THE PREPARATION OF AROMATIC ASTATINE COMPOUNDS THROUGH AROMATIC MERCURY-COMPOUNDS

Gerard W.M. Visser, Eduard L. Diemer, Frans M. Kaspersen
Institute for Nuclear Physics Research (IKO)
P.O. Box 4395
1009 AJ Amsterdam/The Netherlands

SUMMARY

Aromatic astatine compounds can be prepared under mild conditions in high yields by reaction of astatine with aromatic mercury compounds.
Compared to direct electrophilic astatination this procedure is an easy and clean method for the introduction of astatine in aromatic compounds.

Key words: Astatine-211, electrophilic astatination, mercury-compounds, aromatic astatine compounds

INTRODUCTION

Astatine-211 compounds are of potential interest for therapeutic applications because of the decay-properties of this isotope [1]. The synthesis of aromatic astatine compounds is rather complicated. Although astatine is a halogen, the chemical behaviour - probably because of the metal-like character of this element [2] - differs in several aspects from iodine. For the introduction of iodine into aromatic rings, even in carrier-free state, a number of methods is available, such as the reaction of an electrophilic I^+-species generated by oxidation of iodine by chloramine-T, H_2O_2/lactoperoxidase or by electrochemical processes. However, these methods fail for the introduction of astatine [3]. It is possible to introduce At via "At^+" [4], but the oxidising properties of the reagents used for generating the At^+-species ($H_2Cr_2O_7/HNO_3$ or $NaOH/H_2O_2$) are so drastic that also oxidation of the organic substrate occurs [5]. Better results are obtained with the astatine-interhalogen compounds such as AtCl and AtBr [4], but the preparation of these compounds is rather complicated and time-consuming [6].
In our studies of organic astatine-compounds we need a fast and simple method for the introduction of astatine in aromatic compounds starting from astatide (the chemical form in which the element is

0362-4803/80/0517-0657$01.00

Received April 9, 1979
Revised July 3, 1979

usually obtained [7]). In some cases reaction with diazonium compounds gives good results[8], but this method is not generally applicable.
It is known [9] that chloromercury compounds can be converted into the iodide derivatives by reaction with I_2 quite easily, in good yield and in a relative short reaction time. We wish to report here about our results to introduce At into aromatic rings via the corresponding chloromercury compounds. The reaction sequence is given in Figure 1.

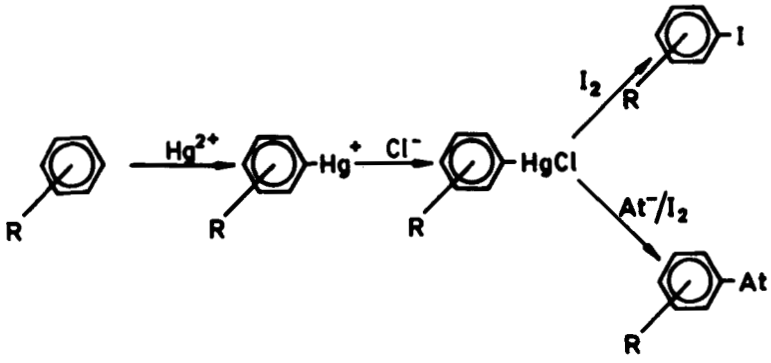

Figure 1 Reaction sequence of the iodination/astatination through chloromercury compounds

EXPERIMENTAL

^{211}At was produced by the ^{209}Bi(α,2n)^{211}At reaction at the synchro-cyclotron of the Free University of Amsterdam and was isolated as ^{211}At-astatide as described earlier [7].
^{131}I-iodide was obtained from Byk-Mallinckrodt (formerly Philips Duphar), in aqueous NaOH without reducing agents. The activities were measured either in a NaI(Tl) well-type crystal on the 365 keV gamma-rays of ^{131}I or the Po X-rays of ^{211}At or by liquid scintillation-counting of the alpha-particles of ^{211}At.

Analysis

o-, m- and p-At-aniline, p-At-anisol, p-At-N,N,-dimethylaniline, m-At-nitrobenzene and o- and p-At-phenol were analysed (and isolated)

by chromatography on SiO_2 (eluent CH_2Cl_2). In case of the TLC-analysis the chromatogram was wrapped in adhesive tape, cut into segments of 0.5 cm and counted. 5-At-uracil was analysed on SiO_2 (eluent, the organic phase of a 5 : 3 : 4 mixture of benzene, butanol-1 and water). At-aminoacids were analysed by electrophoresis (Whatmann 3 MM-paper, 110 V/cm) in a mixture of H_2O, CH_3COOH, HCOOH (8.5 : 1.5 : 0.5) or by paperchromatography (Whatmann 3MM, n-butanol, H_2O, CH_3COOH, 4 : 1 : 1). The position of the mass-peaks was determined by reaction with ninhydrine. The ^{211}At compounds were identified by TLC-analysis and by electrophoresis by comparison of the R_F-values or mobilities with those of the analogous iodo compounds (Table II). Because no differences in R_F-values of the different iodo-nitrobenzenes were found, m-At-nitrobenzene was analysed on TLC as the corresponding aniline after reduction with $SnCl_2$. In some cases (anilines, phenols, uracil) the pK_a-values were determined by measurement of the distribution as a function of pH between an organic phase and an aqueous phase [10].

o- and p-chloromercuriphenol were prepared by reaction of phenol with $Hg(OAc)_2$ as described by Dimroth [11].

m-chloromercurinitrobenzene was prepared by reaction of nitrobenzene with $Hg(ClO_4)_2$ as described by Klapproth et al. [12].

Introduction of At into aromatic compounds

To a solution or suspension of 45 µmoles of substrate in 1 ml of 0.4 N H_2SO_4, 40 µmoles of $HgSO_4$ were added under vigorous stirring; in the case of anisol some ethanol was added to dissolve the anisol. After stirring for several hours at room temperature or at 60 °C (see Table I), 90 µmoles NaCl were added at room temperature, after 5 minutes followed by the At-activity (in aqueous 0.05 M NaOH containing 0.1 mM sulphite) or the ^{131}I-activity. After addition of 10 µmoles KI_3 (1M solution) the mixture was stirred for an additional 30 minutes. The precipitated HgI_2 was dissolved by adding KI and the astatinated compounds,with the exception of the amino-acids, were extracted from the reaction-mixture with an organic solvent (in the case of the anilines after adding Na_2CO_3 to pH = 11.5) (Table I). Subsequently the organic layer was washed with a 1 mM KI-solution (to remove dissolved HgI_2) and Na_2SO_3-solution (to remove all inorganic ^{131}I- and At-activities). Yield determinations were performed by electrophoresis or by measurement of the distribution of the activities over the organic and aqueous phases and subsequent analysis of the organic phase.

Table I Preparation and yields of At-compounds from reactions with chloromercury compounds

Substrate	Preparation of Hg-Cl compound	Method of isolation	Radiochemical yields *	At-products
phenol	acc. to Dimroth[11]	extraction with CH_2Cl_2	95 ± 3%	o- and p-At phenol, AtI-phenol **
nitrobenzene	acc. to Klapproth[12]	extraction with CH_2Cl_2	95 ± 3%	m-At-NO_2-benzene
aniline	3 hours 60 °C	extraction with n-heptane	80 ± 5%	o- and p-At aniline, AtI-aniline **
NN-dimethyl-aniline	3 hours 60 °C	extraction with n-heptane	65 ± 5%	4-At-dimethyl-aniline
anisol	3 hours roomtemp.	extraction with CH_2Cl_2	80 ± 5%	4-At-anisol
uracil	3 hours roomtemp.	extraction with benzene/ butanol-1	85 ± 5%	5-At-uracil
tyrosine	2 hours roomtemp.	electrophoresis H_2O/ CH_3COOH/HCOOH	80 ± 5%	3-At-tyrosine
4-methoxyphenyl-alanine	5 hours 60 °C	DEAE-sephadex 0.9% NaCl	70 ± 5%	At-4-methoxy-phenylalanine
phenylalanine	5 hours 60 °C	DEAE-sephadex 0.9% NaCl	85 ± 5%	4-At-phenyl-alanine

*each yield determination was carried out at least three times

**in the order of 1-5%

Table II Characterisation of the astatine compounds

Compounds	Characterisation		R_F-values *)			pK_a-values [10]	Relative mobilities **)		
			Unsubst.	X=I	X=At	X=At	Unsubst.	X=I	X=At
Phenols	chromatography	phenol	0.25						
	system A	o-X-phenol		0.52	0.46	8.92±0.03			
		p-X-phenol		0.25	0.23	9.53±0.03			
		anisol	0.58						
		p-X-anisol		0.65	0.65				
Anilines	chromatography	aniline	0.20						
	system A	o-X-aniline		0.54	0.50	3.03±0.02			
		m-X-aniline		0.41	0.33	3.90±0.03			
		p-X-aniline		0.36	0.26	4.04±0.02			
		NN-dimethylaniline	0.34						
		p-X-NN-dimethylaniline		0.57	0.55				
Nitrobenzenes	chromatography	nitrobenzene	0.58						
	system A	X-nitrobenzene		0.63	0.63				
Uracils	chromatography	uracil	0.30						
	system B	5-X-uracil		0.57	0.59	8.97±0.01			
Phenylalanines	electrophoresis	tyrosine					1		
	system C	3-X-tyrosine						0.84	0.80
		4-methoxyphenylalanine					1		
		3-X-4-methoxyphenylalanine						0.84	0.81
		phenylalanine					1		
		4-X-phenylalanine						0.86	0.86

*) error ± 0.05; **) mobilities in the order of 20-30 cm

system A: SiO_2/CH_2Cl_2; system B: SiO_2/butanol-1, benzene, H_2O; system C: Whatmann 3 MM/H_2O, CH_3COOH, HCOOH

RESULTS AND DISCUSSION

Introductory experiments were performed with o- and p-chloromercuriphenol. These compounds can be prepared quite easily by reaction of phenol with $Hg(OAc)_2$, followed by reaction with NaCl [11]. Reaction with ^{211}At-astatide and carrier I_2 in $CHCl_3$ at room temperature proceeded smoothly and the corresponding astatinated phenols were obtained in high yields (Table I). This success prompted us to test other substrates. However, mercuration for less activated substrates than phenol requires more drastic conditions in reaction with $Hg(OAc)_2$. It is known [12,13] that mercuration can be facilitated by using more ionic mercuric salts such as $Hg(NO_3)_2$ and $Hg(ClO_4)_2$ in strong acidic solutions. In order to prevent oxidation [13], we tried $HgSO_4$ in 0.4 N H_2SO_4 as mercurating agent. The yields of the astatinated compounds are very good; it is not necessary to isolate the chloromercury compounds but the astatination can be performed in a one-pots reaction. The results are summarized in Table I. By chromatography of the labelled compounds in comparison with the corresponding iodo-compounds the At-compounds were identified and the substitution-pattern in the aromatic nucleus was established(Table II).It could also be excluded (on the basis of the R_F-values of the labelled products) that compounds of the type Ø-Hg-At were formed.
The substitution-pattern in the aromatic compounds is as would be expected for electrophilic substitution. It should be kept in mind that the substitution-pattern is determined by the mercuration-reaction and not by the astatination. Aniline gives o- and p-At-aniline (ratio o/p = 4 at 60 °C). N,N-dimethylaniline results almost exclusively in p-At-dimethylaniline [14]. With anisol the product was identified as p-At-anisol; this is in agreement with the findings of Olah et al. [15] on the reaction of anisol with $Hg(OCOCF_3)_2$. With phenol and aniline small amounts of At-I-compounds were formed. These derivatives are probably formed by astatination and subsequently iodination of the dimercurated compounds [11].
We also tried to synthesize 5-At-uracil, a compound of biological interest [16]. This compound has been prepared by Meyer et al. [17] by the reaction of ^{211}At-astatide with the 5-diazonium salt of uracil in a radiochemical yield of 20 - 30%. Reaction of uracil with $HgSO_4/H_2SO_4/NaCl$ and subsequently with astatide/KI_3 resulted in a 85% yield of 5-At-uracil. Compared with the diazonium-salt reaction this is certainly an improvement. Another advantage of

the mercury-method is the absence of other organic astatine compounds. After removal of the inorganic astatine-species a pure (> 95%) sample of 5-At-uracil is obtained.

Also some amino-acids were astatinated via the mercury compounds. The mercuration of tyrosine proceeds smoothly at room temperature while for the less activated phenylalanine a reaction temperature of 60 ^{o}C is necessary. For the reaction with 4-methoxyphenylalanine a reaction temperature of 60 ^{o}C is also necessary, because the activated para-position [15] is blocked; see the results with anisol. The position of the astatine in tyrosine and methoxyphenylalanine was not established, but on the basis of the substitution-pattern of Hg^{2+}, it is assumed that the products formed in these reactions are 3-At-tyrosine and 3-At-4-methoxyphenylalanine. Klapproth et al. [12] in their study on the mercuration of toluene with $Hg(ClO_4)_2$ and Olah et al. [15] in their study of alkylbenzenes with $Hg(OCOCF_3)_2$ both found a preference of the Hg-group for the para-position. Therefore we believe that the position of At in phenylalanine is mainly para to the alanine part of the molecule.

Also several experiments without iodine-carrier were performed. These revealed that under these conditions also astatinated products were formed, although in somewhat lower yields (20 - 30% decrease). Attempts to synthesize ^{131}I-compounds in the carrier-free state with tyrosine, aniline, nitrobenzene failed completely: yields << 1%. Another indication for the high reactivity of astatine compared with iodine in the reaction with chloromercury compounds can be found in the yields of the ^{211}At compounds compared with those of the ^{131}I compounds in the presence of KI_3. With nitrobenzene - a substrate that can only be iodinated through its chloromercury derivative - a yield of 95% m-At-nitrobenzene was found while for ^{131}I the yield was only 20% (maximal 33%).

The mechanism of the halogenation of chloromercury compounds is uncertain [18]. Both ionic electrophilic and radical mechanisms have been proposed [19,20,21]. From the results with At in the absence of iodine, strong indications can be found for a radical mechanism because At^{o} is easily formed by oxidation of At^{-} at these low pH-values [22]. The formation of AtCl by reaction with NaCl was excluded by astatination of aniline under carrier-free conditions with mercuric acetate-aniline: yield 60% o- and p-At-aniline (ratio o/p under these conditions 2 : 1). In the presence of KI_3 the formation of AtI_2^{-} cannot be excluded. However, this species will also astatinate because of the difference in electronegativity of both elements.

ACKNOWLEDGEMENT

We thank Professor Dr. J.Th. de Boer and Dr. H. Steinberg of the University of Amsterdam for helpful and stimulating discussions. This work is part of the research program of the Institute for Nuclear Physics Research (IKO), made possible by financial support from the Foundation for Fundamental Research on Matter (FOM) and the Netherlands Organization for the Advancement of Pure Research (ZWO).

REFERENCES

1. Smit, J.A., Myburgh, J.A., Neirinckx, R.D., Clin. Exp. Immunol. 14, 107 (1973)
2. Appelman, E.H., Int. Rev. Sci. Inorg. Chem. Ser. 1, vol. 3, ed. V. Guttman, Butterworth, London, 181 (1972)
3. de Boer, J.S.A.M., IKO - Annual Report 1977
4.a. Meyer, G.J., Report Jülich-1418 (1977)
4.b. Meyer, G.J., Rössler, K., Stöcklin, G., Radiochimica Acta 24 81 (1977)
5. See e.g. Visser, G.W.M., Diemer, E.L., Kaspersen, F.M., Int. J. Appl. Rad. Isotop., in press
6. Meyer, G.J., Rössler, K., Radiochem. Radioanal. Lett. 25, 337 (1976)
7. Aaij,C., TSchroots, W.R.J.M., Lindner, L., Feltkamp, T.E.W., Int. J. Appl. Rad. Isotop. 26, 25 (1975)
8. Meyer, G.J., Rössler, K., Stöcklin, G., Radiochem. Radioanal. Lett. 21, 247 (1975)
9. Houben and Weil, page 589, Band V/4, 4e Aufl., George Thieme Verlag, Stuttgart (1960)
10.a. Samson, G., Aten, Jr., A.H.W., Radiochimica Acta 9, 53 (1968)
10.b. Visser, G.W.M., Diemer, E.L., Kaspersen, F.M. to be published
11. Dimroth, O., Chem. Berichte 31, 2154 (1898)
12. Klapproth, W.J., Westheimer, F.H., J. Amer. Chem. Soc. 72, 4461 (1950)
13. Westheimer, F.H., Segel, E., Schramm, R., J.A.C.S. 69, 773 (1947)
14. Dimroth, O., Chem. Berichte 35, 2032 (1902)
15. Olah, G.A., Hashimoto, I., Lin, H.C., Proc. Natl. Acad. Sci. U.S.A., Vol. 74, no. 10, 4121 (1977)
16. Rössler, K., Meyer, G.J., Stöcklin, G., J. Label. Comp. Radiopharm. 13, 271 (1977)
17. Meyer, G.J., Rössler, K., Stöcklin, G., J. Label. Comp. Radiopharm. 12, 449 (1976)
18. Dessy, R.E., Kitching, W., Advances in Organometallic Chem. 4, 267 (1966)

19. Yadav, P.L., Ramakrishna, V., Jha, N.K., Indian J. Chem. Vol. 16A, 623 (1978)
20. Jensen, F.R., Gale, L.H., J. Amer. Chem. Soc. 82, 148 (1960)
21. Winstein, S., Traylor, T.G., J. Amer. Chem. Soc. 78, 2597 (1956)
22. Chalkin, W.A., Herrmann, E., Norseev, J.W., Dreyer, J., Chemiker Zeitung 101, 470 (1977)