SYNTHESES OF ASTATO COMPOUNDS BY MELT METHOD

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SUMMARY

m-Astatobenzoic acid (2), methyl m-astatobenzoate (3), and m-astatohippuric acid (4) were synthesized by the melt method. Reaction of methyl m-bromobenzoate with astatide at 200°C gave methyl m-astatobenzoate. Compounds 2 and 4 were synthesized by similar method. Compounds 2 and 3 were purified and identified by radio-gaschromatography.

Key words: m-astatobenzoic acid, methyl m-astatobenzoate, m-astatohippuric acid, melt method, ^{211}At, cytotoxicity.

INTRODUCTION

The radionuclide, ^{211}At, has been suggested as a means by which selective cytotoxicity may be achieved, owing to the destructive alpha radiation that this isotope emits (1). Astatine is therefore of potential interest in radiation therapy and biology, especially when bound to biomolecules (2-3). The work of Adelstein and coworkers has quantitated the cytotoxicity of astatine (4). However, inorganic forms of ^{211}At, mainly At^- are ionic and do not penetrate the cell membrane. They tend to distribute in the body rather non-specifically

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(5). On the other hand, the organo-astato compounds might overcome transport problems and also increase target specificity. Therefore, it was of interest to synthesize organo-astato compounds and to study their cytotoxicities.

RESULTS AND DISCUSSION

Although the preparation and reliable identification of astatine had been carried out in the early forties, very little is known about the properties of astatine, especially about the chemistry of its organic compounds (6-8). Thus far, astatine has been shown to be able to form aliphatic and aromatic derivatives in both the monovalent and polyvalent states (9). These organo-astato compounds, such as astatobenzene, astato-halobenzenes, and astatobenzoic acid have been synthesized by a method utilizing a modified Sandmeyer reaction (10-12). However, the chemical properties of astatine are partly like those of iodine, and since radioactive iodo-compounds can be synthesized by isotopic exchange methods (13), it was of interest to attempt the preparation of organo-astato compounds by the melt method.

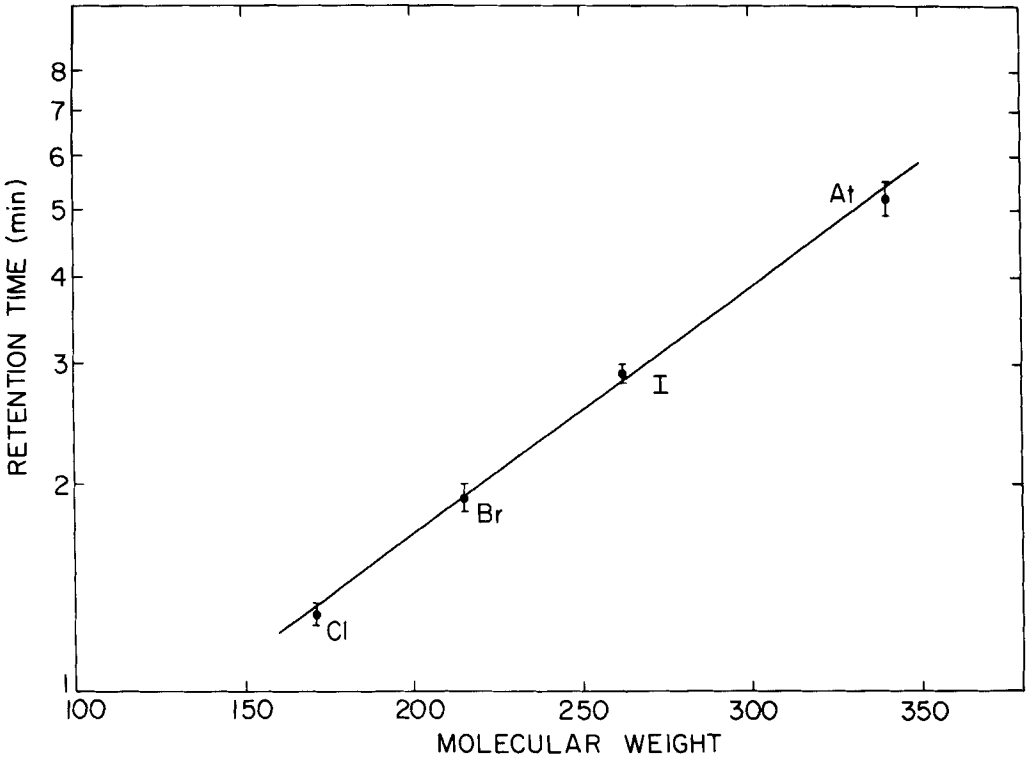
Astato-halobenzenes were recently synthesized from the corresponding compounds of bromine and iodine by heterogeneous isotope exchange (14). p-Astatobenzoic acid (1) was synthesized from p-aminobenzoic acid (12). However, neither the physical properties nor the purity of compound 1 were reported. The synthesis of m-astatobenzoic acid (2) and its methyl ester (3) from the corresponding bromo analog by the melt method (13) and its purification by radio-gaschromatography is reported here.

The reaction of methyl m-bromobenzoate with astatide in a sealed tube at 200-250°C for 60-90 min gave methyl m-astatobenzoate (3) in 30-60% yield. Compound 3 was purified and identified by radio-gaschromatography. The yield of compound 3 depends on the reaction temperature and the amount of NaOH present in the reaction mixture. At lower temperature or higher NaOH content the yield of methyl m-astatobenzoate decreases dramatically. For this reason, astatine was dry distilled (15) and then converted to $^{211}At^-$ by dissolving in 0.1 N NaOH

and 0.01 N $Na_2S_2O_5$ solution. m-Astatobenzoic acid (2) was synthesized by a similar method, converted to the methyl ester and analyzed by radio-glpc.

Since astatine compounds cannot be analyzed by conventional measurements because of the small number of molecules, typically we have identified methyl m-astatobenzoate via chromatographic sequential analysis (3,9). Fig. 1 shows the dependence of the retention times of methyl m-halobenzoates as a function of the respective molecular weights. The experimental values for methyl m-halobenzoates fit the straight line with sufficient accuracy and serve to identify the presence of methyl m-astatobenzoate.

The method reported here can also be used to synthesize m-astatohippuric acid and thus provide another simple method to prepare organo-astato compounds.



EXPERIMENTAL

The ^{211}At (t 1/2 = 7.2 h) was produced via the $^{209}Bi(\alpha,2n)^{211}At$ reaction at the BNL 1.5 m cyclotron using a target of Bi metal melted on an aluminum backing (16). The ^{211}At was isolated from the target material using a modification of the Te column technique developed by Khalkin et al. (17). The Bi metal was dissolved with conc. HNO_3 and the Al backing removed. Excess HNO_3 was removed with the addition of hydroxylamine hydrochloride. Reduction of the astatine was insured by the addition of 1 M $SnCl_2$ and conc. HCl was added to insure the HCl concentration to be 6-8 N. The resulting solution was loaded on a tellurium column (6 cm x 6 mm). The column was then washed with 6 N HCl and distilled H_2O. The astatine was eluted from the column with 1 ml of 2 N NaOH.

In order to reduce the volume of the separated astatine, an alternative method for isolating astatine was used. The irradiated bismuth target was cut in such a way as to leave only that portion of the target that was actually exposed to the α beam. This section was placed in a quartz furnace which was then heated to approximately 600°C. A constant flow of nitrogen gas was passed through the furnace and through a trap kept at liquid nitrogen temperatures. After approximately 1 hour, the trap containing the astatine was removed. The astatine was removed from the trap with 0.15 ml of 0.1 N NaOH and 0.1 N $Na_2S_2O_5$. This served to convert the astatine to astatide. Currently, the latter method is used to synthesize organo-astato compounds.

Radio-gaschromatographic analyses were carried out on simple gas chromatograph made at BNL. This was done to avoid contamination of the other chromatographs which are in daily use. It was equipped with a glass column (10% SF-96 on Chromosorb W, 12 ft x 0.25 in), a thermal conductivity detector and a radioactivity detector (5 in x 5 in NaI (Tl) crystal to detect x-ray emitted from ^{211}At) operating at high temperature (165°C). In order to minimize the decomposition of astatine compounds, the astatine compounds were led directly to radioactivity

detector from the glass column through a heated teflon tube and heated glass tube into the charcoal traps. The other halogen analogs were detected by thermal conductivity detector.

The activities of organo-astato compounds were counted in either a Picker scintillation counter or a Capintec ionization chamber.

m-Astatobenzoic Acid (2)

A solution of 100 μL (275 μCi) of $Na^{211}At$ (in 0.1 N NaOH and 0.01 N $Na_2S_2O_5$ solution) in an ampoule was heated briefly under a slow stream of nitrogen and taken to dryness. m-Bromobenzoic acid (85.73 mg, 0.43 mmol) was added. The ampoule was sealed and the mixture was kept at 208°C for 90 min, followed by cooling to room temperature. The mixture was dissolved in 50 μL of 0.1 N NaOH, extracted with ethyl ether (2 mL) to give 164 μCi (59.6%) of 2. The ethereal solution of 2 was esterified with diazomethane, extracted with 50 μL of 0.1 N NaOH and 0.01 N $Na_2S_2O_5$ solution and then concentrated to give 148 μCi of product. Thirty μl containing 11 μCi of the mixture was injected into radio-glpc and the peak corresponding to methyl m-astatobenzoate (3) was collected (6 μCi, 54.5% recovery from the radio-glpc purification).

Methyl m-Astatobenzoate (3)

A solution of 5 μL (14.95 μCi) of $Na^{211}At$ (in 2 N NaOH solution) in an ampoule was heated briefly under a slow stream of nitrogen and taken to dryness. Methyl m-bromobenzoate (136.6 mg, 0.64 mmol) was then added. The ampoule was sealed and the mixture kept at 250°C for 80 min, followed by cooling to room temperature. The mixture was dissolved in 100 μL of N NaOH and then extracted with ethyl ether to give 13.04 μCi of product. Radio-glpc (10% SF-96 on Chromosorb W, 12 ft. x 0.125 in. column, 170°, 80 ml He/min) analysis of the ethereal solution showed peaks at 3.5, 5.4 and 14 min in the ratio of 4.2:93.9:1.9. The peak at 5.4 min was collected to give 9.3 μCi (62% radiochemical yield) of methyl m-astatobenzoate (3). The specific activity of compound 3 was 4.35×10^8 μCi/μM.

In a separate experiment, the dry distilled astatine (^{211}At°) was converted to astatide, $^{211}At^-$ (in 0.1 N NaOH and 0.01 N $Na_2S_2O_5$ solution) and then allowed to react with methyl m-bromobenzoate.

A solution of 25 μL (480 μCi) of $^{211}At^-$ (in 0.1 N NaOH and 0.01 N $Na_2S_2O_5$ solution) in an ampoule was heated briefly under a slow stream of nitrogen and taken to dryness. Methyl m-bromobenzoate (50 μL) was added. The ampoule was sealed and the mixture was kept at 230°C for 90 min, followed by cooling to room temperature to give 317 μCi of product. Ten μL containing 53.1 μCi of the mixture was injected in radio-glpc (10% SF-96 on Chromosorb W, 12 ft. x 0.25 in column, 170°, 80 ml He/min) and the peak corresponding to methyl m-astatobenzoate was collected (18.9 μCi, 35.6% recovery from the radio-glpc purification).

m-Astatohippuric Acid (4)

An ampoule containing m-iodohippuric acid (27.8 mg, 0.09 mmol) and $^{211}At^-$ (2.37 μCi in 0.1 N NaOH and 0.01 N $Na_2S_2O_5$ solution) was kept at 170°C for 1 hr, followed by cooling to room temperature. The mixture was dissolved in 0.5 N KOH (1 mL), cooled in an ice bath, and acidified with conc. HCl. The precipitates were washed with dil HCl for several times and dried to give m-astatohippuric acid (15.3 μCi, 64.4% radiochemical yield). The purity of compound 4 was determined by radio- thin layer chromatography. Thin-layer chromatography (Eastman cellulose with H_2O:25% NH_4OH:2-BuOH (v/v 3:1.5:7) as developing solvent) showed that compound 4 had R_f 0.73.

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