[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Branched-Chain Fatty Acids. XVI. Synthesis of the Optical Isomers of 15-Methyloctadecanoic Acid[1]

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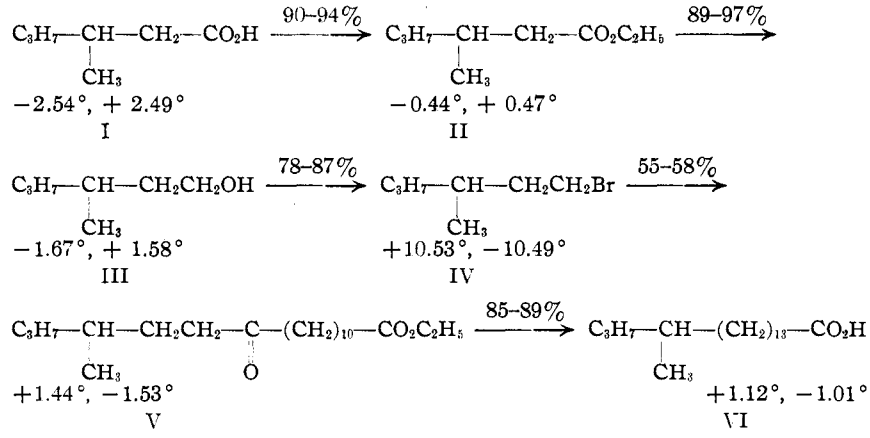
There have previously been obtained[3] one or both of the optical isomers of high molecular weight fatty acids with a branching methyl group in the 2-, 3-, 10- and anteiso[4] positions. The data on these synthetic acids were used[3] to show that Robinson's proposed structure,[5] 3,13,19 - trimethyltricosanoic acid, cannot be correct for phthioic acid,[6] for this proposed structure could have a maximum optical rotation no more than half that observed for phthioic acid. In reaching this conclusion it was assumed that the rotation contributed by optical centers separated by several carbon atoms would be additive and that the optical rotation due to a methyl-substituted carbon would fall off rapidly as the methyl becomes more remote from the ends of the chain. The first assumption seems entirely reasonable, and has been verified by Ställberg-Stenhagen's synthesis[7] of stereoisomers of 2,9-dimethyltetracosanoic acid. The second assumption was based on the fact that the anteiso acid has a molecular rotation of about 11.5° and 10-methyloctadecanoic acid has a molecular rotation of only 0.2°. In the present investigation, this latter assumption has been justified by the synthesis of (+)- and (−)-15-methyloctadecanoic acids, which prove to have a molecular rotation of only 3.2°, less than one-third that for the anteiso isomer.[7a]

The synthetic scheme, as shown in the accompanying chart, is similar to that used previously for synthesis of 10-methyloctadecanoic acid.[8] For each compound, the rotation given first is that of the isomer obtained from (−)-3-methylhexanoic acid. In accordance with the configurative relationships previously discussed,[8] the (+)-15-methyloctadecanoic acid probably belongs to the L-series of compounds.

SCHEME FOR SYNTHESIS OF 15-METHYLOCTADECANOIC ACIDS



The active 3-methylhendecanoic acids used previously[8] were obtained by synthesis from the active 2-decanols, proceeding by way of the secondary bromides, the 2-alkylmalonic esters and the 2-alkylmalonic acids. Although 10–15% racemization occurred in the two-step conversion from alcohol to alkylmalonic ester, the optically pure malonic acids were readily obtained by crystallization, for the optical antipodes were higher melting and much less soluble than the *dl*-mixture. This system was tried in the present synthesis but failed, for the *dl*-substance was a compound melting higher than the optical antipodes. Recrystallization to a constant melting point and rotation of 2-pentylmalonic acid prepared from optically pure 2-pentanol gave material containing about 30% of the *dl*-compound. Fortunately, (+)-3-methylhexanoic acid was readily obtained by crystallization of the quinine salt[9] from acetone, and the (−)-isomer was obtained from fractions rich in it by crystallization of the cinchonidine salt from 60% aqueous ethanol. Although Levene and Marker[10] were able to obtain the pure (−)-isomer from *dl*-3-methylhexanoic acid by use of the cinchonidine salt and we were able to repeat this procedure, prior use of quinine greatly simplifies the operation. It is of interest that although crystallization of

(1) This investigation was supported in part by a research grant from the National Institute of Health, Public Health Service.

(2) Previous publications as Raylene E. Adams.

(3) For references *cf.* Cason and Prout, THIS JOURNAL, **70**, 879 (1948).

(4) The term "anteiso" indicates the *s*-butyl end-group; *cf.* Weitkamp, *ibid.*, **67**, 447 (1945).

(5) Polgar and Robinson, *J. Chem. Soc.*, 389 (1945).

(6) Spielman and Anderson, *J. Biol. Chem.*, **112**, 759 (1936).

(7) Ställberg-Stenhagen, *Arkiv Kemi*, **1**, 187 (1949).

(7a) Ställberg-Stenhagen, *ibid.*, **2**, 95 (1950), has recently described the synthesis of (−)-21-methyltetracosanoic acid, which also has the 2-pentyl end-grouping, and reported the molecular rotation of 3.3°.

(8) Prout, Cason and Ingersoll, THIS JOURNAL, **70**, 298 (1948).

(9) We are greatly indebted to Dr. S. Wilkinson of the Wellcome Research Laboratories, Beckenham, Kent, England, for advising us in a private communication of the efficacy of quinine for resolution of 3-methyl acids.

(10) Levene and Marker, *J. Biol. Chem.*, **91**, 77 (1931).

the cinchonidine salt from aqueous ethanol, as specified by Levene and Marker, gives enrichment in the (−)-isomer in the top fraction, crystallization from acetone–chloroform gives enrichment in the (+)-isomer.

Experimental[11]

(+)-2-Pentanol was obtained by resolution of synthetic 2-pentanol[12] by the procedures described by Pickard and Kenyon[13] and Kenyon.[14] From 295 g. of the *dl*-2-pentyl hydrogen phthalate and 580 g. of brucine, by systematic crystallization from acetone, there was obtained 36.5 g. of the pure **brucine salt of (+)-2-pentyl hydrogen phthalate**, m. p. 153–154°, $[\alpha]^{20}D$ −4.00° in acetone (literature[13] $[\alpha]^{20}D$ −3.91° in acetone). After cleavage of the brucine salt and extraction of the (+)-2-pentanol with ether, most of the ether was removed by fractionation through the column, then chloroform was added and distilled in order to remove last traces of water as the azeotrope with chloroform (b. p. 56°). Otherwise, some pentanol was lost as the azeotrope with water (b. p. 92.5°). The yield from the salt of (+)-2-pentanol, b. p. 115–116°, was 90%, $n^{20}D$ 1.4072, $[\alpha]^{20}D$ +13.56° (homogeneous) (literature[13] $[\alpha]^{20}D$ +13.70°).

(−)-2-Bromopentane was prepared in 82–90% yields by the procedure described for 2-bromodecane,[8] b. p. 60–61° (100 mm.), $n^{21}D$ 1.4422, $[\alpha]^{24}D$ −30.73° (homogeneous).

3-Methylhexanoic Acids (I).—By alkylation of diethyl malonate in ethanol solution, **diethyl 2-pentylmalonate** was obtained in 63–68% yield, b. p. 135–137° (23 mm.), $n^{14}D$ 1.4308, d^{20} 0.976, d^{25} 0.971 (literature[15] $n^{20}D$ 1.4263, d^{20}_4 0.9713). For the ester from (−)-2-bromopentane, $[\alpha]^{23}D$ −0.41° (homogeneous).

The ester was saponified with ethanolic potassium hydroxide, ethanol was removed at reduced pressure, and an aqueous solution of the potassium salt was extracted with ether for fifteen hours in a continuous extractor. After acidification with 6 *N* sulfuric acid, the malonic acid was extracted with ether continuously for forty-eight hours. Removal of ether and crystallization from hexane gave 95% yield of **2-pentylmalonic** acid, m. p. 92.2–93.6° for the *dl*-acid (literature,[15] m. p. 88–89°). For the best sample of acid obtained from (−)-2-bromopentane, m. p. 77.9–79.8°, $[\alpha]^{19}D$ −5.97° in acetone.

Decarboxylation of the malonic acid by heating for two hours at 165–185° and distillation gave 87% yield of 3-methylhexanoic acid, b. p. 92–93° (8 mm.), $n^{27}D$ 1.4209 (literature,[10] b. p. 113° (17 mm.), $n^{25}D$ 1.4214). The acid obtained from recrystallized (−)-2-pentylmalonic acid had $[\alpha]^{18}D$ −1.74° (homogeneous). **(−)-3-Methylhexanoic acid** was obtained from this sample by systematic crystallization of the cinchonidine salt from 60% aqueous ethanol according to the procedure of Levene and Marker.[10] Lower fractions were combined with appropriate fractions rich in the (−)-isomer, which were obtained from the resolution with quinine. Since some cinchonidine base crystallized with nearly all fractions of salt, the rotation of the salt could not be used to follow the resolution. Cleavage of the salt and isolation of the acid was necessary. Acid with an initial rotation greater than −1° was usually resolved after three to six crystallizations of the cinchonidine salt. For the pure antipode, $[\alpha]^{22}D$ −2.54° (homogeneous) (literature,[10] $[\alpha]^{27}D$ −2.52°).

A major portion of the **(+)-3-methylhexanoic acid** was obtained by systematic crystallization from acetone of the quinine salt of *dl*-acid, but appropriate fractions were combined with partially (+)-acid synthesized from (−)-2-pentanol, $[\alpha]^{24}D$ −5.44°, obtained from the mother liquors of the resolution to give (+)-2-pentanol. Starting with *dl*-acid, top fractions became optically pure after three to seven crystallizations. For a total of 78 g. of *dl*-acid and 53.1 g. of (+)-acid, $[\alpha]^{17}D$ +0.40°, there was used 381 g. of quinine, and the total pure (+)-isomer obtained was 23.8 g. For pure **quinine salt of (+)-3-methylhexanoic acid**, $[\alpha]^{20}D$ was −91.6° in chloroform. Acid obtained by cleavage of such salt had $[\alpha]^{25}D$ +2.49° (homogeneous).

Ethyl 3-methylhexanoates (II) were obtained in 90–94% yield by esterification of the acid with 25 equivalents of absolute ethanol containing 10% by weight of concentrated sulfuric acid; b. p. 174–175°, $n^{18}D$ 1.4148. For the **(−)-isomer**, $[\alpha]^{20}D$ −0.44° (homogeneous) (literature,[10] $[\alpha]^{27}D$ −0.42°); for the **(+)-isomer**, $[\alpha]^{21}D$ +0.47° (homogeneous).

3-Methyl-1-hexanols (III).—Twenty grams of ester was hydrogenated at 250° in the presence of 2 g. of copper chromite catalyst.[16] Initial cold pressure was about 2900 lb. p. s. i., maximum hot pressure was about 4500 lb. p. s. i., and hydrogenation was completed in 4–10 hours. The yield was 89–97% of material of b. p. 161–162°, $n^{18}D$ 1.4269. For the **(−)-isomer**, $[\alpha]^{20}D$ −1.67° (homogeneous) (literature[10] $[\alpha]^{29}D$ −1.65°); for the **(+)-isomer**, $[\alpha]^{24}D$ +1.58°.

1-Bromo-3-methylhexanes (IV) were prepared in 78–87% yields by the usual method[17] using 48% hydrobromic acid and sulfuric acid. For the **(+)-isomer**, b. p. 108–110° (100 mm.), $n^{22}D$ 1.4504, $[\alpha]^{22}D$ +10.53° (homogeneous) (literature,[10] b. p. 65° (20 mm.)); for the **(−)-isomer**, $[\alpha]^{22}D$ −10.49° (homogeneous).

11-Carbethoxyhendecanoyl Chloride.—By hydrogenation of 400 g. of diethyl sebacate at 250° in the presence of 36 g. of copper chromite catalyst, there was obtained 251 g. (93.5%) of 1,10-decanediol, which was converted, without purification, to 356 g. (84.5%) of 1,10-dibromodecane, using anhydrous hydrogen bromide.[18] The crude dibromide was converted to the dicyanide and thence to the di-acid and finally to diethyl 1,12-dodecanedioate by the method described for ethyl nonadecanoate.[19] The over-all yield was 72%. The di-ester was saponified in methanolic barium hydroxide by the method of Signer and Sprecher,[20] but pure half ester could not be readily obtained by crystallization, so it was distilled through the column to yield 89 g. (40%) of solid half ester, b. p. 193–196° (2 mm.). The half ester was converted to the ester acid chloride by allowing it to stand overnight with two equivalents of thionyl chloride. Thionyl chloride was removed at reduced pressure, last traces being removed by distillation of two 40-cc. portions of benzene. The residual acid chloride was used for the preparation of keto ester V.

Ethyl 12-keto-15-methyloctadecanoates (V) were prepared according to the improved procedure described for methyl 5-keto-3,3-dimethyloctadecanoate.[21] The Grignard reagent from 12 g. of 1-bromo-3-methylhexane and 1.55 g. of magnesium was converted to the cadmium reagent with 6.5 g. of cadmium chloride, and the cadmium reagent was allowed to react with 18.6 g. of 11-carbethoxyhendecanoyl chloride. After distillation of 9 g. of fore-run, the product was collected at 187–189° (2.5 mm.) in a yield of 12.4–13.2 g. (54.6–58%, based on bromide). Great care was taken to completely remove diethyl 1,12-dodecanedioate, boiling only about 15° below the product. For analysis, there was used a center cut, $n^{25}D$ 1.4518.

Anal. Calcd. for $C_{21}H_{40}O_3$: C, 74.07; H, 12.11. Found: C, 73.81; H, 11.79.

For the (+)-isomer, $[\alpha]^{25}D$ +1.44° in chloroform.

(11) All melting points are corrected and all boiling points are uncorrected. Distillations were through a 65-cm. Podbielniak type column with tantalum wire spiral and partial reflux head. Analyses are by the Microanalytical Division of the Department of Chemistry, University of California.

(12) Prepared as described for 2-decanol (ref. 8).

(13) Pickard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

(14) Kenyon, *Org. Syntheses*, Coll. Vol. I, 418 (1941).

(15) Dewael and Weckering, *Bull. soc. chim. Belg.*, **33**, 495 (1924).

(16) Adkins, *Org. Syntheses*, Coll. Vol. II, 144 (1943).

(17) Kamm and Marvel, *ibid.*, Coll. Vol. I, 30 (1941).

(18) Reid, Ruhoff and Burnett, *ibid.*, Coll. Vol. II, 246 (1943).

(19) Cason, Wolfhagen, Tarpey and Adams, *J. Org. Chem.*, **14**, 151 (1949).

(20) Signer and Sprecher, *Helv. Chim. Acta*, **30**, 1001 (1947).

(21) Cason, Sumrell and Mitchell, *J. Org. Chem.*, **15**, 850 (1950).

For the (−)-isomer, $[\alpha]^{25}D$ −1.53° in chloroform; m. p. 34–36°.

15-Methyloctadecanoic Acids (VI).—Ester V (12 g.) was reduced exactly as described by Huang-Minlon.[22] The diluted and acidified reaction mixture was extracted with ether, and the wet ether solution was passed through a tower containing 150 g. of Amberlite IRA-400 ion exchange resin (*cf.* ref. 21 for details of this procedure). After neutral materials had been washed from the column, the acid was eluted with hydrochloric acid in ether–ethanol solution. The eluate was washed with water until hydrochloric acid had been removed, then ether was evaporated and the residual acid was crystallized from acetone at −25°. The yield of crude acid was 9.0 g. (85.7%), m. p. 39.3–40.5° for the *dl-isomer*. This material was further crystallized from acetone until the m. p. became constant at 40.9–42.4°. A sample placed in a bath at 41.5° melted at once, and a sample which had stood for several days melted at 41.5–43.0°. This behavior indicating polymorphism is the same as that observed in the previous preparation of this compound.[23] Neutral equivalent, 298.0 (calcd. 298.5).

(22) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(23) Cason, Adams, Bennett and Register, *ibid.*, **66**, 1764 (1946).

The pure (+)-isomer melted at 35.2–36.2°, $[\alpha]^{25}D$ +1.12° in chloroform, neutral equivalent 298.0. The (−)-isomer melted at 35.2–36.1°, $[\alpha]^{25}D$ −1.01° in chloroform, neutral equivalent, 298.9. A once-crystallized mixture of equal amounts of the (+)- and (−)-isomers melted at 41.2–42.4°.

The **tribromoanilides** were prepared as previously described,[24] except that the acid chlorides were prepared with thionyl chloride. For the *dl*-isomer, m. p. 103.6–104.4° (literature,[23] m. p. 102.6–103.8°). For the (+)-isomer, m. p. 104.4–105.5°, $[\alpha]^{25}D$ +0.49° in chloroform. For the (−)-isomer, m. p. 104.4–105.3°, $[\alpha]^{25}D$ −0.67° in chloroform.

Summary

The *dl*-, (+)- and (−)-forms of 15-methyloctadecanoic acid have been prepared by use of the keto ester synthesis. 3-Methylhexanoic acid was resolved to furnish the optically active starting materials.

(24) Cason, *ibid.*, **64**, 1106 (1942).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Hydroximyl Chlorides from Nitrostyrenes

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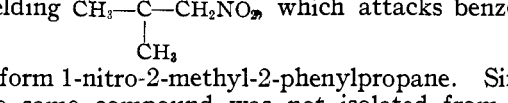
The reaction of nitrostyrene, benzene and aluminum chloride forms the subject matter of this investigation. No comparable reactions were known while the work was in progress, but in 1949 Lambert, Rose and Weedon[2] reported the reactions of benzene and aluminum chloride toward both of the nitroisobutylenes. 3-Nitro-2-methyl-1-propene (I) gave rise to 1-nitro-2-methyl-2-phenylpropane, essentially by addition of benzene across the double bond. 1-Nitro-2-methyl-1-propene (II) yielded phenyldimethylacetohydroximyl chloride, $C_6H_5C(CH_3)_2$—CCl=NOH, by a process involving not only addition but also rearrangement. Some chlorodimethylacetohydroximyl chloride was found also.

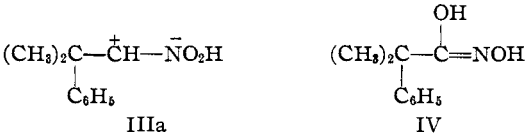
To behave analogously, ω-nitrostyrene, C_6H_5-CH=$CHNO_2$, should change to diphenylacetohydroximyl chloride, $(C_6H_5)_2CH$—CCl=NOH, in view of its structural similarity to 1-nitro-2-methyl-1-propene, $(CH_3)_2C{=}CHNO_2$. This reaction was indeed established. Also, *p*-chloro-ω-nitrostyrene, chlorobenzene and aluminum chloride were found to produce bis-*p*-chlorophenylacetohydroximyl chloride, $(ClC_6H_4)_2CH$—CCl=NOH. The yields realized were 70–85%.

In considering the mechanisms of these reactions from I and II, one may assume that aluminum chloride, either as $AlCl_3$ or as $HAlCl_4$, withdraws electrons from the tertiary carbon of I, yielding CH_3—$\overset{+}{C}$(CH_3)—$CH_2NO_2^-$, which attacks benzene to form 1-nitro-2-methyl-2-phenylpropane. Since the same compound was not isolated from II, it must mean that the nitroalkane, as such, is not involved in the transformation of II into the hydroximyl chloride. To account for the latter, it is assumed that IIa, the resonance modification of II, becomes important in the presence of aluminum chloride and that its initial attack on benzene gives rise to III; but the double bond of III also is subject to reaction with aluminum chloride, thereby bringing its resonance form (IIIa) into play. The electron deficient carbon of IIIa promotes an intramolecular oxidation and reduction leading to IV (or a complex of it with aluminum chloride). Conversion of IV into the hydroximyl chloride by reaction with aluminum chloride is the final step

I II



IIa III



IIIa IV

(1) Holders of Commercial Solvents Corporation Fellowships, 1942–1944 (D. W.), 1947–1948 (M. N.).

(2) Lambert, Rose and Weedon, *J. Chem. Soc.*, 42 (1949).