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CARRIER-FREE ASTATINATION OF STEROID HORMONES

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SUMMARY

The alpha emitting radiohalogen ^{211}At has potential use as a radiotherapeutic agent when linked to biologically active molecules. The range of compounds which may be astatinated is limited by relative lack of knowledge of organoastatine syntheses. The production of astatovinyl steroids was carried out via electrophilic substitution of tri-n-butylstannylvinyl steroids with astatide in the presence of mild oxidizing agents. The astatinated steroids are synthesized rapidly and in carrier-free fashion yielding compounds of high radiochemical purity.

Key words: ^{211}At, 17-alpha-^{211}At-vinylestradiol, 11-beta-methoxy-17-alpha-^{211}At-vinylestradiol, destannylation.

INTRODUCTION

^{211}Astatine labeled compounds are of current medical interest because of the recent demonstration that ^{211}At-tellurium colloids and ^{211}At monoclonal antibodies are efficacious in experimental model systems [1-3]. A relatively pure alpha emitter [4] with a short physical half-life (7.2 h), ^{211}At is particularly interesting for internal emitter radiotherapy because energy deposition from the alpha particle emissions occurs over a distance that approximates several cell diameters.

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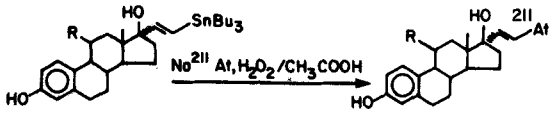
In contrast to the iodination of biologically active molecules, the astatination of organic compounds is relatively difficult to achieve. The short physical half-life demands rapid and simple methodologies which yield radiochemically pure compounds. Aromatic compounds have been astatinated by electrophilic substitution of mercury and thallium [5-8], decomposition of diazonium salts [9,10] and thermal halogen exchange [11,12]. Electrophilic destannylation reactions have been used for the preparation of halogenated organic compounds and the synthesis of aryltrialkylstannane intermediates for subsequent rapid preparation of radiolabeled steroids and their analogs [13-16]. The requirements of radiochemical purity and a rapid and simple methodology for potential therapeutic astatinated compounds led us to investigate the use of mild oxidizing agents in the carrier-free synthesis of astatinated vinylsteroid hormones from tri-n-butylstannylvinyl steroid precursors. This paper reports the successful preparation of 17-alpha-^{211}At-vinylestradiol (^{211}AtVE2) and 11-beta-methoxy-17-alpha-^{211}At-vinylestradiol (^{211}AtMVE2) in high radiochemical yield under carrier-free conditions (Figure 1).

EXPERIMENTAL

^{211}At was prepared at the Chemistry Department, Brookhaven National Laboratory, Upton, NY, on a 60 in. cyclotron using 26.5 ± 0.5 MeV alpha particle bombardment and the ^{209}Bi (alpha, 2n) ^{211}At nuclear reaction. Details of astatine production have previously been reported [17]. ^{211}At was recovered as Na^{211}At in a solution of 0.1 M sodium hydroxide and 0.1 mM sodium bisulfite. ^{211}At activity was quantified with a NaI (Tl) crystal adjusted for the 687 and 569 KeV gamma rays from the decay of ^{211}At and ^{211}Po.

17-alpha-E-tributylstannylvinylestradiol was prepared by a single step procedure starting from 17-alpha-ethynylestradiol. The



R = H, OCH_3

Figure 1. Schema of Synthesis

procedure involved 3 h reflux of a mixture of 17-alpha-ethynylestradiol (10 mmol), tributyltinhydride (12 mmol), azobisisobutyronitrile (5 mg) and tetrahydrofuran (10 ml) [18]. At the end of this period the reaction was complete and a 3:2 mixture of E and Z isomers of 17-alpha-tributylstannylvinyl estradiol was obtained. The mixture was separated by preparative TLC on silica gel and the required E isomer was isolated in 60% yield. On comparison by IR and NMR spectra this compound was found to be identical to that of the reported compound [19]. 11-beta-methoxy-17-alpha-E-tributylstannylvinylestradiol was prepared through the reaction of 11-beta-methoxyestrone [20] and E-bis-(tributylstannyl)ethylene in the presence of butyllithium as previously described [21]. Both 17-alpha-E-stannylvinylestradiol and 11-beta-methoxy-17-alpha-E-stannylvinylestradiols were treated at 0 ^{o}C with iodine in chloroform to furnish the respective 17-alpha-E-iodovinylestradiols. Their purity and retention times were checked by reverse phase HPLC and structure was confirmed by IR and NMR spectra.

Astatinations were performed in 2 ml reacti-vials (Pierce Chemicals) fitted with a teflon septa. Typically 0.1 nmol of 17-tri-n-butylstannylvinylestradiol or 11-beta-methoxy-17-tri-n-butylstannylvinylestradiol in 100 ul MeOH and 100 uCi of $Na^{211}At$ were allowed to react by the addition of 10 ul of a solution of 30% H_2O_2 in glacial acetic acid (2:1, vol:vol). Two identical reactions were carried out using 0.1 nmol

of NaI as carrier. The reaction was left at room temperature for 10 min and was stopped by adding 25 ul of 1 mM sodium bisulfite and extracting 3 times with 1 ml chloroform. The chloroform extracts were combined, dried by passing through anhydrous magnesium sulfate and concentrated under nitrogen to 100 ul. Product isolation and identifications were achieved by HPLC on a C-18 bondapak reverse phase column with a mobile phase of 20% H_2O, 80% MeOH. Products were dynamically monitored for radioactivity using a NaI (Tl) well crystal connected to a chart recorder. The ^{211}At hormones were identified by comparison of their retention times to those of the corresponding ^{125}I-iodocompounds.

The astatinated steroids were isolated as single peaks from the HPLC column. 17-alpha-^{211}At-vinylestradiol and 11-beta-methoxy-17-alpha-^{211}At-vinylestradiols synthesized in the absence of carrier were isolated in 78% and 82% yields, respectively. The presence of carrier NaI did not affect the yields appreciably - small increases in synthetic yields were observed in both the cases (82% and 90%, respectively). A very small shoulder peak observed in the radiochromatogram could be an isomeric impurity originally present in the stannyl precursors and was undetectable in the cold compounds because of its limited quantity. The HPLC

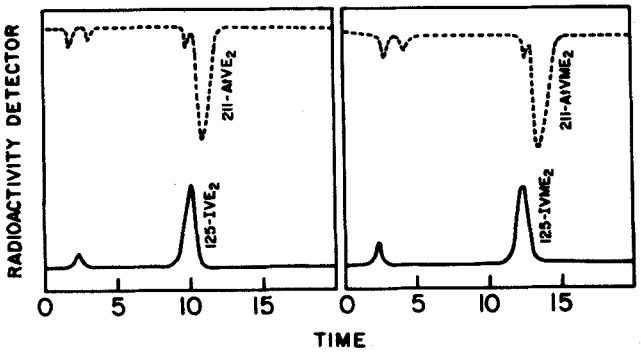


Figure 2. Separation of ^{211}AtVE2 and ^{211}AtMVE2.

analysis demonstrated that the astatinated compounds were similar to the iodinated forms (Figure 2) with respect to their retention times on the column.

CONCLUSION

These results demonstrate that destannylation reactions can be used to produce carrier-free astatine substituted compounds. The facility with which the trialkylstannyl moiety can be introduced into aromatic and vinylic compounds makes this method a general technique which may be applicable to the astatination of a wide variety of biologically active compounds. We have previously demonstrated the utility of this synthetic scheme for the synthesis of astatinated aromatic compounds (22). The ability to synthesize stable and radiochemically pure astato-compounds in a carrier-free environment will facilitate further investigations with ^{211}At labeled drugs and proteins as tumor therapeutic agents.

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