# The Synthesis of Fluoro-bromo Derivatives of Benzoic Acid to be Evaluated as Radiographic Opaques*

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**Seven new compounds: 3,5-dibromo-4-fluorobenzoic acid and its methyl, ethyl, *n*-propyl, and isopropyl esters, 3,5-dibromo-4-fluorohippuric acid, and 3,5-dibromo-4-fluorobenzamide have been synthesized. Three new compounds which were intermediates have also been made. They are: 3,5-dibromo-4-toluenediazonium fluoborate, 3,5-dibromo-4-fluorotoluene and 3,5-dibromo-4-fluorobenzoyl chloride. The opaque properties of 3,5-dibromo-4-fluorobenzoic acid, 3,5-dibromo-4-fluorohippuric acid, and ethyl 3,5-dibromo-4-fluorobenzoate were equal or superior to those of tetraiodophenolphthalein when radiographed in equivalent amounts in single tests on mice and indicate that the compounds are worthy of further study.**

SOON AFTER the discovery of X-rays by Roentgen their application to medical diagnosis was begun. Contrast media, agents placed within the body to cause a certain area of that body to appear on an X-ray film, have been developed from relatively crude materials such as metal sounds and bags of lead solutions (1) to the selective agents currently being used. What was said to be the greatest advance in the field of radiographic opaques was the introduction by Graham, Cole, and Copher (2), in 1924, of tetrabromophenolphthalein as a diagnostic aid. Here was an agent which when taken by mouth would concentrate in the gallbladder in sufficient quantities to allow it to be visualized by X-rays.

Most radiographic opaques used today are iodinated compounds. In many cases they give satisfactory radiographs but it is well known that their use is too often attended by untoward side reactions. These include lacrimation, salivation, coughing spells, nausea, vomiting, fall in blood pressure, flushing of the face, choking sensation, and cyanosis. Although these symptoms usually disappear after a time, fatalities have occurred (3).

It has been said that the opacity of an element is proportional to the cube of its atomic weight (4). This is probably a misinterpretation of Hull's law which shows that the coefficient of absorption of all elements for X-rays varies approximately as the cube of the atomic number except in the immediate vicinity of one of the characteristic wave lengths of an element (5). It has been shown by Binz, *et al.* (6), and Hull's law affirms it, that bromine has better opaque properties than iodine.

It has been reported that fluorine stabilizes other halogens in aliphatic compounds when the two are on adjacent carbon atoms (7). This led to the supposition that fluorine has the same effect when attached to an aromatic ring. Verification of this supposition seems to be offered by the work of Mittelstaedt and Jenkins (8). Results of toxicity tests of some fluoro-iodo compounds which they prepared showed a low order of toxicity. These facts led to the belief that a more satisfactory radiographic opaque might be discovered through the synthesis of certain bromo-fluoro compounds.

## EXPERIMENTAL

**Preparation of 3,5-Dibromo-4-toluenediazonium Fluoborate.**—An adaptation of the method of Schiemann and Winkelmuller (9) for the preparation of aromatic fluorine compounds was used. 4-Amino-3,5-dibromotoluene, prepared according to Hickinbottom (10), 255 Gm. (1.0 mole), was diazotized at 0–5° in 525 Gm. (2.5 moles) of fluoboric acid, 42%, with 69 Gm. (1.0 mole) of sodium nitrite. The diazonium fluoborate was collected on a Büchner funnel, washed with successive portions of cold distilled water, methyl alcohol and ether and air-dried for twenty-four hours. The yield was 350 Gm. (97.5%), decomposition temperature, 195–200°.

**Preparation of 3,5-Dibromo-4-fluorotoluene.**—The 3,5-dibromo-4-toluenediazonium fluoborate was thermally decomposed in a suitable apparatus (9). The crude 3,5-dibromo-4-fluorotoluene was washed out of the apparatus with ether. After filtering the ether solution and drying it over anhydrous sodium sulfate, the ether was removed by distillation and the residue vacuum distilled. The yield was 70 Gm. (28.1%), b. 118–125° at 21 mm. pressure.

**Preparation of 3,5-Dibromo-4-fluorobenzoic Acid.**—The oxidation was carried out by a general procedure (11). The 3,5-dibromo-4-fluorotoluene, 70 Gm. (0.28 mole), was oxidized in 500 cc. of acetic acid with 39 Gm. (0.39 mole) of chromic anhydride.

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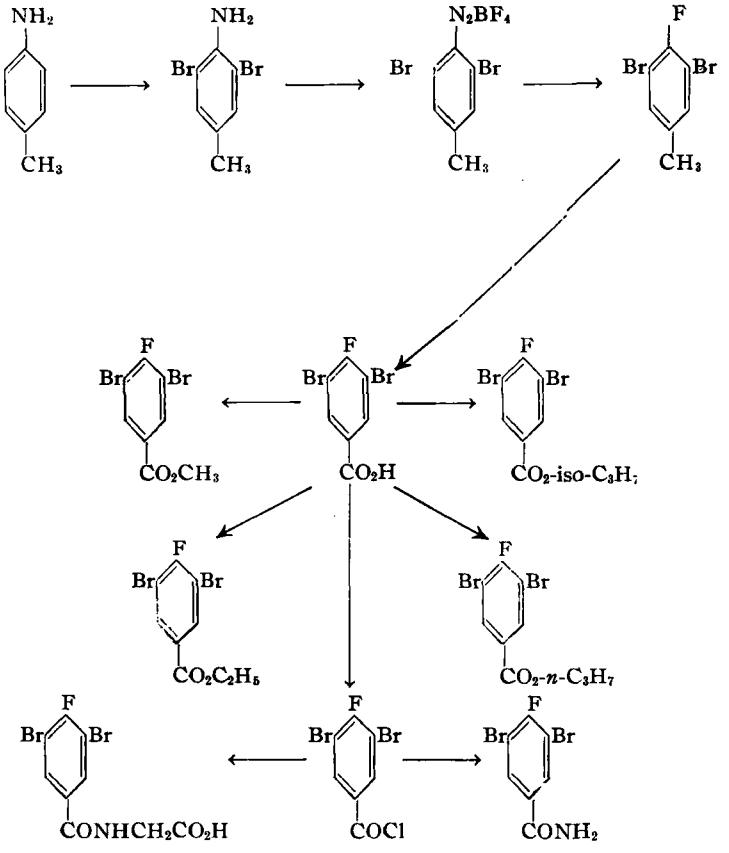
OUTLINE OF LABORATORY WORK




The crude acid was precipitated by the addition of distilled water and collected on a Büchner funnel. It was purified by dissolving it in ammonia solution, digesting with activated charcoal, filtering and precipitating it again with hydrochloric acid. The yield was 28.6 Gm. (36.8%), m. 234.5–235°.

*Anal.*—Calcd. for $C_7H_3O_2Br_2F$: neutr. equiv., 297.91. Found: neutr. equiv., 296.3.

**Preparation of Esters of 3,5-Dibromo-4-fluorobenzoic Acid.**—A modification of an esterification process described in Adkins and McElvain (12) was used. The 3,5-dibromo-4-fluorobenzoic acid, 2.97 Gm. (0.01 mole), was refluxed in 20 cc. of the appropriate alcohol saturated with hydrogen chloride. The esters were recrystallized from ethyl alcohol. Methyl ester: yield, 28%, m. 88–88.5°; ethyl ester: yield, 55%, m. 80–80.5°; *n*-propyl ester: yield, 12%, m. 34–35°; isopropyl ester: yield, 21%, m. 56–57°.

**Preparation of 3,5-Dibromo-4-fluorobenzoyl Chloride.**—An adaption of the method described in Gattermann and Wieland (13) was employed. The 3,5-dibromo-4-fluorobenzoic acid, 14.9 Gm. (0.05 mole), was refluxed with 17.8 Gm. (0.15 mole) of thionyl chloride in 50 cc. of dry benzene for sixteen hours. The excess thionyl chloride was removed by distillation and the residue dissolved in dry benzene for use in the following experiments.

**Preparation of 3,5-Dibromo-4-fluorohippuric Acid.**—The 3,5-dibromo-4-fluorohippuric acid was prepared according to the method which Ingersoll and Babcock (14) used to prepare hippuric acid. One-half of the benzene solution of 3,5-dibromo-4-fluorobenzoyl chloride prepared above and a solution of 4 Gm. (0.1 mole) of sodium hydroxide in 10 cc. of distilled water were added simultaneously to a stirred solution of 7.5 Gm. (0.1 mole) of glycine in 75 cc. of distilled water. The additions were made at such a rate that the reaction mixture was always slightly alkaline. The crude acid was precipitated by acidification and collected on a Büchner funnel. It was digested in carbon tetrachloride in which it is insoluble and the carbon tetrachloride removed by filtration. The 3,5-dibromo-4-fluorohippuric acid was recrystallized from boiling distilled water. The yield was 2.0 Gm., m. 210–211°.

*Anal.*—Calcd. for $C_9H_6O_3NBr_2F$: N, 3.95. Found: N, 3.87.

**Preparation of 3,5-Dibromo-4-fluorobenzamide.**—The 3,5-dibromo-4-fluorobenzamide was prepared according to the method described in Gattermann and Wieland (15) for the preparation of benzamide. The remainder of the benzene solution of 3,5-dibromo-4-fluorobenzoyl chloride prepared above was mixed with 20 Gm. of powdered ammonium

carbonate in an evaporating dish and heated with stirring until the odor of the 3,5-dibromo-4-fluorobenzoyl chloride was no longer discernible. The mixture was then stirred with distilled water and the undissolved portion collected on a Büchner funnel. The 3,5-dibromo-4-fluorobenzamide was recrystallized from ethyl alcohol. The yield was 1.5 Gm., m. 207.5–208°.

*Anal.*—Calcd. for $C_7H_4ONBr_2F$: N, 4.717. Found: N, 4.72.

**Test for Opacity of 3,5-Dibromo-4-fluorobenzoic Acid, 3,5-Dibromo-4-fluorohippuric Acid and Ethyl 3,5-Dibromo-4-fluorobenzoate.**—Solutions or suspensions of these in peanut oil were compared with the opaque properties of an aqueous solution of tetraiodophenolphthalein. The latter solution was made to contain 100 mg. of iodine per cubic centimeter and the others contained an equimolecular quantity of bromine. One-half cubic centimeter portions of the opaque solutions or suspensions were placed in the stomach and peritoneum of anesthetized mice and radiographed. Results of the tests revealed that the bromo-fluoro compounds gave better radiographs of the stomach than the iodo compound.

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# Experimental Oral Cholecystography with a New Contrast Medium, Teridax (Triiodoethionic Acid)*

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**Teridax (triiodoethionic acid), a new, oral cholecystographic medium was evaluated in non-anesthetized, trained dogs. At 100 mg./Kg., Teridax visualized the gall bladder more distinctly than 300 mg./Kg. iodoalphionic acid. The new compound at 150 mg./Kg. was as effective as 300 mg./Kg. of iodopanoic acid. Maximal opacity occurred between eight and ten hours with both Teridax and iodoalphionic acid. The safety of Teridax is indicated by acute toxicity data obtained in mice, rats, guinea pigs, and dogs. Blood determinations showed normal total and differential white blood cell counts, red blood cell counts, blood sugars, and hemoglobin values in all animals. Gross and microscopic examination showed no pathological changes in any organs examined. Liver and kidney function tests in dogs chronically medicated with Teridax were normal. No emetic reactions occurred in dogs, nor was there any evidence of gastric irritation. Pharmacodynamic tests with anesthetized dogs have not shown any deleterious effects upon respiration or the cardiovascular system. Clinical data indicate a close parallel between the gall-bladder opacity and definition, absence of colon opacity or gastrointestinal irritation, and the safety of Teridax in laboratory animals and in man.**

ORAL CHOLECYSTOGRAPHIC agents have attained wide clinical acceptance in the routine diagnosis of gall-bladder disease. For the past decade, Priodax (iodoalphionic acid), has been the standard cholecystographic contrast medium. Compared to tetraiodophenolphthalein, iodoalphionic acid produces fewer undesirable side effects, and serious toxicity is rare. Nevertheless, the occurrence of these side actions continued to be objectionable and prompted continued synthetic programs directed toward more satisfactory substances. In our laboratories, experimental studies (1) were directed toward finding a compound which would provide: (*a*) freedom from nausea, diarrhea, dysuria, emesis, irritation of mucous membranes; low systemic toxicity; (*b*) clearly defined shadow, but one which would not be so dense as to obscure

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