color with alcoholic ferric chloride. The bulk of the product could not be crystallized.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6. Found: C, 83.5; H, 5.3.

Summary

The α-hydroxymethylene derivatives of cholestenone, 8-keto-11-methyl-8,9,10,11-tetrahydrobenz[a]anthracene, α-tetralone, and 8-methyl-11-keto-8,9,10,11-tetrahydrobenz[a]anthracene and 1-keto-1,2,3,4-tetrahydrophenanthrene have been prepared for testing as agents in the chemotherapy of cancer.

The hydroxymethylene derivative of 8-keto-11-methyl 8,9,10,11-tetrahydrobenz[a]anthracene has shown an interesting lability of ether formation and cleavage.

OAK RIDGE, TENNESSEE RECEIVED APRIL 3, 1950

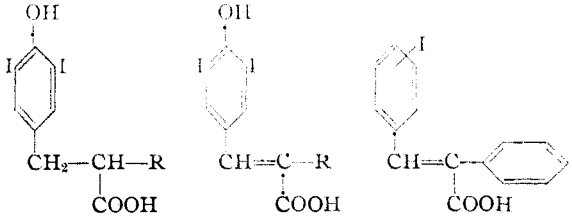
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

X-Ray Diagnostics. IV. Cholecystographic Agents

BY DOMENICK PAPA, HILDA BREIGER, ERWIN SCHWENK AND VIRGINIA PETERSON

In continuation of studies[1] on the correlation of structure and cholecystographic property of organic iodine compounds, we have prepared for pharmacological evaluation a limited number of compounds of four different types. In none of these four groups of compounds do the structures depart radically from the known clinically efficacious cholecystographic medium, α-phenyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid[2] (I).

The first two types of iodinated compounds are of general formulas II and III[1e] wherein Z is either sulfur or oxygen. The structural similarity of these two types of compounds to I is apparent from an inspection of the formulas, II being identical to I except for the presence of a hetero atom, whereas III differs from I in having both a hetero atom and a double bond in the aliphatic portion of the molecule.



I, R = C_6H_5– III, R = C_6H_5Z– VI
II, R = C_6H_5Z– IV, R = C_6H_5; $CH_2C_6H_5$–
V, R = alkyl group

The third group of compounds are of general formula IV, wherein R is phenyl, benzyl and the corresponding *p*-iodo derivatives. These substances embrace the basic Priodax structure, but are unsaturated aliphatic acid derivatives. In the latter respect, substances of type IV are structurally related to the recently described[1c] 3,5-diiodo-4-hydroxyphenylalkenoic acid (V) and the diiodo-diarylacrylic acids[1a] (VI).

Several additional compounds of general formula IV were synthesized in which the radiopaque element is bromine, chlorine or a combination of either of these elements and iodine. Although iodine is recognized as the radiopaque element of choice, bromo and chloro compounds have been used clinically with success as contrast agents. In addition, the chemical and patent literature is replete with reports of bromo and chloro compounds which have been proposed or studied as contrast agents. It was also of interest to compare the solubility of these compounds with the corresponding iodo compounds in view of the apparent correlation of this physical property and cholecystographic properties.[1b]

The diiodo compounds of formula II were secured from the known substituted propionic acids[3] by iodination with potassium triiodide in alkaline solution. The compounds of formulas III, IV and IX were prepared by the conventional Perkin reaction of the anhydrous alkali metal salt of the appropriately substituted acetic acids and benzaldehydes. The condensation of the free acid with the substituted benzaldehyde in the presence of an equimolecular amount of anhydrous triethylamine or potassium acetate[4] was used in the synthesis of α-phenoxy-3,5-diiodo-4-hydroxycinnamic acid and X. The yield in these instances was not comparable to those obtained using the anhydrous alkali metal salts of the acids.

The fourth type of compound to be investigated differs from types I–V in that the hydroxyl group has been replaced by an amino group.[5] Two propionic acids, VII and VIII, an acrylic acid, IX, and a substance, X, having both a hydroxyl and an amino group were prepared.

The intermediates, α-phenyl-β-(*p*-aminophenyl)-propionic acid (XI) and α-(*p*-aminophenyl)-β-

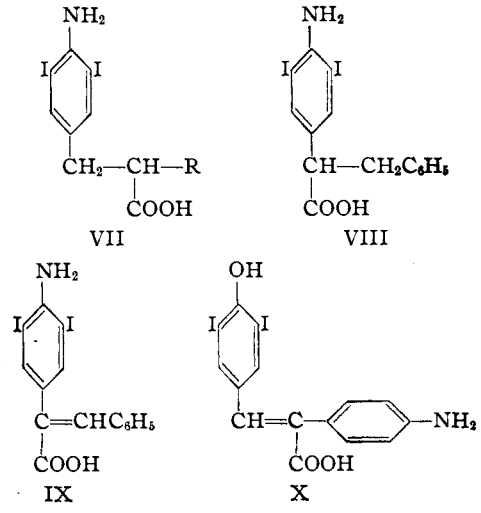
(1) (a) Schwenk and Papa, U. S. Patent 2,436,270, Feb. 17, 1948; (b) Papa, *Arch. Biochem.*, **23**, 163 (1949); (c) Papa, Schwenk, Breiger and Peterson, THIS JOURNAL, **72**, 2619 (1950); (d) Papa, Schwenk and Klingsberg, *ibid.*, **72**, 2623 (1950); (e) Papa and Schwenk, U. S. Patent 2,503,296, April 11, 1950.

(2) See references in 1c.

(3) Papa and Schwenk, THIS JOURNAL, **69**, 3022 (1947).

(4) Papa, Breiger and Peterson, *J. Org. Chem.*, **14**, 363 (1949) (see references 6 and 7 in this paper).

(5) (a) While this work was in progress, the diiodoamino acid VII was reported by Barnett, Robinson and Wilson, *J. Chem. Soc.*, 203 (1947); (b) diiodoamino acids VII and VIII have been reported recently by Lewis, Pratt, Homiller, Tullar and Archer, THIS JOURNAL, **71**, 3749 (1949).



phenylpropionic acid (XII), for the synthesis of VII and VIII were obtained as follows: Condensation of *p*-nitrobenzaldehyde[6] and potassium phenylacetate gave a mixture of the low and high melting forms of α-phenyl-*p*-nitrocinnamic acid (XIII) which without purification was reduced to XI with Raney nickel catalyst in alkaline solution[5b] at room temperature and 1,500 p.s.i. of hydrogen in 84% yield and with Raney alloy in aqueous alkali[7] in 68% yield. Treatment of XIII with Adams platinum oxide catalyst in ethanol gave an intermediate reduction product which on further reduction with sodium amalgam gave XI in 76% yield.

The isomeric acid XII was secured by a similar sequence of reactions; *p*-nitrophenylacetic acid and benzaldehyde gave α-(*p*-nitrophenyl)-cinnamic acid (XIV), which was reduced to XII by the three procedures described for XI. In the case of the platinum oxide reduction of XIV, the intermediate product, α-(*p*-aminophenyl)-cinnamic acid, was isolated and characterized.

Unlike the corresponding hydroxy compounds, the iodination of XI and XII and the purification of VII and especially VIII is comparatively difficult. Iodination with potassium triiodide in alkaline solution or with powdered iodine in dilute ammonium hydroxide[8] solution gave only intractable products. The acid XI with iodine chloride in acetic acid solution gave VII in 52% yield as a light tan product, whereas XII on treatment with iodine chloride in aqueous hydrochloric acid yielded VIII in unsatisfactory purity. Our results with the iodination of XI and XII parallel those of other investigators.[5] However, it has been reported[5b] that iodination of XII in a two-phase system using iodine chloride in aqueous hydrochloric acid with chloroform or tetrachloroethane gives VIII in both satisfactory purity and yield.

The pharmacological evaluation of the four groups of compounds was carried out essentially as previously described.[1a] The substance under test was fed to dogs in 2-g. quantities in gelatine capsules and the animals observed for a period of 48 hours. Compounds 13, 14 and 15 (the arabic numbers refer to the compounds in the table and experimental section) gave good gall bladder visualization within 5–7 hours, with little or no substance present in the transverse colon. Substances 1, 2, 3, 4, 5 and 16 gave fair to faint gall bladder shadows in about 8 hours, whereas the remaining compounds gave no gall bladder visualization. The greatest concentration of the latter group of substances was in the intestinal tract and elimination was principally *via* the colon. A detailed report on the pharmacology of these compounds will appear elsewhere.

As a result of these studies, those previously reported,[1] and others which will be the subject of subsequent publications, it has been established that neither a hydroxyl group nor saturation in the aliphatic portion of the organic iodine compound is essential for cholecystographic properties.[9] As has been recently pointed out,[5b] it is likely that the sole function of the hydroxyl group in these substances is to facilitate the introduction of the radiopaque element. Similarly, the amino group does not confer any unique properties to such substances, although to a somewhat lesser degree it also facilitates halogen substitution.

Experimental

The compounds in Table I were prepared by the following procedure except as noted: In a 500-cc., three-necked flask with stirrer, thermometer and condenser carrying a calcium chloride tube, there was added 0.1 mole of the anhydrous potassium salt of the appropriately substituted acetic acid, 0.1 mole of the substituted benzaldehyde and 150 cc. of acetic anhydride. The mixture was heated for the specified time and temperature and after cooling to about 60°, the excess acetic anhydride was decomposed with water. The crude condensation product was taken up in ether, the ether extract washed several times with water and after evaporating the ether, the residue was heated on the steam-bath with sufficient 5% sodium hydroxide solution so that the final solution had a *p*H of 10. The alkaline solution was filtered and acidified with dilute hydrochloric or acetic (for the amino compounds) acids.

(13) **α-Phenoxy-β-(3,5-diiodo-4-hydroxyphenyl)-propionic Acid.**—To a solution of 12.8 g. (0.05 mole) of α-phenoxy-β-(4-hydroxyphenyl)-propionic acid in 400 cc. of 0.5 *N* sodium hydroxide solution, there was added dropwise with stirring a solution of 25.4 g. of iodine and 25.4 g. of potassium iodide in 150 cc. of water. The solution was stirred for an additional hour and filtered through Supercel. The filtrate was cooled to 5–10° and acidified to litmus paper with sulfur dioxide. The white crystalline product was filtered, washed with water and dried; yield 21.5 g. (84%), m. p.[10] 133–135°; recrystallized from a

(6) Generous samples of *p*-nitrobenzaldehyde have been obtained from the National Aniline Division of the Allied Chemical and Dye Corporation through the kindness of Mr. J. D. Nantz of the Buffalo plant.

(7) Papa, Schwenk and Whitman, *J. Org. Chem.*, **7**, 587 (1942).

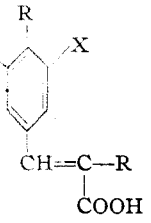
(8) British Patent 559,024.

(9) Compare Natelson, *et al.*, U. S. Patent 2,400,433, May 16, 1946, and Epstein, Natelson and Kramer, *J. Am. Roentgenol.*, **56**, 202 (1946), in which it is suggested that the presence of the diiodohydroxyphenyl moiety is a prerequisite for cholecystographic compounds.

(10) All melting points are corrected.

TABLE I

COMPOUNDS OF FORMULA



No.	R′	X	R	Reacn. time, hr.	Temp., °C.	Yield, %	M. p.,[a] °C.	Recryst. solvent	Formula	Analyses, % Calcd.	Found
1	OH	I	C_6H_5O[b]	35–40	110	33[c]	224.5–226.5	Acetone–H_2O	$C_{15}H_{10}O_4I_2$	I, 50.00	49.88
2	OH	I	C_6H_5S–	30	110	65	219.5–220.5	C_2H_5OH–H_2O	$C_{15}H_{10}O_3SI_2$	C, 34.36; H, 1.92	34.64, 2.37
3	OH	I	C_6H_5–[d]	6	110	69	225–227	Acetone–H_2O	$C_{15}H_{10}O_3I_2$	I, 51.8	51.7
4	OH	I	p-IC_6H_4–	10	115	58	240–242	Acetone–H_2O	$C_{15}H_9O_3I_3$	I, 61.6	61.9
5	OH	I	$C_6H_5CH_2$–	80	100	72	240–241	Acetone–H_2O	$C_{16}H_{12}O_3I_2$	I, 50.2	50.5
6	OH	Cl	C_6H_5–	6	110	56	224–225.5	CH_3OH–H_2O	$C_{15}H_{10}O_3Cl_2$	C, 58.25; H, 3.26	58.47, 3.21
7	OH	Br	C_6H_5–	6	110	66	219–220	CH_3OH–H_2O	$C_{15}H_{10}O_3Br_2$	C, 45.34; H, 2.53	45.05, 2.65
8	OH	Cl	p-IC_6H_4–	10	115	42	231–232	C_2H_5OH–H_2O	$C_{15}H_9O_3Cl_2I$	C, 41.38; H, 2.09	41.70, 2.36
9	OH	Br	p-IC_6H_4–	10	115	51	252–253.5	Acetone–H_2O	$C_{15}H_9O_3Br_2I$	C, 34.36; H, 1.73	34.18, 1.64
10	OH	Cl[e]	C_6H_5	6	110	68	180–181	CH_3OH–H_2O	$C_{15}H_{11}O_3Cl$	C, 65.56; H, 4.04	65.48, 3.77
11	OH	I	p-$NH_2C_6H_5$–[f]	6	105	49	218–219	C_2H_5OH–H_2O	$C_{15}H_{11}O_2NI_2$	N, 2.76	2.66
12	H	H	3,5-I_2-4-$NH_2C_6H_5$–	10	110	14	>300	[g]	$C_{15}H_{11}O_2NI_2$	N, 3.85	3.62

[a] All melting points reported are for the analytically pure compounds. [b] The condensation was carried out with phenoxyacetic acid (0.1 mole), 3,5-diiodo-4-hydroxybenzaldehyde (0.1 mole) and 30.3 g. (0.3 mole) of triethylamine. [c] This represents the yield of crude condensation product, m. p. 203–213°. [d] After decomposing the excess acetic anhydride, the mixture was poured into dilute hydrochloric acid. The crude crystalline product was filtered, added to 500 cc. of 10% sodium hydroxide solution and the mixture heated on the steam-bath for one hour. The alkaline solution was filtered and then mixed with an equal volume of hot (95°) saturated sodium chloride solution. The disodium salt precipitates out on cooling. Recrystallized from 10% sodium chloride solution for analysis. *Anal.* Calcd. for $C_{15}H_8O_3I_2Na_2$: Na, 8.58. Found: Na, 8.51. The free acid was obtained by dissolving the salt in water at 70–80°, filtering and acidifying the filtrate. [e] This is a monochloro compound prepared from 3-chloro-4-hydroxybenzaldehyde. [f] Condensed *p*-aminophenylacetic acid (0.1 mole), 3,5-diiodo-4-hydroxybenzaldehyde (0.1 mole), freshly fused potassium acetate (0.1 mole) and 150 cc. of acetic anhydride. [g] Purified by solution in sodium carbonate and reprecipitation with acetic acid.

mixture of benzene–petroleum ether, m. p. 135–136°. *Anal.* Calcd. for $C_{15}H_{12}O_4I_2$: I, 49.81. Found: I, 50.00.

(14) **α-Phenylmercapto-β-(3,5-diiodo-4-hydroxyphenyl)-propionic Acid.**—Iodination of α-phenylmercapto-β-(4-hydroxyphenyl)-propionic acid was carried out as described for the oxygen compound; yield 78%, m. p. 130–131° after recrystallization from chloroform–petroleum ether. *Anal.* Calcd. for $C_{15}H_{12}O_3SI_2$: C, 34.23; H, 2.45. Found: C, 34.49; H, 2.45.

(15) **α-(Phenyl)-β-(3,5-diiodo-4-aminophenyl)-propionic Acid.**—A mixture of 70.5 g. (0.5 mole) of *p*-nitrobenzaldehyde, 87 g. (0.5 mole) of anhydrous potassium phenylacetate and 300 cc. of acetic anhydride was heated for 6–8 hours at 105–110°. The reaction mixture, after decomposing the excess acetic anhydride, was poured into 2 l. of dilute hydrochloric acid and the semi-crystalline α-phenyl-*p*-nitrocinnamic acid was filtered. The crude acid was dissolved in sodium carbonate solution, treated with Norite, filtered and the filtrate acidified with acetic acid. The yellow nitro acid was obtained in a yield of 86% and was reduced without further purification. Recrystallization of a small sample from ethanol gave a pale yellow crystalline product, m. p. 214.5–215.5°; previously reported m. p. 213–214° and 208–210°. The lower melting form of the nitro acid was not obtained pure.

Reduction of the crude nitro acid was carried out: (a) with Raney nickel catalyst in alkaline solution at room temperature and 1,500 p. s. i. of hydrogen essentially as previously described,[5b] yield 84%, m. p. 212–213°; (b) with Raney nickel aluminum alloy in aqueous alkali using sodium acetate to buffer the acidified (hydrochloric acid) reaction mixture; yield 68%, m. p. 213–214.5°; (c) with Adams platinum oxide catalyst in 95% ethanol at room temperature and 40–50 p. s. i. of hydrogen. The product obtained with the latter catalyst was probably α-phenyl-*p*-aminocinnamic acid (1 mole of hydrogen absorbed) and without further purification was reduced to the α-phenyl-β-(*p*-aminophenyl)-propionic acid with 5% sodium amalgam in ethanol at reflux temperature for six hours. The over-all yield of XI by the combined reductions was 76%, m. p. 213–214°. Mixed melting points of the products from experiments a, b and c showed no depression. An analytical sample of the amino acid was prepared by recrystallization from ethanol, m. p. 214–215°, previously reported m. p. 204–205°.[11] *Anal.* Calcd. for $C_{15}H_{15}O_2N$: C, 74.65; H, 6.27; N, 5.80. Found: C, 74.55; H, 6.29; N, 5.96.

To a solution of 24.1 g. (0.1 mole) of XI in 125 cc. of acetic acid, there was added 32.4 g. (0.2 mole) of freshly distilled iodine chloride. The mixture was heated to 40–50° for one hour and after keeping at room temperature overnight was slowly added to 300 cc. of 10% sodium bisulfite solution. The light brown diiodo acid was filtered, washed with water and crystallized from aqueous methanol; yield 52%, m. p. 173.5–175°. The analytical sample was prepared by recrystallization from ligroin (b. p. 65–70°) in which the diiodo acid is sparingly soluble, m. p. 176–177.5°, previously reported m. p. 175–176.9°,[5b] 172–173°.[5a] *Anal.* Calcd. for $C_{15}H_{13}O_2NI_2$: I, 51.5. Found: I, 51.7.

(16) **α-(3,5-Diiodo-4-aminophenyl)-β-phenylpropionic Acid.**—The condensation of *p*-nitrophenylacetic acid (90.5 g.), benzaldehyde (53 g.), triethylamine (50 g.) and acetic anhydride (300 cc.) was carried out at 105–110° for 16 hours. The crude mixture of nitro acids was worked up as described for the isomeric compound, yield 86 g. (63%), and was reduced in alkaline solution with Raney nickel catalyst at room temperature and 1,500 p. s. i. of hydrogen; yield 82%, m. p. 201–203°; recrystallized for analysis from aqueous acetic acid, m. p. 206–208°, previously reported m. p. 202–204°.[5b] *Anal.* Calcd. for $C_{15}H_{15}O_2N$: C, 74.65; H, 6.27. Found: C, 74.39; H, 6.36.

Reduction of the nitro acid with Adams platinum oxide catalyst in ethanol gave α-(*p*-aminophenyl)-cinnamic acid in 78% yield, m. p. 220–225°; recrystallized for analysis from ethanol, m. p. 226–227°. *Anal.* Calcd.

(11) Ref. 5b reports m. p. 200–203° for the amino compound resulting from the reduction and m. p. 204–205° for the amino compound regenerated from the hydrochloride.

for $C_{15}H_{13}O_2N$: C, 75.28; H, 5.48. Found: C, 75.44; H, 5.39. This cinnamic acid yielded the propionic acid on treatment with sodium amalgam in ethanol after refluxing for 6–8 hours; melting point and mixed melting point with product from Raney catalyst reduction, 205–206.5°.

Iodination of the α-(*p*-aminophenyl)-β-phenylpropionic acid by the procedure of Barnett, Robinson and Wilson[5a] gave 28% of the α-(3,5-diiodo-4-aminophenyl)-β-phenylpropionic acid, m. p. 133–138°. After several recrystallizations from ether–petroleum ether, the product was obtained as tan crystals, m. p. 139–141° after sintering at 135°, previously reported 144–146.2°.[5b] *Anal.* Calcd. for $C_{15}H_{13}O_2NI_2$: I, 51.5. Found: I, 50.9.

Acknowledgment.—The authors wish to express their appreciation to Dr. Richard Tislow for permission to publish the preliminary data on the pharmacology of the compounds and to Mr. Edwin Conner for most of microanalyses reported herein.

Summary

A series of α-(dihalogen-hydroxyphenyl)-, α-aryl-, α-aralkyl-, α-phenoxy- and α-phenylmercaptoacrylic acids, β-(diiodo-hydroxyphenyl)-α-phenoxy- and α-phenylmercaptopropionic acids and diiodo-amino-diaryl- propionic and acrylic acids have been synthesized and examined pharmacologically for cholecystographic properties.

BLOOMFIELD, N. J. RECEIVED APRIL 10, 1950

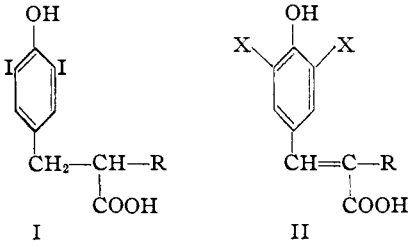
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

X-Ray Diagnostics. V. Halogenated Polycyclic Compounds[1]

BY DOMENICK PAPA, HILDA BREIGER, ERWIN SCHWENK AND VIRGINIA PETERSON

Of the numerous compounds which have been suggested or used clinically as gall bladder contrast agents, only the halogenated phenolphthaleins[2] and the iodinated cinchopen derivatives[3] have more than two six-membered rings. Notwithstanding the known clinical toxicity of these two types of compounds, it was of interest to establish whether α-naphthyl, α-tetralyl and α-diphenyl derivatives of β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid would be suitable for gall bladder visualization. Although it has been shown that the 3,5-diiodo-4-hydroxyphenyl moiety is not essential for cholecystographic property, we have retained this grouping in the polycyclic compounds because of the ease of preparation of such compounds and the clinical efficacy and safety of this configuration.

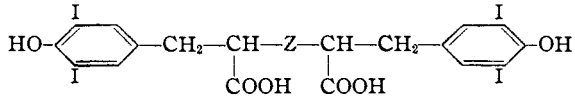
The halogenated polycyclic compounds prepared in this study are of general formulas I and II wherein X is halogen and R is a naphthyl, tetralyl or diphenyl radical. In addition, the



I

II

compounds III and IV were also prepared, the phenyl and diphenyl radicals being substituted in the para positions.



III, Z = $-C_6H_5-$ IV, Z = $-C_6H_4-C_6H_4-$

The diiodo acids of formula I, wherein R is naphthyl or tetralyl, were secured from the known appropriately substituted propionic acids[4] by iodination with potassium triiodide in alkaline solution. The diphenyl compound of formula I was prepared in the conventional manner. The Perkin condensation of diphenyl-4-acetic acid with *p*-hydroxybenzaldehyde gave α-diphenyl-4-hydroxycinnamic acid, which on reduction with Raney alloy and subsequent iodination yielded the α-diphenyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid in good yield.

The tetraiodo acids III and IV were obtained by the same sequence of reactions from *p*-phenylene diacetic acid and *p,p'*-diphenyldiacetic acid, respectively. The intermediate products, bis-α,α'-(*p*-hydroxybenzal)-*p*-phenylenediacetic acid, bis - α,α' - (*p* - hydroxybenzal) - *p,p'* - diphenyldiacetic acid and the corresponding benzyl derivatives were high melting compounds and although analytically pure samples were obtained, the melting points could not be used as a criterion of purity. Iodination of the two benzyl derivatives yielded tan to brown crystalline products which could not be recrystallized to constant melting point. In fact, repeated recrystallization of the tetraiodo acids resulted in decomposition with the liberation of iodine.

The acrylic acid derivatives of formula II were secured readily by the condensation of the anhydrous potassium salt of the arylacetic acid and the halogenated *p*-hydroxybenzaldehyde. In addition to the iodo compounds of Formula

(1) For the previous papers in this series see THIS JOURNAL, **72**, 4906 (1950), ref. 1.

(2) Graham and Cole, *J. Am. Med. Assoc.*, **82**, 613 (1924).

(3) Dohrn and Diedrich, U. S. Patent 2,220,086, Nov. 5, 1940; Orator and Walchshofer, *Deut. Z. Chir.*, **205**, 86 (1927).

(4) Papa, Breiger and Peterson, *J. Org. Chem.*, **14**, 362 (1949).