Synthesis and Physical Properties of Normal Higher Primary Alcohols. III. Synthesis of Normal Higher Primary Alcohols of Even Carbon Numbers from Dodecanol to Hexatriacontanol

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In the previous investigation of this series[1,2] the author confined his attention to the synthesis of normal higher alcohols of odd carbon numbers. In view of the interesting results on the physical properties, especially the transition phenomena of these alcohols in the solid state, it was felt desirable to extend the study to alcohols of even carbon numbers, and thirteen members with even carbon atoms ranging from C_{12} to C_{36} were synthesized and their transition points were observed.

The alcohols were all prepared by the lithium aluminum hydride reduction of the corresponding fatty acids or their ethyl esters, of which acids from C_{12} to C_{22} were obtained by careful purification of commercial specimens.

Tetracosanoic acid ($C_{23}H_{47}CO_2H$) was synthesized from docosyl bromide ($C_{22}H_{45}Br$) by the modified malonic ester synthesis[3]. The method employed for the synthesis of the fatty

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1) A. Watanabe, This Bulletin, 32, 1295 (1959).
2) A. Watanabe, ibid., 33, 531 (1960).
3) W. Bleyberg et al., *Ber.*, 64, 2506 (1931).

acids with more than 24 carbon atoms is Bowman's synthesis:

$$C_2H_5O_2C(CH_2)_nBr \xrightarrow{\text{Ethyl malonate}} \underset{\text{(I)}}{}$$

$$C_2H_5O_2C(CH_2)_nCH(CO_2C_2H_5)_2 \xrightarrow{\text{Benzyl alcohol}} \underset{\text{(II)}}{}$$

$$C_6H_5CH_2O_2C(CH_2)_nCH(CO_2CH_2C_6H_5)_2 \xrightarrow{RCOCl} \underset{\text{(III)}}{}$$

$$C_6H_5CH_2O_2C(CH_2)_nC(CO_2CH_2C_6H_5)_2COR \xrightarrow{H_2(Pd)} \underset{\text{(IV)}}{}$$

$$HO_2C(CH_2)_nC(CO_2H)_2COR \xrightarrow{\text{Decarboxylation}} \underset{\text{(V)}}{}$$

$$RCO(CH_2)_{n+1}CO_2H \xrightarrow[\text{reduction}]{\text{Huang-Minlon}} \underset{\text{(VI)}}{}$$

$$R(CH_2)_{n+2}CO_2H \xrightarrow[LiAlH_4]{\text{Esterification}} R(CH_2)_{n+3}OH$$
$$\text{(VII)} \qquad\qquad \text{(VIII)}$$

Although this method was extensively applied in the preparation of odd members[1,2], the yields of the ketonic acids were low and fluctuated (maximum 37%) compared with those obtained by Bowman (70%). Nunn[4] and Hougen[5] reported similar low yields, and ascribed them to the ketonic hydrolysis of the ketoesters, although their studies appeared not to be extensive. Since it was felt necessary to increase the yield and convenience in order to develop the present study, several improvements in the synthetic technique were made and the results are reported in this paper.

It was found that partial hydrolysis of triester II occurred in spite of precautions during the reaction of alcoholysis as evidenced by the isolation of the carboxylic acid from the reaction mixture in an amount of 30% to the starting triester and by the recovery of a nearly corresponding amount of benzyl alcohol. It seemed quite probable that the presence of this acid and the alcohol was detrimental to the subsequent malonic ester condensation. The procedures were then improved as follows, giving the desired product with a fairly good and consistent yield.

After the alcoholysis the acid was removed with a sodium carbonate solution and benzyl alcohol was distilled off under reduced pressure. Tribenzyl ester III, freed from the acid and benzyl alcohol and obtained as an oil, was condensed with an acid chloride by means of sodium ethoxide to give compound IV. Hydrogenolysis of compound IV and subsequent decarboxylation yielded ketonic acid VI in a yield of 65% based on the acid chloride. Details of the procedures are given in the Experimental Part.

In order to avoid the hydrolysis of triester II, the use of sulfuric acid, hydrogen chloride, and zinc chloride as the catalysts for the alcoholysis were attempted with no success. Metallic sodium, instead of sodium ethoxide, was used in the malonic ester condensation without success, probably because the hydrogen from the reaction of sodium with the malonic ester cleaved the benzyl groups.

Another factor which affects the yield is the instability of compound IV as shown by the fact that this compound was decomposed even at room temperature by the hydrochloric acid liberated from the unchanged acid chloride on washing the reaction mixture with water. At temperature low enough to be harmless to the compound it was quite difficult to decompose the acid chloride with water when the carbon chain of the acid was long. Therefore, it is advisable to use slightly less than one equivalent of the acid chloride to obtain a good yield.

It has been known that Bowman's synthesis suffers from the catalyst poisoning which can not be avoided on account of the difficulty in purification of compound IV, and it was experienced in the previous study[2] that a long period was required for complete hydrogenolysis when the intermediate acid chloride could not be purified by distillation. However, in the present experiments, it was found advantageous to purify compound IV with activated aluminum oxide, permitting the complete hydrogenolysis with great saving in time and catalysts and with no lowering of the yield of ketonic acid V.

The ketonic acids thus obtained were all converted into the corresponding fatty acids by Huang-Minlon reduction[6] and the desired alcohols were obtained easily by the lithium aluminum hydride reduction of the fatty acids or their ethyl esters. The alcohols were purified with great care to obtain the final products with sharp melting points and excellent analytical values. For hexacosanol $C_{26}H_{53}OH$ and higher alcohols high vacuum (2×10^{-3} mmHg) distillation as well as recrystallization was employed.

An alternative chain-lengthening process for the synthesis of octacosanol $C_{28}H_{57}OH$ is Cason's method[7], which consists in the condensation of a dialkyl cadmium with a halfester-acid chloride. The accompanying flow chart indicates the reaction:

4) J. R. Nunn, *J. Chem. Soc.*, **1951**, 1742.
5) F. W. Hougen et al., ibid., **1953**, 98.
6) Huang-Minlon, *J. Am. Chem. Soc.*, **66**, 839 (1944).
7) J. Cason, ibid., **68**, 2078 (1946).

TABLE I

Alcohol	Formula	Calcd. C	Calcd. H	Found C	Found H	M. p., °C	F. p., °C	T. p., °C
Dodecyl	$C_{12}H_{26}O$	77.35	14.07	77.46	14.00	22.5(24.0[a])	22.3	
Tetradecyl	$C_{14}H_{30}O$	78.43	14.11	78.36	13.90	39.0(37.7[b])	37.5	33.5
Hexadecyl	$C_{16}H_{34}O$	79.26	14.14	79.02	14.22	48.5(49.0[c])	48.0	42.5
Octadecyl	$C_{18}H_{38}O$	79.92	14.16	80.11	14.25	58.5(58.5[d])	58.0	50.0
Eicosyl	$C_{20}H_{42}O$	80.46	14.18	80.41	14.02	65.3(66.5[e])	64.2	55.5
Docosyl	$C_{22}H_{46}O$	80.90	14.20	80.86	14.07	70.4(70.8[e])	69.3	61.0
Tetracosyl	$C_{24}H_{50}O$	81.28	14.21	81.43	14.29	76.0(75.3[e])	75.7	68.0
Hexacosyl	$C_{26}H_{54}O$	81.60	14.22	81.70	14.48	78.8(79.2[e])	78.2	73.0
Octacosyl	$C_{28}H_{58}O$	81.87	14.23	81.75	14.10	82.5(82.6[e])	82.0	
Triacontyl	$C_{30}H_{62}O$	82.11	14.24	82.22	14.19	86.3(86.5[e])	85.5	
Dotriacontyl	$C_{32}H_{66}O$	82.32	14.25	82.40	14.21	88.2(89.2[e])	87.0	
Tetratriacontyl	$C_{34}H_{70}O$	82.51	14.26	82.35	14.20	91.0(91.7[e])	89.5	
Hexatriacontyl	$C_{36}H_{74}O$	82.68	14.26	82.40	14.22	91.6(92.6[e])	89.5	

Melting points are uncorrected.

When a sample was cooled below its freezing point from the melt, a transition appeared with the change of the transparent waxy material into the opaque crystalline state. Transition points of the alcohols higher than hexacosanol could not be observed.

a) F. Krafft, *Ber.*, **16**, 1718 (1883).
b) W. E. Garner et al., *J. Chem. Soc.*, **1927**, 1357.
c) F. Krafft, *Ber.*, **16**, 1721 (1883).
d) P. A. Levene et al., *J. Biol. Chem.*, **59**, 914 (1924).
e) F. Francis et al., *Proc. Roy. Soc.*, **A 158**, 691 (1937).

TABLE II

Ethyl alkane-tricarboxylates	Acid chlorides (Cno.)	Ketonic acid (Cno.)	M. p., °C	Fatty acid	M. p., °C
n-Undecane	Myristoyl (C_{14})	$CH_3(CH_2)_{12}CO(CH_2)_{11}CO_2H(C_{26})$	95.5	Hexacosanoic	86.5(87.7)*
〃	Palmitoyl (C_{16})	$CH_3(CH_2)_{14}CO(CH_2)_{11}CO_2H(C_{28})$	99.5	Octacosanoic	90.2(90.9)
〃	Stearoyl (C_{18})	$CH_3(CH_2)_{16}CO(CH_2)_{11}CO_2H(C_{30})$	102.6	Triacontanoic	93.0(93.6)
n-Octane	Tricosanoyl (C_{23})	$CH_3(CH_2)_{21}CO(CH_2)_8CO_2H(C_{32})$	105.5	Dotriacontanoic	96.0(96.2)
n-Undecane	Docosanoyl (C_{22})	$CH_3(CH_2)_{20}CO(CH_2)_{11}CO_2H(C_{34})$	107.5	Tetratriacontanoic	97.8(98.2)
〃	Tetracosanoyl (C_{24})	$CH_3(CH_2)_{22}CO(CH_2)_{11}CO_2H(C_{36})$	110.0	Hexatriacontanoic	98.5(99.9)

* F. Francis et al., *Proc. Roy. Soc.*, **A 158**, 691 (1937).

$$C_{18}H_{37}OH \xrightarrow{HBr} C_{18}H_{37}Br \rightarrow C_{18}H_{37}MgBr \xrightarrow{CdCl_2} (C_{18}H_{37})_2Cd \xrightarrow{ClOC(CH_2)_8CO_2C_2H_5}$$

$$C_{18}H_{37}CO(CH_2)_8CO_2C_2H_5 \xrightarrow[\text{reduction}]{\text{Huang-Minlon}}$$

$$C_{27}H_{55}CO_2H \xrightarrow[LiAlH_4]{\text{Ethyl ester}} C_{28}H_{57}OH$$

The alcohol obtained by this method was shown to be identical with that obtained by Bowman's method by the mixed melting point and the X-ray data[8].

Melting points, transition points and analytical data of the alcohols synthesized here are given in Table I. The transition points of the alcohols with more than 22 carbon atoms have been unknown. All the alcohols described in this paper and two previous papers, namely odd and even members from C_{11} to C_{37}, are being studied for their physical properties and part of the results has been published from the Department of Physics of Kyoto University[9-11]. Thermal data will be reported in this Bulletin in near future.

Experimental

Since the reactions used for the synthesis of the lower members are well known, descriptions of the experiments are omitted. Bowman's[4] method was applied with some improvements for the synthesis of the alcohols with more than 24 carbon atoms. As the conditions except those for isolation of the products, were essentially the same throughout the series, the synthesis of octacosanol is described as an illustration. Combinations of the starting materials and the intermediates are listed in Table II.

Ethyl n-Undecane-1, 1, 11-tricarboxylate. — It was

8) A. Watanabe, unpublished.

9) K. Tanaka, T. Seto and T. Hayashida, *Bull. Inst. Chem. Res. Kyoto Univ.*, **35**, 123 (1957).
10) K. Tanaka, T. Seto, A. Watanabe and T. Hayashida, ibid., **37**, 281 (1959).
11) K. Asai, *J. Phys. Soc. Japan*, **14**, 1084 (1959).

prepared by condensation of ethyl bromoundecanoate with ethyl malonate as already described[2]).

B. p. 187°C/1 mmHg, n_D^{28} 1.4435.

Benzyl n-Undecane-1, 1, 11-tricarboxylate.—In a 200 ml. three-necked flask, equipped with a mechanical stirrer, a dropping funnel and a reflux condenser fitted with a calcium chloride tube, were placed 0.65 g. of sodium sand (finely powdered in toluene) and 50 ml. of thiophene-free dry benzene. To the mixture was added from the dropping funnel 10 g. of ethyl *n*-undecane-1, 1, 11-tricarboxylate. The mixture was allowed to stand at room temperature for about 6 hr. with stirring and then moderately heated to the complete disappearance of the sodium. After 8.7 g. of freshly distilled benzyl alcohol was added, the condenser was replaced by a Fenske column and the mixture was heated to distill off ethanol as the benzene ethanol azeotrope. During the distillation reflux-ratio was controlled from 6 : 1 to 20 : 1 (2~3 drops per minute). When no more ethanol distilled over, the boiling point reaching 79°C and the absence of the ethanol in the final portion of the distillate being confirmed by the index of refraction, the mixture was cooled and acidified with dilute sulfuric acid. The benzene layer was separated, washed with water, with sodium carbonate solution, again with water to neutral reaction, and dried over sodium sulfate.

After evaporating the benzene, the residue was heated to 120°C in an oil bath under reduced pressure (3 mmHg), the flask being immersed into the bath as deeply as possible to remove the benzyl alcohol completely. Recovered benzyl alcohol weighed 2.5 g. The Tribenzyl ester III remained in the flask as an oil which weighed 11 g. On acidification of the above alkali washing with sulfuric acid, an oily substance separated out which gradually crystallized on standing several days. Recrystallization from ethyl acetate-petroleum ether gave the product in white crystals, m. p. 89°C. It was found not to depress the melting point when mixed with the acid obtained by hydrolysis of the triester.

13-Keto-octacosanoic Acid $C_{15}H_{31}CO(CH_2)_{11}CO_2H$. —In a 200 ml. three-necked flask, 0.41 g. of freshly cut sodium was placed. Absolute ethanol (5 ml.) was added to give a clear solution. All excess of the ethanol was distilled off until a crust of sodium ethoxide was formed on the surface of the residue. Then 15 ml. of dry thiophene-free benzene was added from the dropping funnel. To this suspension a solution of 11 g. of the tribenzyl ester in 10 ml. of benzene was added and the mixture was allowed to stand at room temperature with occasional shaking, while the solid gradually went into solution. The benzene was removed under reduced pressure at room temperature, leaving a brown syrup in the flask. Two portions of 10 ml. of fresh benzene were added and removed under reduced pressure to remove the last traces of ethanol. Thus the sodium salt of the tribenzyl ester was obtained as a brown viscous material, to which 30 ml. of fresh benzene was added, giving a colored solution. Then the flask was equipped with a stirrer and a reflux condenser fitted with a calcium chloride tube. A solution of 5.2 g. of palmitoyl chloride (prepared from pure acid and thionyl chloride, b. p. 148°C/ 1.5 mmHg) in 10 ml. of benzene was added from the dropping funnel with stirring and the mixture was refluxed for 30 min. with continued stirring.

After the reaction mixture attained room temperature the flask was immersed in an ice bath. Ice-cooled water containing 1 g. of sulfuric acid was added gradually with vigorous stirring, the temperature of the mixture being maintained at 3 to 5°C. The contents of the flask were then transfered to a separating funnel. The layers were separated with the aid of a small amount of ethanol and the benzene layer was washed with water to neutral reaction with occasional cooling to prevent the temperature from rising above 5°C. After the solution was dried over sodium sulfate the benzene was removed under reduced pressure at about 30°C of bath temperature. The condensation product remained as an oil (15 g.). A solution of 5 g. of the above product in a mixture of 15 ml. of ethyl acetate and 15 ml. of absolute ethanol was shaken with Pd-C (0.2 g.) and Pd-$SrCO_3$ (0.2 g.) in a hydrogen atmosphere at room temperature. Catalyst poisoning was so often encountered that it was necessary to add fresh catalysts frequently until a nearly theoretical amount of hydrogen was absorbed. The total amount of the catalyst used was 2.7 g. The time required for the complete hydrogenolysis was about 4 hr. The solution freed from the catalyst was refluxed for 30 min. to decarboxylate the product. Upon cooling the solution to room temperature white crystals appeared. These were collected and washed with ethyl acetate. The ketonic acid obtained showed the melting point of 91 to 94°C. Yield was 1.5 g. The filtrate and washing were combined and concentrated to a syrup. To this was added 10 ml. of acetic acid containing 1 ml. of sulfuric acid and the mixture was refluxed for 40 min. The solid residue obtained on removing acetic acid was taken up in benzene and the solution was washed and dried over sodium sulfate. Concentration and subsequent cooling of the benzene solution gave white crystals which melted at 93 to 97°C and weighed 0.6 g. The substance was combined with the acid obtained from the ethyl acetate solution and the combined crystals were recrystallized twice from benzene. The pure ketonic acid showed the melting point of 99.5°C. The yield was 1.8 g. or 65% based on palmitoyl chloride.

Found: C, 76.60; H, 12.45. Calcd. for $C_{28}H_{54}O_3$: C, 76.65; H, 12.41%.

Palmitic acid (0.15 g.) was recovered from the filtrate of the ketonic acid.

Purification of the Condensation Product (IV).— The product (5 g.) was dissolved in 20 ml. of pure benzene (dried over sodium wire) and the solution was shaken with active alumina for a short period. The alumina was filtered off and the filtrate was evaporated under reduced pressure at about 30°C of bath temperature to give a colorless liquid. This was hydrogenated in the same manner as described above. Absorption of the first 280 ml. of hydrogen proceeded rapidly (30 min.) with 0.4 g. of the catalyst. The second 140 ml. was absorbed in about 1 hr. with the addition of 0.3 g. of the catalyst. The product was treated in the same way as the

above. The yield of the pure ketonic acid was 1.8 g. (65%).

Octacosanol $C_{28}H_{57}OH$. — Octacosanoic acid ($C_{27}H_{55}CO_2H$) was obtained from 3 g. of the ketonic acid by the Huang-Minlon reduction[6] in a yield of 77% (2.2 g.). Details were given in the previous paper[2] for the reaction of other higher alcohols. The melting point was 90.2°C (recrystallized from toluene).

Found: C, 79.10; H, 13.34. Calcd for $C_{28}H_{56}O_2$: C, 79.18; H, 13.29%.

The acid was converted into its ethyl ester by a usual method. The lithium aluminum hydride reduction[2] of 2 g. of the pure ester (recrystallized from benzene, m. p. 64°C) afforded 1.4 g. of the desired alcohol after recrystallization from benzene. The melting point was 82.5°C. Further purification of the alcohol was tried by high vacuum distillation (2×10^{-3} mmHg) followed by recrystallizations. Although the melting point and analytical data were not changed, the physical data[8] indicated that these procedures seemed to be necessary to obtain a pure sample.

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