[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Some Isomeric Branched Hexadecanols

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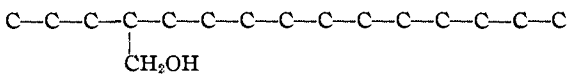
In a previous paper[1] we were led to the provisional view that certain aliphatic alcohols, such as cetyl alcohol, might possess mild purgative properties. On the basis of this hypothesis we have prepared all the eight primary hexadecanols which are theoretically possible when a —CH_2OH group is successively attached to each carbon in pentadecane.



$$\underset{\displaystyle CH_2OH}{\text{C—C—C—C}}\text{—C—C—C—C—C—C—C—C—C—C—C}$$

Only the first member of this series, cetyl alcohol had been previously prepared.

Preparation

The correct conditions for the simplest method of preparation, *i. e.*, reduction of the branched chain aldehyde obtained by heating the glycidic ester condensation product of the corresponding ketone and chloroethyl acetate,[2] could not be found. Consequently, the branched chain acid[3] corresponding to the alcohol was prepared by means of the malonic ester synthesis, and the ethyl ester of this substituted acetic acid reduced by the method of Bouveault and Blanc.[4]

The required thirteen normal halides, from methyl to tridecyl, were prepared in the usual way[5] from the corresponding alcohols. The alcohols above butyl, with the exception of heptyl, were made from ethyl esters of the corresponding acids by reduction with metallic sodium in butyl alcohol.[4] Heptanol was prepared according to the method of Clarke and Dreger.[6] With the exception of undecylic acid the odd acids were prepared by the malonic ester synthesis or the nitrile reaction. *Ethyl Undecylate.* The crude undecylenic acid was distilled, esterified, and the ethyl ester cut 185–190° (100 mm.),[7] iodine no. 113. The ester was hydrogenated with a nickel catalyst, and reduced to the alcohol in the usual way.[4] The resultant undecyl alcohol, iodine no. 5.1, was dissolved in absolute ethyl alcohol and hydrogenated (Adams platinum oxide) to an iodine no. of 1.0.

Substitution of the Halides in Malonic Ester

One of the most annoying factors involved in the use of the malonic ester synthesis is the large volumes of anhydrous ethyl alcohol required. This difficulty has been overcome by the use of butyl alcohol, which is obtained anhydrous by mere distillation. The ethyl malonate should first be converted to the butyl ester[8] but in the present work ethyl malonate was used in butyl alcohol solution, with a resultant formation of ethyl butyl, diethyl and dibutyl esters of the mono-substituted malonic ester. Fortunately, the dibutyl ester predominated. Substitution of halides was in the usual way.

Saponification.—The disubstituted ester was refluxed for three hours with 25% alcoholic potassium hydroxide (with occasional addition of a little water to prevent separation of potassium malonate). The ethyl and butyl alcohols were steam distilled.[9] The remaining dipotassium-disubstituted-malonate was refluxed with concentrated hydrochloric acid in 100% excess until the fatty acid layer was clear. The disubstituted acid was separated, and heated to 190° in an oil-bath.

Esterification of α,α′ Dialkyl Acetic Acids.—The branched chain acids are more difficult to esterify than are normal acids. The usual procedure (refluxing with 95% ethyl alcohol containing 3% hydrochloric acid), was modified by the addition of anhydrous calcium chloride, 1.5 mols for 4 mols of water. After refluxing for twenty-four hrs., the aqueous layer was removed, and the procedure repeated. This procedure applied to a straight chain acid (as palmitic) gives 98–99% esterification, but

TABLE I

YIELDS OF INTERMEDIATES AND HEXADECANOLS

$RR_1CHCOOH$		$RR_1CHCOOC_2H_5$			RR_1CHCH_2OH		
R =	R_1 =	Yield, %	B. p. °C.	Mm.	Yield, %	B. p., °C.	Mm.
CH_3-	$C_{13}H_{27}$-	70	185–187	12	66	185–187	15
C_2H_5-	$C_{12}H_{25}$-	67	191–199	15	53	186–188	15
C_3H_7-	$C_{11}H_{23}$-	60	181–183	14	32	181–184	15
C_4H_9-	$C_{10}H_{21}$-	57	180–185	15	30	181–183	15
C_5H_{11}-	C_9H_{19}-	57	180–182	14	33	181–182	15
C_6H_{13}-	C_8H_{17}-	49	181–183	14	27	181–183	15
C_7H_{15}-	C_7H_{15}-	40	182–183	14	28	181–182	15

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(1) W. M. Cox and E. E. Reid, THIS JOURNAL, **54**, 220 (1932).

(2) G. Darzens, *Compt. rend.*, **139**, 1214 (1905); *Frdl.*, **8**, 1257; M. A. Verley, *Bull. soc. chim.*, **35**, 487 (1924).

(3) This series of hexadecanoic acids was prepared by W. M. Stanley, M. S. Jay and R. Adams, THIS JOURNAL, **51**, 1261 (1929), who did not, however, make the corresponding esters and alcohols.

(4) Bouveault and Blanc, *Compt. rend.*, **136**, 1676 (1903); **137**, 60 (1903).

(5) "Organic Syntheses," John Wiley and Sons, Inc., 440 Fourth Ave., New York City, 1921, Vol. I, p. 1.

(6) H. T. Clarke and E. E. Dreger, Ref. 5, 1926, Vol. VI, p. 52.

(7) G. R. Yohe and R. Adams, THIS JOURNAL, **50**, 1503 (1928), reduced undecenyl alcohol with hydrogen and platinum.

(8) J. D. Meyer and E. E. Reid, *ibid.*, **55**, 1574 (1933); Ref. 5, 1935, Vol. XV, p. 51.

(9) This procedure was found more satisfactory than that employed by R. Adams, W. M. Stanley, S. G. Ford and W. R. Peterson, THIS JOURNAL, **49**, 2934 (1927). Alcoholic potassium hydroxide saponification was used by R. Adams, W. M. Stanley and H. A. Stearns, *ibid.*, **50**, 1475 (1928).

TABLE II

PROPERTIES OF BRANCHED CHAIN HEXADECANOLS AND THEIR ACETATES

RR_1CHCH_2OH					Analysis[b]		Acetates[a]		
R =	R_1 =	$n^{25}D$	d^{25}_4	M. p., °C.	C	H	d^{25}_4	$n^{25}D$	Sapon. no.[e]
H	$C_{14}H_{29}$	1.4283[d]	0.798[d]	49.3[d]	79.41	13.58	0.8574	1.4390	197.2
CH_3	$C_{13}H_{27}$	1.4453	.8320	12–13	79.23	13.91	.8527	1.4378	184.2[f]
C_2H_5	$C_{12}H_{25}$	1.4484	.8366	− 0.2	79.25	13.94	.8584	1.4391	193.7
C_3H_7	$C_{11}H_{23}$	1.4478	.8349	5.5	79.20	13.90	.8567	1.4385	191.6
C_4H_9	$C_{10}H_{21}$	1.4476	.8345	−14.5–14	79.05	13.96	.8567	1.4381	194.3
C_5H_{11}	C_9H_{19}	1.4476	.8341	− 9–8[c]	78.78	14.09	.8563	1.4380	195.5
C_6H_{13}	C_8H_{17}	1.4470	.8336	−30–26[c]	79.24	13.90	.8560	1.4379	195.4
C_7H_{15}	C_7H_{15}	1.4470	.8342	−25–18[c]	78.79	13.69	.8565	1.4380	194.7

[a] Prepared by refluxing with acetic anhydride and sodium acetate, and distilling directly under reduced pressure. [b] Analyzed by Dr. Ing. A Schoeller, Berlin, Germany. Calculated for $C_{16}H_{34}O$: C, 79.26; H, 14.14. [c] Readings approximate. Alcohols supercool to glassy solids. [d] "I. C. T." $n^{78.9}D$ $d^{78.9}_4$. [e] Calculated saponification no. 197.5. [f] This was reacetylated and the product redistilled but without essential change. The densities of the other acetates are 0.0222 greater than those of the alcohols according to which the density of this acetate is 0.0015 low which indicates 6.8% of unchanged alcohol. The saponification number found indicates 93.2% ester. According to this the true density is 0.8542.

with the substituted acids, much poorer yields were obtained (see Table I).

Reduction.—Reduction of the distilled esters was accomplished by the Bouveault-Blanc reaction. With the exception of the α-methylpentadecylate, the reaction was very sluggish, and instead of cooling the reaction flask, it had to be heated. The yields were poor (Table I). Separation of unreduced acid from the alcohol formed by the reaction could not be accomplished in the usual way, *i. e.*, by taking advantage of the insolubility of the calcium soaps in toluene. This method of separation was effective only in the case of the α-methylpentadecylate. The calcium salts of the other branched chain acids are soluble in toluene. To effect this separation it was necessary to convert the unreduced acid into the zinc salt, during steam distillation of the solvent butyl alcohol, and then to distil the branched chain alcohol, directly, under reduced pressure. The zinc salt remains liquid, and apparently undergoes no decomposition at moderately high temperatures. It may be removed from the still, after distillation of the alcohol, and converted to the ester by refluxing with ethyl alcohol containing hydrochloric acid.

The properties of the seven branched chain hexadecanols and their acetates are compiled in Table II. The purgative qualities of the alcohols and acetates was not marked. 2-Ethyl-2-dodecylethanol-1 and 2-hexyl-2-octylethanol-1 were reported by Macht and Barba-Gosè[10] as stimulating intestinal peristalsis in rats.

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Summary

Substituted ethanols of the type $\begin{matrix}R\\R_1\end{matrix}\!\!>\!CHCH_2OH$, where R and R_1 are straight chain aliphatic residues and total 14 carbon atoms, have been synthesized and their physical properties studied.

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[10] D. I. Macht and J. Barba-Gosè, *Proc. Soc. Exptl. Biol. Med.*, **28**, 772 (1931).