and then by dilution of a solution in 5 cc. of cold chloroform with 20 cc. of petroleum ether (b.p. 40–60°). The pure product (wt. 1.87 g.) melted at 81.2–81.6° cor. *Anal.* Calcd. for $C_7H_{13}OHgI$: C, 19.1; H, 2.97. Found: C, 18.6; H, 3.01.

β-1-Iodomercuri-2-methoxycyclohexane.—This preparation was carried out like that for the α-diastereomer to give a 4.25 g. (96% of theoretical yield) of product, m.p. 95–96°. This was dissolved in 6 cc. of chloroform at 25° and the solution diluted with 16 cc. of petroleum ether (b.p. 40–60°). Repetition of this purification yielded 1.84 g., m.p. 96.6–97.2° cor. *Anal.* Calcd. for $C_7H_{13}OHgI$: C, 19.1; H, 2.97. Found: C, 18.6; H, 3.06.

β-1-Methoxy-2-acetoxymercuricyclohexane.—When a suspension of 3.32 g. (0.0095 mole) of *dl,ld*(β)1-methoxy-2-chloromercuricyclohexane and 1.64 g. (0.0098 mole) silver acetate in 50 ml. of water are stirred for forty-eight hours it gradually acquires a purplish color owing to the formation of silver chloride. This was removed by filtration, and the clear colorless filtrate concentrated under reduced pressure at 50° to a volume of 10 cc. This aqueous solution was extracted three times with 5-ml. portions of chloroform. The chloroform layers were combined and concentrated to 5-ml. volume and then diluted to 25 cc. with 90–100° petroleum ether. A white crystalline solid weighing 2.95 g. or 83 mole per cent. was filtered off which melted at 82–83.5° cor. Recrystallization from chloroform and 60–70° petroleum ether raised the melting point to 83.0–83.6° cor.

Anal. Calcd. for $C_9H_{16}O_3Hg$: C, 28.9; H, 4.3; Hg, 53.9. Found: C, 28.8; H, 4.2; Hg, 53.9.

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RECEIVED MARCH 8, 1950

Gallium Citrate and Radio-gallium (Ga^{72}) Citrate[1,2]

Interest in the physiological characteristics of gallium and radiogallium (Ga^{72}) in relation to normal and neoplastic bone metabolism[3] has resulted in studies of compounds suitable for administration of this element to experimental animals. Gallium citrate was prepared and found superior in many respects to all other compounds tried, including gallium lactate.[4] Neogi and Nandi[5] mention gallium citrate but give few details of its preparation and properties.

Freshly precipitated gelatinous gallium hydroxide[2] was treated with citric acid in the ratio of 1 mole gallium to 1.2 moles citric acid. The mixture was allowed to stand at room temperature two hours, evaporated on a steam-bath to a thin sirup, filtered while warm and the clear filtrate then poured into ten volumes of cold ethanol. This precipitated the gallium citrate and dissolved the excess citric acid. The mixture was allowed to stand in the cold overnight, centrifuged and the solid washed twice with ethanol in the centrifuge cup, again centrifuged and finally the excess alcohol was removed by suction. After the excess solvent was removed the filter cake was finally dried by evaporation at reduced pressure. In order to obtain a usable product moisture must be excluded during the drying process. Such gallium as may remain in the ethanol may be easily recovered on evaporation of the solvent.

The product obtained by the above procedure without further purification contained 25 to 26% gallium, was completely water soluble, was stable at *p*H 7–8, and was suitable as a water solution (*p*H 7.4) for subcutaneous or intramuscular injection at concentrations of 20 mg. Ga/cc. From 50 g. of the metal there was obtained 122 g. of the citrate (yield 66%), an amorphous white powder, slightly hygroscopic. The product does not melt, caramelization begins at 200°. Solubility at 20°, in water is 92.4 g./100 cc., in 95% ethanol is 0.12 g./100 cc., in absolute ethanol is 0.07 g./100 cc. Gallium citrate is insoluble in benzene, acetone and ether. Further purification was accomplished by repeated precipitation from cold absolute ethanol. Analytical results after three purifications indicate a somewhat unstable basic citrate which loses water easily.

Anal. Calcd. for $Ga(C_6H_6O_7)(OH)$: Ga, 25.18; C, 26.03; H, 2.55. Found: (sample dried at 100° over $CaCl_2$): Ga, 26.49; C, 23.29; H, 2.73.

On continued heating there is a reversible loss of 1 molecule of H_2O at 130°, and a second molecule at 200°. Heating above 200° produces irreversible dehydration, so that the third and fourth molecule of H_2O are lost at 250° and 280°.

As a concentrated solution of the citrate cools, no crystallization takes place. On evaporation the solution concentrates to a viscous mass, which on cooling solidifies into an amorphous transparent solid. No means of crystallizing gallium citrate has been found.

When gallium citrate is dissolved in water (75 mg./ml.) the resulting solution has a *p*H of 2.5. A solution suitable for physiological studies is prepared by bringing a solution of this concentration to *p*H 7–7.4 with 0.1 *N* NaOH. Such a solution is suitable for intramuscular or subcutaneous injection if some local anesthetic is used. Procaine hydrochloride is compatible with the gallium citrate at *p*H 7.4 and thus may be administered simultaneously with the gallium if so desired. These solutions do not cause precipitation of fresh horse serum or egg albumin.

Radiogallium Citrate.—Commercially available metal (98.6%, Eagle–Picher) was used to obtain a purified gallium nitrate which would have no long life radioactive contaminants following neutron bombardment. The metal was dissolved in mixed hydrochloric and nitric acids and precipitated as a hydroxide, using ammonia in slight excess. This suspension was heated to boiling, then filtered and the resulting flocculent gallium hydroxide was heated at 1000°, cooled and stored in a desiccator. Using this oxide as standard Ga_2O_3 sufficient of the material was dissolved in nitric acid and diluted so that the final solution contained 15 mg. Ga/cc. Solution of this refractory oxide is slow but may be accomplished by dissolving in a rather large volume of nitric acid and concentrating the solution by evaporation on a steam-bath. When dissolving metallic gallium, discard the residue which resists solution in the acids as this mass contains the majority of the impurities. Spectroscopic analysis by the National Bureau of Standards of Ga_2O_3 prepared as described, indicated the following (in p. p. m.): Ag, 0.1; Al, 2; Cu, 8; Fe, 0.5; In, 0.5; Mg, 1; Pb, 3; Si, 1; Mn, trace; not detected, As, Au, Be, Bi, Cd, Co, Cu, Ge, Hg, Mo, Na, Ni, P, Sb, Sn, Ti, Tl, V, Zn.

Five cc. of the standard $Ga(NO_3)_3$ solution was placed in quartz ampoules, dried at 140°, sealed and forwarded to the Atomic Energy Commission for neutron bombardment. These ampoules must have an outside diameter of not more than 18 mm., and an over-all length not to exceed 80 mm., the wall thickness of 1 mm. has withstood all shocks of handling and such pressures as may be built up therein. After irradiation, the ampoules were returned by air freight and used immediately. The quartz ampoule when removed from the shipping container was placed in lead shields, the end crushed and 1 cc. of the 20% HCl added. The ampoule was heated gently to near boiling to facilitate the solution of the gallium complex. The mixture was transferred quantitatively to a 50-cc. graduated cylinder. After adding 1 cc. of brom cresol purple (*p*H 5.6–6.5) indicator, 2 cc. of 20% citric acid were added. The solution was neutralized with sodium hy-

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(1) Presented at the Medicinal Chemical Section, American Chemical Society, September 20, 1949.

(2) The opinions or conclusions contained in this report are those of the author. They are not to be construed as necessarily reflecting the views or endorsement of the Navy Department. Not copyrighted.

(3) Dudley, *et al.*, *J. Pharm. & Expt. Therap.*, **95**, 482, 487 (1949); **96**, 135, 224 (1949).

(4) Dudley and Garzoli, THIS JOURNAL, **70**, 3942 (1948).

(5) Neogi and Nandi, *J. Indian Chem. Society*, **13**, 399 (1936), **14**, 492 (1937).

droxide to a red purple color (*p*H 6.5–7.0) and brought to a final volume of 20 cc. Inasmuch as the average activity of the gallium as received was 18 millicuries (mc.) this yielded a solution containing approximately 1 mc./cc. which was used in physiological studies. By plotting a decay curve of samples prepared as described above, we have obtained a curve, log activity *vs.* time, for 15 half lives of Ga^{72}. No significant deviation from the straight line of a half life of 14.3 hours was observed, indicating no significant amounts of long life contaminants.

No attempt has been made to isolate the citrate of Ga^{72} since this would entail lengthy procedures and provide opportunities for serious radiation exposures. The citrate solutions containing Ga^{72} as described above contained considerable quantities of other ions, (Cl, NO_3, Na). The citrate ions in this solution serve to stabilize the mixture, preventing the precipitation of gallium hydroxide at *p*H 7–8, as would result if the citrate were not present. In a series of toxicological studies with stable gallium using a mixture containing the above mentioned ions plus citric acid or a solution containing only purified gallium citrate we have observed no difference in the effects or toxic properties when a comparison is made on an mg. Ga/kg. basis.

The penetrating β-γ spectrum of Ga^{72} (2.5 mev. γ, 3.1 mev. β) makes necessary the utmost effort for protection of personnel and especially for those carrying out chemical manipulations. The handling of the ampoules and all containers requires the use of suitable tongs. All glass apparatus, cylinders, beakers, etc., were placed in lead pots having a 25-mm. wall thickness. The chemical operations were carried on behind a wall of lead blocks 5 cm. in thickness. It has been found that when the above precautions were observed, a total body radiation of less than 20 milliroentgens (mr.) was received by personnel carrying out the chemical manipulations. Exposure to the hands was 20 to 40 mr., usually within a space of thirty minutes. Personnel injecting solutions of 0.5 mc./cc. activity in quantities up to 10 mc. per injection received less than 20 mr. total body radiation and less than 40 mr. on the hands, when using lead shielded syringes.[6] Therefore, it is recommended that personnel doing the chemical manipulations not carry out other studies or injections. No more than one unit of Ga^{72} (10–30 mc.) should be processed by one group in a single 24-hour period.

Studies using Ga^{72} must be carried out far removed from photographic storage and processing facilities since the hard gamma will penetrate the usual shielding, even that adequate for X-ray.

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(6) Dudley, Bronson and Taylor, *Science*, **110**, 16 (1949).

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RECEIVED MARCH 3, 1950

Certain 4,4'-Dinitrodiphenyl Sulfides and Sulfones

Bis-(2-methoxy-4-nitrophenyl) Sulfide.—An alcoholic solution of 8 g. (0.0345 mole) of 2-bromo-5-nitroanisole (m. p. 104°)[1] and the potassium ethyl xanthate prepared from 1.96 g. of potassium hydroxide and 2.66 g. of carbon disulfide was refluxed for a total of ninety-six hours. At intervals during this refluxing the mixture was filtered to remove the product. At one point an additional 2 g. of the nitrobromoanisole was added making a total of 10 g. A total of 5.1 g. (70.2%) of bright yellow sulfide (recrystallized from acetic acid) was obtained, m. p. 204–205°.

Anal. Calcd. for $C_{14}H_{12}O_6N_2S$: S, 9.54. Found: S, 9.61.

Bis-(2-methoxy-4-nitrophenyl) Sulfone.—Oxidation of the above sulfide (3.0 g.) was performed with chromic anhydride in acetic acid at reflux. Pouring onto ice and recrystallization from glacial acetic acid afforded 2.4 g. (75%) of fine white crystals melting at 231–232°.

Anal. Calcd. for $C_{14}H_{12}O_8N_2S$: S, 8.70. Found: S, 8.26, 8.39.

2-Iodo-2'-methoxy-4,4'-dinitrodiphenyl Sulfide.—An alcohol solution of 4.62 g. (0.025 mole) of 2-methoxy-4-nitrothiophenol (prepared from 2-bromo-5-nitroanisole by the methods of Price and Stacey)[2] 8.45 g. (0.025 mole) of 2-iodo-4-nitrobromobenzene and 2.6 g. (0.02 mole) of suspended potassium carbonate was heated under reflux for about five hours. After isolation in the usual way and recrystallization there was obtained 2.9 g. (33.6%) of light-brown microcrystalline powder melting at 191–192°.

Anal. Calcd. for $C_{13}H_9O_5N_2IS$: S, 7.42. Found: S, 6.67.

Oxidation of the above sulfide to **2-iodo-2'-methoxy-4,4'-dinitrodiphenyl sulfone** was carried out in the customary manner with chromic anhydride in acetic acid. From 2.9 g. of the sulfide there was obtained 3.0 g. (96.5%) of recrystallized light pink colored sulfone melting at 270–271°.

Anal. Calcd. for $C_{13}H_9O_7N_2IS$: S, 6.89. Found: S, 6.82.

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(1) Hanford and Adams, THIS JOURNAL, **57**, 1592 (1935), found m. p. 104°.

(2) Price and Stacey, *ibid.*, **68**, 498 (1946).

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RECEIVED MARCH 20, 1950

Triphenyl-*o*-methoxymethylphenyltin

Incidental to studies concerning water-soluble organotin compounds, triphenyl-*o*-methoxymethylphenyltin was prepared from the Grignard reagent which was obtained (1) directly from the organic halide, and (2) by means of a halogen–metal interconversion reaction.

Triphenyl-*o*-methoxymethylphenyltin.—To *o*-methoxymethylphenylmagnesium bromide prepared by refluxing for six hours 1.95 g. (0.080 gram atom) of magnesium and 15.1 g. (0.075 mole) of *o*-bromobenzyl methyl ether in 150 cc. of ether and 60 cc. of benzene, was added 20.0 g. (0.0518 mole) of triphenyltin chloride. From the mixture, after stirring for several hours, followed by hydrolysis with aqueous ammonium chloride, there was obtained, after two crystallizations from benzene–ethanol, 8.5 g. or a 35% yield of triphenyl-*o*-methoxymethylphenyltin melting at 93–95°. Another recrystallization from the same solvent, subsequent to vacuum drying, raised the melting point to 94.5–95.5°.

Anal. Calcd. for $C_{26}H_{24}OSn$: Sn, 25.22. Found: Sn, 25.88 and 25.90.

Since direct formation of the Grignard reagent was slow, it was also prepared by means of the halogen–metal interconversion reaction. To 15.1 g. (0.0752 mole) of *o*-bromobenzyl methyl ether in 50 cc. of ether, was added 0.0752 mole of *n*-butyllithium in 145 cc. of ether. After the mixture was stirred for twenty-five minutes, 0.085 mole of anhydrous magnesium bromide in 75 cc. of ether was added. By the procedure outlined above, after the addition of 19.0 g. (0.0493 mole) of triphenyltin chloride, there was obtained 8.8 g. or a 38% yield of triphenyl-*o*-methoxymethylphenyltin melting at 94–95.5°.

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RECEIVED MARCH 6, 1950

m-Phenyl-phenylacetic Acid

m-Acetylbiphenyl[1] (3.2 g.) with 1 g. of sulfur and 10 ml. of morpholine was refluxed for seven hours. The mixture was poured into 30 ml. of methanol and water was added until the product precipitated as a gummy

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(1) Huber, Renoll, Rossow and Mowry, THIS JOURNAL, **68**, 1109 (1946).