ADVANCES IN INORGANIC CHEMISTRY, VOL. 31

ASTATINE: ITS ORGANONUCLEAR CHEMISTRY AND BIOMEDICAL APPLICATIONS

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I. Introduction

Astatine ($^{200-219}_{85}$At), the fifth and heaviest member of the Periodic Table Group VIIB (the halogens), is the earth's rarest naturally occurring element. All its isotopes are radioactive (Table I), hence the Greek name $\alpha\sigma\tau\alpha\tau\omega\zeta$, meaning *unstable* (*44, 45*). The possibility of their existence was predicted from the β-decay of polonium (*55*). Its three naturally occurring isotopes, ^{215}At, ^{218}At, and ^{219}At, are the extremely short-lived natural daughters of AcA (*77*), RaA (*76, 173*), and AcK (*72*), respectively.

The mass–energy dependence for heavy nuclei shows that, in element $Z = 85$, the proton:neutron ratio is such that nuclear stability is not expected. The most long-lived isotopes possess a number of neutrons close to the magic number of 126, corresponding to the formation of a closed nuclear shell configuration (*20, 75*). The relationship between the emitted α-particle energy and mass number of the astatine isotope is shown in Fig. 1. The lightest isotopes have very short half-lives and disintegrate with the expulsion of high-energy α-particles, as would be expected since the products of α-emission have a next-to-magic-number of protons. Moreover, in possessing a considerable neutron deficiency, these isotopes would certainly be unstable upon capture of an orbital electron. On passing the neutron-surplus region ($A - Z = 126$) the curve shows a break, which reveals a sharp decrease in the strength of bonding of nucleons within the nucleus. All the isotopes with $A > 211$ have very short half-lives; the heaviest isotopes $\geq^{219}$At show some stability toward α-decay. However, in this range transitions by β-decay are also possible (*177, 118*). It has been suggested that astatine, like technetium and promethium, cannot have β-stable nuclei at all (*51*).

TABLE I

DECAY, HALF-LIVES, AND PRODUCTION OF ASTATINE ISOTOPES[a]

Isotope	Half-life[b]	Decay	Production
^{219}At	0.9 min	97% α, 3% β	Natural daughter of AcK
^{218}At	1.5–2.0 s	99.9% α, 0.1% β	Natural daughter of RaA
^{217}At	0.032 s	α	Daughter of ^{221}Fr in ^{233}U series
^{216}At	3×10^{-4} s	α	Daughter of ^{220}Fr in ^{228}Pa series
^{215}At	1×10^{-4} s	α	Daughter of ^{219}Fr in ^{227}Pa series
^{214}At	Short (2×10^{-6} s)	α	Daughter of ^{218}Fr in ^{228}Pa series
^{213}At	0.11×10^{-6} s	α	Decay product of ^{225}Pa
^{212}At	0.315 s	α	Bi(α,n)
^{212m}At	0.12 s	α	Bi(α,n)
^{211}At	7.21 h	40.9% α, 59.1% EC	Bi(α,2n); ^{211}Rn (EC)
^{210}At	8.3 h	99.9% EC, 0.1% α	Bi(α,3n); ^{210}Rn (EC)
^{209}At	5.4 h	95% EC, 5% α	Bi(α,4n); ^{209}Rn (EC)
^{208}At	1.63 h	99% EC, 0.5% α	Bi(α,5n); daughter of ^{212}Fr
^{207}At	1.8 h	α, EC	Bi(α,6n); Au + ^{14}N; ^{207}Rn (EC)
^{206}At	31 min	EC, α	Bi(α,7n); Au + ^{12}C, ^{14}N, ^{16}O
^{205}At	26 min	α, EC	Bi(α,8n); Au + ^{12}C, ^{14}N, ^{16}O Pt + ^{14}N
^{204}At	9.1 min	EC, α	Bi(α,9n); Au + ^{12}C, ^{14}N, ^{16}O
^{203}At	7.3 min	α, EC	Bi(α,10n); Pt + ^{14}N; Au + ^{12}C, ^{14}N, ^{16}O
^{202}At	3.0 min	α, EC	Au + ^{12}C, ^{14}N, ^{16}O
^{201}At	1.5 min	α	Au + ^{12}C, ^{14}N, ^{16}O
^{200}At	0.8 min	α	Au + ^{12}C

[a] All astatine isotopes, with the exception of ^{213}At, produce other radionuclides by their decay, consequently complicated decay curves can arise. In astatine isotopes, electron capture (EC) always produces K-radiation.

[b] h, Hours; min, minutes; s, seconds.

Many aspects of the nuclear physics, and inorganic and organic chemistry, of the astatine radionuclides have been the subject of a number of excellent reviews (*5, 6, 17, 18, 49, 79, 80, 90, 110*).

II. Isotopes: Production, Extraction, and Identification

Preparation of the isotopes of astatine is more difficult than with most radionuclides, as they cannot be synthesized by neutron irradiation; this precludes the use of a nuclear reactor. To date, the bulk of

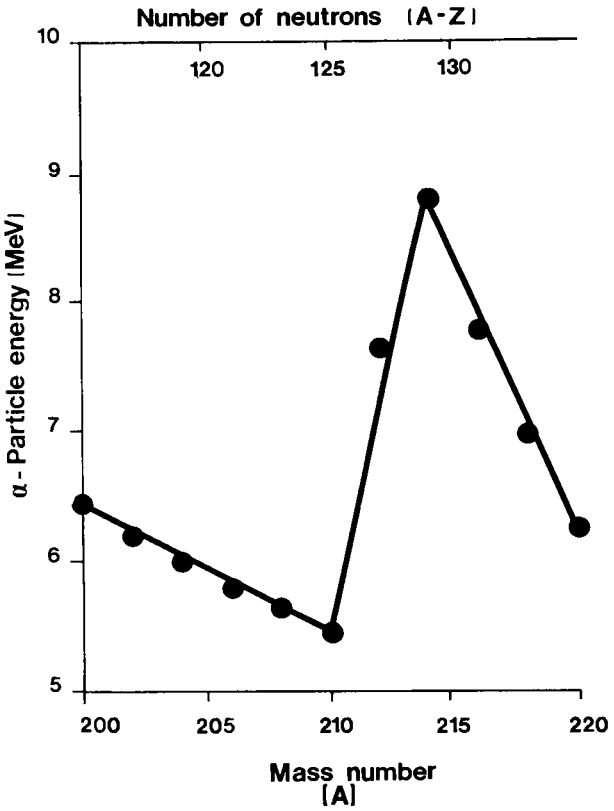


FIG. 1. Relationship between the energy of the α-particles emitted by astatine isotopes and their mass number (A) and neutron content (A – Z).

astatine research has been carried out using cyclotrons or synchrocyclotrons at large nuclear research centers.

Numerous nuclear reactions have been employed to produce astatine. Three of these are particularly suited for routine preparation of the relatively long-lived isotopes with mass numbers 209, 210, and 211. The most frequently used is the $^{209}Bi(\alpha,xn)^{213-x}At$ ($x = 1$–4) reaction, in which bismuth (*44, 74, 120*) or bismuth oxide (*7, 125*) is bombarded by 21- to 40-MeV α-particles. The $^{209}Bi(He^{+},xn)^{213-x}At$ reaction can also be used to produce isotopes of astatine (*152*); the nuclear excitation functions (*62*) favor a predominant yield of ^{209}At and ^{210}At. The routine preparation of astatine is most conveniently carried out through the $^{209}Bi(\alpha,xn)^{213-x}At$ nuclear reactions, from which a limited spectrum of astatine nuclides may be derived. The excitation functions for these nuclear reactions have been studied extensively (*78, 89, 120*). The

incident α-particle threshold energies for (α,2*n*), (α,3*n*) and (α,4*n*) reactions correspond to 21, 29, and 34 MeV, respectively (see Fig. 2). For routine chemical studies with astatine, an isotopic mixture will suffice. Large quantities of astatine isotopes can be synthesized by using both internal (*100, 129*) and external target systems (*22*). Activities up to 1 Ci ml^{-1} have been produced using an internal target (*48*). However, for biomedical studies, only. ^{211}At possesses advantageous decay properties; ^{210}At decays by electron capture to ^{210}Po, which subsequently decays by the emission of 5.355- to 5.519-MeV α-particles, with a half-

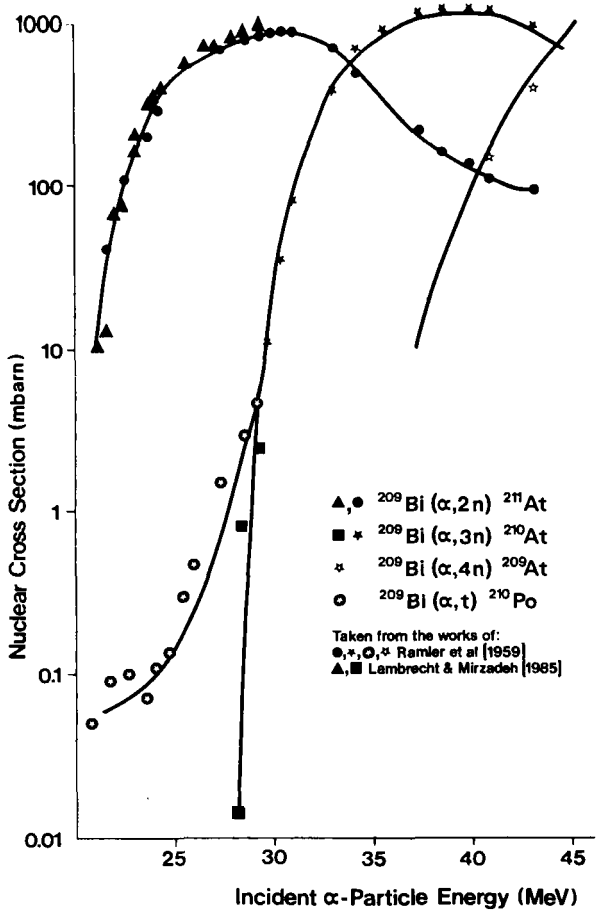


FIG. 2. Excitation functions for the production of ^{209}At–^{211}At by α-particle bombardment of ^{209}Bi.

life of 138.4 days. Thus ^{210}At clearly represents a potentially significant radiation hazard, particularly if ingested. Astatine-211 can be exclusively produced by the irradiation of bismuth with 28-MeV α-particles, where the (α, $2n$) nuclear reaction cross-section (σ) is near its optimum at 790 mbarn. It has been possible to prepare the high-activity yields of ^{211}At potentially required for biomedical application by using an external oscillating α-beam cyclotron target system which also incorporates an almost 4π combined helium/water target cooling (*33*); beam currents up to 30 μA have been routinely employed.

Astatine can be readily and routinely obtained in an inorganic form suitable for chemical and biomedical application from the α-irradiated bismuth target by either extractive (*7, 113, 116*) or dry (*2, 3, 48, 74, 93, 120*) distillation techniques. Both methods have their relative merits (*33, 101*).

The wet technique involves dissolution of the bismuth target in a mineral acid such as HNO_3 or $HClO_4$, followed by extraction of astatine in its highly reactive zero-oxidation state with an organic solvent such as isopropyl ether. The back-extraction of astatine from the organic layer can be achieved with NaOH containing a little Fe^{3+}; $Fe(OH)_3$ retains the impurities and the loss of At does not exceed 5%. The yield has been reported at ~90% (*116*). Alternatively, distillation of the separated organic layer enables At^0 to be carried over, either via adsorption or formation of adducts, into a cold trap. The final valence of astatine can easily be determined: Oxidation to At^+ or reduction to At^- can be achieved by addition of 1 *M* $HNO_3/10^{-3}$ *M* $H_2Cr_2O_7$ or by aqueous 0.2 *M* Na_2SO_3, respectively. The organic solvent is removed by distillation through the nonpolar/polar media. Yields of approximately 60% have been obtained for At^-, At^+, and At^0 (*101*) and high activities can be obtained, though the method is more suitable for low-activity requirements.

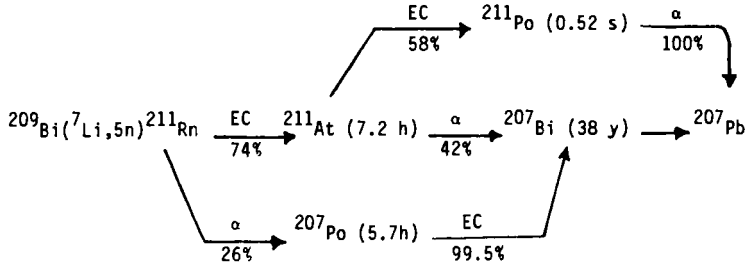
Distillation of astatine from molten metallic bismuth is the most widely used technique for separation of the radionuclide. In order to separate astatine from the mass of bismuth, lead, and polonium, use is frequently made of its high volatility. Distillations have been carried out at temperatures ranging from 300 to 600°C, in a stream of N_2 or He (*11*), or under *in vacuo* (*74, 78*) conditions. Astatine has been collected by direct adsorption from the gas phase onto platinum or silver (*2, 3, 48, 78*), condensed on a glass cold finger probe or into frozen solutions at the temperature of liquid N_2 (*101*), as well as absorbed into aqueous solutions of NaOH or Na_2SO_3 (*1*). More recently, high yields of $^{211}At^-$ have been obtained by trapping distilled At^0 on a silica–gel column, then eluting with aqueous NaOH into a small volume (*33, 89*).

Meyer and Rössler (*101*) showed that the overall yields for wet and dry extractive procedures are comparable, being approximately 60% for $^{211}At^{-}$. Some workers have found that yields vary somewhat, due to adsorption of evaporated At^{0} onto vessel walls, and to the possibility of the retention of astatine within the target due to the formation of nonvolatile compounds (*11*). However, the dry evaporation method is more applicable to studies with high-activity targets; it is rapid and lends itself to further development within the scope of remote handling techniques. Aspects of both extraction approaches have been discussed widely (*2, 7, 33, 89, 101, 116, 120, 160*).

Another method employed to prepare astatine uses secondary nuclear reactions and spallation processes. Heavy metals such as lead, bismuth, thorium, and uranium can be bombarded with high-energy particles, such as 160-MeV protons, 190- to 270-MeV Ar^{+}, and 430- to 500-MeV Kr^{+} (*23, 24, 91, 92*). These processes lead to a wide range of radionuclides, including some astatine isotopes. Fission of thorium can also be achieved by 660-MeV protons (*16, 28, 85*). However, the formation cross-section for the spectrum of astatine isotopes is a factor of two to three times less than the total formation cross-section for products of spallation and fission (*177*). Radiochemically pure astatine can be obtained only by its separation from most elements of the periodic table. After dissolving the target material, astatine can be separated and purified by repeated adsorption on, and elution from, tellurium-filled columns (*79, 174*). More recently, its isolation from other spallation products has been achieved by the simple and elegant technique of gas thermochromatography (*98*).

High-energy nuclear reactions can similarly be utilized to synthesize the neutron-deficient noble gas isotopes among the spectrum of spallation products. Isolation of the radon isotopes from the mixture is easily performed by gas chromatography in columns packed with molecular sieves (*82*). The longest lived of the radon isotopes, ^{211}Rn ($\tau_{1/2}$ = 14.6 hours), decays by electron capture to ^{211}At. Radon and astatine isotopes can also be obtained by heavy-ion induced nuclear reactions (*52, 99*) or photospallation (*172*). Particularly promising is the production of ^{211}Rn, and hence ^{211}At, by the $^{209}Bi(^{7}Li,5n)^{211}Rn$ reaction, using 53- to 60-MeV ^{7}Li ions (σ = 500-600 mbarns) accelerated from a three-stage Tandem Van der Graaff system (*103*). In contrast to spallation reactions on uranium and thorium, which have been used for producing ^{211}Rn, the other competing nuclear reactions ($^{7}Li,xn$), ($^{7}Li,p\alpha n$), and ($^{7}Li,\alpha xn$) (where x = 1–4) lead to either very short-lived radon, astatine, polonium, bismuth, and lead isotopes, which decay by α-emission, or to radionuclides with a considerably longer

half-life. The limited product spectrum allows the effective separation of ^{211}Rn by a simple degassing of the bismuth target at 500°C and trapping of the products in silver-wool and tellurium filters. Radon-211 can be obtained with high radiochemical purity, is a convenient generator for ^{211}At (Scheme 1), and delivers its maximum activity after 14 hours. About 50% of the maximum ^{211}At activity is, however, still available after 40 hours (*99*).



SCHEME 1

Identification and quantitation of the three main astatine isotopes, ^{209}At, ^{210}At, and ^{211}At, can be achieved by the appropriate measurement of α-, γ-, or X-ray activity. X-rays and γ-rays can be counted conveniently by well-type crystal counters, whereas α-counting[1] requires that astatine samples be measured as infinitely thin or thick preparations. Astatine-211 can be measured by counting its 79- to 92-keV ^{211}Po *K–L,M,N* X-rays, and, importantly, discriminated from ^{210}At and ^{209}At by their γ-emissions (245, 1180; 195, 545, and 782 keV, respectively). Identification and aspects of counting other astatine isotopes have been briefly discussed elsewhere (*6, 110*).

III. Synthetic Organic Radiochemistry

Astatine, generally speaking, is a difficult isotope to study from a chemical viewpoint because no stable isotopes exist. Although the study of the chemical properties of astatine began over 40 years ago (*44*), the element's precise behavior is still in doubt. The chemical similarity between astatine and its nearest halogenic neighbor, iodine, is not always obvious. In many cases the astatine tracer has not

[1] α-Emissions arising from long-lived ^{210}Po may complicate determinations, but if ^{211}At is allow to decay completely (>99.9% in 48 hours), discrimination can be achieved.

followed the iodine carrier as would be expected. The situation is further complicated by the fact that the chemical properties of the halogens do not follow an easily recognizable pattern; in many respects bromine does not interpolate between chlorine and iodine (*49*). However, the general trend in the periodic system suggests that astatine is more metallic in character than iodine.

The chemistry of ^{211}At, as a consequence of its production by nuclear reaction processes and its short physical half-life, must invariably be carried out on a tracer scale. At high concentration, the intensive accompanying α-particle radiation would give rise, in aqueous solutions, to labile and highly reactive peroxides, and to heat that would interfere with the understanding and elucidation of reaction stoichiometry, due to the production of very short-lived metastable radiolytic species. The concentration of usable ^{211}At is clearly limited by these factors. For ^{211}At, whose specific activity is 1.5×10^{16} α-particles min^{-1} cm^{-3}, a 1*M* ^{211}At solution would lead to unacceptably intense radiation dose and heat. The highest concentration of ^{211}At that has been prepared is 10^{-8} *M* (*2, 3*); that needed for typical chemical experiments is in the range 10^{-13}–10^{-15} *M*. The concentration of ^{211}At in 1 ml of a solution with an activity of 40 μCi is only 10^{-10} *M* or 0.002 ppb. Therefore, extremely pure reagents are required, otherwise reactions with impurities may lead to severe irreproducibility, and incomprehensible chemical behavior and identification problems.

The low concentration of ^{211}At has several consequences important in the understanding of its chemistry.

1. The diatomic molecule At_2, although purported to have been identified (*115*), is on statistical grounds unlikely to exist, and in terms of organic syntheses there would be a negligible probability of diastatination occurring.
2. Equilibrium reactions such as

$$R^- + At^+ \rightleftharpoons RAt \rightleftharpoons R^+ + At^- \qquad (1)$$

do not occur, because if the At is removed from its substrate R, the reverse reaction with the same substrate is statistically highly improbable. If it occurs, complete decomposition of an At compound can be considered irreversible.

3. Disproportionation, a common process in inorganic halogen chemistry, does not proceed. For example, IOH(HIO) is an unstable, strongly electrophilic compound and, when no substrate is present,

readily disproportionates:

$$3IOH \longrightarrow 2HI + HIO_3 \quad (2)$$

At low concentrations such a disproportionation would be virtually impossible. Therefore, when AtOH is formed it will have a relatively long lifetime.

4. Normal physicoorganic methods used for the formal identification of organic compounds are not applicable to organic astatine chemistry. The mass quantities required for the characterization of compounds by UV, NMR, and IR spectroscopy are in the region 10^{-6}–10^{-3} g; molar concentrations of $\sim 10^{-11}$ preclude the application of such techniques. Mass spectrometry has not yet been developed to operate at such a concentration, except under special laboratory conditions (*4*).

The only method that can be used routinely to identify organoastatine compounds is measurement of radioactivity based upon its distribution over two or more phases. Such techniques are gas–liquid chromatography (GLC), high-pressure liquid chromatography (HPLC), thin-layer chromatography (TLC), and electrophoresis.

In order to identify synthesized astatocompounds it has been necessary to adopt criteria and guidelines for both synthesis and identification.

1. A series of analogous, well-characterized iodo compounds should be prepared under conditions identical to those used for astatocompounds.
2. Syntheses should be carried out under the mildest conditions possible; the use of drastic and strongly oxidative conditions may lead to ill-defined reaction mixtures.
3. Wherever possible, specific astatocompounds should be synthesized by different radiochemical routes (*128*).
4. The chromatographic or electrophoretic behavior of a specific astatocompound must be considered similar, but not necessarily the same, as that of its analogous iodo and bromo derivative. This procedure has been developed and termed *sequential analysis* (*99, 102*); in order to avoid a coincidental fitting of chromatographic data, several solvent systems should be used.
5. The physical and chemical behavior of astatocompounds must be considered comparable to the corresponding lower halogenic compounds.

The adoption of such criteria has ensured that more consistent and reproducible results are obtained in synthetic inorganic and organic astatine chemical studies (*17, 18, 33, 99, 160*).

A. Compounds of Multivalent Astatine

As astatine exhibits a more pronounced positive character compared with the other halogens, early studies were directed toward the preparation of organometallic derivatives of astatine in the valence states +3 and +5. The compounds $RAtCl_2$, R_2AtCl, and $RAtO_2$ (where $R = C_6H_5$ or $p\text{-}CH_3C_6H_4$) were prepared according to the reaction schemes in Eq. (3); macroquantities of iodine carrier labeled with ^{131}I were always added (*112, 114*). Consequently, formation of the analogous

$$R_2ICl + At^- \longrightarrow Cl^- + R_2IAt \xrightarrow{170^\circ C} RAt + RI \xrightarrow[Cl_2]{0^\circ C} RAtCl_2 \qquad (3)$$

iodine compounds along with those of the astato compounds occurred at each stage during the synthesis. In order to prepare $RAtCl_2$, KI containing At^- was added to a solution of R_2ICl. The crystalline product R_2I_2 (R_2IAt) was centrifuged, washed, and heated in sealed glass ampuls for a few minutes at 170–190°C. The thermal decomposition product RI(RAt) was dissolved in $CHCl_3$ and chlorinated at 0°C in order to obtain $RICl_2(RAtCl_2)$. The analogous iodo compound was present as a yellow precipitate which was crystallized from $CHCl_3$ together with the product. To a hot $CHCl_3$ solution of $RAtCl_2$ was slowly added R_2Hg [see Eqs. (4–6].

$$RAtCl_2 + R_2Hg \longrightarrow R_2AtCl + RHgCl \qquad (4)$$

$$RAtCl_2 + RHgCl \longrightarrow R_2AtCl + HgCl_2 \qquad (5)$$

$$RAtCl_2 + OCl^- + 2OH^- \longrightarrow RAtO_2 + 3Cl^- + H_2O \qquad (6)$$

After cooling, $HgCl_2$ precipitated out leaving a mixture of $RAtCl_2$ and R_2AtCl, together with their iodo analogs, in solution. The extraction of R_2AtCl was performed into an aqueous phase and identified by TLC. If a solution of NaOH and CH_3COOH is added to the crystals of $RICl_2(RAtCl_2)$, and the mixture heated to its boiling point and chlorinated in order to oxidize $I^{3+}(At^{3+})$ into $I^{5+}(At^{5+})$, then a white crystalline precipitate of $RIO_2(RAtO_2)$ formed on cooling. This was recrystallized from a small amount of water.

The carrier compounds were useful for identifying the corresponding astatine derivatives by means of paper chromatography (*112*) and TLC (*114*); the β- and α-activities of ^{131}I and ^{211}At products, respectively, were measured.

B. Compounds of Monovalent Astatine

1. Aliphatic Compounds

a. Alkyl Astatides. The simplest molecule, the methyl astatide ion CH_3At^+, has been identified by time of flight mass spectrometry (*4*); the observation of its mass line was a result of an astatine reacting with organic impurities within the ion source. Methyl astatide is one of the products formed from recoil ^{211}At atoms, originating from the $^{211}Rn(EC)^{211}At$ nuclear transformation, reacting with various long-chain and cyclic aliphatic hydrocarbons, and benzene (*88*). In addition to the formation of CH_3At, the higher homologs, C_2H_5At, isomers of C_3H_7At, C_4H_9At, $C_6H_{13}At$, c-C_5H_9At, and c-$C_6H_{11}At$ were also produced as a result of a spectrum of ^{211}At recoil reactions with the parent hydrocarbons. The separation of reaction products and their identification was effected by GLC; the relative amounts of the individual products varied for different starting hydrocarbons and depended very much upon experimental conditions. However, as a rule, the highest yield was of the astatinated derivative of the original hydrocarbon (*88*).

Normal alkyl astatides n-$C_nH_{2n+1}At$ ($n = 2$–6) have been prepared by homogeneous halogen-exchange reactions (*127*); molecular iodine containing AtI was added to the corresponding n-alkyl iodides at room temperature according to Eq. (7), where $R = C_2H_5$–C_6H_{13}; ethyl

$$RI + At^- \longrightarrow RAt + I^- \tag{7}$$

alcohol accelerated the exchange reaction. Normal alkyl astatides have also been prepared by gas chromatographic halogen exchange, where At^- had been previously adsorbed on the solid phase of a short precolumn packed with kieselguhr and the respective alkyl iodide was allowed to flow through the GLC column in a carrier gas stream. Halogen exchange occurred best at 130–200°C; products separation was achieved by using a longer sequential analytical chromatographic column (*125, 127*). Preparation of n-alkyl astatides ($n = 2$–5) and i-alkyl astatides, i-$C_nH_{2n+1}At$ ($n = 3$–5), has been achieved by a simplified GLC halogen-exchange method using only one analytical column with At^- adsorbed at its inlet (*54*).

The boiling temperatures (T_b) for alkyl astatides obtained by halogen-exchange methods have been determined by extrapolation from the T_b values of the corresponding lighter alkyl halides using the technique of sequential GLC analysis (*53, 83, 125, 127*). Typical values are given in Table II; an extensive tabulation of extrapolated data has been collected by Berei and Vasáros (*17, 18*).

A similar linear dependence of T_b on the logarithmic GLC retention time for alkyl iodides and alkyl astatides has been observed (*54*). The calculation of an experimental parameter Z' (*83*) for astatine has also

TABLE II

EXTRAPOLATED PHYSICOCHEMICAL PROPERTIES OF ALIPHATIC ASTATIDES[a,b,c]

Compound	Mean T_b (°C)	H_{vap} (kJ mol^{-1})	D_{C-At} (kJ mol^{-1})	IP (eV)
CH_3At	66 ± 3 (*86*) 65.8 (*115*) 73 ± 5 (*8*) 72 ± 2 (*66*) 77 ± 5 (*67*)	28.9 (*115*)	139.3 (*115*) 205 (*67*) 176 (*141*)	8.85 (*115*) 8.8 (*67*)
C_2H_5At	98 ± 2 (*125, 127*) 95.4 (*115*) 103 ± 5 (*8*)	31.6 (*115*)	167 (*141*)	8.8 (*115*) 8.65 (*67*)
n-C_3H_7At	123 ± 2 (*125, 127*) 124.3 (*115*)		163 (*141*) 161.5 (*139*)	
i-C_3H_7At	112 ± 2 (*54*) 110.4 (*115*)		159 (*141*) 151.9 (*139*)	
n-C_4H_9At	152 ± 3 (*125, 127*) 152.5 (*115*)		161 (*141*)	
i-C_4H_9At	142 ± 3 (*54*) 140.4 (*115*)			
n-$C_5H_{11}At$	176 ± 3 (*125, 127*) 182 (*115*)			
i-$C_5H_{11}At$	163 ± 3 (*125, 127*) 163 (*115*)			
n-$C_6H_{13}At$	202 ± 2 (*125, 127*)			
CH_2AtCl CH_2AtBr CH_2AtI	137 168 208 } (*115*)		130.1 124.7 118.0 } (*115*)	

[a] References in parentheses.
[b] GLC data (*54, 125, 127*).
[c] Thermal decomposition data (*139*).

been calculated through studies dealing with the gas chromatographic behavior of alkyl astatides in relation to that of other alkyl halides. Using this derived parameter for extrapolation, T_b, heat of vaporization (ΔH_{vap}), ionization potential (IP), and C–At bond dissociation energies (D_{C-At}) have been estimated for a number of simple organoastatine molecules (*115*). The T_b, IP, and D_{C-At} for ethyl astatide have also been calculated by other extrapolation techniques, based upon the relationships between different physicochemical constants (*8, 66, 67*)[2]. Similar methods have also been used to calculate the D_{C-At} values for a number of alkyl astatides (*141*). More recently, the dissociation energy of the carbon–astatine bond in *n*- and *i*-propyl astatide has been established by measurement of the kinetics of the pyrolytic decomposition of these compounds (*140*); the values obtained were of a scale similar to those obtained by extrapolation (see Table II).

b. Astatocarboxylic Acids. The halogen atoms of haloacetic acids are readily replaced by heavier halogens in aqueous solution. Astatoacetic acid was prepared by reacting At^- in the presence of an iodide carrier with an aqueous solution of iodoacetic acid at 40°C (*125, 126*).

$$At^- + ICH_2COOH \longrightarrow AtCH_2COOH + I^- \quad (8)$$

The product was extracted with ethyl ether and after evaporation of the solvent the dry residue was recrystallized from CCl_4; $AtCH_2COOH$ was identified by ion-exchange chromatography. Its dissociation constant was determined by the measurement of its distribution between diisopropyl ether and aqueous solutions of varying acidity; K_a was found to be $1.5–1.8 \times 10^{-4}$ mol liter^{-1} between 0 and 27°C (*125, 126*).

2. Aromatic Compounds

a. Astatobenzene. Astatobenzene has been successfully synthesized by a number of well-established preparative routes (Table III). The

[2] In a study directed toward predicting physicochemical properties of volatile compounds of the superheavy elements (*8*), monotonic relationships between physicochemical constants were derived for alkyl derivatives of elements which belonged to the same group of the periodic system. A number of estimates were also made for the corresponding astatine derivatives. Since both the electronegativity (χ) and atomic volume (v_A) influence the van der Waal's interactions of their organic derivatives, T_b was plotted against $f(Zv_A\chi^{-1})$, where Z is the atomic number of element A. Smooth curves were obtained for methyl and ethyl halides (*8*); the values v_A and χ are themselves extrapolated from corresponding values for other halogens. Similarly derived expressions were related for IP $[f(Zr_A^2\chi^{-1})]$ and D_{C-At} $[f(Z\chi^{-1})]$, where r_A is the covalent atomic radius of A.

TABLE III SYNTHESES OF ASTATOBENZENE

Method	Substrate	Experimental conditions	Yield (%)	Reference
Electrophilic substitution (At^+)				
Homogeneous	C_6H_6	$CH_3COOH/HClO_4$ mixture containing $Cr_2O_7^{2-}$, heated to 120°C for 90 minutes	50	*140*
Heterogeneous	C_6H_6	$HClO_4$ or H_2SO_4 at 180–190°C for 20 minutes	90	*148*
"Electrophilic" halogen exchange (ipso-attack)				
$\overset{\delta+}{At}—\overset{\delta-}{Cl}$	C_6H_5Cl	AtCl, AtBr at	29, 19	*99, 104*
	C_6H_5Br	60°C for 1 hour	45, 30	
Nucleophilic substitution (At^-)				
Homogeneous halogen exchange	C_6H_5I	$At^-(I_2)/\gamma$-radiation		*125, 128*
	C_6H_5Cl		73	
	C_6H_5Br	n-$C_4H_9NH_2$ at 210°C	85	*143, 144*
	C_6H_5I	for 30–60 minutes	99	
	C_6H_5I	At^-(KI), GLC synthesis/separation at 130–200°C		*125, 128*
Heterogeneous halogen exchange	C_6H_5Br	At^-(NaI) at 155°C for 2 hours	60	*84*
	C_6H_5Br	At^-(NaOH) sealed ampul at 250°C for 30 minutes	70	*141, 142*
	$(C_6H_5)_2I_2$	At^-(KI)/hot C_2H_5OH, decomposition of crystallized product at 175°C in sealed tube		*125, 128*
Via diazonium intermediate	$C_6H_5NH_2$	Diazotization and decomposition in the presence of At^-/KI	80	*69, 71*
	$C_6H_5NH_2$			*125, 128*
	$C_6H_5NHNH_2$			*125, 128*
Recoil astatination [At]*	$(C_6H_5)_3Bi$	Via $^{209}Bi(\alpha,2n)^{211}At$		*125, 128*
	C_6H_6		44	*88, 111*
	C_6H_6		23	
	C_6H_5Cl	Via $^{211}Rn(EC)^{211}At$	35	*150*
	C_6H_5Br		40	
	C_6H_5I		45	
	C_6H_5Cl		60	*145*

production of astatobenzene in high yields has been achieved best through halogen-exchange (At for I or Br) reactions, in both homogeneous and heterogeneous systems. Electrophilic substitution can also be very successful particularly if the heterogeneous systems contain strong acids. Astatobenzene has been identified by GLC.

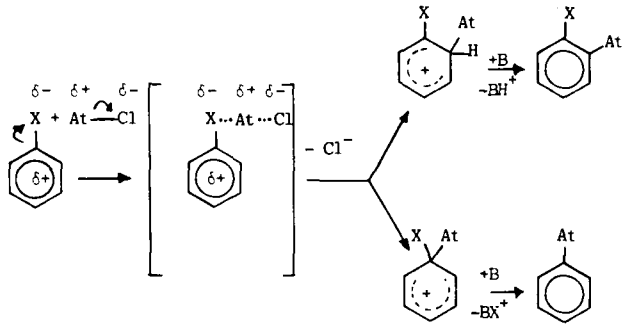
The electrophilic substitution of benzene by At^+ in a homogeneous mixture of $HClO_4$ and CH_3COOH containing $Cr_2O_7^{2-}$ as an oxidizing agent has resulted in good yields (*139*). The reactants, sealed within glass ampuls, were heated for 30–60 minutes at 100–120°C; astatobenzene was obtained in ~50% yield. More efficient electrophilic astatination has been achieved in heterogeneous systems with radiochemical yields of approximately 90% if astatine is present in the aqueous phase containing either H_2SO_4 or $HClO_4$, even in the absence of $Cr_2O_7^{2-}$ oxidizing agent (*148*). This latter finding has been interpreted on the basis of the complex structure[3] of the monovalent At^+ in aqueous solutions by the fact that, in the presence of strong acids, the equilibrium in Eq. (9) shifted to the right. It has been assumed that the

$$HOAt + H_3O^+ \rightleftharpoons [H_2OAt]^+ + H_2O \qquad (9)$$

heterolytic fission of hypoastatous acid $[H_2OAt]^+$, resulting in the formation of the reactive entity At^+, is the rate-determining step in the astatination mechanism, immediately preceeding its substitution into the aromatic ring. The activation energy (E_a) for the electrophilic astatination of benzene has been obtained from kinetic studies and found to be 134 ± 8 kJ mol^{-1} (*148*).

Electrophilic halogen-exchange reactions in monohalobenzenes by the interhalogen compounds AtCl and AtBr yielding astatobenzene have been described (*99, 104*). This unexpected observation has been explained by Meyer *et al.* (104) in terms of an "*ipso*-attack" of the highly polarized interhalogen molecule at the electronegative site of the substrate, and consequent complex formation (Scheme 2). This results in electrophilic replacement of the halogen atom competing with the normal aromatic substitution of hydrogen in the ortho position (*99, 104*). It has been assumed that both reactions are assisted by a Lewis

[3] A relatively stable aqua complex or protonated hypoastatous acid $[H_2OAt]^+$ has been assumed; similarly, a protonated hypoiodous acid has been reported to exist in aqueous solutions (*15*). The equilibrium constant for the deprotonation reaction [Eq. (9)] has been estimated by extrapolation of data accrued from the lighter halogens to be $< 10^{-3}$ (*80*), indicating that $[H_2OAt]^+$ is a fairly weak acid. Another structure, the symmetric diaqua cationic complex $[H_2O-At-OH_2]^+$, has also been proposed (*79, 80*).



SCHEME 2. X = F, Cl, Br; B = Lewis Base.

base, which is always present in the reaction mixture. However, more recent studies have found that the yields for the halogen as well as for the hydrogen replacement are not reproducible; this is probably due to the ill-defined chemical state of astatine under the specified experimental conditions (*43*).

Astatobenzene has also been prepared by heterogeneous halogen-exchange reaction between At^- adsorbed on solid sodium iodide, and bromobenzene at its boiling point (*84*). A further development in this technique has been to allow the reaction of bromobenzene in sealed ampuls at 250°C with At^- adsorbed on sodium hydroxide; this resulted in high yields of about 70% (*141, 142*).

Nucleophilic astatination of halobenzenes C_6H_5X (X = Cl, Br, I) in homogeneous mixtures with n-$C_4H_9NH_2$, $(C_2H_5)_2NH$, and $(C_2H_5)_3N$ at 210°C has led to the formation of astatobenzene with radiochemical yields of 75–90% (*143, 144*). A two-step process has been postulated [Eqs. (10) and (11)], with the latter reaction [Eq. (11)] as the rate-determining step:

$$C_6H_5X + NRR'R'' \longrightarrow [C_6H_5NRR'R'']^+ X^- \quad (10)$$

$$[C_6H_5NRR'R'']^+X^- + At^- \longrightarrow C_6H_5At + NRR'R'' + X^- \quad (11)$$

where R, R′, R″ = H, C_2H_5, or n-C_4H_9. Kinetic investigations have supported this assumption as the activation energy for halogen exchange remained the same regardless of the different halogen leaving groups. The reaction, however, is significantly influenced by the nature of the amine; this is probably related to steric effects (see Table IV).

TABLE IV

ACTIVATION ENERGIES FOR NUCLEOPHILIC ASTATINATION OF HALOBENZENES: THE INFLUENCE OF ALIPHATIC AMINES

Reaction	E_a (kJ mol^{-1})
$At^- + C_6H_5Br + (C_2H_5)_3N$	111.7
$At^- + C_6H_5Br + (C_2H_5)_2NH$	21.8
$At^- + C_6H_5Br + C_4H_9NH_2$	17.2
$At^- + C_6H_5Cl + C_4H_9NH_2$	17.6
$At^- + C_6H_5I + C_4H_9NH_2$	17.2

Accordingly, the highest yields were those obtained using *n*-butylamine (*143*).

Samson and Aten (*126, 127*) were the first to use recoil astatination to synthesize astatobenzene, by irradiating $(C_6H_5)_3Bi$ with α-particles accelerated in a synchrocyclotron. Astatobenzene, as well as the products of recoil astatine formed in the nuclear reaction, were separated and identified by GLC. Hot homolytic replacement reactions by recoil ^{211}At *in situ* have also been used to produce astatobenzene (*111, 145, 150*). Recoil astatine is produced from the electron capture decay of ^{211}Rn, which is one of the spallation products formed by bombardment of thorium or uranium with 660-MeV protons (*16, 28, 85*). After the separation of ^{211}Rn from other spallation products and its subsequent purification (*82*), carrier-free ^{211}Rn has been introduced into thoroughly evacuated glass ampuls filled with benzene or with the corresponding benzene derivative. The ampules were sealed and the ^{211}Rn ($\tau_{1/2}$ = 14.6 hours) was allowed to decay for 14–20 hours until the radioactive equilibrium with ^{211}At ($\tau_{1/2}$ = 7.2 hours) was attained. Organic and inorganic fractions were separated by extraction of the substrate with CCl_4 and aqueous NaOH solutions containing a small amount of Na_2SO_3 as a reducing agent. Identification and determination of yields of individual organic products were performed by GLC and HPLC. The highest yield was obtained with chlorobenzene as the substrate, when diluted with compounds of a lower IP than that of astatine, thus promoting neutralization of the originally multicharged recoil ^{211}At (*145*).

Most of the physical properties of astatobenzene have been determined (*vide supra*) by extrapolation from data derived for other halobenzenes. These extrapolations are based upon a comparison of their respective gas chromatographic behavior. Vasáros *et al.* (*136*) used

a variety of stationary phases to establish the retention indexes (I_x)[4] for substituted benzene derivatives, including those of astatine. A linear correlation between I_x and T_b for monosubstituted benzenes has been established (*17*). The dissociation energy of the C—At bond in astatobenzene has been determined experimentally by measuring the kinetics of its thermal decomposition using a modified version of the toluene carrier gas technique (*139, 151*). The properties of astatobenzene established so far are listed in Table V.

b. Astatotoluenes. Preparation of the isomers of astatotoluene from the corresponding toluidines has been achieved through decomposition of their diazonium salts (*99, 105, 163*), but with relatively low radiochemical yields (10–20%). The toluidines were dissolved in HCl or H_2SO_4 and converted into the corresponding diazonium salts by addition of aqueous $NaNO_2$ at −5°C. Excess $NaNO_2$ was destroyed by the addition of urea, then At^- (in Na_2SO_3 solution) was added and the mixture slowly heated to between 50 and 80°C and then cooled. The products were extracted with diethyl ether and subsequently washed with NaOH solution and dried over $CaCl_2$. Analysis of the final product was carried out by GLC (*99, 105*) and by TLC (*163*). Under such experimental conditions $[OH^-] \gg [At^-]$ as the latter is present only in tracer amounts (10^{-15}–10^{-11} *M*). Consequently, the low radiochemical yields can be explained by the almost overwhelming competitive hydrolysis of the diazonium salts to the corresponding phenols.

In order to explain some of the peculiarities of the decomposition reaction and isomer distribution of the products (*99, 105*), a reaction mechanism has been postulated that involves complex formation between At^- and the diazonium ion, followed by electron transfer, leading to the release of nitrogen, while the phenyl radical recombines with astatine according to Eq. (12).

$$\begin{array}{l} o\text{-}CH_3C_6H_4\text{—}\overset{+}{N}\equiv N + At^- \longrightarrow [o\text{-}CH_3C_6H_4\text{—}N{=}N^+]At^- \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \Big\downarrow e^- \\ o\text{-}CH_3C_6H_4At \longleftarrow o\text{-}CH_3C_6H_4^{\cdot} + At^{\cdot} + N_2 \end{array} \qquad (12)$$

[4] The retention time of the measured compound with that of a standard compound (usually an *n*-hydrocarbon) under the same conditions, the retention index I_x was calculated as:

$$I_x = 100\left[\frac{\ln(x) - \ln(n)}{\ln(n+1) - \ln(n)} + n\right]$$

where $t(x)$ is the retention time of component x, $t(n)$ is the retention atoms, similarly for $(n + 1)$. All measurements were made under the same conditions; $t(n) \leq t(x) \leq t(n + 1)$.

The physicochemical properties of astatotoluene isomers have been estimated by extrapolation from those of the corresponding lighter halotoluenes based upon their GLC behavior (*99, 137, 138*), calculated directly from the GLC retention volumes (*137*), and determined experimentally by measurement of their thermal decomposition (*151*); these are given in Table V.

Homogeneous halogen exchange has been employed in order to prepare the isomers of $AtC_6H_4CF_3$ from the corresponding isomers of $ClC_6H_4CF_3$ in the presence of the *n*-butylamine (*149*). Radiochemical yields of 30, 45, and 36% for *ortho-*, *meta-*, and *para*-astatotrifluorotoluene, respectively, were significantly lower than yields observed for astatobenzene formation under similar conditions (*vide supra*). Gas–liquid chromatography was not only used to identify the products but also to estimate the physicochemical parameters ΔH_{vap} and T_b (*149*); the dissociation energy of the C—At bond was determined by measuring the kinetics of their thermal decomposition (*151*). These values are summarized in Table V.

c. Astatohalobenzenes. This group of organic astatine compounds has been the one most extensively studied (*17*); the isomers of AtC_6H_4X (X = F, Cl, Br, I) were obtained in essentially the same way as with astatobenzene (*vide supra*).

Whereas negligible radiochemical yields have been reported for the attempted electrophilic substitution of halobenzenes in homogeneous systems (*140*), astatination of fluorobenzene in heterogeneous mixtures with strong inorganic acids occurs at ~90% yield. This can be effected at 190°C over a 30-minute period; the *ortho*:*meta*:*para* (25:5:70) distribution of the AtC_6H_4F isomers reflected the electrophilic character of the reacting astatine. Under the same conditions, the distribution of *ortho*:*meta*:*para* AtC_6H_4Cl isomers was 30:20:50 from C_6H_5Cl; the yield was 72%. The corresponding yield sharply decreased for similar reactions with the isomers of AtC_6H_4Br and AtC_6H_4I (8.1 and 2.5%, respectively). The decreasing capability of halobenzenes to undergo electrophilic substitution has been correlated with the increasing atomic number of the bound halogen (*148*).

Hydrogen substitution in C_6H_5F, C_6H_5Cl, and C_6H_5Br by AtCl and AtBr is less efficient than the competing halogen-replacement reactions in these systems (*vide supra*); the total radiochemical yields are only a few percent and are poorly reproducible (*43, 99, 104*).

Specific astatohalobenzenes can be conveniently prepared by using heterogeneous halogen-exchange reactions, starting from the corresponding bromohalobenzene isomer, under the same conditions used for

TABLE V

EXTRAPOLATED PHYSICOCHEMICAL PROPERTIES OF ASTATOBENZENE AND OTHER ASTATINATED SUBSTITUTED AROMATIC MOLECULES[a,b,c,d]

Compound	Mean T_b (°C)	H_{vap} (kJ mol^{-1})	R_{C-At} (cm^3 mol^{-1})	μ_{C-At} (D)	D_{C-At} (kJ mol^{-1})	IP (eV)
C_6H_5At	222 ± 3 (*87*) 212 ± 3 (*125, 128*) 217 (*141*) 219 ± 3 (*99*) 216 ± 2 (*137*) 211 (*115*)	41.6 (*115*) 43.4 (137)	20.1 (*138, 145*)	1.60 (*99*) 1.66 (*138*) 1.53 (*17*)	205 (*141*) 187.9 ± 21.3 (*139*) 180.7 ± 9.1 (*151*)	8.8 (*115*)
o-$AtC_6H_4CH_3$	237 ± 4	46.3	20.3		180.7 ± 9.8	
m-$AtC_6H_4CH_3$	240 ± 4 (*99, 137*)	46.6 (*137*)	19.9 (*138*)		181.2 ± 8.6 (*151*)	
p-$AtC_6H_4CH_3$	237 ± 4	46.7	19.9	1.51 (*17*)	181.6 ± 9.5	
o-$AtC_6H_4CF_3$	485 ± 2	44.5			176.6 ± 8.8	
m-$AtC_6H_4CF_3$	478 ± 1 (*149*)	43.3 (*149*)			177 ± 8.6 (*151*)	
p-$AtC_6H_4CF_3$	481 ± 1	42.6			176 ± 9.0	
o-AtC_6H_4F	213 ± 2	44.6			179.5 ± 8.8	
m-AtC_6H_4F	206 ± 2 (*137*)	43.4 (*137*)	20.3 (*138*)		179.9 + 9.0 (*151*)	
p-AtC_6H_4F	209 ± 2	42.5			179.9 ± 8.2	

o-AtC_6H_4Cl	258 ± 2	50.8		173.6 ± 8.6
m-AtC_6H_4Cl	255 ± 3 (*137*)	49.0 (*137*)	20.2 (*138*)	175.3 ± 8.7 (*151*)
p-AtC_6H_4Cl	253 ± 2	47.5		179.5 ± 9.1
o-AtC_6H_4Br	303 ± 3			176.1 ± 7.9
m-AtC_6H_4Br	304 ± 3 (*99*)			177.0 ± 8.6 (*151*)
p-AtC_6H_4Br	305 ± 3			178.2 ± 9.3
o-AtC_6H_4I	336 ± 4			
m-AtC_6H_4I	337 ± 4 (*99*)			
p-AtC_6H_4I	337 ± 4			
o-$AtC_6H_4NO_2$	303			
m-$AtC_6H_4NO_2$	297 (*99*)			
p-$AtC_6H_4NO_2$	303			

[a] References in parentheses.

[b] GLC data (*87, 99, 125, 128*).

[c] GLC-retention index (I_X) data (*137, 138*).

[d] Thermal decomposition data (*139, 151*).

preparing astatobenzene. The radiochemical yields for *meta-*, *para-* and for *ortho*-astatohalobenzenes have been found to be 60–70% and 40–50%, respectively (*141, 142*). Likewise, homogeneous nucleophilic substitution of the bromine atom has also been used to prepare astatohalobenzenes; no cross-isomerization has been observed in the course of these halogen-exchange reactions (*146*).

Astatohalobenzenes can be synthesized directly in ^{211}At recoil (Table III) experiments either via hydrogen replacement by recoil astatine in monohalobenzenes or by halogen replacement in dihalobenzenes. In the former, total yields range from 5 to 15%, with an almost statistical mixture of *ortho-*, *meta*, and *para*-astatohalobenzene products (*145, 150*). The production of AtC_6H_4F from the corresponding ClC_6H_4F isomers has been achieved with yields of 14% without noticeable isomerization of the products (19).

Astatohalobenzenes have also been prepared from the corresponding haloaniline isomers by decomposition of their diazonium salts under conditions similarly described for astatotoluenes (*vide supra*). Here again, relatively low radiochemical yields (10–26%) were obtained. Again, this has been attributed to the competing reaction of hydroxyl ions present in the aqueous solution in a much higher concentration than At^-, leading to the by-product formation of phenols (*99, 100, 105*).

All astatohalobenzenes were identified by GLC; their thermodynamic properties were estimated by extrapolative gas chromatographic data related to the corresponding dihalobenzene isomers (*17, 99, 137, 138*) (see Table V).

d. Astatophenols and Derivatives. Electrophilic astatination of phenol can be accomplished with AtCl or AtBr; the product is a mixture of *ortho-* and predominantly *para*-AtC_6H_4OH, with 20–30% radiochemical yields (*99, 104*). However, the ortho and para isomers have been prepared in much higher yield by astatination of the corresponding chloromercuri derivatives (*160, 166*). Phenol is easily mercurated in the para position by $Hg(CH_3COO)_2$, followed by reaction with NaCl (*47*). Addition of At^- in NaOH solution (containing SO_3^{2-}) to the chloromercuric derivative was followed by I_2 carrier in $CHCl_3$ and by KI_3. The mixture was stirred at room temperature for 30–40 minutes, and the HgI_2 precipitate was either filtered off or dissolved in excess KI solution. The astatinated products formed according to Eq. (13) are

$$C_6H_5OH \xrightarrow{Hg(CH_3COO)_2} p\text{-}HgC_6H_4OH \xrightarrow{NaCl} p\text{-}HgClC_6H_4OH \xrightarrow{At^-} p\text{-}AtC_6H_4OH \quad (13)$$

extracted from the mixture with CH_2Cl_2 and identified by TLC. Among

the products, small amounts of astatoiodophenols (<5%) were also noted. These were presumably formed by astatination and subsequent iodination of dimercurated phenol. Astatine was observed to have a higher reactivity with chloromercuri derivatives than iodine in similar reaction systems. Furthermore, astatination, though in lower yields, was also possible without iodine carrier whereas radioiodine in tracer amounts failed to react with some aromatic substances (e.g., aniline, nitrobenzene). Reaction of astatine with chloromercuric compounds in the absence of an iodine carrier provides further indication that a radical mechanism for the astatination of these aromatic moieties may be implicated, particularly as this could be explained by the easy oxidation of At^- to At^0 at lower pH values (*166*).

meta-Astatophenol has been synthesized by the diazonium salt intermediary of *meta*-aminoaniline, according to the reaction

$$m\text{-At-}C_6H_4NH_2 \xrightarrow[-5°C]{NaNO_2} m\text{-At-}C_6H_4N_2^+ \xrightarrow[45°C]{H_2O} m\text{-At}C_6H_4OH \qquad (14)$$

This preparative scheme leads to only 30% yield due to the side reactions between the *meta*-astatoaniline diazonium salt and astatophenol, which cannot be eliminated even by continuous extraction of the product with *n*-heptane (*167*). All the astatophenols synthesized to date have been identified by either HPLC (*99, 104*) or TLC (*160, 166, 167*). Their dissociation constants (K_a) have been established from extraction experiments by measuring the relative distribution of compounds between aqueous borax buffer solutions and *n*-heptane as a function of acidity. On the basis of these derived values, the Hammett σ-constants and hence the field (F) and resonance (R) effects have been estimated for these compounds (*167*) (see Table VI). The field effect for astatine was found to be considerably weaker than that for other halogens; the resonance effect was similar to that for iodine (*162*).

para-Astatoanisole has been prepared by nucleophilic astatination of the Tl^{III}-di(trifluoroacetic) acid derivative of anisole; the product (70–90% yield) was identified by TLC (*162*).

e. Astatoanilines and Derivatives. Although *ortho*- and *para*-$AtC_6H_4NH_2$ can be prepared by recoil astatination of aniline (*99, 150*) or by its electrophilic substitution via AtCl and AtBr (*99, 104*), these are relatively inefficient synthetic procedures and poor yields are obtained. Slightly better yields (10–15%) have been recorded for the reaction of At^- with the corresponding arsanilic acids at 60°C (*167*). A much more efficaceous synthetic route is via the appropriate chloromercuri derivatives (*166, 167*), as used initially for obtaining astatophenols (*47, 160, 166*). However, in this case, mercuration is necessarily performed

TABLE VI

DISSOCIATION CONSTANTS (K_a) AND ESTIMATED HAMMETT σ-CONSTANTS, FIELD (F), AND RESONANCE (R) EFFECTS FOR ASTATOPHENOLS[a]

Compound		pK_a	σ	F	R
AtC_6H_4OH	*ortho*	8.92 ± 0.03			
	meta	9.33 ± 0.03	0.26	0.28	−0.08
	para	9.53 ± 0.03	0.18		
$AtC_6H_4NH_2$	*ortho*	3.03 ± 0.03			
	meta	3.90 ± 0.03	0.24	0.25	−0.05
	para	4.04 ± 0.02	0.18		
AtC_6H_4COOH	*ortho*	2.71 ± 0.02			
	meta	3.77 ± 0.02			
	para	4.03 ± 0.02			

[a] Data from refs. *160* and *167*.

under more drastic conditions because of the lower reactivity of aniline compared with phenol. Single-pot reactions can be performed; mercuration can be achieved with $Hg(NO_3)_2$ or $Hg(ClO_4)_2$ in strong acid solutions at 60°C after 3–4 hours of stirring, following by addition of At^-. The astatoanilines have been obtained with radiochemical yields of approximately 80% and extracted from the reaction mixture with *n*-heptane. Small amounts of astatoiodoanilines (*166*) were formed (<5%), again apparently from dimercurated intermediates (*vide supra*).

meta-Astatoaniline has been synthesized by reduction of *meta*-astatonitrobenzene (*vide infra*) with $SnCl_2$ at 60°C; a 90% yield has been reported (*167*).

The astatoanilines were identified by HPLC (*99, 104, 150*) and TLC (*160, 166, 167*). The pK_a values established by extraction experiments using *n*-heptane and citrate buffer solutions are given in Table VI, along with estimates of the Hammett σ-values, field, and resonance effects.

para-Astato-*N,N*-dimethylaniline has been synthesized by astatination of a chloromercuri derivative with a 65% radiochemical yield and identified by TLC (*166*).

f. Astatonitrobenzenes. Under conditions of halogen exchange similar to those described for synthesizing astatobenzene, the heterogeneous At for Br exchange has been employed in order to obtain all three isomers of astatonitrobenzene from the corresponding bromo compounds with yields on the order of 70%. Isotopic exchange was

carried out at 50–60°C in order to avoid thermal decomposition of both the substrate and product. Identification was undertaken using GLC and HPLC, although partial decomposition of the product occurred (*147*). *meta*-Astatonitrobenzene was also obtained via its chloromercuric derivative, which was obtained by the mercuration of nitrobenzene using $HgClO_4$ in strong acidic solution (*81*). The final product was obtained with a 95% radiochemical yield and separated by extraction with CH_2Cl_2 and identified by TLC (*166, 167*). The T_b values of the astatonitrobenzene isomers were determined by extrapolation of GLC retention indexes (*147*) (see Table V).

g. Astatobenzoic Acids and Derivatives. All three isomers of astatobenzoic acid have been prepared through their respective diazonium intermediates using a procedure similar to that described for the astatotoluene isomers (*69, 71*). Yields of up to 90% have been reported (*153, 159, 163, 167*); TLC and column chromatography have been employed for their identification. *ortho*-Astatobenzoic acid has also been obtained in high yield (70–90%) by reaction of At^- with the Tl^{III} di(trifluoroacetate) derivative of benzoic acid (*162*). Heterogeneous isotopic exchange has also facilitated the rapid and high yield (~60%); the synthesis of *meta*-astatobenzoic acid, its methyl ether, and *meta*-astatohippuric acid from their bromo analogs was carried out *in vacuo* at 200–250°C (*134*). The time period for such syntheses did not exceed 1.5 hours and the final products, *meta*-astatobenzoic and its methyl ether and *meta*-astatohippuric acid, were identified by GLC and TLC, respectively (*134*). The pK_a values of astatobenzoic acids (Table VI), as estimated from extraction experiments using citrate buffer solutions and *n*-heptane, have also been used for identification purposes (*167*).

Astatobenzoic acid isomers have also been prepared by heterogeneous isotopic exchange by using the corresponding iodobenzoic acid. Halogen exchange has been effected under molten conditions, or with the substrate dissolved in a molten inert high-dielectric solvent, such as acetamide; yields of 60–70% have been obtained (*35*).

h. Astatinated Aromatic Amino Acids and Proteins. The most effective method for the incorporation of astatine into aromatic amino acid molecules is via their chloromercuri derivatives; phenylalanine, 4-methoxyphenylalanine, tyrosine, and 3-iodotyrosine have been astatinated in this manner (*164, 166*). As the hydrogen atoms in the benzene ring of 4-methoxyphenylalanine and phenylalanine are relatively deactivated, mercuration could be achieved only by prolonged stirring (5 hours) of suspensions of these substrates with $HgSO_4$ in 0.4 *N*

H_2SO_4 at 60°C. 4-Astatophenylalanine and 3-astato-4-methoxyphenylalanine were obtained by subsequent reaction of the nonisolated mercurated compounds with At^- over a period of about 30 minutes. The respective radiochemical yields were on the order of 85 and 70%; both astatoamino acids were identified by paper electrophoresis (*166*).

Mercuration of tyrosine and 3-iodotyrosine has been achieved smoothly at room temperature, and subsequent astatination (*vide supra*) led to 3-astatotyrosine and 3-astato-5-iodotyrosine, respectively. Yields were on the order of 60–80%; these compounds were identified by paper electrophoresis and paper chromatography (*166*). In these molecules, the precise position of the astatine atom in the aromatic ring has not been determined, but it was assumed on the basis of the electrophilic substitution pattern for mercuration. Synthesis of astatotyrosine by electrophilic astatination of L-tyrosine, using H_2O_2 as the oxidizing agent, has also been reported; yields were very low and the product appeared to be unstable under the experimental conditions described (*155*). Visser *et al.* (*164*) have discussed this problem thoroughly and their later investigations on the stability of astatinated amino acids in different media indicated that compounds such as 3-astatotyrosine and 3-astato-5-iodotyrosine, although stable in acid solutions, decomposed rapidly at pH $\geq$ 8, especially in the presence of oxidizing agents (*154, 161, 164*). Anecdotally, the synthesis of an astatoiodotyrosine, in which astatine was allowed to react with tyrosine in the presence of *N*-iodosuccinimide, has also been reported (*68, 70*).

In view of the potential therapeutic applications of ^{211}At (*vide infra*) the synthesis of stable astatinated protein molecules has attracted much effort (see Table VII). Proteins labeled with ^{211}At can be prepared most reliably and unambiguously via incorporation of previously prepared *para*-AtC_6H_4COOH by an acylation reaction with protein amino groups (*53, 156, 158, 159, 178*). Labeling proteins by this method was first reported by Hughes *et al.* (*69, 71*).

Acylation of protein amino groups by the mixed anhydride of *para*-AtC_6H_4COOH can be achieved by the following reaction sequence [Eqs. (15)–(17)].

$$p\text{-}AtC_6H_4COOH + N(C_4H_9)_3 \longrightarrow p\text{-}AtC_6H_4COO[HN(C_4H_9)_3] \quad (15)$$

$$p\text{-}AtC_6H_4COO[HN(C_4H_9)_3] + C_2H_5COOCl \longrightarrow p\text{-}AtC_6H_4COOCOC_2H_5 + [HN(C_4H_9)_3]Cl \quad (16)$$

$$p\text{-}AtC_6H_4COOCOC_2H_5 + H_2N\text{-protein} \longrightarrow C_2H_5OH + CO_2 + p\text{-}AtC_6H_4CONH\text{-protein} \quad (17)$$

i-Butyl chlorocarbonate in 1,4-dioxane was added to a mixture of pure *para*-AtC_6H_4COOH in tetrahydrofuran containing $N(C_4H_9)_3$. This was allowed to stand for half an hour at room temperature; solvents were removed by vacuum pumping, then the protein in borate buffer (pH = 9) was added. Acylation was completed within 1 hour at 4°C; the ^{211}At-protein was separated from low-molecular-weight components by gel filtration, using sterile phosphate-buffered saline as eluent. Overall labeling yields are highly variable, and have ranged from 10 to 28% (*153, 157, 178*). Astatination under carrier-free conditions and using HPLC for the preparation of *p*-AtC_6H_4COOH (*63*) has resulted in a more consistent product yield (~30%).

Electrolytic generation of $^{211}At^+$ for direct labeling of proteins (*1, 135*) and surface proteins on lymphocytes (*113*) has been best achieved at low electrode potentials (~1 V), thus avoiding the electrolytic denaturation of the ^{211}At-proteins (*1*). In bioorganic systems, the ^{211}At label has been lost rapidly (*113, 135*). A more reliable method for electrophilic astatination of proteins has involved using H_2O_2 as an oxidizing agent in a solution of At^- containing KI as a carrier in neutral sodium phosphate buffer (*1*). Label yields of 60% were obtained for a synthesis period of 0.5–1.0 hour. Labeled proteins were separated by gel filtration.

Whereas electrophilic astatination of protein moieties has also been performed by others, the true nature of the At—protein bond has remained in doubt and, consequently, controversial views have been expressed about the mechanism of At-labeling. Initially it was assumed that At^+ was originally bound to protein tyrosine residues but was readily released due to the lability of the C—At bond. The free astatine as At^0 then reacted nonspecifically with other functional groups in the protein, eventually being trapped in the tertiary structure (*156*). However, it has been considered unlikely that electrophilic astatination of tyrosine occurs, as under similar experimental conditions decomposition of otherwise synthesized astatotyrosine has been observed in the presence of oxidizing agents (*161, 164*). Visser *et al.* (*169*) suggested two different types of labeling mechanisms. Relatively stable high radiochemical yields of astatinated proteins containing SH groups have been obtained even in the absence of oxidizing agents; formation of S—At bonds is implicated. In contrast, labeling of proteins with no free SH groups requires the presence of H_2O_2 as an oxidizing agent. In this latter case, the astatination process is slower and the yield and stability of the astato-labeled product are much lower. It has been assumed that the At^{3+} species $HAtO_2$[AtO(OH)] in the presence of H_2O_2 (pH = 7) forms a complex bond with oxygen and nitrogen atoms of

TABLE VII

ASTATINATION OF PROTEIN MOLECULES

Astatination method		Protein	Isolation	Yield (%)	Reference
Electrophilic (At^+)	At/H_2O_2	Bovine serum albumin		80–90	*169, 171*
		β-Lactoglobulin		70–90	
		Hemoglobin		80–90	
		Cytochrome *c*	Gel filtration	1–35	*169*
		Lysozyme		1–25	
		Rat IgG and light chain fragment			*156*
	At/KI	Lymphocytes		~60	*113*
		Streptokinase			
		Phytohemoagglutin			
		Tuberculin (PPD)			
		Keyhole limpet Hemocyanine			
		Human γ-globulin	Gel filtration		*1*
		Tuberculin			

Acylation via p-AtC_6H_4COOH	Bovine serum albumin	Gel filtration		*53, 69, 71, 178*[a]
	γ-Globulin			*71*
	Fibrinogen			*71*
	Rabbit anti-mouse Thymocyte IgG	Gel filtration	12–28	*153*
	Concavalin A	Gel filtration		*157, 159*
	Human serum albumin			*159*
	BK 19.45 IgG			*159*
	BK 19.9 IgG			*14, 158*
	Rabbit IgG (polyclonal) (carrier free)	HPLC (p-AtC_6H_4COOH) Gel filtration	~30	*63*
At^-/KI	Ovalbumin			*70*
	γ-Globulin			*70*
At^-/N-I-succinimide	γ-Globulin			*68, 70*

[a] Acylation via p-$AtC_6H_4SO_2Cl$.

the proteins (*165*), similar to some oxometallic species. Such complex bonds are easily destroyed by reducing agents at pH > 8 and are not even stable enough to survive gel separation methods (*169*).

i. Astatonaphthoquinones. Astatination of 6-chloromercuri-2-methyl-1,4-naphthoquinone has been achieved in high yield (~70%) by refluxing an ethanolic suspension of the substrate with At^-/ICl for 2 hours; the product was identified by TLC (*31*). A more rapid and efficaceous synthesis was achieved by *in vacuo* heterogeneous isotopic exchange with 6-iodo-2-methyl-1,4-naphthoquinone at its melting point (*35*). The preparation of 6-astato-2-methyl-1,4-naphthoquinol diphosphate (6-^{211}At-MNDP) has been accomplished by two methods. The first involves reduction, phosphorylation, and hydrolysis of previously synthesized 6-astato-2-methyl-1,4-naphthoquinone; overall, this five-step procedure took ~7 hours, thereby reducing the original high radiochemical efficiency and resulting in only ~15% yield (*31*). Its identification was determined by TLC (see Fig. 3). Alternatively, high-activity and specific activity 6-^{211}At-MNDP has been quickly synthesized by solid-phase thermal isotopic At^-/6-I-MNDP exchange *in vacuo* (*32*) (see Fig. 4). The presence of SO_3^{2-} markedly diminished the

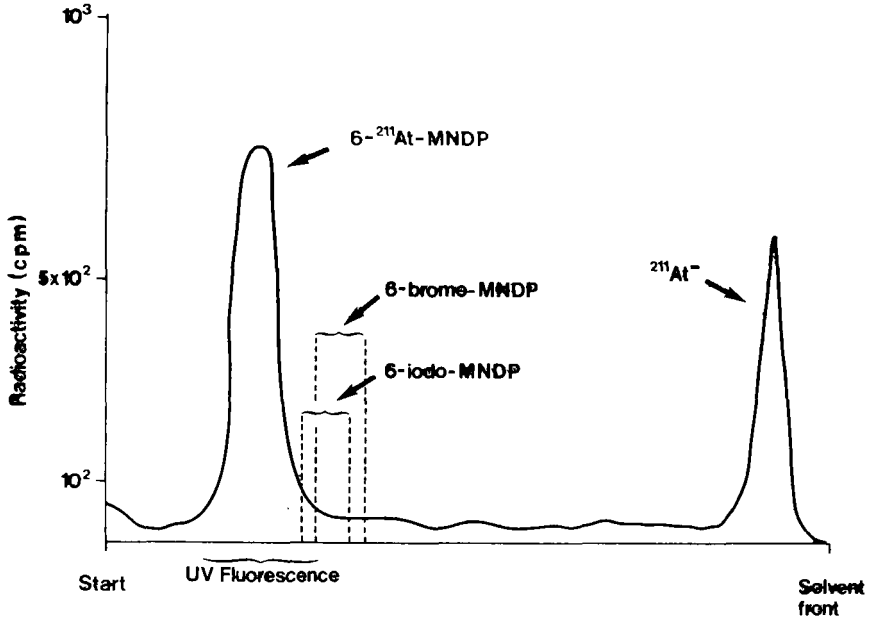


FIG. 3. Sequential TLC analysis [silica gel UV_{250} plates and *n*-BuOH/CH_3COOH/H_2O (10:7:3 v/v)]: identification of 6-^{211}At-MNDP (*32, 33*).

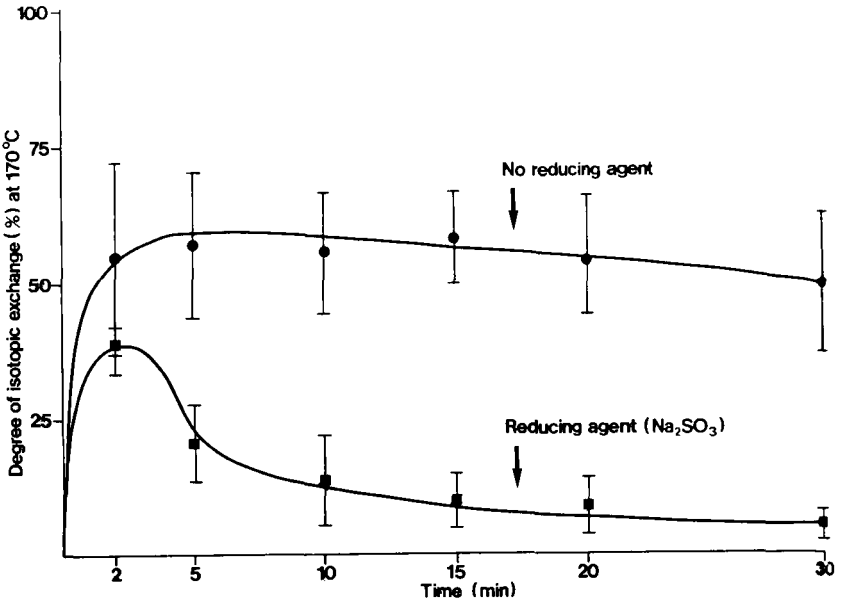
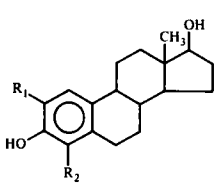


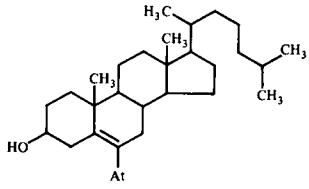
FIG. 4. Synthesis of 6-^{211}At-MNDP by *in vacuo* thermal heterogeneous isotopic exchange ($^{211}At^-$/I) (*32*).

product yield due to substrate decomposition. After purification by ion-exchange chromatography, radiochemical yields of 40–60% non-carrier-free 6-^{211}At-MNDP were obtained after a 10-minute reaction period. It has been postulated that the isotopic-exchange mechanism is facilitated through nucleophilic attack by At^- at the 6-position of 6-I-MNDP, where resonance stabilization of the intermediary adduct would be additionally favored by protonation of the naphthalene nucleus (*33*).

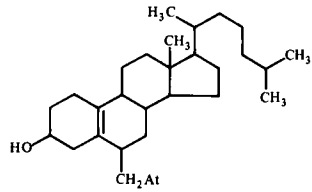
j. Astatosteroids. Several complex steroid molecules have been astatinated via their chloromercuriderivatives; a mixture of 2-astatoestradiol (I), 4-astatoestradiol (II), and 2-astato-4-iodoestradiol (III) was obtained with yields of 55, 19, and 18%, respectively (*170*). Estradiol was mercurated by $Hg(CH_3COO)_2$ in a C_2H_5OH–water solution for 16 hours at room temperature, and then allowed to react with At^- in H_2SO_4 in the presence of KI_3 for 1 hour. The products were separated and identified by TLC (*170*).

Generally speaking, astatoestradiols are less stable than the analogous iodine compounds. Their relative deastatination has been measured in mixtures with methanol and aqueous buffer solutions; no decomposition was observed at room temperature in acidic media up to





(IV)



(V)

(I): R_1 = At; R_2 = H
(II): R_1 = H; R_2 = At
(III): R_1 = At; R_2 = I

neutral pH. However, at 50°C and at pH 7, more than 75% of astatine was lost from the molecule over 20 hours. It was found that higher pH and the presence of H_2O_2 enhanced breakage of the C—At bond (*170*). Similarly, 6-astatocholesterol (**IV**) was also synthesized with 95% radiochemical yield and identified by TLC. However, heating the compound in ethanol–water solutions to 70°C and incubation at room temperature with H_2O_2 or with $NaHSO_3$ (*170*) did not produce deastatination. *In vivo* animal studies have also confirmed the nonlability of the 6-position C—At bond in the cholesterol molecule (*171*).

More recently, 6-astatomethyl-19-norcholest-5(10)-en-3β-ol (**V**) has been prepared rapidly, in high yield (60–70%), and at high specific activity by halogen exchange (At^-/I) in the presence of crown ethers. The crown ethers may fulfill a catalytic role by acting as specific cationic "sinks," and thus facilitating rapid nucleophilic exchange. The product was identified by TLC with an R_F value very close to that of the iodinated derivative (*95*).

3. Heterocyclic Compounds

a. Astatoimidazoles. Mercuration of imidazoles can be achieved over 3–5 hours by reaction with either $HgSO_4$ in H_2SO_4 solution at 55°C or with $Hg(CH_3COO)_2$ in aqueous $NaCH_3COO$ solution (pH = 5) at 50°C (*46*). Chloromercuri derivatives can be isolated, identified, and subsequently astatinated at room temperature using At^- with a molecular iodine carrier in sulfuric acid solution for 30 minutes. Using this method, 4-astatoimidazole, 5-astato-4-methylimidazole, and 5-astatohistidine have been prepared with yields ranging from 50 to 80%. These were identified by TLC and paper electrophoresis. Additionally, 2-astato-4-iodoimidazole and 2-astato-5-iodo-4-methylimidazole were also formed (~5%), presumably due to side reactions with the iodine carrier (*168*). These astatinated imidazoles were found to be stable in

aqueous solutions at room temperature in the pH range 0–14, over a period of 15 hours. If the temperature was increased to 80°C, subsequent addition of Na_2SO_3 or H_2O_2 led to their rapid decomposition (*168*). It was also noted that excess iodine also gave rise to decomposition of 5-astatohistidine in a similar manner, as has been reported for the analogous iodine compound 5-iodohistidine (*130*).

b. Astatopyrimidines, Their Nucleosides, and Nucleotides. Preparation of 5-astatouracil was initially effected by astatination of the 5-aminouracil via its diazonium salt, in a manner similar to that described for obtaining astatohalobenzenes; the radiochemical yield was about 30% (*99, 102, 123*), and the product was identified by HPLC using the sequential analysis of uracil and other halouracils (*99, 102, 122*). Alternatively, 5-astatouracil can be synthesized from its chloromercuri derivative, with a much higher yield (~80%) and a very pure product (>95%) because of the absence of side reactions. Uracil can easily be mercurated with $HgSO_4$ in 0.4 *N* H_2SO_4 at room temperature for 3 hours; the chloromercuri compound can then be allowed to react with At^- according to the method employed for preparing astatophenol derivatives. The final product, 5-astatouracil, was isolated from the reaction mixture by extraction with benzene or *n*-butanol and identified by TLC (*166*). Attempts to produce astatouracil by allowing AtCl or AtBr to react with uracil or iodouracil have been unsuccessful (*99*).

In vitro studies have indicated that 5-astatouracil is chemically stable over the pH range 1–11.5 at room temperature, and 1–7 at 50°C over a period of 20 hours; these results are similar to those for the iodo analog. Heating to 50°C at pH > 11.5 resulted in loss of 20–30% of bound astatine after 20 hours. This has been attributed to direct attack of OH^- on the 5-position of the pyrimidine nucleus, as in the case of 5-iodouracil, Both halouracils are stable in the presence of SO_3^{2-} and H_2O_2 (*170*). From distribution studies utilizing benzene and aqueous borax buffers, the pK_a of 8.97 has been established for 5-astatouracil at 0°C (167).

In a similar manner, 5-astatouridine and its mono- and triphosphate derivatives (At-UMP and At-UTP) have been synthesized from the corresponding chloromercuri derivatives, which were formed first by the reaction of uridine, UMP, and UTP with $Hg(CH_3COO)_2$ in $NaCH_3COO$ buffer (pH 5) at 50°C over 3–5 hours (*170*). Astatination was accomplished in 1 hour with 75% radiochemical yield. 5-Astatouridine and 5-astato-UMP were purified and isolated by TLC; 5-astato-UTP was isolated by paper electrophoresis. Whereas the sta-

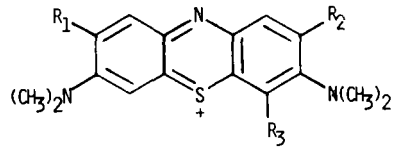
bility of 5-astatouridine was very similar to that of 5-astatouracil, the astatinated nucleotides were found to be sensitive to hydrolysis. Dephosphorylation of 5-astato-UTP and 5-astato-UMP was significant (50%) within 20 hours if acidic solutions (pH ~1) were kept at 50°C (*170*).

The nucleotide 5-astato-2-deoxyuridine has been obtained from 2-deoxyuridine in a manner similar to that described for preparing 5-astatouridine with a radiochemical yield of ~85% (*170*). Attempts to synthesize 5-astato-2-deoxyuridine from the diazonium salt of 5-amino-2-deoxyuridine led only to a 2–3% yield of desired product, whereas 20–25% of the bound astatine was found in the form of 5-astatouracil (*99, 123*). This was apparently due to hydrolysis of the *N*-glycosyl bond in the course of the diazotization reaction. The final product, 5-astato-2-deoxyuridine, was identified by TLC, paper electrophoresis (*170*), and HPLC (*99, 122, 123*).

Other nucleotides, such as 5-astatocytosine, 5-astatocytidine, as well as the monophosphate derivatives of 5-astatocytidine (At-CMP) and of 5-astato-2-deoxycytidine (At-dCMP), have been similarly prepared via astatination of their chloromercuri derivatives (*170*). Product yields are of a similar order; final compounds were isolated and identified by TLC and by paper electrophoresis. It was found that 5-astatocytosine and 5-astatocytidine were stable at room temperature over a wide pH range. Their behavior in the presence of reducing or oxidizing agents paralleled that of their iodo analogs; deastatination occurred. In acidic solutions (pH = 1), dephosphorylation of 5-astato-CMP has been observed in addition to the slow decomposition of the sugar–pyrimidine bond. However, these effects were pronounced for 5-astato-dCMP which was found to decompose completely within 20 hours at 50°C in acid solutions, followed by the formation of 5-astatocytosine and 5-astato-2-deoxycytidine.

Variously astatinated nucleic acids, At-DNA and At-RNA, have been obtained via their chloromercuri derivatives with radiochemical yields of >90%. These compounds have been isolated and proved stable to purification by gel filtration. There was no evidence of any deastatination at pH 2–11 on incubation for 20 hours, nor at neutral pH in the presence of small amounts of reductants or oxidants at room temperature. However, heating to 50°C caused slow deastatination with 15–20% astatine loss in 20 hours. On heating of the At-nucleic acids there was some degree of degradation but this did not appear to involve breakage of the C—At bond (*170*).

c. Astatophenazathioniums. Syntheses of astatinated derivatives of 3,7-bis(dimethylamino)phenazathionium chloride (methylene blue) have been attempted by several synthetic routes (*41, 94*).



(VI): R_1, R_2 = H; R_4 = ^{211}At

(VII): R_1 = I; R_2 = ^{211}At; R_3 = H

Astatination of the diazonium salt of 4-amino-methylene blue led to only ~10% yield of 4-astato-methylene blue (**VI**). Alternatively, 4-astato-methylene blue was rapidly synthesized by heterogeneous nucleophilic isotopic exchange in the presence of 18-crown-6 ether at 80°C, with 4-iodo-methylene blue. The product was separated and identified by TLC; yields ranged from 50 to 65% (*41*). Additionally, 2-astato-8-iodo-methylene blue (**VII**) has similarly been prepared in 60% yield from 2,8-diiodo-methylene blue (*41*).

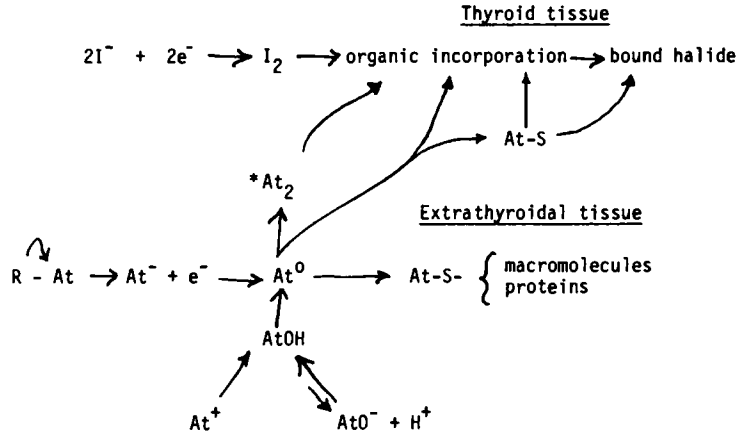
Attempts at electrophilic astatination of methylene blue with ^{211}At/chloramine-T have proved ineffective (*41*).

IV. Biological Behavior

Astatine, regardless of its electronic state (*vide infra*), appears to possess many physiobiochemical properties similar to those of its nearest homolog, iodine (*34, 57, 60, 119, 176*). However, astatine also exhibits a proclivity to accumulate in macrophage-laden tissue, such as lungs, liver, and spleen (*37, 60, 119*); this has been attributed to its amphoteric character.

In rats, guinea pigs, monkeys, and man uptake of [^{211}At]-astatide anion into thyroid tissue has been demonstrated as high, but to a lesser degree than that for radioactive iodine (*57, 59, 60, 132*). Unlike radioactive iodine, the tissue:plasma ratios for [^{211}At]-astatide anion have all been found generally greater than unity (*60*). Its uptake into human thyroid tissue is relatively greater (*59*). Small doses of ^{211}At have been observed to greatly modify thyroid function in animals, with no apparent damage to important contiguous functional anatomical structures such as parathyroid tissue (*58*). Like radioactive iodine, uptake of ^{211}At into the thyroid gland can be blocked by the prior administration of iodide, thiocyanate (*60, 133*), or perchlorate ions (*33, 37*). Astatine can be leached from thyroid tissue by thiocyanate, (*133*) presumably due to the formation of stable At–SCN complexes. Paradoxically, other agents that interfere with the organic binding of iodine

in thyroid tissue, such as thiouracil or propylthiouracil, cause increased uptake of ^{211}At into thyroid tissue (*59, 132*). The possible biochemical fate of *in vivo* ^{211}At can be schematically summarized as shown in Scheme 3. If ^{211}At is administered as a radiocolloid, it has been found to localize in liver (*60*) and lungs (*33*); this behavior is common to most colloids *in vivo* (*33*).



SCHEME 3.

It has been demonstrated that ^{211}At is embryotoxic in pregnant mice, and there also exists a dose-related occurrence of associated fetal malformations (*29, 30*). Long-term studies in female rats that had received 0.5 μCi g^{-1} ^{211}At$^-$ systemically indicated a significant incidence of radiation-induced mammary carcinomata (39/45; 44%) and endometrial polyps (43/55; 76.4%) at 14 months after treatment. No thyroid tumors were found (*50*). Detailed macroscopic radiation dosimetric studies related to the biodistribution of ^{211}At$^-$ in animal models have been reported (*29, 33, 39*).

V. Biomedical Applications—Cancer Therapy

Astatine-211 ($\tau_{1/2}$ = 7.21 hours) possesses many of the desired physical (Fig. 5), chemical, and radiobiological properties thought pertinent to its possible application in cancer therapy (*26, 33, 34, 36, 40*). Astatine-211 decays along two branches: (1) by direct α-particle decay (41.94 $\pm$ 0.50%; 5.87 MeV) to ^{207}Bi ($\tau_{1/2}$ = 38 years), which decays by electron

* Formation of At_2 is statistically highly unlikely.

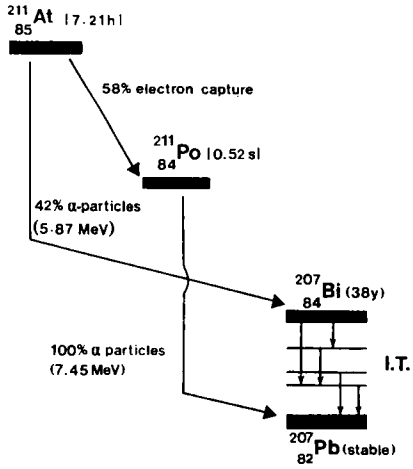


FIG. 5. Decay scheme for ^{211}At.

capture to ^{207}Pb; and (2) by electron capture to ^{211}Po ($\tau_{1/2} = 0.52$ second), which is in transient equilibrium with ^{211}At and which subsequently decays by the emission of α-particles almost entirely of energy 7.45 MeV to form stable ^{207}Pb. There is one α-particle per disintegration. The ranges of the α-particles of ^{211}At in unit density tissue are either 55 μm, corresponding to energy 5.87 MeV for 42% of the disintegrations, or 80 μm, corresponding to energy 7.45 MeV for approximately 58% of the disintegrations. The total mean absorbed radiation dose in tissue is 150.6 cGy g μCi^{-1} (*119*). The contribution from the long-lived decay of ^{207}Bi is negligible (<0.002%).

The mean dose-average linear energy transfer (LET_∞) of ^{211}At-emitted α-particles is approximately 98.84 keV μm^{-1} unit density tissue (*73, 175*). This value is probably very close to the optimum for endoradiotherapeutic effects (*56*). *In vitro* cell studies have demonstrated that the cell-killing effect of such high-LET radiation is independent of dose rate. As a result of its intense focal ionizing nature, cell damage is lethal, being predominantly attributed to nonrejoining double strand breaks in DNA (*121*). There has been no evidence of repair of sublethal damage or potentially lethal cellular damage (*9, 10, 21*).

Conclusions drawn from *in vitro* cell studies with heavy ion beams of varying LET_∞ have indicated that approximately 100 keV μm^{-1} was optimal in achieving a maximum relative biological effect (RBE), as demonstrated by the blocking of cells in $G_2 + M$ and subsequent lethal effects (*21, 96, 97*). The efficient arrest of cultured human squamous cell carcinoma of the larynx (HEp2) and murine rectal adenocarcinoma

TABLE VIII

THERAPEUTIC STUDIES WITH ASTATINE AND ITS LABELED COMPOUNDS

Compound	Tumor	Species	Experimental details	Reference
$^{211}At^-$	Papillary thyroid adenocarcinoma	Man	Anecdotal study in a patient with cervical node metastases. No significant uptake of At into an excised node. Poorly differentiated tumor	*59*
$^{211}At^-$	Rectal adenocarcinoma	Mouse	Biodistribution studies in thyroid-blocked (ClO_4^-) animals. High uptake in spleen, lungs, and stomach. No therapeutic effect over 1- to 20-μCi dose range	*33, 37–39, 109*
$^{211}At^-$, At^0, At^+	Sarcoma 180	Mouse	Biological fate was identical regardless of administered valence state. No tumor affinity; high uptake into spleen, lung, liver, stomach, and thyroid	*119*
^{211}At–tellurium colloid	Ovarian adenocarcinoma	Mouse	Therapeutic studies with 25–200 μCi ^{211}At–Te colloid. Injected by an intraperitoneal route. Ascitic tumor. 100% cures in 25- to 50-μCi dose range; acceptable morbidity. Greater than 50 μCi radiation-induced lethality observed	*25, 27*
$^{211}At^-$	Benign epithelial cyst	Man	Trial local instillation into anterior segment of the eye. Retarded reaccumulation of cystic fluid, but cyst not destroyed, with such a modest dose (10 μCi)	*131*

5-^{211}At-uracil, 5-^{211}At-UdR	Sarcoma 180	Mouse	**Rapid deastatination of compounds.** Biodistribution profile similar to that for $^{211}At^-$. No preferential tumor uptake, although three times that for the analogous iodo compound	*99, 124*
6-^{211}At-MNDP	Rectal adenocarcinoma	Mouse	Biodistribution studies: significant tumor uptake over 12 hours. Heterogeneous distribution within tumor tissue, related to alkaline phosphatase positive areas. Therapy with 0.125-20 μCi. Survival (Φ)-dose (D) relationship of a Langmuir-type saturation equation $\Phi_n = \xi_n D(1 + \zeta_n D)^{-1}$ at n months. At 12 months, 50% survival plateau at $D > 2.5$ μCi. Permanent healing	*33, 34, 37-40, 106-109*
^{211}At-BK 19.9 monoclonal antibody	Human promyelocytic leukemia (HL60)	Nude mouse	Significant localization of ^{211}At in tumor by 12 hours postinjection. Generally, a higher uptake into spleen, lungs, and thyroid, suggestive of metabolic deastatination or free p-AtC_6H_4OH impurities	*13, 158, 159*
^{211}At-anti-thy 1,1 (OX7) monoclonal antibody	T-cell lymphoma	Mouse	Therapeutic studies. 78% and 47% of mice that received a single i.v. injection of 2.2-2.4 μCi, 48 h after injection of lymphoma cells survived >200 days (controls $^{211}At^-$ survived only ~25 days)	*63, 65*
4-^{211}At-methylene blue	B16 melanoma	Mouse	High specific activity compound; marked therapeutic efficacy by lung colony assay. Localization of 4-^{211}At-methylene blue in intracellular melanin. No cytotoxic effect with $^{211}At^-$	*94*

(CMT-93) cells in G_2+M after exposure to small doses of $^{211}At^-$ has been quantitatively confirmed by flow cytofluorometric methods (*35*).

In vitro clonal tumor cell studies have demonstrated the severe cytotoxicity of α-particles delivered by $^{211}At^-$; single exponential cell survival–dose curves were obtained, with D_0 (37% survival) values of 29–48 cGy and 57–73 cGy for Chinese hamster V-79 (*61*) and HEp2 cells, respectively (*33*). In both studies the oxygen enhancement ratio (OER) was found to be slightly greater than unity, probably resulting from the low-LET components of ^{211}At decay (see Fig. 5). In biological systems, such α-particle emissions enable comparable cytotoxicities to be effected in both hypoxic and euoxic tumor cell populations.

The results from similar clonogenic survival studies with an [^{211}At]-IgG monoclonal antibody to human leukemia cells (*158*) have given a mean D_0 of 12 ^{211}At atoms $cell^{-1}$; the RBE has been determined as approximately 4, when compared to the γ-radiations from cobalt-60 (*13*). A range of RBE values (2.8–5.2) for ^{211}At α-particles compared with other low-LET (γ,β^-) radiations has been obtained for a variety of tissues under different *in vitro* and *in vivo* experimental conditions (*12, 13, 29, 61, 64*).

Apart from isolated studies of the selective suppression of graft-versus-host mechanisms by ^{211}At-labeled proteins in organ transplantation (*113*), and various *in vitro* immunological investigations (*1, 135*), the main *in vivo* applications of ^{211}At has been directed toward tumor therapy (*25, 27, 33, 38–40, 65, 108, 109*). Astatine-211 can be stably incorporated into potentially useful biologically active organic compounds via covalent ^{211}At—C bonds, both rapidly and with high yield and specific activity (*32, 33, 160*). In several complex ^{211}At-biomolecules, the ^{211}At—C bond has been found to be metabolically stable *in vivo* (*37, 63, 160, 171*). Applications of such compounds and ionic astatine as potential endoradiotherapeutic drugs have been widely studied in both animal and human tumor models (see Table VIII).

It has been shown that [^{211}At]-endoradiotherapy can be curative in tumor bearing animals, without untoward acute or chronic side effects (*27, 33, 39, 65*). On the basis of results derived from localized ^{211}At–Te colloid therapy (*25, 27*), such an approach might be advocated for the treatment of malignant intraperitoneal disease, and perhaps chronic synovitis, in human subjects (*27*). From the point of view of the systemic application of ^{211}At, encouraging results have been derived from investigations with tumor-surface antigen-specific ^{211}At-labeled monoclonal antibodies (*65*). Likewise, the concurrent development and investigation of a novel class of metabolically directed radiohalogenated potential anti-cancer drugs have proved most promising. Of these,

6-^{211}At-MNDP (*31–33, 36, 108*), whose mechanism of intracellular localization is related to the presence of oncogenically expressed tumor-membrane alkaline phosphatase isoenzymes (*42, 108*), has been demonstrated strikingly effective in an animal tumor model (*33, 34, 38, 39*). It has also served as a concomitant analytical probe for identifying the intracellular locus of radiotherapeutic action of this class of drug by α-particle track autoradiography (*33, 106–109*). Phase I and II human therapeutic trials are shortly envisaged (*33, 34*).

Clearly, there is much scope for the future development of ^{211}At-labeled molecules, and for investigation of their possible role in cancer therapy (*33*).

NOTE ADDED IN PROOF. The facile astatination of *para*-AtC_6H_4COOH and 3-At-tamoxifen by astatination of 4-(n-C_4H_9)$_3$Sn-benzoic acid oxazoline and 3-(n-C_4H_9)$_3$Sn-tamoxifen via an electrophilic destannylation route under mild conditions has recently been reported (*179*). Product isolation and identification were achieved HPLC and TLC; radiochemical yields were 80% and 60%, respectively. Attempted astatination under carrier(I_2)-free conditions gave negligible yields (0.5–1%). Results suggested that the electrophilic species was either AtI or AtI_2 as analogous iodo-destannylation reaction kinetics exhibit a second-order dependence upon iodide concentration (*180*).

ACKNOWLEDGMENTS

I am most grateful to Professor J. S. Mitchell, FRS, for his continued advice and encouragement. Also, many thanks to Dr. Klara Berei, with whom I recently had useful discussions. Mary-Ann Starkey's valuable contribution to the preparation of the final manuscript is much appreciated.

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