

pounds prepared. These data were obtained using a Hilger E3 spectrograph, Hilger sector photometer and Eastman Kodak Co. panchromatic plates. An underwater spark served as light source.

Summary

1. Phenylglyoxal reacts with urea in cold basic solution to form 4-phenylhydantoin, and, when refluxed in basic solution to form on cooling and acidifying 2-keto-4-phenyl-4,5-dihydroxytetrahydroglyoxaline which on melting loses water to become 4-phenylhydantoin.

2. Phenylglyoxal and urea refluxed in glacial

acetic give a polymer of 4-phenylhydantoin. The same polymer is obtained by heating 4-phenylhydantoin with 6 *N* hydrochloric acid.

3. Phenylglyoxal reacts in hot alkaline solution with phenyl urea to form 2-keto-3,4-diphenyl-4,5-dihydroxytetrahydroglyoxaline which on being melted loses water to become 3,4-diphenylhydantoin.

4. Phenylglyoxal reacts with methyl urea in hot alkaline solution to form 3-methyl-4-phenylhydantoin.

BOULDER, COLORADO

RECEIVED FEBRUARY 16, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF RADIOLOGY, SCHOOL OF MEDICINE AND DENTISTRY, AND FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF ARTS AND SCIENCE, THE UNIVERSITY OF ROCHESTER]

Iodinated Organic Compounds as Contrast Media for Radiographic Diagnoses. I. Iodinated Aracyl Esters^{1a}

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With the object of developing absorbable insoluble liquid contrast media for use in radiographic diagnoses, three classes of iodinated organic compounds have been studied: (1) esters of iodinated *o*-acyl derivatives of glycolic acids; (2) esters of iodinated phenoxy fatty acids; and (3) esters of iodinated phenyl fatty acids. Most of the work was confined to ethyl esters, since these are relatively fluid and easily purified.

Esters of Iodinated O-Acylglycolic Acids.—The iodinated O-acylglycolic acids were obtained by heating the sodium salt of the several iodinated acids with an ester of chloroacetic acid. The method is described by the equation $R-CO_2Na + Cl-CH_2CO_2R' \rightarrow R-CO_2-CH_2CO_2R'$, and has previously been employed for the synthesis of ethyl O-benzoyl-glycolate.^{1c} Compounds prepared in this way were ethyl O-(*o*-iodobenzoyl)-glycolate, ethyl O-[β -(*p*-iodophenyl)-propionyl]-glycolate, and the ethylene glycol ester of O-(*o*-iodobenzoyl)-glycolic acid. All were obtained in yields of 50–70%.

An attempt was made to prepare ethyl O-(κ -iodoundecyl)-glycolate by the interaction of sodium κ -iodoundecylate and ethyl chloroacetate, but widespread decomposition occurred when the two were heated together. The analogous re-

action between sodium undecylenate and ethyl chloroacetate proceeded satisfactorily, however.

Ethyl Esters of Iodophenoxy Fatty Acids.—From *o*-iodophenol the two iodinated phenoxy fatty acid esters, ethyl γ -(*o*-iodophenoxy)-*n*-butyrate and ethyl κ -(*o*-iodophenoxy)-undecylate, were prepared. The former was obtained from the corresponding acid, which in turn was synthesized from sodium *o*-iodophenoxide and trimethylene bromide by a series of reactions modelled after those employed by Marvel and Tannenbaum² in the preparation of γ -phenoxy-*n*-butyric acid. A similar reaction with ethylene bromide in place of trimethylene bromide was carried through the stage of α -bromo- β -(*o*-iodophenoxy)-ethane; with this a small amount of α,β -di-(*o*-iodophenoxy)-ethane was obtained. Ethyl κ -(*o*-iodophenoxy)-undecylate was obtained by the interaction of sodium *o*-iodophenoxide and ethyl κ -bromoundecylate.

Ethyl Esters of Iodinated Phenyl Fatty Acids.—By the addition of iodobenzene to ethyl undecylenate and to ethyl oleate, respectively, in the presence of aluminum chloride at *ca.* 5°, reaction products were isolated, which are doubtless mixtures of isomers. With ethyl undecylenate and iodobenzene, a 40% yield of a product boiling at 205–213° (1.5 mm.) was obtained. It is probably a mixture of the ν - and κ -(iodophenyl)-esters,³ in analogy with the reaction prod-

(1a) Aided by a grant from the Research Laboratory of the Eastman Kodak Company.

(1b) This work is taken from part of the Ph.D. dissertation of John T. Plati, 1940. Present address: The Massachusetts Institute of Technology, Cambridge, Massachusetts.

(1c) Wislicenus and Andrieff, *Ann.*, **183**, 284 (1865).

(2) Marvel and Tannenbaum, *This Journal*, **44**, 2647 (1922).

(3) The composition of this mixture will be the subject of a future communication.

ucts obtained under similar conditions from benzene and ethyl undecylenate.⁴ The iodine is probably attached *para* to the side chain, although oxidative degradation yielded *p*-iodobenzoic acid in poor yield (12%). In an analogous reaction in which bromobenzene was substituted for iodobenzene, a 45% yield of mixed ethyl bromophenylundecylates was obtained.

On substituting ethyl oleate for ethyl undecylenate in the reaction with iodobenzene, a high boiling residue formed the main fraction (55–60%), and a mixture of mono-addition products b. p. 243–258° (2 mm.), was obtained in a yield of 22–25%. The analyses for iodine on the mono-addition product were 4% under theory, however, and it is possible that some deiodination may have occurred during the reaction; on the other hand, the low value of iodine may have been due to incomplete combustion of the iodinated product in the analysis. The liquid is presumably largely a mixture of *para*-iodinated derivatives of ethyl ϵ - and ι -phenylstearate,⁵ for the addition of benzene to ethyl oleate has been shown by Harmon and Marvel⁶ to give these isomers.

Attempts were made to bring about addition of iodobenzene to ethyl crotonate, but these were unsuccessful. Closely related iodophenyl fatty acids and their ethyl esters were obtained by combining succinic anhydride or δ -carboethoxyvaleryl chloride with iodobenzene in the presence of aluminum chloride, followed by reduction of the ketonic acids to iodinated phenyl fatty acids by Clemmensen's method. In each case, some deiodination and disproportionation occurred. Thus, from the reaction mixture of iodobenzene and succinic anhydride, 1,2-diiodobenzene, 1,4-diiodobenzene, β -benzoylpropionic acid, and β -(*p*-iodobenzoyl)propionic acid were separated. Clemmensen reduction of the iodinated ketonic acids was rather unsatisfactory in both cases, and poor yields of the iodinated phenyl fatty acids were obtained.

Physiological Application.⁶—The compounds were tested as prepared by intrathecal injection in dogs, since the spinal canal represents the most sensitive site in which they might ultimately be used. Of the group, the mixture of isomeric ethyl iodophenylundecylates gave very satisfactory results in the animal testing. Following this animal work, this mixture has been employed in

numerous human cases. The product seems to be particularly satisfactory for myelography in that it is more fluid than previous compounds which have been employed,⁷ and may be injected and removed after injection with comparative ease. Apart from these mechanical advantages, the product has the added feature that it is completely absorbed within a year after intrathecal injection.

Experimental⁸

Esters of Iodinated O-Acylglycolates.—The esters of the O-acylglycolates were obtained by heating for several hours under reflux at 160–170° mixtures of the dry sodium salts of the individual acids with a slight excess of an ester of chloroacetic acid. For purification the reaction products were taken up in ether or chloroform, washed free of unreacted material, and distilled at reduced pressure or crystallized from alcohol.

Ethyl O-(*o*-Iodobenzoyl)-glycolate.—From the dry sodium salt prepared from 79.5 g. (0.32 mole) of *o*-iodobenzoic acid and 63 g. (0.51 mole) of ethyl chloroacetate, 67 g. (63%) of colorless ethyl O-(*o*-iodobenzoyl)-glycolate was obtained; b. p. 169° (0.02 mm.); sp. gr. $^{20}_{20}$ 1.647; n^{25}_D 1.5637.

Anal. Calcd. for $C_{11}H_{11}O_4I$: I, 38.0. Found: I, 37.8.

Glycol Di-(chloroacetate).—A mixture of 141.7 g. (1.5 moles) of chloroacetic acid, 46.5 g. (0.75 mole) of ethylene glycol, and 204 g. (1.5 moles) of anhydrous zinc chloride was heated on the steam-bath for five to six hours. After cooling, water was added to dissolve the zinc chloride, and the mixture extracted with ether. The ether layer was separated and washed with dilute sodium carbonate solution and then with water until neutral. The ether was allowed to evaporate, and the liquid residue (67.5 g.) was taken up in 50 cc. of ether. An equal volume of petroleum ether was added and the mixture cooled in an ice-salt-bath. A yield of 56 g. (35%) of needle-like crystals, m. p. 42.5–43°, was thus obtained. Meerwein and Sönke⁹ obtained the same compound, m. p. 45–46.5°, as one of the products of the interaction of ethylene oxide and chloroacetic acid.

Glycol Di-O-(*o*-iodobenzoyl)-glycolate.—From 1.08 g. (0.005 mole) of glycol di-chloroacetate and 2.70 g. (0.01 mole) of sodium *o*-iodobenzoate, 2.2 g. (69%) of a product melting at 77–78° was obtained. Crystallization from methyl alcohol gave crystals of m. p. 80–81°.

Anal. Calcd. for $C_{20}H_{16}O_6I_2$: I, 39.8. Found: I, 39.8.

(7) Cf., *inter al.*, "New and Non-Official Remedies," American Medical Association, 1940, p. 295–296; Goodman and Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1941, p. 619.

(8) In this and subsequent publications of this series, iodine analyses have been used for definition of the compound rather than the classical C and H analyses. Experience with more than three hundred iodinated compounds has shown that the iodine content is a most sensitive criterion, since iodine is usually the element most abundantly present, and since methods for iodine determination are extremely accurate. Many of the analyses reported in this paper were carried out by Dr. Leonard Weisler and by Mr. Hugh Mosher. In all cases, the analyses were conducted by fusion with sodium peroxide in the Parr bomb and determination of the iodine by the Volhard method.

(9) Meerwein and Sönke, *J. prakt. Chem.*, **137**, 316 (1933).

(4) Fournau and Baranger, *Bull. soc. chim.*, [4] **40**, 1163 (1931).

(5) Harmon and Marvel, *THIS JOURNAL*, **54**, 2526 (1932).

(6) The physiological results will be reported elsewhere.

Ethyl *p*-Iodobenzylmalonate.—From a solution of 5.75 g. (0.25 atom) of sodium in 50 cc. of absolute ethyl alcohol, 76.2 cc. (0.50 mole) of ethyl malonate and 74 g. (0.25 mole) of crude *p*-iodobenzyl bromide,¹⁰ ethyl *p*-iodobenzylmalonate was prepared in the usual way in a yield of 50.8 g. (54%); b. p. 180–183° (3 mm.); sp. gr. ²⁰₂₀ 1.469; *n*²⁵_D 1.5355.

Anal. Calcd. for C₁₄H₁₇O₄I: I, 33.7. Found: I, 34.1.

***p*-Iodobenzylmalonic Acid.**—Alkaline hydrolysis of ethyl *p*-iodobenzylmalonate in 80% ethanol gave a 96% yield of *p*-iodobenzylmalonic acid, which melted without purification at 164–165° with evolution of gas. The acid, m. p. 164.4°, has been prepared previously by a Sandmeyer reaction on *p*-aminobenzylmalonic acid.¹¹

β -(*p*-Iodophenyl)-propionic Acid.—Decarboxylation of *p*-iodobenzylmalonic acid at 160–170° gave a quantitative yield of β -(*p*-iodophenyl)-propionic acid; m. p. 137–138°. After crystallization from 60% acetic acid, the acid melted at 138–141°. When prepared from *p*-nitrohydrocinnamic acid, β -(*p*-iodophenyl)-propionic acid is reported¹² to melt at 140–141°.

Ethyl O-[β -(*p*-Iodophenyl)-propionyl]-glycolate.—From the sodium salt of β -(*p*-iodophenyl)-propionic acid and a 60% excess of ethyl chloroacetate, ethyl O-[β -(*p*-iodophenyl)-propionyl]-glycolate was obtained in 51% yield as a low melting solid, b. p. 227–232° (20 mm.). The pure compound, m. p. 41–42°, was obtained by digesting the crude product with saturated sodium bicarbonate solution and by crystallizing from dilute alcohol.

Anal. Calcd. for C₁₃H₁₅O₄I: I, 35.0. Found: I, 35.4.

Ethyl O-Undecylenylglycolate.—From 23.2 g. (0.19 mole) of ethyl chloroacetate and the dry sodium salt obtained by evaporating 25 g. (0.14 mole) of undecylenic acid with an equivalent amount of aqueous sodium hydroxide, ethyl O-undecylenylglycolate was obtained as a colorless oil in a yield of 22.4 g. (61%); b. p. 145° (0.2 mm.); sp. gr. ²⁰₂₀ 0.974; *n*²⁵_D 1.4438.

Anal. Calcd. for C₁₅H₂₅O₄: C, 66.63, H, 9.69. Found: C, 66.27, H, 9.69.

Reaction of Sodium κ -Iodoundecylate and Ethyl Chloroacetate.—A mixture of 18.3 g. (0.15 mole) of ethyl chloroacetate and 33.4 g. (0.1 mole) of sodium κ -iodoundecylate, prepared from κ -iodoundecylic acid¹³ by evaporating with an equivalent amount of aqueous sodium hydroxide, was heated for one hour in an oil-bath held at 140–150°. A vigorous reaction took place at first, and the temperature of the reaction mixture rose to 150–160°. Considerable decomposition occurred, and only an impure dark-colored product could be isolated when the reaction mixture was worked up.

γ -(*o*-Iodophenoxy)-*n*-propyl Bromide.—To a boiling mixture of 45.7 g. (0.208 mole) of *o*-iodophenol, 54 g. (0.268 mole) of trimethylene bromide and 100 cc. of water, a solution of 7.9 g. (0.197 mole) of sodium hydroxide in 25 cc. of water was added with stirring over a period of three hours. The reaction was completed by refluxing for five hours, cooled, and the upper water layer separated and

discarded. The lower layer was first distilled at the water pump. In this manner, 33.9 g. of forerun, containing unreacted *o*-iodophenol and trimethylene bromide, was obtained. Continued distillation at lower pressure gave 41.5 g. (58%) of γ -(*o*-iodophenoxy)-*n*-propyl bromide, which boiled at 154–156° (0.2 mm.).

Ethyl γ -(*o*-Iodophenoxy)-*n*-butyrate.—Using a procedure paralleling that of Marvel and Tannenbaum² for the preparation of ethyl phenoxybutyrate from phenol and trimethylene bromide, γ -(*o*-iodophenoxy)-*n*-propyl bromide, b. p. 154–156° (0.2 mm.), was obtained in 58% yield from *o*-iodophenol and trimethylene bromide. Conversion to γ -(*o*-iodophenoxy)-*n*-butyronitrile, b. p. 160° (0.2 mm.), was effected in 55% yield by interaction with sodium cyanide. From the nitrile, ethyl γ -(*o*-iodophenoxy)-*n*-butyrate, b. p. 158° (0.1–0.2 mm.), was obtained in nearly quantitative yield by ethanolysis in the presence of sulfuric acid; sp. gr. ²⁰₂₀ 1.549; *n*²⁵_D 1.5598.

Anal. Calcd. for C₁₂H₁₅O₃I: I, 38.0. Found: I, 38.1.

Reaction of *o*-Iodophenol with Ethylene Bromide: (a) α,β -Di-(*o*-iodophenoxy)-ethane.—A solution of 110 g. (0.5 mole) of *o*-iodophenol and 188 g. (1.0 mole) of ethylene bromide in 500 cc. of absolute alcohol containing 11.5 g. (0.5 atom) of sodium was refluxed with stirring for five hours. The reaction product was cooled and the crystals filtered. Trituration with water gave 9.2 g. (10%) of α,β -di-(*o*-iodophenoxy)-ethane; m. p. 109–115°. After crystallization from alcohol, the product melted at 120–121°.

Anal. Calcd. for C₁₄H₁₂O₂I₂: I, 54.5. Found: I, 54.6.

(b) **α -Bromo- β -(*o*-iodophenoxy)-ethane.**—On chilling the alcoholic filtrates to 0°, 40.4 g. of α -bromo- β -(*o*-iodophenoxy)-ethane of m. p. 45–47° was obtained. On working up the residue by dilution with water and by distillation *in vacuo* of the separated oil, the yield was raised to 80 g. (34%). Crystallization from alcohol gave a product melting at 50–51°.

Anal. Calcd. for C₈H₈OBrI: halogen, 63.3. Found: halogen, 63.1.

Ethyl κ -(*o*-Iodophenoxy)-undecylate.—By heating a mixture of 73.3 g. (0.25 mole) of ethyl κ -bromoundecylate with 55 g. (0.25 mole) of dry sodium *o*-iodophenoxide for eight hours with stirring at ca. 110° and by extracting the reaction product with ether and distilling at reduced pressure, a light brown oil, boiling at 235–240° (2 mm.), was obtained. Although a slight amount of decomposition evidently occurred during the distillation, the oil analyzed correctly for ethyl κ -(*o*-iodophenoxy)-undecylate; yield, 51.5 g. (48%); sp. gr. ²⁰₂₀ 1.302; *n*²⁵_D 1.5251.

Anal. Calcd. for C₁₉H₂₉O₃I: I, 29.4. Found: I, 29.7.

κ -(*o*-Iodophenoxy)-undecylic Acid.—Hydrolysis of ethyl κ -(*o*-iodophenoxy)-undecylate with alcoholic alkali and crystallization of the product from alcohol gave a 59% yield of κ -(*o*-iodophenoxy)-undecylic acid; m. p. 49–50.5°.

Anal. Calcd. for C₁₇H₂₅O₃I: neut. equiv., 404. Found: neut. equiv., 405.

Ethyl Iodophenylundecylate.—To 275 g. (1.35 moles) of iodobenzene, cooled to 0° by means of an ice-salt-bath,

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

(11) Abderhalden and Brossa, *Ber.*, **42**, 3413 (1909).

(12) Gabriel and Herzberg, *ibid.*, **16**, 2040 (1883).

(13) Ashton and Smith, *J. Chem. Soc.*, 1308 (1934).

52.5 g. (0.39 mole) of powdered anhydrous aluminum chloride was added. Over a period of about thirty-five minutes, during which the temperature was maintained at 7–8°, 60 cc. (0.25 mole) of ethyl undecylenate was introduced with stirring. The mixture was poured with stirring into a mixture of 200 g. of cracked ice and 100 cc. of 6 *N* hydrochloric acid. When the decomposition was over, the iodobenzene layer was separated and washed with a saturated aqueous solution containing 15 g. of sodium bisulfite and then with water until the washings were neutral to litmus. After drying with sodium sulfate, it was distilled at reduced pressure. At 205–213° (1.5 mm.), 39 g. (40%) of almost colorless oil was collected; sp. gr. $^{20}_{20}$ 1.263; n^{25}_{D} 1.5232.

Anal. Calcd. for $C_{19}H_{29}O_2I$: I, 30.5. Found: I, 30.2.

The residue from the distillation weighed 39–40 g. (40%), but could not be distilled without decomposition. It probably consists of iodobenzene condensed with more than one molecule of ethyl undecylenate.

Alkaline hydrolysis of ethyl iodophenylundecylate followed by alkaline permanganate oxidation gave a 12% yield of impure *p*-iodobenzoic acid; m. p. 252–261°. By sublimation the melting point was raised to 264°, and this product gave no depression in a mixed melting point with *p*-iodobenzoic acid.

Ethyl Bromophenylundecylate.—This product was prepared from bromobenzene and ethyl undecylenate in a manner analogous to that used with ethyl iodophenylundecylate; yield, 45%; b. p. 186–189° (1.5 mm.); sp. gr. $^{20}_{20}$ 1.137; n^{25}_{D} 1.5042.

Anal. Calcd. for $C_{19}H_{29}O_2Br$: Br, 21.6. Found: Br, 21.4.

Ethyl Iodophenylstearate.—From ethyl oleate and iodobenzene in the presence of aluminum chloride, a 22% yield of ethyl iodophenylstearate was obtained as a yellow oil; b. p. 242–258° (2 mm.); sp. gr. $^{20}_{20}$ 1.09. The product analyzed about 4% low for iodine, which may be due either to partial decomposition or to incomplete combustion in the analysis.

Anal. Calcd. for $C_{26}H_{48}O_2I$: I, 24.7. Found: I, 20.5.

In addition to the above fraction, a residue weighing 50–60 g. was obtained. This material varied in viscosity with the period of heating to which it was subjected during distillation. It probably consists of iodobenzene condensed with two or more molecules of ethyl oleate.

Reaction of Succinic Anhydride with Iodobenzene.—To 50 g. (0.5 mole) of succinic anhydride in 693 g. (3.4 moles) of iodobenzene, 147 g. (1.10 moles) of powdered anhydrous aluminum chloride was added rapidly with stirring. The temperature spontaneously rose to 74°, and the reaction was completed by heating with stirring on a steam-bath for half an hour. The reaction product was broken up in ice-hydrochloric acid, and the excess iodobenzene removed by steam distillation. The heavy, dark residue was cooled, separated from the supernatant liquid, and digested with 500 cc. of hot 10% sodium carbonate solution. After cooling to 16°, the insoluble residue was filtered, and the filtrate acidified with concentrated hydrochloric acid. In this way a crude mixture of β -benzoylpropionic acid and β -(*p*-iodobenzoyl)-propionic acid was obtained in a yield of 87.1 g.; m. p. 110–140°. The crude product could be

resolved most easily by extraction with hot water. For example, 41 g. of crude acid was refluxed for half an hour with 500 cc. of water, the hot solution filtered, and the residue crystallized twice from 50 cc. of alcohol. In this manner, 9.7 g. (13%) of β -(*p*-iodobenzoyl)-propionic acid, m. p. 174–177°, was obtained. From the aqueous filtrate 10.1 g. of β -benzoylpropionic acid, m. p. 109–110°, separated on cooling. For the preparation of the pure β -(*p*-iodobenzoyl)-propionic acid, however, the crude mixture was esterified both with ethyl and with methyl alcohol, and the separation in each case was effected by distillation at reduced pressure. The esters were purified by crystallization from twice their weight of ethyl alcohol. Ethyl β -(*p*-iodobenzoyl)-propionate was found to melt at 64–65°.

Anal. Calcd. for $C_{12}H_{13}O_2I$: I, 38.2. Found: I, 38.1.

Methyl β -(*p*-iodobenzoyl)-propionate melted at 67.5–68.5°.

Anal. Calcd. for $C_{11}H_{11}O_2I$: I, 39.9. Found: I, 39.6.

β -(*p*-Iodobenzoyl)-propionic Acid.—Alkaline hydrolysis of the esters in aqueous alcohol gave the free acid. After crystallization from alcohol, it melted at 177–178°.

Anal. Calcd. for $C_{10}H_9O_2I$; neut. equiv., 304. Found: neut. equiv., 304.

1,4- and 1,2-Diiodobenzene.—The insoluble residue from the sodium carbonate digestion was dissolved in hot alcohol. On cooling to 20°, a mixture of oil and crystals separated. The crystals were filtered, and, after crystallization from alcohol, were found to melt at 128°. The product was identified with 1,4-diiodobenzene, m. p. 128°, by a mixed melting point. The oil was distilled under reduced pressure, and an amber colored liquid, which solidified on standing, was collected at 153° (15 mm.); yield 15.4 g.; m. p. 23°; sp. gr. 2.4. The properties of the compound correspond closely to those of 1,2-diiodobenzene; m. p. 23.4° (1,3-diiodobenzene, m. p. 34°).¹⁴

Clemmensen Reduction of β -(*p*-Iodobenzoyl)-propionic Acid: Ethyl γ -(*p*-Iodophenyl)-*n*-butyrate.—Clemmensen reduction of β -(*p*-iodobenzoyl)-propionic acid with amalgamated zinc and concentrated hydrochloric acid gave crude γ -(*p*-iodophenyl)-*n*-butyric acid, which was purified by conversion to the ethyl ester and by distillation of the latter at reduced pressure; yield 32%; b. p. 183° (10 mm.).

Anal. Calcd. for $C_{12}H_{15}O_2I$: I, 39.9. Found: I, 40.0.

γ -(*p*-Iodophenyl)-*n*-butyric Acid.—Hydrolysis of the ester with alcoholic sodium hydroxide gave γ -(*p*-iodophenyl)-*n*-butyric acid; m. p. 80–83°. After crystallization from 60% aqueous acetic acid, the melting point was raised to 89–89.5°.

Anal. Calcd. for $C_{10}H_{11}O_2I$: neut. equiv., 290. Found: neut. equiv., 288.

Aqueous alkaline permanganate oxidation of γ -(*p*-iodophenyl)-*n*-butyric acid resulted in a 63% yield of *p*-iodobenzoic acid.

Reaction of δ -Carboethoxyvaleryl Chloride with Iodobenzene.—To 38.6 g. (0.20 mole) of δ -carboethoxyvaleryl chloride¹⁵ and 220 g. (1.08 moles) of iodobenzene, 53.4 g. (0.40 mole) of aluminum chloride was added in small por-

(14) Narbutt, *Ber.*, **52**, 1028 (1919).

(15) Blaise and Köhler, *Bull. soc. chim.*, [4] **7**, 219 (1910).

tions with stirring. The temperature was held at 15° during the addition of the aluminum chloride, and was then lowered to 10°, while stirring was continued for three hours. After decomposing the reaction mixture with ice-hydrochloric acid, the product was worked up by the same procedure used with the reaction product from succinic anhydride and iodobenzene. For purification, the crude acid fraction was esterified with ethyl alcohol and distilled under reduced pressure. A fraction, boiling at 188–206° (1.5 mm.), was obtained in a yield of 26.8 g. From this, after digestion with 10% sodium bisulfite solution, and crystallization from alcohol, a yield of 23 g. (32%) of pure ethyl δ -(*p*-iodobenzoyl)-*n*-valerate, m. p. 66–67°, was obtained.

Anal. Calcd. for $C_{14}H_{17}O_2I$: I, 35.2. Found: I, 35.2.

δ -(*p*-Iodobenzoyl)-*n*-valeric Acid.—Hydrolysis of ethyl δ -(*p*-iodobenzoyl)-*n*-valerate with sodium hydroxide in 50% alcohol gave a nearly quantitative yield of δ -(*p*-iodobenzoyl)-*n*-valeric acid; m. p. 154–156°.

Anal. Calcd. for $C_{12}H_{13}O_3I$: neut. equiv., 332. Found: neut. equiv., 332.

By oxidation of δ -(*p*-iodobenzoyl)-*n*-valeric acid with aqueous alkaline permanganate, a 67% yield of *p*-iodobenzoic acid was obtained.

Ethyl ϵ -(*p*-Iodophenyl)-*n*-caproate.—By Clemmensen reduction, δ -(*p*-iodobenzoyl)-*n*-valeric acid was converted

to ϵ -(*p*-iodophenyl)-*n*-caproic acid. The product was isolated and purified as the ethyl ester which was obtained in 14% yield; b. p. 205–210° (10 mm.).

Anal. Calcd. for $C_{14}H_{19}O_2I$: I, 36.7. Found: I, 37.0.

ϵ -(*p*-Iodophenyl)-*n*-caproic Acid.—Hydrolysis of the ethyl ester with alcoholic sodium hydroxide gave ϵ -(*p*-iodophenyl)-*n*-caproic acid. The pure product, m. p. 66–67°, was obtained by crystallization first from petroleum ether (b. p. 40–60°) and finally from 60% acetic acid.

Anal. Calcd. for $C_{12}H_{15}O_2I$: neut. equiv., 318. Found: neut. equiv., 320.

Summary

With the object of developing an absorbable liquid contrast medium for radiographic diagnoses, a number of esters of iodinated aromatic derivatives of glycolic acid, of iodinated phenoxy fatty acids, and of iodinated phenyl fatty acids have been prepared. Of these, ethyl iodophenylundecylate, a mixture of isomers obtained by the addition of iodobenzene to ethyl undecylenate in the presence of aluminum chloride, appears to satisfy most of the clinical requirements.

ROCHESTER, N. Y.

RECEIVED NOVEMBER 21, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, PURDUE UNIVERSITY AGRICULTURAL EXPERIMENT STATION]

Studies on the Carotenoids. III. Distribution of Pure Pigments between Immiscible Solvents^{1,2}

BY JONATHAN W. WHITE, JR.,³ AND F. P. ZSCHEILE

Most methods for the determination of carotene depend upon a partition between two immiscible solvents for its separation from other pigments. Peterson⁴ has discussed such methods from a historical and critical viewpoint. Many methods in use today employ 85 to 90% methanol or ethanol and a hydrocarbon as the two phases. Following the work of Clausen and McCoord⁵ who used diacetone alcohol in the determination of carotene in blood, Hegsted, Porter, and Peterson,⁶ Zimmerman, Tressler and Maynard,⁷ and Beadle

and Zscheile⁸ have employed aqueous diacetone alcohol as the hypophasic solvent.

Despite the wide use of such partition methods in the carotene determination, very little quantitative work has been done with pure pigments. Clausen and McCoord⁵ determined the distribution coefficients for "carotene" and "xanthophyll" between hexane and aqueous solutions of methanol, ethanol, and diacetone alcohol. The method developed from these studies was based upon a single distribution between hexane and a 100:14 solution of diacetone alcohol and water.

The determination of the carotenoids in corn grain is complicated by the presence of relatively large amounts of cryptoxanthol. Efforts to include this pigment in an analytical method have been based on the degree of adsorption of the pigment by calcium carbonate⁹ or magnesium carbonate.¹⁰ However, no attempt is usually made

(1) Based upon a portion of a thesis to be submitted by Jonathan W. White, Jr., to the faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, May, 1942.

(2) Journal Paper Number 10 of the Purdue University Agricultural Experiment Station.

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