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Preparation of Esters by Hemiacetal Oxidation

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The direct formation of esters by the oxidation of primary alcohols has been shown to occur by the reaction sequence: alcohol → aldehyde ⇌ hemiacetal → ester, rather than by the commonly accepted path: alcohol → aldehyde → acid → ester. Hemiacetal oxidation presents a possible alternative to acid-alcohol esterification as a biogenetic pathway for the formation of certain long chain esters.

The oxidation of *n*-butyl alcohol with dichromate and sulfuric acid was reported[2] to give *n*-butyl butyrate in 75% yield after two-six hours heating. This process is the basis of the *Organic Syntheses* preparation[3] of the ester (41–47% yield); in both instances the reaction is assumed to involve an esterification as the final step. The method, and the presumed course of the reaction, was derived from early observations on the oxidation of primary alcohols. For example, *n*-propyl propionate (75–76%) and *n*-butyl butyrate (87–88%) were obtained[4] by the oxidation of the corresponding alcohols at 0°, and *n*-hexyl hexanoate was obtained as a by-product in the oxidation of *n*-hexyl alcohol.[5] Decanol was reported[6] to give an excellent yield of decyl decanoate on oxidation at 100°. The aldehyde (frequently the objective in early work[6]) was recognized as an intermediate step in the oxidative process, and it was concluded that the oxidation proceeded to the acid and that esterification followed.

It was observed by one of us[7] that mild oxidation (chromic acid–sulfuric acid, 10–15°) of 3-phenylpropanol-1 gave a 53% yield of 3-phenylpropyl β-phenylpropionate, and it was suggested that the reaction course involved hemiacetal oxidation rather than esterification:

$$R_1CHO + R_2{-}CH_2OH \rightleftharpoons R_1CHOCH_2R_2 \longrightarrow R_1COOCH_2R_2$$

(OH on the hemiacetal)

The reversible formation of hemiacetals is known to occur readily as a proton-catalyzed reaction.[8] The fact that hemiacetal oxidation might be a road to esters was recognized by Schulz,[9] who oxidized decanol to decyl decanoate (32%) and a lauryl alcohol–decanal mixture (1:1) to obtain both lauryl decanoate and dodecanoate. No systematic investigation of this reaction, however, has been undertaken. It has been shown[10] that two stable cyclic hemiacetals, and also an equimolecular mixture of an aldehyde and an alcohol, showed much faster oxidation rates than did the aldehyde or alcohol alone; moreover, the formation of hemiacetals from an alcohol and an aliphatic aldehyde is known to occur readily,[11] and has been followed by physical measurements.[8] These facts argue strongly for the hemiacetal as the precursor of ester formed by oxidation of an alcohol.

These reactions are of interest for two reasons. First, a simple preparation of symmetrical esters would be of some value in synthetic work, requiring only the use of the alcohol (readily purified by distillation and checked for homogeneity by vapor phase chromatography) as starting material, and affording an extremely pure ester, free from homologous contaminants so often introduced by the use of incompletely purified acids. Second, the formation of long chain esters of the cetyl palmitate type occurs in mammalian metabolism (whale), and hemiacetal oxidation has never been considered as a possible biogenetic pathway for this or any other naturally occurring ester. The present preliminary study was undertaken to determine if the hemiacetal oxidation hypothesis was tenable, and to discover suitable experimental conditions for the preparation of long chain esters by this route.

The oxidation of a heptanol-1: heptanal mixture (1:1) with chromic acid-sulfuric acid was examined under a variety of conditions (Table I). The best yield of *n*-heptyl heptanoate, 73%, was obtained with the most polar solvent used, acetic acid, and when a similar oxidation was carried out with the alcohol alone the yield of ester was 90%. When a ten-fold excess of the alcohol was used with one equivalent of both aldehyde and oxidant, the

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(2) J. Reilly and W. J. Hickinbottom, *Sci. Proc. Roy. Dub. Soc.*, **16**, 233 (1921).

(3) G. R. Robertson, *Org. Syntheses*, Coll. Vol. I, 138 (1941).

(4) J. Pierre and E. Puchot, *Ann.*, **163**, 271 (1872).

(5) A. Franchimont and T. Zincke, *Ann.*, **163**, 193 (1872).

(6) L. Bouveault, *Bull. Soc. Chim.*, [2], **31**, 1306 (1904).

(7) J. Cymerman Craig, E. G. Davis, and J. S. Lake, *J. Chem. Soc.*, 1874 (1954).

(8) E. R. Alexander, *Principles of Ionic Organic Reactions*, J. Wiley and Sons, Inc., New York, N. Y., 1950, p. 158.

(9) L. Schulz, *Ann. Repts. Ess. Oils*, Schimmel and Co., **1938**, 119.

(10) W. A. Mosher and D. M. Preiss, *J. Am. Chem. Soc.*, **75**, 5605 (1953).

(11) Schimmel and Co., *Ann. Repts. Ess. Oils*, **1933**, 71.

yield of ester fell to 40%, and 56% of heptanal di-*n*-heptyl acetal was formed as well. These results suggested that the expected aldehyde ⇌ hemiacetal ⇌ acetal equilibrium was present. When sulfuric acid was omitted from the reaction mixture in acetic acid solution, the yield fell from 90% for the alcohol alone to 33%. It is well known that the intensity of carbonyl absorption of alcoholic solutions of aldehydes and ketones is greatly reduced on the addition of mineral acid,[12] and the reaction of hemiacetal formation is taken to proceed through an oxonium salt intermediate, explaining the sulfuric acid effect. Hemiacetals may be isolated as chemical individuals; Erickson and Campbell[13] characterized the hemiacetal of lauraldehyde and lauryl alcohol (formerly regarded as a higher-melting crystalline modification of lauraldehyde).

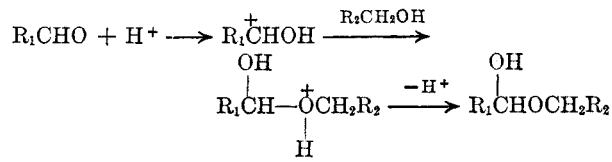


TABLE I

ESTER FORMATION FROM HEPTANOL-1 AND HEPTANAL

Solvent	Temp.	Mole Ratio Aldehyde	Mole Ratio Alcohol	Mole Ratio Oxidant	Yield, %
Acetone	10	1	1	1	47
Acetone	10	1	1	2	48
Benzene	25	1	1	1	33
Benzene	10	1	1	1	50
Acetic acid	10	1	1	1	73
Acetone	10	0	1	2	72
Acetic acid	10	0	1	2	90
Acetic acid[a]	10	0	1	2	33
Acetic acid	10	1	10	1	40[b]

[a] The sulfuric acid was omitted. [b] 56% of heptanal di-*n*-heptyl acetal was also obtained.

When the components required for esterification were maintained under the same reaction conditions, but without the oxidant, no ester was found; this was tried with a 1:1 mixture of heptanol-1 and heptanoic acid. Moreover, no trace of *n*-heptyl acetate could be detected by vapor phase chromatography when acetic acid was used as solvent in the formation of *n*-heptyl heptanoate from heptanol-1. Mosher and Preiss[10] have similarly reported that oxidation of *n*-butyl alcohol in 70% acetic acid gave only *n*-butyl butyrate, no *n*-butyl acetate being found. The failure to esterify in the absence of the oxidant and the lack of ester formation with the acetic acid present effectively exclude the possibility of an acid-catalysed esterification as the mechanism, and afford conclusive evidence that the step leading to the ester is an oxidative one.

When benzyl alcohol was used as the starting alcohol, oxidation to the aldehyde occurred, but no ester was formed. This was in agreement with earlier work,[11] and the result has been ascribed to the failure of aromatic aldehydes to form hemiacetals. The lack of success of Mosher and Preiss' attempt[10] to obtain an ester from the oxidation of a mixture of ethanol and 2,4,6-trimethylbenzaldehyde is probably due to the same reason.

Methanol might be expected to form a hemiacetal more readily than other alcohols, and it should be possible to prepare methyl esters by hemiacetal oxidation. This was tested by examining the oxidation of heptanal-methanol mixtures. The expected ester was formed in 28–61% yield (depending on the conditions); unchanged aldehyde was present at all times, showing that methanol was being oxidized at a comparable rate to that of the hemiacetal. That oxidation of the aldehyde to the acid did not occur preferentially to hemiacetal oxidation was indicated by an experiment in which one-half of the theoretical amount of oxidant was used; the products were the ester (52%) and recovered aldehyde (45%). In this and other experiments, gas phase chromatography was particularly useful in determining the composition of product mixtures. When phenylacetaldehyde dimethyl acetal was used with methanol in acetic acid solution, and with the usual oxidant, the products included 35% of methyl phenylacetate and 32% of unchanged acetal.

This method of making methyl esters, although not of preparative significance, may be useful in special instances. It is doubtless the reaction involved in the conversion of *dl*-pseudoyohimbaldehyde into *dl*-pseudoyohimbine by means of chromic acid–sulfuric acid in methanol-acetone solution.[14]

The fact that lauraldehyde and lauryl alcohol form a well defined hemiacetal suggested that the reaction might be applicable to long-chain compounds. When cetyl alcohol was used, the product was cetyl palmitate (48–51%) identical with a synthetic sample. The shortest chain alcohol used was *n*-butyl alcohol, and the ester yield in this case was 57–61%.

It has been reported,[15–17] that the rate of hemiacetal formation decreases markedly with increased branching around the hydroxyl group, but there is also a description[18] of hemiacetal

(12) O. Wheeler, *J. Am. Chem. Soc.*, **79**, 4191 (1957).

(13) J. L. E. Erickson and C. R. Campbell, *J. Am. Chem. Soc.* **76**, 4472 (1954).

(14) E. C. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm, and P. E. Aldrich, *J. Am. Chem. Soc.*, **80**, 5006 (1958).

(15) W. Herold, *Z. Elektrochem.*, **39**, 566 (1933).

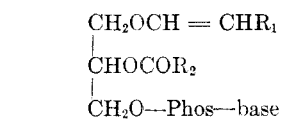
(16) B. N. Rutovski and K. S. Zabrodina, *J. Appl. Chem. U.S.S.R.*, **11**, 302 (1938).

(17) F. E. McKenna, H. V. Tartar, and E. C. Lingafelter, *J. Am. Chem. Soc.*, **75**, 604 (1953).

(18) G. W. Mast and F. E. Anderson, U. S. Patent 2,657,241 (1953); Chem. Abstr., **48**, 12168 (1954).

formation from tertiary alcohols. The oxidation of a cyclohexanol-heptanal mixture (1:1) gave 50% of cyclohexyl heptanoate. When the reaction was extended to cholesterol, oxidation to 4-cholesten-3-one[19] and other products[20] was a competitive reaction. However, yields of up to 10% of cholesteryl heptanoate were obtained. No attempt was made to extend this reaction to longer chain substances.

It is not yet possible to say whether ester formation occurs in this way in any biological environment. Nevertheless, there are indications that this reaction pathway is compatible with observations relating to long chain compounds. There are two circumstances that are particularly pertinent. One of these is the occurrence of plasmalogens in mammalian tissues. These compounds are vinyl ethers possibly derived from a C-1 reaction with a long chain aldehyde followed by dehydration of the hemiacetal intermediate:



Early investigations suggested a hemiacetal formulation; the current view[21,22] is that a vinyl ether structure is present, and that the principal groups correspond in chain length to C:18 and C:16 parent aldehydes.[23,24] An analogous saturated ether structure is also known to exist; a recent paper described such a C-1 long chain (C:16 or C:18) ether derivative.[25] While the occurrence of plasmalogens cannot be taken as evidence that the esterification process leading to phopholipids of the lecithin-cephalin group occurs by hemiacetal oxidation at the C-1 position, it is nevertheless possible that a hemiacetal dehydration process of this kind may be connected with the plasmalogen level in a given tissue.

The formation of long chain esters of the cetyl palmitate type in whales and elsewhere is generally regarded to occur by a reaction involving some kind of active palmitate, but the possibility of an alternate pathway involving hemiacetal oxidation has apparently been completely overlooked. In this connection, recent studies of the bacterial oxidation of long chain hydrocarbons are of interest.[26] The product of bacterial metabolism of hexadecane was cetyl palmitate. The oxidation process required oxygen of the air (by O^{18} experiments) as is typical of biological hydroxylations. The O^{18} experiments showed some dilution; this may have occurred by aldehyde hydration. When octadecane was used as a substrate, the metabolic products were octadecyl stearate and octadecyl palmitate. Current knowledge permits only the view that the reaction sequence leading to cetyl palmitate from hexadecane is essentially hexadecane → cetyl alcohol → palmitaldehyde → palmitic acid → cetyl palmitate, with the esterification occurring through an intermediate that might be palmitoyl Co-A. It seems equally possible that the metabolic oxidation sequence might be: Hexadecane → cetyl alcohol → palmitaldehyde → hemiacetal of palmitaldehyde and cetyl alcohol →cetyl palmitate.

If hydration of the aldehyde occurs as a reversible process, followed by formation and oxidation of the hemiacetal, then the O^{18} originally present in the aldehyde will be distributed at random with O^{16} from water in the medium, leading to a 75% incorporation of O^{18} in the final ester, in agreement with the experimental result.[26]

The chemical evidence suggests that oxidation of a hemiacetal is considerably easier than the corresponding aldehyde oxidation, and that hemiacetal formation and oxidation can occur concurrently for both long and short chain aldehyde-alcohol combinations. From a metabolic point of view, it might be advantageous to have two alternate routes of ester formation, with different degrees of specificity. The hemiacetal pathway might be relatively nonspecific. Further investigations in the general field of hemiacetals and thiohemiacetals are in progress.

EXPERIMENTAL[27]

Chromic–sulfuric acid solution. This contained 20 g. of chromic acid in 150 ml. of aqueous solution containing 35 ml. of sulfuric acid.

Oxidation of heptanol-1 and heptanal. (*A*). To a well stirred solution of 1.16 g. 0.01 mole) of heptanol-1 and 1.14 g. (0.01 mole) of heptanal in 10 ml. of acetone cooled to 0°, 5 ml. of the chromic–sulfuric acid solution were added over a period of 15 min., keeping the internal temperature below 10°. After stirring for 15 min. longer at 10° (internal), the mixture was treated with 50 ml. of water and extracted with ether. The combined ether extracts were washed with sufficient 10% sodium hydroxide solution to remove all acid, and then with water, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was kept at 100° (bath temperature) under a short column at

(19) A. Butenandt and J. Schmidt-Thome, *Ber.*, **69**, 882 (1936).

(20) W. C. J. Ross, *J. Chem. Soc.*, 739 (1946).

(21) G. V. Marinetti, J. Erbland, and E. Stotz, *J. Am. Chem. Soc.*, **80**, 1624 (1958).

(22) M. M. Rapport, B. Lemer, N. Alonzo, and R. E. Franzl, *J. Biol. Chem.*, **225**, 859 (1957).

(23) H. Debuch, *Biochem. J.*, **67**, 27P (1957).

(24) G. M. Gray, *Biochem. J.*, **70**, 425 (1958).

(25) H. E. Carter, D. B. Smith, and D. N. Jones, *J. Biol. Chem.*, **232**, 681 (1958).

(26) J. E. Stewart, R. E. Kallio, D. P. Stevenson, A. C. Jones, and D. O. Schissler, *J. Bacteriol.*, **78**, 441 (1959); J. E. Stewart and R. E. Kallio, *J. Bacteriol.*, **78**, 726 (1959).

(27) Melting points were taken on a Kofler block. Ultraviolet and infrared spectra were measured on a Cary model 11 recording spectrophotometer and on a Perkin-Elmer model 21 or Beckman model IR7 double beam recording spectrophotometer by Mrs. K. Warren. Vapor phase chromatograms were run at 150–180° on a Barber-Colman model 10 gas chromatograph, the stationary phase being a glutaric acid–diethylene glycol polyester on Chromosorb-W (15%) and the column being 2 m. long.

0.5 mm. for half an hour, leaving 1.08 g. (47%) of a colorless oil identified as *n*-heptyl heptanoate, b.p. 96–97° (1 mm.), n_D^{20} 1.4320, by identity of its infrared spectrum and its retention time, with that of an authentic sample.

(*B*). An experiment identical with (A), but using 10 ml. of chromic–sulfuric acid solution, gave 1.10 g. (48%) of *n*-heptyl heptanoate, n_D^{20} 1.4322, identified as before.

(*C*). A solution of 2.32 g. (0.02 mole) of heptanol-1 and 2.28 g. (0.02 mole) of heptanal in 40 ml. of benzene was cooled in ice and 10 ml. of the chromic–sulfuric solution was added over 15 min., keeping the internal temperature below 25°. After being stirred for a further 2 hrs., the mixture was worked up as described above, to yield 1.5 g. (33%) of *n*-heptyl heptanoate, n_D^{22} 1.4309, identified as before.

(*D*). An experiment identical with (A), but using 20 ml. of benzene as solvent instead of acetone, gave, after oxidation at 10°, a red benzene layer. The color was not removed by water or bicarbonate solution, but was instantly removed by 1% sodium hydroxide solution. This was presumably a chromate ester.[28] The product was 1.14 g. (50%) of *n*-heptyl heptanoate, n_D^{20} 1.4322, identified as before.

(*E*). An experiment identical with (A) but using 5 ml. of acetic acid as solvent instead of acetone, gave 1.67 g. (73%) of *n*-heptyl heptanoate, n_D^{20} 1.4322, identified as before.

Oxidation of heptanol-1 (*A*). A well stirred solution of 2.32 g. (0.02 mole) of heptanol-1 in 10 ml. of acetone cooled to 0° was treated dropwise over 15 min. with 10 ml. of chromic–sulfuric acid solution, keeping the internal temperature below 10°. After stirring (10°) for a further 15 min., the product was isolated as before to give 1.65 g. (72%) of *n*-heptyl heptanoate, n_D^{22} 1.4310.

(*B*). Repetition of the experiment using 5 ml. of acetic acid as solvent instead of acetone, gave 2.05 g. (90%) of *n*-heptyl heptanoate, n_D^{20} 1.4328.

(*C*). A solution of 20 g. of chromic acid in 150 ml. of solution, containing 70 ml. of glacial acetic acid, was made up. This contained an equivalent amount of acetic acid instead of the sulfuric acid used previously. An experiment identical with (*B*), but using 10 ml. of this chromic–acetic acid solution, was carried out. The acetic acid was neutralized at 5° with 10% sodium hydroxide solution. The product was 0.77 g. (33%) of *n*-heptyl heptanoate, n_D^{20} 1.4327.

Heptanol-1 and heptanoic acid. A stirred solution of 1.16 g. (0.01 mole) of heptanol-1 and 1.33 g. (0.01 mole) of heptanoic acid in 5 ml. of acetic acid was treated at 10° with 5 ml. of water containing 1.2 ml. of sulfuric acid, but no chromic acid. Stirring was continued for 30 min., and the mixture was worked up as described. A trace (90 mg.) of an unidentified residue, n_D^{22} 1.4650, remained. No *n*-heptyl heptanoate or acetate was detected.

Oxidation of excess of heptanol-1 and heptanal. A stirred mixture of 11.6 g. (0.1 mole) of heptanol-1 and 1.14 g. (0.01 mole) of heptanal in 10 ml. of acetic acid was treated at 10° with 5 ml. of chromic-sulfuric solution over 15 min. After a further 15 min. stirring at 10°, excess heptanol was distilled off at 53° (1.5 mm.), (8.25 g. was collected). The residue boiled at 100–150° (1 mm.), n_D^{24} 1.4348. The yield was 2.9 g. Infrared spectroscopy showed strong absorption bands at 1745 cm.$^{-1}$ (ester) and at 1047, 1073, and 1119 cm.$^{-1}$ (acetal). The material gave a positive hydroxamic acid test for esters, and a positive 2,4-dinitrophenylhydrazone test after heating. Treatment of 0.164 g. of the mixture with 25 ml. of a solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid at 100° for 20 min. gave 0.083 g. (56%) of heptanal 2,4-dinitrophenylhydrazone (m.p. and mixed m.p. 107–108°). The mixture consisted of 1.72 g. (56%) of heptanal di-*n*-heptyl acetal and 1.18 g. (40%) of *n*-heptyl heptanoate. The composition was confirmed by gas chromatographic analysis.

Oxidation of phenylacetaldehyde dimethylacetal. A stirred mixture of 6.64 g. (0.04 mole) of phenylacetaldehyde dimethylacetal and 1.3 g. of methanol (0.04 mole) in 6 ml. of acetic acid was treated at 10° over 15 min. with 60 ml. of chromic–sulfuric acid solution. The mixture was treated at 0° with 45 ml. of 10% sodium hydroxide solution, and the products were isolated as usual. Distillation gave 4.7 g. of oil, b.p. 217–219° (760 mm.), n_D^{25} 1.5077. Infrared spectroscopy showed the presence of ester and acetal, with a trace of free aldehyde, and gas chromatography indicated the composition of the mixture to be 9.5% of aldehyde, 46% of acetal, and 44% of methyl phenylacetate. Estimation of total aldehyde was carried out as described above, and 0.33 g. of the mixture yielded 0.315 g. of the 2,4-dinitrophenylhydrazone of phenylacetaldehyde (using 2,4-dinitrophenylhydrazine reagent in 2*N* hydrochloric acid), corresponding to 52.5% content of aldehyde plus acetal, in good agreement with the gas chromatographic analysis. The total yields were 2.1 g. (35% overall) of methyl phenylacetate, 2.15 g. (32% recovery) of phenylacetaldehyde dimethylacetal, and 0.45 g. (9.5%) of free phenylacetaldehyde.

Oxidation of benzyl alcohol. Treatment of 2.16 g. (0.02 mole) of benzyl alcohol in 5 ml. of acetic acid with 10 ml. of chromic–sulfuric acid solution at 10° for 15 min., followed by stirring for a further 15 min. at 10°, gave 1.15 g. of a mixture of benzaldehyde, benzyl alcohol, and a little benzoic acid. No benzyl benzoate was detected.

Oxidation of heptanal and cyclohexanol. Oxidation of 1.14 g. (0.01 mole) of heptanal and 1.0 g. (0.01 mole) of cyclohexanol in 5 ml. of acetic acid at 10° with 5 ml. of chromic–sulfuric acid solution gave 1.05 g. (50%) of cyclohexyl heptanoate, b.p. 98° (0.5 mm.), n_D^{25} 1.4450, identical in properties with an authentic sample (infrared spectroscopy and gas chromatography).

Oxidation of heptanal and cholesterol. (A). To a stirred solution of 4 g. (0.035 mole) of heptanal and 2.02 g. (0.005 mole) of cholesterol in 40 ml. of acetic acid at 15°, 2.5 ml. of chromic–sulfuric acid solution were added over 5 min., and stirring was continued for a further 10 min. at 15°. After addition of 140 ml. of 10% sodium hydroxide solution at 0°, the mixture was extracted with methylene chloride and ether, and the products were isolated as usual. The material (2.15 g., 85%) showed infrared absorption bands at 1676, 1735, 3450, and 3600 cm.$^{-1}$, and the ultraviolet spectrum (isooctane) showed λ_{max} 232 mμ, ε 2250 (calc. on mol. wt. 384), corresponding to 14% of conjugated cholestenone.[29] Chromatography on silicic acid (100–200 mesh) of 100 mg. of the reaction product [using 6% benzene–hexane (v/v)] gave 4 mg. of cholesteryl heptanoate as needles, m.p. and mixed m.p. 110–111°, and identical in infrared spectrum with an authentic specimen.

(B). A mixture of 2.28 g. (0.02 mole) of heptanal and 1.01 g. (0.0025 mole) of cholesterol in 25 ml. of acetic acid and 50 ml. of acetone at 5° was treated with 0.25 ml. of *N* sulfuric acid and stirred for 5 min. at 5°. The solution was then treated with 1.25 ml. of chromic–sulfuric acid solution at 5° over 5 min., and stirred for a further 10 min. at the same temperature. Working up as before gave 1.15 g. of solid residue, showing identical infrared absorption with that of the product (A).

Chromatography of 100 mg. of the crude reaction product on silicic acid afforded 8 mg. (7.5%) of pure cholesteryl heptanoate, m.p. 109–110.5°, identical with authentic material in melting point and infrared spectrum.

(C). An experiment identical with (A), with 1.14 g. (0.01 mole) of heptanal and 0.386 g. (0.001 mole) of cholesterol in 20 ml. of acetic acid and 20 ml. of acetone, was carried out. The oxidation was effected at 5° during 5 min. with 0.6 ml. of chromic–sulfuric acid solution, with further stirring at 5° for 10 min. After chromatography on silicic acid, 35 mg. (7.5%) of cholesteryl heptanoate, m.p. and mixed m.p. 110.5–111.5°, was obtained.

(28) W. A. Waters, *Quart. Revs.* **12**, 277 (1958); F. Holloway, M. Cohen, and F. H. Westheimer, *J. Am. Chem. Soc.* **73**, 65 (1951); M. Cohen and F. H. Westheimer, *J. Am. Chem. Soc.* **74**, 4380 (1952).

(29) H. Mohler, *Helv. Chim. Acta*, **20**, 289 (1937).

(D). An experiment identical with (C), but in which the solution of heptanal and cholesterol was allowed to stand 30 min. at 25° after the addition of 0.25 ml. of 5*N* hydrochloric acid, was carried out. The crude product contained 8.5% of conjugated cholestenone (ϵ 1370 at 232 mμ); 49 mg. (10%) of cholesteryl heptanoate was obtained as before, and had m.p. and mixed m.p. 110–111°.

Oxidation of cetyl alcohol. A solution of 4.84 g. (0.02 mole) of cetyl alcohol in 20 ml. of acetic acid and 10 ml. of acetone at 15° was treated with 10 ml. of chromic–sulfuric acid solution over 15 min., and stirred a further 15 min. at 25°. Addition of 130 ml. of 10% sodium hydroxide solution at 0°, followed by working up as usual, gave 2.33–2.48 g. (48.5–51.5%) of cetyl palmitate, m.p. and mixed m.p. 49.5–50.5°, identical in infrared spectrum with an authentic specimen.

Oxidation of heptanal and methanol. (*A*). A mixture of 2.28 g. (0.02 mole) of heptanal and 0.64 g. (0.02 mole) of methanol in 5 ml. of acetic acid was treated at 10° with 10 ml. of chromic-sulfuric solution during 15 min. After a further 15 min. stirring at 10°, the mixture was worked up as usual. Distillation gave 2.3 g., b.p. 48–62° (12 mm.), n_D^{24} 1.4098, shown by gas chromatography to consist of 1.5 g. (65%) of recovered aldehyde and 0.8 g. (28% yield) of methyl heptanoate, identical in retention time with an authentic specimen.

(*B*). Repetition of the experiment with 6.4 g. (0.2 mole) of methanol gave 2 g. of product, b.p. 63–65° (12 mm.), n_D^{25} 1.4096, consisting of 0.5 g. (22%) of recovered aldehyde and 1.5 g. (52% yield) of the methyl ester.

(*C*). When a mixture of 2.28 g. (0.02 mole) of heptanal and 6.4 g. (0.2 mole) of methanol in 3 ml. of acetic acid was treated with 20 ml. of chromic-sulfuric acid solution at 10° during 20 min., (stirred for a further 10 min. at 10°), the product was 2.5 g., b.p. 56–66° (12 mm.), n_D^{24} 1.4097, consisting of 1.65 g. of methyl heptanoate (57%) and 0.85 g. (37%) of heptanal (by gas chromatography).

(*D*). Repetition of experiment (C) using 30 ml. of chromic-sulfuric acid solution (added over 30 min. at 10°), afforded 2.6 g. of product, n_D^{24} 1.4102, containing 1.75 g. (61%) of methyl ester and 0.85 g. (37%) of recovered aldehyde.

(*E*). When experiment (C) was repeated with only 5 ml. of chromic-sulfuric acid solution, the product was 2.45 g., b.p. 56–66° (12 mm.), n_D^{24} 1.4098, consisting of 1.7 g. of recovered aldehyde (*i.e.* 1.14 g. (0.01 mole) plus 0.56 g. (45% of 0.01 mole) and 0.75 g. (52% yield of 0.01 mole) of methyl heptanoate.

Oxidation of n-butyl alcohol. A solution of 14.8 g. (0.2 mole) of *n*-butyl alcohol in 10 ml. of acetic acid was cooled to 10°, and 100 ml. of chromic-sulfuric acid solution was added over 30 minutes at 10°. At 0–10°, 28 ml. of 50% sodium hydroxide solution was added, and the mixture was extracted with ether. The combined extracts were washed with 10% sodium hydroxide solution, with water, and dried over magnesium sulfate. Distillation through a short Vigreux column gave 8.2–8.8 g. (57–61%) of *n*-butyl butyrate, b.p. 164–166°, n_D^{25} 1.4032, identical in its infrared spectrum and retention time with an authentic sample.

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Polyfunctional Acids and Alcohols from Tetrachloro-*o*-xylene, Tetrachloro-*p*-xylene, and Trichloromesitylene

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Procedures are described for the ω-chlorination of tetrachloro-*o*-xylene, for the ω-bromination of tetrachloro-*o*-xylene, tetrachloro-*p*-xylene, and trichloromesitylene and for replacement of the bromine by hydroxyl (*via* the acetates), by carboxymethyl (*via* malonic ester alkylation), by phenyl (*via* the Friedel-Crafts reaction), and by *n*-propoxy (*via* reaction with sodium propoxide in *n*-propyl alcohol).

In connection with studies of condensation polymers, we have prepared the polyfunctional carboxylic acids and alcohols, which are described in the experimental section. The structural feature which these compounds have in common is a fully-substituted, highly chlorinated benzene ring. The aromatic ring, when properly inserted as an element in a polymer chain, is known to raise the melting point and increase the thermal stability of a polymer.[2] As these compounds are highly chlorinated, they also offer the possibility of conferring flame retarding properties on a polymer.

The synthetic approach adopted was to use the methyl groups in three known compounds, tetrachloro-*o*-xylene,[3] tetrachloro-*p*-xylene,[3a,c,4] and trichloromesitylene[3a,c,5], as handles for the introduction of either the alcohol or acid functions. When adapted to the xylenes, the general ring-chlorination procedure of Silberrad[6] proved more convenient than the methods described in the references above. Although we did succeed in preparing both 1-methyl-2-chloromethyl-3,4,5,6-tetrachlorobenzene and 1,2-bis(chloromethyl)-3,4,5,6-tetrachlorobenzene, and 1,4-bis(chloromethyl)-2,3,-5,6-tetrachlorobenzene was known,[4c] the synthetic

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(2) R. Hill and E. E. Walker, *J. Polymer Sci.*, **3**, 609 (1948); E. F. Izard, *J. Polymer Sci.*, **8**, 503 (1952).

(3) (a) R. L. Datta and F. Fernandes, *J. Org. Chem.*, **38**, 1810 (1916). (b) L. E. Hinkel, *J. Chem. Soc.*, **117**, 1296 (1920). (c) P. G. Harvey, F. Smith, M. Stacey, and J. C. Tatlow, *J. Applied Chem.*, **4**, 325 (1954).

(4) (a) E. Bures and T. Rubes, *Casopis Ceskoslov Lekarnictva*, **8**, 225, 228 (1928); *Chem. Abstr.*, **23**, 3674 (1929). (b) *Ibid., Collection Czechoslov Chem. Communications*, **1**, 648 (1920); *Chem. Abstr.*, **24**, 1851 (1930). (c) P. Ruggli and F. Brandt, *Helv. Chim. Acta.*, **27**, 274 (1944).

(5) E. T. BcBee and R. E. Leech, *Ind. Eng. Chem.*, **39**, 393 (1947).

(6) O. Silberrad, *J. Chem. Soc.*, **127**, 1267 (1925).