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Iodinated Organic Compounds as Contrast Media for Radiographic Diagnoses. II. Ethyl Esters of Iodinated Straight and Branched Chain Phenyl Fatty Acids[1]

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In continuation of the study of esters of iodinated phenyl fatty acids as absorbable liquid contrast media for radiographic diagnosis,[3] a method for the direct iodination of phenyl fatty acids was essential. Such a method has been found in a modification of the process of Varma and Panickar[4] for the direct iodination of benzenoids. In the procedure adopted, a boiling glacial acetic acid solution of iodine, the phenyl fatty acid, and sulfuric acid was treated with coarse sodium nitrite. For the most part the iodination study was confined to the ω-phenyl-*n*-fatty acids ranging from phenylacetic to ζ-phenyl-*n*-heptoic acids. The crude products obtained were probably mixtures of isomeric *ortho* and *para* iodinated derivatives, but on purification only the latter was isolated from each mixture. Attachment of the iodine in the *para* position was established in each case, either by direct comparison with known compounds or by oxidative degradation to *p*-iodobenzoic acid. Yields of 39–50% were obtained from the iodination of ω-phenyl-*n*-fatty acids with an uneven number of carbon atoms in the side chain, and of 14–45% of the acids with an even number of carbon atoms. The yields and physical data of the several acids, together with the physical constants of the corresponding ethyl esters, are given in Table I. It is noteworthy that the melting points of the iodinated ω-phenyl-*n*-fatty acids show alternations reminiscent of those of the *n*-fatty acids or of the aliphatic dicarboxylic acids.[5]

Using δ-phenyl-*n*-valeric acid as a typical phenyl fatty acid, variations of the iodination procedure were studied. Substitution of sodium iodate for sodium nitrite in the iodination mixture gave satisfactory results, but the use of nitric acid as an oxidant was unsatisfactory where more than 0.3 mole of the fatty acid was involved. Similarly, indirect iodination *via* the nitro compound resulted in poor yield.

Only the ω-phenyl-*n*-fatty acids up to ζ-phenyl-*n*-heptoic acid were iodinated. In the course of the physiological work, promising results were obtained with ethyl δ-(*p*-iodophenyl)-*n*-valerate, and an improved synthesis of the intermediate, δ-phenyl-*n*-valeric acid was developed. Although this acid may be prepared from γ-phenyl-*n*-propyl bromide and malonic ester[6] in good yield, it was found that the catalytic hydrogenation of cinnamalacetic acid in ethanol with Raney nickel at 110° was a far superior method of obtaining δ-phenyl-*n*-valeric acid.[7] Cinnamalacetic acid, in turn, was prepared from cinnamalacetone by hypochlorite oxidation of the crude reaction product of cinnamaldehyde and acetone.[8] By the procedure finally adopted an over-all yield of 70% for the three steps was obtained, and by this method δ-phenyl-*n*-valeric acid becomes one of the most accessible of the ω-phenyl-*n*-fatty acids.

A number of iodinated phenyl fatty acids with branched chains were also prepared. Two of these were obtained by decarboxylation of the malonic acids resulting from the interaction of ethyl- and *n*-butyl-malonic esters, respectively, with *p*-iodobenzyl bromides; and the third, by direct iodination of α-ethyl-δ-phenyl-*n*-valeric acid with nitrous acid as an oxidant.

The ethyl esters of the iodinated phenyl fatty acids were tested as prepared by intrathecal injection in dogs and by injection in other areas of other experimental animals. Ethyl δ-(*p*-iodophenyl)-*n*-valerate and ethyl ζ-(*p*-iodophenyl)-*n*-heptoate gave the most satisfactory results, but were somewhat toxic in the spinal canal. Ethyl δ-(*p*-iodophenyl)-*n*-valerate seems to be satisfactory for radiographic delineation of the nasal sinuses, of the Fallopian tubes, and of various other cavities of the body. The rate of absorp-

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(2) This work is taken from part of the Ph.D. dissertation of John T. Plati, 1940. Present address: Research Laboratory, Swift and Co., Chicago, Ill.

(3) Previous paper, THIS JOURNAL, **64**, 1436 (1942).

(4) Varma and Panickar, *Q. J. Ind. Chem. Soc.*, **3**, 342 (1926).

(5) *Cf.*, Brode and Leermakers in Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1937, Vol. II, p. 1719.

(6) v. Braun and Kruber, *Ber.*, **45**, 386 (1912); Jones and Pyman, *J. Chem. Soc.*, **127**, 2597 (1925).

(7) Borsche, *Ber.*, **45**, 621 (1912), and Skraup and Schwamberger, *Ann.*, **462**, 135 (1928), have carried out the hydrogenation of cinnamalacetic acid with colloidal palladium in aqueous potassium carbonate, and in methanol, respectively.

(8) Diehl and Einhorn, *Ber.*, **18**, 2320, 2324 (1885).

tion from these areas varies somewhat but is sufficiently rapid that absorption is complete in fourteen to eighteen days.

Experimental[9]

ω-Phenyl-*n*-fatty Acids

Phenylacetic and **β-phenylpropionic acids** were used as purchased from the Eastman Kodak Company.

γ-Phenyl-*n*-butyric Acid.—Benzene was condensed with succinic anhydride, and the product converted to γ-phenyl-*n*-butyric acid by the Clemmensen method according to Martin's[10] procedure.

δ-Phenyl-*n*-valeric Acid. 1. By Malonic Ester Synthesis.[6]—From γ-phenyl-*n*-propyl bromide and ethyl malonate, ethyl γ-phenyl-*n*-propylmalonate, b. p. 203–204° (15 mm.), was obtained in a yield of 69%. The ester was saponified, and, without purification, the malonic acid was decarboxylated by heating *in vacuo* at 160–170°. The δ-phenyl-*n*-valeric acid was purified by distillation, b. p. 188–189° (19 mm.), and was obtained in a yield of 86%; on standing the product solidified, m. p. 59–60°.

2. From Cinnamaldehyde. A. Cinnamalacetone.—To 60 liters of water contained in a 25-gallon crock fitted with a stirrer, was added 2525 cc. (35 moles) of acetone, 1 kg. (7.6 mole = 960 cc.) of cinnamaldehyde, and 1800 cc. of 10% sodium hydroxide solution in the order given. The mixture was stirred for twenty-four hours. At the end of this time the odor of cinnamaldehyde had disappeared, and an abundant yellow, granular precipitate of cinnamalacetone had formed. The precipitate was filtered, washed with 2–4 liters of cold water, well pressed, and used moist for the next step.

B. Cinnamalacetic Acid.—The moist cake from A was dissolved in 5 liters of methyl alcohol at 40–50°. The warm solution was then poured into a well-stirred solution of 7 liters of commercial 12–14% sodium hypochloride solution and 5 liters of water. A turbid suspension resulted, and the temperature of the reaction mixture rose to 60–65° in five to ten minutes. As the temperature attained its maximum, chloroform was evolved and continued to be evolved during the remainder of the reaction. At intervals of five to six minutes, 2-liter portions of a second solution of 7 liters of 12–14% sodium hypochlorite and 5 liters of water were added. When the temperature of the reaction mixture had fallen to 40°, sulfur dioxide was passed in until a sample acidified with hydrochloric acid was neutral to starch–iodide paper; about 60–80 g. of sulfur dioxide was required. The solution was then acidified to congo red paper by the addition of 1250–1500 cc. of concd. hydrochloric acid solution. The stirrer was stopped and the reaction mixture allowed to cool overnight. The precipitated acid was filtered and washed free of reactants by resuspending twice in 12 liters of water. After the final filtration, the precipitate was covered with a rubber dam, sucked as dry as possible, and then air-dried for several days. (Cinnamalacetic acid when dried briefly on the steam-bath softens at 154°, and melts at 161–163°.)

C. δ-Phenyl-*n*-valeric Acid.—The air-dried product from B was catalytically hydrogenated at 110° in ethanol using Raney nickel as a catalyst. Reduction was usually complete in half an hour. Distillation of the product gave 936 g., or 70% based on cinnamaldehyde, of δ-phenyl-*n*-valeric acid, b. p. 147–150 (3 mm.). A residue weighing 154 g. was discarded.

ε-Phenyl-*n*-caproic and ζ-Phenyl-*n*-heptoic Acids.—Using Martin's[10] modification of Clemmensen reduction δ-benzoyl-*n*-valeric acid was converted to ε-phenyl-*n*-caproic acid, and ε-benzoyl-*n*-caproic acid to ζ-phenyl-*n*-heptoic acid. Both phenyl fatty acids were isolated in about 75% yield. δ-Benzoyl-*n*-valeric acid was obtained equally well by Grateau's[11] method and by Hill's[12] procedure. ε-Benzoyl-*n*-caproic acid was prepared in 25% yield as one of the products of the interaction of benzoyl chloride and cyclohexanone in the presence of sodamide according to Bauer's[13] method.

Iodinated ω-Phenyl-*n*-fatty Acids and their Ethyl Esters

Direct Iodination with Sodium Nitrite—Sulfuric Acid as Oxidant.—The modification of the method of Varma and Panickar[4] that was employed was as follows. To a solution of 1 mole of the ω-phenyl-*n*-fatty acid in ten volumes of glacial acetic acid contained in a 3-necked flask fitted with stirrer and condenser was added 1 volume of concentrated sulfuric acid and 1 equivalent of iodine. To this mixture 0.9–1 part of solid granular[14] sodium nitrite was added in one portion. With vigorous mechanical stirring the reaction mixture was rapidly heated to the boiling point and held at this temperature until the iodine color disappeared (twenty to thirty minutes). Occasionally, it was necessary to add a small amount of solid sodium nitrite toward the end of the reaction to bring about complete decoloration. Usually some iodine sublimed to the walls of the condenser and this was brought into reaction by shutting off the condenser until the hot acetic acid vapors had washed off the crystals. When the reaction was completed, the hot mixture was poured into crushed ice and the solidified iodinated acid was filtered. For purification the higher melting iodinated acids were crystallized first from ligroin, or gasoline, and then from 60% aqueous acetic acid, while the lower melting acids were converted to their ethyl esters and, after purification of these by distillation, regenerated by hydrolysis. The yields and physical constants of the iodinated acids are given in Table I.

Identity of the reaction products as para iodinated derivatives was established by means of physical constants in the case of *p*-iodophenylacetic acid[15]; by direct comparison in the cases of β-(*p*-iodophenyl)-propionic, γ-(*p*-iodophenyl)-*n*-butyric, and ε-(*p*-iodophenyl)-*n*-caproic

(9) The iodine analyses were carried out by fusion with sodium peroxide in the Parr bomb, and the iodine determined by the Volhard method. Some of the analytical work was performed by Dr. Leonard Weisler and Mr. Hugh Mosher.

(10) Martin, THIS JOURNAL, **58**, 1428 (1936); "Org. Syntheses," **17**, 97 (1937).

(11) Grateau, *Compt. rend.*, **191**, 947 (1930).

(12) Hill, THIS JOURNAL, **54**, 4105 (1932).

(13) Bauer, *Ann. chim.*, [9] **1**, 408 (1914).

(14) The particle size of the sodium nitrite is perhaps the critical factor of the operation. With powdered sodium nitrite the evolution of oxides of nitrogen is so rapid that not all the iodine enters into the action. Good results were uniformly obtained by breaking up caked sodium nitrite in a mortar until the largest particle size was about 1 cc. in volume.

(15) Jackson and Mabery, *Am. Chem. J.*, **2**, 253 (1880); Datta and Chatterjee, THIS JOURNAL, **41**, 292 (1919).

TABLE I

ω-(*p*-IODOPHENYL)-*n*-FATTY ACIDS AND THEIR ETHYL ESTERS

Fatty acid side chain	Acids: % Yield on direct iodination	Acids: M. p., °C.	Acids: Neut. equiv. Calcd.	Acids: Neut. equiv. Found	Ethyl ester: B. p. °C.	Ethyl ester: Mm.	Ethyl ester: Sp. gr.$^{20}_{20}$	Ethyl ester: $n^{25}D$	Ethyl ester: % Iodine Calcd.	Ethyl ester: % Iodine Found
Acetic	39–45	135[a]	262	...	...	...	...	...	...	...
Propionic	50	139–141	276	274	140	2	1.532	1.5597	41.7	41.9
Butyric	27	89–90.5	290	288	146–148	0.8	1.486	1.5528	39.9	40.0
Valeric	50	109.5–110.5	304	302	158	2	1.436	1.5471	38.2	38.5
Caproic	14	66–67	318	320	158–160	2	1.401	1.5413	36.7	37.0
Heptoic	39	93–94.5	332	334	175–177	2.5	1.367	1.5376	35.2	35.0

[a] Data from Jackson and Mabery, *Am. Chem. J.*, 2, 253 (1880).

acids[3]; and by oxidative degradation with alkaline permanganate to *p*-iodobenzoic acid in the cases of δ-(*p*-iodophenyl)-*n*-valeric and ξ-(*p*-iodophenyl)-*n*-heptoic acids.

The ethyl esters prepared from the *p*-iodophenyl-*n*-fatty acids were obtained as colorless oils when purified by distillation in a Hickman boiling-point still at low pressure. Exposure to sunlight quickly brought about the development of an orange coloration. The taste of the esters varied with the length of the side chain: the lower members had a taste similar to that of iodobenzene, while the higher members had initially a bland flavor which was soon followed by a sharp, stinging sensation. The physical constants and analytical data relating to the ethyl esters are given in Table I.

Direct Iodination with Iodic Acid.—One experiment with iodic acid as oxidant was carried out. A mixture of 8.6 g. (0.04 mole) of potassium iodate, 35.6 g. (0.2 mole) of δ-phenyl-*n*-valeric acid, 20.3 g. (0.16 atom) of iodine, 250 cc. of 60% acetic acid, and 10 cc. of concentrated sulfuric acid was refluxed with stirring for three hours and forty-five minutes.[16] Sulfur dioxide was then passed in until the iodine color disappeared, and the mixture was cooled until crystallization was complete. The crystals were filtered and purified by recrystallization from 200 cc. of 60% acetic acid. A yield of 35.9 g. (59%) of crude δ-(*p*-iodophenyl)-*n*-valeric acid, sintering at 97° and melting at 100–107°, resulted.

Indirect Iodination: δ-(*p*-Iodophenyl)-*n*-valeric Acid from δ-(*p*-Aminophenyl)-*n*-valeric Acid.—By means of the Sandmeyer reaction δ-(*p*-aminophenyl)-*n*-valeric acid was converted to the corresponding iodo compound in nearly quantitative yield. The crude product, m. p. 104–108°, was purified by crystallization from gasoline, and was obtained in the form of slightly brown crystals which showed no depression in a mixed melting point with δ-(*p*-iodophenyl)-*n*-valeric acid prepared by direct iodination.

The δ-(*p*-aminophenyl)-*n*-valeric acid was obtained from **δ-(*p*-nitrophenyl)-*n*-valeric acid.** The latter was prepared by adding with stirring 64.1 g. (0.36 mole) of δ-phenyl-*n*-valeric acid to a mixture of 130 cc. of concentrated nitric acid (d. 1.4) and 65 cc. of fuming nitric acid (d. 1.5). As the acid dissolved, the mixture became dark red, and the temperature rose to 80°. By external cooling the temperature was reduced to 60° and held at this point for twenty minutes. On pouring the nitration mixture into 300 g. of crushed ice, an oil separated which soon solidified. The solid was filtered, and digested moist in 65 cc. of boiling carbon tetrachloride. On cooling to 18°, nearly pure δ-(*p*-nitrophenyl)-*n*-valeric acid separated. Recrystallization from 30 cc. of carbon tetrachloride, with cooling to 18° as before, gave 22.4 g. (28%) of pure product, m. p. 84–85°.

Anal. Calcd. for $C_{11}H_{13}O_4N$: neut. equiv., 223. Found: neut. equiv., 224.

Oxidation of δ-(*p*-nitrophenyl)-*n*-valeric acid with aqueous chromic acid at 75–120° gave a 93% yield of *p*-nitrobenzoic acid, m. p. 233–234°.

Reduction of δ-(*p*-nitrophenyl)-*n*-valeric acid with ferrous hydroxide in ammoniacal solution gave a 42% yield of **δ-(*p*-aminophenyl)-*n*-valeric acid,** m. p. 109–110°. By crystallization from water, the melting point was raised to 113–113.5°.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.4; H, 7.82. Found: C, 68.4; H, 7.79.

Iodinated Branch Chain Phenyl Fatty Acids and Their Ethyl Esters

Using a standard procedure[17] for alkylating malonic esters, ethyl ethylmalonate was treated with *p*-iodobenzyl bromide[18] and with γ-phenyl-*n*-propyl bromide, and ethyl *n*-butylmalonate with *p*-iodobenzyl bromide.

Ethyl ethyl-(*p*-iodobenzyl)-malonate was obtained in 64% yield as a viscous oil, b. p. 176–180° (2 mm.); sp. gr. $^{20}_{20}$ 1.404; $n^{25}D$ 1.5348.

Anal. Calcd. for $C_{16}H_{21}O_4I$: I, 31.4. Found: I, 31.3.

Ethyl ethyl-(γ-phenyl-*n*-propyl)-malonate was obtained in 58% yield; b. p. 193–196° (11 mm.); $n^{24}D$ 1.4840.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.9; H, 8.55. Found: C, 70.9; H, 8.54.

Ethyl *n*-butyl-(*p*-iodobenzyl)-malonate was obtained in 67% yield as a viscous oil of b. p. 178–182° (2 mm.); sp. gr.$^{20}_{20}$ 1.362; $n^{25}D$ 1.5228.

Anal. Calcd. for $C_{18}H_{25}O_4I$: I, 29.4. Found: I, 29.4.

Hydrolysis of the iodinated compounds to the malonic acids, decarboxylation, and esterification with ethyl alcohol gave the ethyl esters of the branched chain acids.

Ethyl α-(*p*-iodobenzyl)-*n*-butyrate was isolated in 52% yield as a colorless oil, b. p. 182–183° (14 mm.); sp. gr.$^{20}_{20}$ 1.415; $n^{25}D$ 1.5425.

Anal. Calcd. for $C_{13}H_{17}O_2I$: I, 38.2. Found: I, 37.9.

(16) Subsequent work has shown that the heating period should be reduced to ten to twenty minutes.

(17) *Cf.*, Adams and Kamm, Gilman-Blatt, "Organic Syntheses: Collective Volume I," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 250.

(18) Wheeler and Clapp, *Am. Chem. J.*, **40**, 460 (1908).

Ethyl α-(*p*-iodobenzyl)-*n*-caproate was obtained in 68% yield as a colorless oil, b. p. 156° (2 mm.); sp. gr.$^{20}_{20}$ 1.352; $n^{25}D$ 1.5333.

Anal. Calcd. for $C_{15}H_{21}O_2I$: I, 35.2. Found: I, 35.4.

Hydrolysis and decarboxylation of ethyl ethyl-(γ-phenyl-*n*-propyl)-malonate gave **α-ethyl-δ-phenyl-*n*-valeric acid** in 80% yield, b. p. 189–190° (14 mm.); $n^{25}D$ 1.5033.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.7; H, 8.79; neut. equiv., 206. Found: C, 75.6; H, 8.62; neut. equiv., 207.

Ethyl α-Ethyl-δ-(*x*-iodophenyl)-*n*-valerate.—The iodination of α-ethyl-δ-phenyl-*n*-valeric acid was carried out in the presence of sodium nitrite. The iodinated acid was obtained as a heavy oil, which was converted to the ethyl ester without purification. A 61% yield of ethyl α-ethyl-δ-(*x*-iodophenyl)-*n*-valerate was obtained as a viscous oil, b. p. 162–164° (2 mm.); sp. gr. $^{20}_{20}$ 1.362; $n^{25}D$ 1.5352. The position of the iodine atom was not determined.

Anal. Calcd. for $C_{15}H_{21}O_2I$: I, 35.2. Found: I, 35.2.

Summary

For study as absorbable liquid contrast media in radiographic diagnoses, the ethyl esters of the ω-(*p*-iodophenyl)-*n*-fatty acids from *p*-iodophenylacetic to ζ-(*p*-iodophenyl)-*n*-heptoic acids have been prepared from the corresponding uniodinated phenyl-*n*-fatty acids by direct iodination in the presence of sodium nitrite–sulfuric acid. Several branched chain iodophenyl fatty acids and their ethyl esters have been prepared, also. Of these various esters, ethyl δ-(*p*-iodophenyl)-*n*-valerate seems to be suitable for restricted use as a contrast medium. In the course of the work an improved synthesis of δ-phenyl-*n*-valeric acid has been developed.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Vitamin E. XLI. Synthesis of 1-Chloro-3,7,11,15-tetramethylhexadecanol-3, and its Condensation with Trimethylhydroquinone to Form α-Tocopherol[1]

BY LEE IRVIN SMITH AND JOSEPH A. SPRUNG

As is well known, tocopherols are synthesized by condensation of an appropriate hydroquinone with phytol or one of its derivatives—a phytyl halide or phytadiene. Since all of the derivatives are made from phytol itself, these syntheses all require an adequate source of phytol. Although enough phytol is available for relatively small scale operations, the supply of phytol would be a limiting factor in the manufacture of α-tocopherol on a scale comparable to that involved in the manufacture of some of the other vitamins, and for this purpose, a synthetic substitute would be desirable. The synthesis of phytol from hexahydropseudoionone by Fischer and Löwenberg[2] is well known, and, although this synthesis has recently been modified and improved,[3] it still leaves much to be desired in its adaptability to large scale operations.

Citral is the most readily available commercial material whose structure contains repeating "isoprene" units; this C_{10}-compound therefore was chosen as the most promising starting material for the synthesis of any substance containing twenty carbon atoms with a regular sequence of "isoprene" units. Moreover, in view of results previously obtained on the condensation of "potential dienes" with hydroquinones to give chromans[4] it was known to be unnecessary to synthesize an unsaturated substance; any compound, having the requisite carbon chain ending with two functional groups—halogen and/or hydroxyl, in the 1,3-positions, would suffice. With these facts in mind, a synthesis of 1-chloro-3,7,11,15-tetramethylhexadecanol-3 (X) was undertaken; the synthesis is outlined in the chart. Several of the reactions in the chart required a considerable amount of study before the proper conditions were found.

In order to use trimethylene glycol, it was first necessary to convert it into a mono ether (I). The group R in this ether had to be one which (a) could be introduced in good yield, (b) would not be extensively cleaved when the halide II or Grignard reagent was formed, and (c) would cleave fairly readily from VI under the proper condition. Three ethers were prepared; those in which R in I was methyl, ethyl and benzyl. Of these, the ethyl

(1) XL, THIS JOURNAL, **65**, 441 (1943). This work was made possible by financial aid, through the Graduate School, from the General Research Fund of the University of Minnesota, for which the authors make grateful acknowledgment.

(2) (a) Fischer and Löwenberg, *Ann.*, **464**, 69 (1928); (b) **475**, 183 (1929).

(3) Karrer and Ringier, *Helv. Chim. Acta*, **22**, 610 (1939).

(4) Smith, Ungnade, Stevens and Christman, THIS JOURNAL, **61**, 2615 (1939).