

This reaction temperature was maintained one hour longer, then a few cc. of the reaction mass was poured into water, the precipitate was filtered, washed and slurried in dilute alkali containing sodium hydrosulfite. The absence of an orange vat indicated completion of the reaction.

The reaction mass was poured into water (3 l.) and the charge was heated to boiling where the reaction product formed a lump of tar. After washing by decantation with cold water, it was slurried in warm water (3 l.) containing an excess of sodium hydroxide, where it dispersed to a very fine powder that caused difficulty in filtration. The slurry was therefore again acidified cold with hydrochloric acid, and the precipitate was filtered, washed and dried. Crude, greenish-black 4,5-benzthiophanthrone (130 g.) was isolated. Upon Soxhlet extraction with benzene, and evaporation of the benzene extract, a bright yellow 4,5-benzthiophanthrone (75 g.), m.p. 139–140°, was obtained, equal to a 63.5% yield from thiophanthraquinone. After crystallization from "Dependip" (3500 cc.) (a high boiling gasoline), it formed yellow needles, m.p. 140° (recovery 50 g.). It could be distilled at atmospheric pressure without decomposition, and was soluble in 96% sulfuric acid as well as in 36% hydrochloric acid.

*Anal.* Calcd. for  $C_{15}H_8O_5$ : S, 13.56. Found: S, 13.43.

**Thiophanthraquinone-5-carboxylic Acid by Oxidation of 4,5-Benzthiophanthrone.**—4,5-Benzthiophanthrone (5 g.) was dissolved in glacial acetic acid (50 cc.). A solution of chromic acid (25 g.,  $CrO_3$ ) in water (25 cc.) and acetic acid (25 cc.) was added in three hours during which time the reflux temperature dropped from 120 to 105°. After refluxing for one hour, water (700 cc.) was added and the precipitate which formed was filtered, washed first with 10% sulfuric acid, then with water. The crude thiophanthraquinone-5-carboxylic acid was dissolved in aqueous sodium carbonate (100 cc.), filtered from a small amount of insoluble matter, and precipitated again with hydrochloric acid; (yield 1.05 g.), m.p. 255–268°. After two crystallizations from nitrobenzene (9 cc.), thiophanthraquinone-5-carboxylic acid (0.8 g.) was obtained, m.p. 283–284°. Its solutions in aqueous

sodium hydroxide turned deep red upon the addition of sodium hydrosulfite.

*Anal.* Calcd. for  $C_{13}H_8O_4S$ : C, 60.45; H, 2.32; S, 12.40. Found: C, 60.48; H, 2.40; S, 12.46.

**Thiophanthraquinone-5-carboxylic Acid from 5-Aminothiophanthraquinone.**—5-Aminothiophanthraquinone (2 g.) obtained by ring closing 6-nitro-2-(2-thenoyl)-benzoic acid to 5-nitrothiophanthraquinone and reducing the latter,<sup>4</sup> was dissolved in 96% sulfuric acid (11 g.), and diazotized at about 10° with finely powdered sodium nitrite (0.3 g.). The diazotization was finished by heating the solution to 40°. The diazonium salt was precipitated by carefully adding ice (10–15°) to the reaction mass. It was filtered, sucked as dry as possible and added to a solution of copper sulfate (4.5 g.), sodium bicarbonate (2.5 g.) and potassium cyanide (3.5 g.) in water (140 cc.). The reaction mass was held at room temperature overnight and then heated to 60° for 30 minutes. Crude 5-cyanothiophanthraquinone (1.19 g.), m.p. 200–215°, was separated by filtration.

This crude 5-cyanothiophanthraquinone was dissolved in 90% sulfuric acid (10 g.) and heated to 70–80° for 20 minutes. The hot solution was treated with sodium nitrite (0.3 g.). Upon dilution with water crude thiophanthraquinone-5-carboxylic acid (0.66 g.), m.p. 270–280°, was obtained. After recrystallizations from *o*-dichlorobenzene and from methanol it melted at 283–284° (0.36 g.).

*Anal.* Calcd. for  $C_{13}H_8O_4S_2$ : C, 60.45; H, 2.32; S, 12.40. Found: C, 60.26; H, 2.38; S, 12.10.

**Thiophanthraquinone-8-carboxylic Acid from 8-Aminothiophanthraquinone.**—In a manner similar to that described above, 8-aminothiophanthraquinone, prepared by ring closing 3-amino-2-(2-thenoyl)-benzoic acid,<sup>4</sup> was converted to the thiophanthraquinone-8-carboxylic acid. After several crystallizations from chlorobenzene, and from ethanol it melted at 273–274°.

*Anal.* Calcd. for  $C_{13}H_8O_4S_2$ : C, 60.45; H, 2.32; S, 12.40. Found: C, 59.99; H, 2.51; S, 11.92.

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[CONTRIBUTION FROM THE MALLINCKRODT LABORATORY OF HARVARD UNIVERSITY]

## Tri-1-naphthylgermanium Compounds and Steric Hindrance<sup>1</sup>

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Tetra-1-naphthylgermane and several tri-1-naphthylgermanium compounds have been prepared. A comparison of the chemical properties of tri-1-naphthylgermanium compounds with those of the analogous silicon compounds shows a much lower degree of steric hindrance to the reactions of the germanium compounds.

Although tetra-2-naphthylsilane has been prepared from 2-naphthyllithium and silicon tetrachloride,<sup>2</sup> all attempts to prepare tetra-1-naphthylsilane have given only the tri-1-naphthylsilicon derivative. The results have been attributed to the large steric requirements of the 1-naphthyl groups.<sup>3</sup> The same investigators reported other evidence of steric hindrance to reactions occurring at a silicon atom bonded to three 1-naphthyl groups. Thus tri-1-naphthylchlorosilane can be hydrolyzed to the corresponding silanol only under relatively vigorous conditions; and tri-1-naphthylsilanol is not converted to the disiloxane by treatment with acid, nor does it react quantitatively with the Karl Fischer reagent, which can be used to titrate unhindered organosilicon hydroxides.<sup>4</sup>

Also, tri-1-naphthylsilane is not hydrolyzed readily by bases, as unhindered organosilanes are.

Because of the slightly larger covalent bonding radius of germanium than that of silicon,<sup>5</sup> a comparative study of the reactions of tri-1-naphthylgermanium compounds is of interest. The results of this study indicate much less steric hindrance to most reactions occurring at a germanium atom bonded to three 1-naphthyl groups. If it is assumed that analogous organic compounds of silicon and germanium react by similar mechanisms, this confirms the explanation offered by Gilman and Brannen for the behavior of the tri-1-naphthylsilicon compounds.

Attempts to prepare tetra-1-naphthylgermane directly from germanium tetrabromide, either with 1-naphthyllithium or with 1-naphthylmagnesium bromide, were unsuccessful; but interaction of

(1) This work was partly supported by a grant from the Office of Naval Research.

(2) H. Gilman and C. G. Brannen, *THIS JOURNAL*, **72**, 4280 (1950).

(3) H. Gilman and C. G. Brannen, *ibid.*, **73**, 4640 (1951).

(4) H. Gilman and L. S. Miller, *ibid.*, **73**, 2367 (1951).

(5) 1.17 Å. for silicon and 1.22 Å. for germanium: L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 164.

tri-1-naphthylbromogermane (made by the Grignard method) with 1-naphthyllithium gave a small yield of tetra-1-naphthylgermane. Tri-1-naphthylbromogermane could be titrated rapidly and quantitatively with dilute alcoholic sodium hydroxide solutions. The resulting tri-1-naphthylgermanol reacted quantitatively with the Karl Fischer reagent<sup>6</sup> and was very readily converted to the corresponding oxide. The reaction of the germanol with the Fischer reagent confirms the prediction of Gilman and Miller<sup>1</sup> that organic hydroxy derivatives of germanium, like those of silicon, tin and lead, can be determined with this reagent.

Tri-1-naphthylsilanol is unchanged by treatment with boiling formic acid, while unhindered silanols are converted to the corresponding siloxanes. Tri-1-naphthylgermanol under the same conditions gave insoluble, refractory organogermanium oxide polymer, indicating that some naphthyl groups had been lost from the germanium atoms. The cleavage of aromatic groups under acidic conditions has been observed in organosilicon compounds,<sup>7</sup> and organogermanium compounds would be expected to undergo acidic cleavage even more readily, because of the increased polarity of the carbon-germanium bond.

Tri-1-naphthylbromogermane with lithium aluminum hydride in ether gave tri-1-naphthylgermane. This compound hydrolyzed with the formation of hydrogen when it was warmed with basic solutions, unlike tri-1-naphthylsilane.

Almost all of the experiments thus indicate that there is relatively little steric hindrance to reactions of tri-1-naphthylgermanium compounds. Possible indications of steric hindrance in this series, compared to other arylgermanium compounds, are the difficulty in preparing tetra-1-naphthylgermane and the fact that tri-1-naphthylgermanol could be isolated from the hydrolysis of the bromide. In the triphenylgermanium series, hydrolysis of the halides led directly to bis-(triphenylgermanium) oxide.<sup>8</sup>

Johnson and Nebergall showed that tricyclohexylgermanium bromide is unchanged by treatment with cyclohexyllithium solutions.<sup>9</sup> The formation of tetra-1-naphthylgermane under the same conditions may therefore be taken as an indication of the lower steric requirements of the 1-naphthyl group, in reactions of this nature, compared to the cyclohexyl group.

All of the compounds reported below are new; the only naphthylgermanium compounds previously reported in the literature are bis-(1-naphthylgermanium) oxide and sulfide.<sup>10</sup>

### Experimental<sup>11</sup>

**Tri-1-naphthylbromogermane.**—The reaction was carried out under nitrogen in a three-necked flask fitted with a dropping funnel, reflux condenser and gas inlet tube. To

(6) K. Fischer, *Angew. Chem.*, **48**, 394 (1935).

(7) H. Gilman and F. J. Marshall, *This Journal*, **71**, 2066 (1949); H. Gilman and J. F. Nobis, *ibid.*, **72**, 2629 (1950).

(8) G. T. Morgan and H. D. Drew, *J. Chem. Soc.*, **127**, 1760 (1925).

(9) O. H. Johnson and W. H. Nebergall, *This Journal*, **70**, 1706 (1948); **71**, 1720 (1949); W. H. Nebergall and O. H. Johnson, *ibid.*, **71**, 4023 (1949).

(10) H. Bauer and K. Burschies, *Ber.*, **65B**, 956 (1932).

(11) Combustion analyses were carried out by the M. I. T. micro-analytical laboratory. Melting points were determined with Anschütz thermometers.

the Grignard reagent prepared from 50 g. (0.24 mole) of 1-bromonaphthalene and 7 g. of magnesium, in 250 ml. of ether, was added over 20 minutes a solution of 14 g. (0.36 mole) of germanium tetrabromide in 110 ml. of benzene. The mixture was heated to reflux for six hours, then decomposed with ice and HCl. The organic layer was separated, washed rapidly once with water, filtered, and dried over calcium chloride. The solution was concentrated and finally heated to 130° at 3 mm. pressure to remove naphthalene. The brown resinous residue was taken up in warm ethyl acetate, filtered through charcoal, and allowed to stand for a month in a refrigerator. During this time four roughly equal crops of powdery crystals were removed by filtration, yielding a total of 7.3 g. (38%) of crude tri-1-naphthylbromogermane, m.p. 230–238°. Several recrystallizations from ethyl acetate raised the m.p. to 242–243.5°. The pure product was in the form of colorless irregular prisms, showing low birefringence and parallel extinction; probably orthorhombic.

*Anal.* Calcd. for C<sub>30</sub>H<sub>24</sub>GeBr: C, 67.47; H, 3.96; Br, 15.0. Found: C, 67.38; H, 4.00; Br, 14.9.

**Tri-1-naphthylgermanol.**—In 40 ml. of Mallinckrodt reagent grade acetone, 0.2610 g. (0.489 mmole) of pure tri-1-naphthylgermanium bromide was dissolved with the aid of heat. The solution was cooled and titrated rapidly with 11.90 ml. of 0.0416 N alcoholic NaOH, to a sharp phenolphthalein end-point. A blank run on the same volume of acetone required 0.20 ml.; the amount required to hydrolyze the bromide was therefore 11.70 ml., or 0.487 mmole. The solution was allowed to evaporate slowly at room temperature. After several days well-formed, colorless triclinic needles of tri-1-naphthylgermanol had formed. The product was pure when pressed dry on filter paper; yield 0.20 g., 95%. When heated the crystals effloresced at 130–140°, losing water, and giving a white powder which melted at 206–208°.

*Anal.* Calcd. for C<sub>30</sub>H<sub>22</sub>GeO: C, 76.48; H, 4.71. Found: C, 76.45; H, 4.89.

This compound could be recrystallized only by solution in solvents (ethanol or benzene) at room temperature and slow evaporation. Crystallization from boiling solvents gives an impure product with higher carbon and hydrogen content, indicating some loss of water and formation of bis-(tri-1-naphthylgermanium) oxide.

**Reaction of Tri-1-naphthylgermanol with Karl Fischer Reagent.**—0.1908 g. of finely-powdered tri-1-naphthylgermanol was suspended in 50 ml. of Merck reagent grade methanol which had been brought to the end-point with Karl Fischer reagent. After shaking for 30 minutes, the mixture was titrated to the same end-point with freshly-standardized Fischer reagent. The results indicated the presence of 0.39 mmole of apparent water, or 0.96 mole per mole of germanol.

A sample which had been heated for a day at 170° (well above the temperature of efflorescence) decolorized only traces of the reagent, indicating that it had been largely converted to bis-(tri-1-naphthylgermanium) oxide.

**Tri-1-naphthylgermanol and Formic Acid.**—To 10 ml. of 87% formic acid was added 0.3 g. of tri-1-naphthylgermanol. The mixture was heated under reflux for two hours, but the germanol did not dissolve. The suspension was cooled, diluted with water, neutralized with Na<sub>2</sub>CO<sub>3</sub>, and extracted with benzene. The benzene layer included white material in suspension which did not dissolve when the benzene was heated to boiling. The solid was filtered off and dried; the yield was 0.2 g. Less than 0.02 g. of other products were recovered by evaporating the benzene filtrate.

The principal product was insoluble in all of the organic solvents tried. It was unchanged in appearance when heated to 300°. The combustion analysis gave C, 64.53; H, 4.81. These results are consistent with the assumption that the solid was a mixture of 1-naphthylgermanium oxide polymers.

**Tetra-1-naphthylgermane.**—1-Naphthyllithium was prepared from 1.4 g. (6.7 mmoles) of 1-bromonaphthalene and 0.1 g. of finely-cut lithium in 25 ml. of ether at reflux temperature, under an atmosphere of nitrogen. After the removal of excess lithium, a solution of 1.0 g. (1.9 mmoles) of tri-1-naphthylbromogermane in 15 ml. of benzene was added, and the mixture was heated under reflux for four hours. A white solid (LiBr) slowly precipitated during this period. The mixture was allowed to stand overnight, then

poured into 20% HCl. The organic layer was separated, washed with water, and evaporated to dryness. The residue was steam distilled to remove naphthalene. The resulting gummy solid was dissolved in 400 ml. of petroleum ether containing 10% by volume of chloroform. The mixture was poured through a 30-cm. column packed with alumina, and eluted with the same solvent mixture. Forty-ml. fractions were collected and allowed to evaporate to dryness. Fractions 3-11 contained pale yellow crystalline material, while succeeding fractions were resinous and darker in color. The crystalline material from fractions 3-11 was combined and recrystallized from 3:1 isopropyl alcohol-ethyl acetate mixture, using charcoal. The yield was 0.40 g. (38%) of fine colorless needles, m.p. 252-256°. Three more recrystallizations from the same solvent mixture gave a product melting sharply at 270°. Attempts to purify crude tetra-1-naphthylgermane by crystallization without chromatographing gave only impure, low melting products. Tetra-1-naphthylgermane was sparingly soluble in alcohols but soluble in most other organic solvents.

*Anal.* Calcd. for  $C_{40}H_{28}Ge$ : Ge, 12.49. Found: Ge, 12.32.

This compound is relatively inert chemically. It was unreactive toward alcoholic KOH, bromine in  $CCl_4$ ,  $KMnO_4$ , and dilute or concentrated mineral acids. It slowly dissolved in a warm mixture of sulfuric and fuming nitric acids in the course of the analysis.

**Tri-1-naphthylgermane.**—One gram of tri-1-naphthylgermanium bromide, in 20 ml. of ether, was added dropwise to 20 ml. of ether containing 0.2 g. of  $LiAlH_4$ . A white solid precipitated immediately. The mixture was heated under reflux for two hours, after which the excess hydride was decomposed by the dropwise addition of ethanol followed by water. The ethereal layer was separated, dried over  $CaCl_2$ , and evaporated to dryness. The residue was crystallized from benzene, yielding 0.7 g. of colorless crystalline tri-1-naphthylgermane, m.p. 240-246° (82%). Recrystallization from benzene and then from chloroform-petroleum ether gave colorless needles melting at 249-250°.

*Anal.* Calcd. for  $C_{30}H_{22}Ge$ : C, 79.17; H, 4.87. Found: C, 78.74; H, 5.05.

Tri-1-naphthylgermane showed little reaction with cold basic solutions; however, the compound gave a steady stream of hydrogen bubbles when warmed gently with KOH in moist piperidine.<sup>3</sup> Also, a  $CCl_4$  solution of the germane rapidly decolorized bromine in the cold with the evolution of HBr.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MALLINCKRODT CHEMICAL WORKS]

## X-Ray Contrast Media. I. Iodinated Acylaminobenzoic Acids<sup>1</sup>

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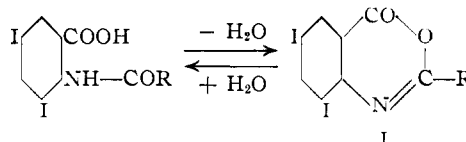
Sixteen new iodinated acylaminobenzoic acids have been prepared for investigation as X-ray contrast media. The introduction of a lower acyl group markedly lowers the toxicity of the parent iodinated aminobenzoic acid and increases the solubility of its sodium salt. From among the compounds reported, sodium 3-acetylamino-2,4,6-triiodobenzoate has been found to possess to a high degree the properties of low toxicity and high solubility desired for a urographic contrast medium. 2-Acylamino-3,5-diiodobenzoic acids are readily dehydrated to form cyclic anhydrides analogous to acetylanthranil. Analytical control procedures are given for preparing iodine monochloride reagent.

This is the first report of an investigation having for its objective the synthesis of organic compounds of possible use as X-ray contrast media for the visualization of various tissues, organs or cavities of the human body. Consideration of the aminobenzoic acids suggested a sufficient number of iodine-containing derivatives possibly to correlate structure to physical and pharmacological properties. Useful compounds have been found in the group of iodinated acylaminobenzoic acids reported in this paper.

The iodinated aminobenzoic acids or their derivatives had not found application in radiography previous to the present study. A Swiss patent<sup>2</sup> claims, as a useful medium, the monoethanolamine salt of 4-amino-3,5-diiodobenzoic acid. This compound (as the diethanolamine salt) was included in the present study for comparison. Its relatively high toxicity explains why it has not found acceptance. In 1944 Klemme and Bang<sup>3</sup> prepared azo dyes by coupling 4-amino-3,5-diiodobenzoic acid with naphthalene intermediates. Although it was stated that these compounds were to be tested as X-ray contrast media, no report has yet appeared.

The literature records several monoiodinated acetylaminobenzoic acids but these were not included in the present study because of their low iodine content. The only recorded acylaminobenzoic acid containing two or more iodine atoms is 2-acetylamino-3,5-diiodobenzoic acid described by Goldberg and his associates.<sup>4</sup>

The iodinated acylaminobenzoic acids, the properties of which are summarized in Table I, were prepared by the action of the appropriate acid anhydride or chloride upon the iodinated aminobenzoic acid with or without a diluent. The acid anhydrides usually require the presence of a trace of strong acid such as sulfuric acid for rapid reactions. The action of an excess of acetic anhydride upon 2-amino-3,5-diiodobenzoic acid produced a non-acidic compound apparently resulting from the loss of water from the acetylated amino acid with the formation of an inner anhydride (I,  $R = CH_3$ )



(1) Presented before the Division of Medicinal Chemistry, American Chemical Society, Milwaukee, March 31, 1952.

(2) Swiss Patent No. 175,169, July 16, 1935; C. A., 30, 246 (1936).

(3) C. J. Klemme and H. Bang, *J. Org. Chem.*, 9, 254 (1944).

(4) A. A. Goldberg, H. S. Jefferies, H. S. Turner and D. M. Besly, *Quart. J. Pharm. Pharmacol.*, 19, 483 (1946).