Reaction of Benzeneselenenyl Halides with Estrogens

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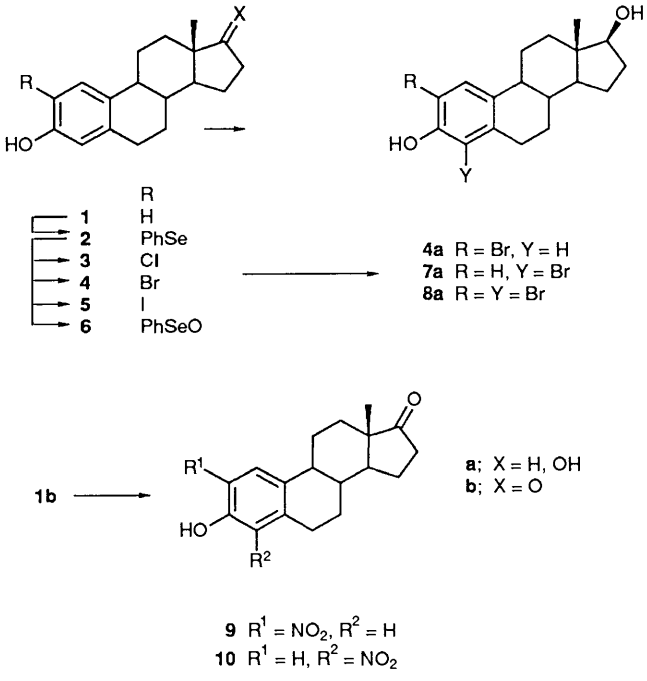
The reaction of estradiol and estrone with benzeneselenenyl chloride affords mainly 2-phenylselenenyl adducts which are readily converted into the corresponding 2-halogenated estrogens upon treatment with a variety of reagents.

Functionalization of the aromatic carbon atoms in estradiol is an area of considerable importance in steroid chemistry. Biologically active 2- and 4-substituted estrogen derivatives are commonly prepared from the corresponding 2- and 4-amino derivatives which, in turn, are readily obtained by the reduction of the 2- or 4-nitro analogues.[1] Conventional methods for the preparation of the latter, using nitric acid, give mixtures of 2- and 4-nitro and 2,4-dinitro derivatives which are difficult to separate. Substantial progress has been made in the regioselective introduction of various substituents at C-2 and C-4 using straightforward procedures. In particular, a number of papers describing selective nitration at the C-2 position have appeared. Using *N*-nitropyrazole, silver nitrate in the presence of BF_3·Et_2O, or the inexpensive reagent clay-supported ferric nitrate (Clayfen) yields of 35–55% have been reported.[2,3] High regioselectivity has also been achieved using mercuriation reactions. Thus 3-methoxyestradiol 17-acetate reacts with mercuric acetate to yield a 2-substituted mercuric derivative while the same reaction with estradiol or its acetate gives mixtures of 2- and 4-substituted derivatives. These mercuric derivatives subsequently undergo halogenation.[4] More recently, selective 2-iodination has been reported using iodine–copper(II) acetate.[5] An alternative route to 2-iodo derivatives involves the treatment of estradiol [protected as the 3,17-bis(methoxymethyl) ether or the 3-methoxymethyl ether] with s-butyllithium and, thereafter, trimethylsilyl chloride. The resulting 2-trimethylsilyl derivatives can conveniently be converted into the 2-bromo or 2-iodo derivative in 22 and 18% overall yield, respectively.[6]

We have previously reported that the A-ring iodination of estradiol diacetate with thallium trifluoroacetate in TFA and subsequent reaction with KI or (^{125}I)NaI exclusively yields the 2-iodo isomer.[7] More recently this reaction has been extended to include the 2-chloro, 2-bromo and 2-cyano derivatives.[8] We now report on the reaction of estradiol **1a** and estrone **1b** with benzeneselenenyl chloride (PhSeCl). With a molar ratio of 1 : 1.2 (reagent) two compounds, a major product **2a** or **2b** and a minor product, were observed with both substrates. When the amount of PhSeCl was increased, a third product was obtained and characterized as a 2-chloro analogue **3a** or **3b**. The yield of **3** was dependent on the amount of PhSeCl used in the reaction mixture and its formation parallelled a decrease in product **2**. The yield of the minor product was unaffected by the amount of reagent. The 2-phenylselenenyl intermediates were isolated and identified as 2-phenylselenenylestrogen derivatives **2a,b** on the basis of NMR (^{1}H and ^{13}C) and mass spectrometry. The structure of the minor product was tentatively assigned as 4-phenylselenenylestradiol and estrone on the basis of NMR and MS. However, these products did behave unusually in that they did not react with added benzeneselenenyl chloride to yield the corresponding 4-chloro derivatives, nor did we observe any trace of these products from the initial reaction.

We extended this study to include benzeneselenenyl bromide as a reagent, with the presumption that similar addition products would be obtained. Instead, we observed normal bromination products (2- and 4-bromo, and 2,4-dibromo derivatives).[9] Under similar reaction conditions benzeneselenenyl iodide failed to react. The pure 2-chloro, -bromo or -iodo derivatives were obtained *via* the reaction of compounds **2a,b** with various reagents. Treatment of **2a,b** with ICl or PhSeCl gave the 2-chloro derivatives **3a,b**, while 1M bromine in acetic acid or benzeneselenenyl bromide or iodine monobromide gave the 2-bromo derivatives **4a,b**, and the reaction with iodine gave the 2-iodo derivatives **5a,b** in excellent yield. Surprisingly, treatment of compounds **2a,b** with trimethylsilyl halides (chloride or iodide) gave the starting materials **1a,b** exclusively. Treatment of **2a,b** with NIS oxidizes the selenium to selenoxide **6a,b** which failed to react further. This is expected in view of the known stability of benzeneselenenyl complexes.[10]



Among the various solvents explored for the reaction between benzeneselenenyl halides and estrogens (*i.e.* MeOH, DMF, ether, $CHCl_3$, EtOAc), the highest yields were obtained in $CHCl_3$. To further evaluate the synthetic utility of the benzeneselenenyl halides, we also tried to use this reagent with metal nitrites and nitrates for regioselective nitration. Treatment of estrone with benzeneselenenyl chlorides and silver nitrate in acetonitrile resulted in 94% conversion into the 2-nitro (80%) and 4-nitro (15%) derivatives.

Our results show that the halogenations initially involve PhSeCl addition to the substrate followed by the interaction

with a further PhSeX (X = Cl, Br) molecule, to yield the final halogenated product, rather than a direct halogenation as previously suggested.[11] Although the overall yields of the 2-substituted estrogens are moderate, the method reported here is significant in that the starting materials do not require protection of functional groups, and the reaction sequences consist of simple steps.

Experimental

General Experimental Details.—M.p.s were determined on a Fisher-Johns apparatus and are uncorrected. Spectral data (^1H and ^{13}C NMR, Bruker WM 25 spectrometer with Me_4Si as an internal standard, *J* values are given in Hz; EIMS, Hewlett Packard model 5988 quadrupole instrument) were recorded. The high resolution mass spectra (HRMS) were determined with a V9 micro-mass Model ZAB-1F apparatus at 70 eV ionization voltage. Silica gel (60–200 mesh) was used for column chromatography. High performance liquid chromatography (HPLC) was performed on a reverse phase column (C-18, ODS-2 Spherisorb, 5 μm, 25 × 0.94 cm, CSC, Montreal) and the compounds were detected at 280 nm. All chemicals used are commercially available and were of the highest-chemical grade. Steroids were purchased from Steraloids.

Reaction of Estradiol **1a** *or Estrone* **1b** *with Benzeneselenenyl Chloride.* To a solution of estradiol **1a** (272 mg, 1 mmol) or estrone **1b** (270 mg, 1 mmol) in dry chloroform (10 ml) was added benzeneselenenyl chloride (230 mg, 1.2 mmol) with stirring. The reaction mixture was stirred at room temperature for *ca.* 6 h during which time the colour of the solution changed slowly from brown to yellow. The reaction mixture was poured into water (30 ml) and extracted with chloroform (2 × 20 ml), and the combined extracts were washed with water (20 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed over silica gel (40 g), 5–8% ethyl acetate–hexanes eluting a mixture of two components which was further purified on a reverse phase C-18 column by HPLC.

2-Phenylselenenylestradiol **2a** (300 mg, 70%) HPLC, gradient of 30% water in MeOH to 100% MeOH (40 min) R_t 29 min: m.p. 72–73 °C (from ether–hexane); δ($CDCl_3$) 0.79 (s, 3 H, 18-CH_3), 3.72 (t, *J* 8, 17α-H), 6.24 (br s, 1 H, 17β-OH), 6.81 (s, 1 H, 4-CH), 7.1–7.26 (m, 5 H, SePh) and 7.5 (s, 1 H, 4-CH); δ_C($CDCl_3$) 11.0 (C-18), 23.03 (C-15), 26.2 (C-11), 26.9 (C-7), 29.5 (C-6), 30.42 (C-16), 36.5 (C-12), 38.5 (C-8), 43.6 (C-9), 49.9 (C-13, C-14), 81.7 (C-17), 114.7 (C-4), 126.4 (C-1), 129.7 (C-10), 134.3 (C-5) and 154.3 (C-3); *m/z* (relative intensity) 430 (22), 429 (24), 428 (100), 426 (57), 425 (19), 424 (21), 375 (11) and 348 (30). [Found: *m/z* (HRMS) 428.1266. Calc. for $C_{24}H_{28}SeO_2$: *m/z* 428.1254].

4-Phenylselenenylestradiol (45 mg, 10%) HPLC, gradient of 30% water in MeOH to 100% MeOH (40 min) R_t 35 min (noncrystalline solid); δ($CDCl_3$) 0.75 (s, 3 H, 18-CH_3), 3.72 (t, *J* 8, 1 H, 17α-H), 6.96 (d, *J* 8.5, 1 H, 2-CH), 7.08–7.26 (m, 5 H, SePh) and 7.35 (d, *J* 8.5, 1 H, 1-CH); *m/z* (relative intensity) 430 (21), 429 (23), 428 (90), 426 (50), 425 (20), 369 (7), 253 (14) and 157 (100) [Found: *m/z* (HRMS) 428.1266. Calc. for $C_{24}H_{28}SeO_2$: 428.1254].

2-Phenylselenylestrone **2b** (285 mg, 67%) HPLC, gradient of 30% water in MeOH to 100% MeOH (40 min) R_t 26 min: m.p. 165–170 °C (from methanol); δ($CDCl_3$) 0.91 (s, 3 H, 18-CH_3), 6.82 (s, 1 H, 4-CH), 7.17–7.53 (m, 5 H, SePh) and 7.54 (s, 1 H, 1-CH); δ_C 13.8 (C-18), 21.53 (C-15), 25.90 (C-11), 26.30 (C-7), 29.44 (C-6), 31.45 (C-16), 35.79 (C-12), 38.13 (C-8), 43.77 (C-9), 47.9 (C-13), 50.38 (C-14), 114.8 (C-4), 126.6 (C-1), 129.21 (C-10), 134.8 (C-5), 141.4 (C-2), 154.56 (C-3) and 220.68 (C-4); *m/z* (relative intensity) 428 (21), 427 (29), 426 (100), 424 (48), 423 (21), 420 (20) and 346 (34) [Found: *m/z* 426.1113. Calc. for $C_{24}H_{26}SeO_2$: 426.1098].

4-Phenylselenenylestrone (50 mg, 12%) HPLC, gradient of 30% water in MeOH to 100% MeOH (40 min) R_t 29 min: m.p. 65–75 °C; δ($CDCl_3$) 0.90 (s, 3 H, 18-CH_3), 6.92 (d, *J* 8.5, 1 H, 2-CH), 7.13–7.26 (m, 5 H, SePh) and 7.35 (d, *J* 8.5, 1-CH); *m/z* (relative intensity) 428 (21), 427 (28), 426 (100), 424 (48), 423 (19), 422 (19), 341 (9) and 239 (10) (Found: *m/z* (HRMS) 426.1113. Calc. for $C_{24}H_{26}SeO_2$: 426.1098).

2-*Chloroestradiol* **3a** *and* 2-*Chloroestrone* **3b**.—A solution of 2-phenylselenenylestradiol **1a** (43 mg, 0.1 mmol) or 2-phenylselenenylestrone **1b** (42 mg, 0.1 mmol) in chloroform (10 ml) was treated either with iodine monochloride (32 mg, 0.2 mmol) or benzeneselenenyl chloride (39 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 3 h, poured into water (10 ml), and extracted with chloroform (3 × 10 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure and the product was purified on silica gel (20 g). The fractions eluted with hexane–ethyl acetate (80:20) were collected and the 2-chloroestradiol **3a** or the 2-chloroestrone **3b** were obtained from the corresponding intermediate. Compound **3a** (24 mg, 78%), crystallized from methanol, had m.p. 168–173 °C (lit.,[8] 187–189 °C); δ($CDCl_3$) 0.77 (s, 3 H, 18-CH_3), 6.73 (s, 1 H, 4-CH) and 7.20 (s, 1 H, 1-CH); *m/z* (EI) (relative intensity) 306 (M^+, 86), 308 (M^+, 26), 247 (69) and 206 (31) and 194 (80). Compound **3b** (22 mg, 72%), m.p. 220–222 °C (lit.,[12] 223–224 °C); δ($CDCl_3$) 0.91 (s, 3 H, 18-CH_3), 6.75 (s, 1 H, 4-CH) and 7.2 (s, 1 H, 1-CH); *m/z* (relative intensity) 304 (M^+ 93), 306 (M^+ 31), 247 (25), 206 (24) and 194 (25).

2-*Bromoestradiol* **4a** *and* 2-*Bromoestrone* **4b**.—A solution of 2-phenylselenenylestradiol **1a** (43 mg, 0.1 mmol) or 2-phenylselenenyl estrone **1b** (42 mg, 0.1 mmol) in chloroform (5 ml) was treated either with iodine monobromide (41 mg, 0.2 mmol) or benzeneselenenyl bromide (47 mg, 0.2 mmol) as described above. The products were extracted with chloroform (2 × 10 ml) and after work-up as described above were purified on silica gel (15 g). On elution with hexane–ethyl acetate (80:20) compound **4a** crystallized from ether–hexane (25 mg, 72%), m.p. 193–196 °C (lit.,[6] 195–197 °C); *m/z* 351, 353 (M^+) and compound **4b** (24 mg, 70%), m.p. 190 °C (lit.,[6] 194–195 °C); *m/z* 349, 351 (M^+).

2-*Iodoestradiol* **5a** *and* 2-*Iodoestrone* **5b**.—A solution of 2-phenylselenenylestradiol **1a** (43 mg, 0.1 mmol) or 2-phenylselenenylestrone **1b** (42 mg, 0.1 mmol) in chloroform (10 ml) was stirred while a 1M iodine solution in chloroform was added at room temperature over a period of 1 h. When the colour of the iodine persisted, the reaction mixture was worked up as described above and purified on silica gel. Elution with 10–20% ethyl acetate in hexane furnished compound **5a** crystallized from ethanol (28 mg, 70%), m.p. 172–173 °C (decomp.) (lit.,[8] 177–178 °C), compound **5b**, m.p. 166–168 °C (lit.,[8] 167–168 °C).

Reaction of 2-*Phenylselenenylestradiol* **2a** *and* 2-*Phenylselenenylestrone* **2b** *with Trimethylsilyl Chloride or Iodide.*—To a solution of **2a** (43 mg, 0.1 mmol) or **2b** (42 mg, 0.1 mmol) in chloroform (10 ml) was added either trimethylsilyl chloride (21 mg, 0.2 mmol) or trimethylsilyl iodide (40 mg, 0.2 mmol). After being stirred at room temperature for 10–15 min the reaction mixture was extracted with chloroform (3 × 10 ml) and the combined extracts were worked up as described above. The compounds were purified on silica gel (15 g) with 20% ethyl acetate in hexane as eluent to furnish **1a**, m.p. 175–176 °C (18 mg, 66%) or **1b**, m.p. 256 °C (16 mg, 60%). Compounds **1a** and **1b** were identical (m.p., MS, HPLC) to authentic samples obtained from a commercial source (Steraloids).

2-Phenylseleninylestradiol **6a** *and 3-Hydroxy-2-phenylseleninylestrone* **6b**.—A solution of 2-phenylselenenylestradiol **2a** (43 mg, 0.1 mmol) in acetonitrile (10 ml) was stirred with *N*-iodosuccinimide (45 mg, 0.2 mmol) at room temperature for 1 h. The reaction mixture was poured into water and the products were extracted with chloroform (2 × 10 ml) and worked up in the usual manner. The crude material was purified on silica gel (15 g), elution with 15–20% ethyl acetate in hexane furnishing compound **6a** (22 mg, 50%); *m/z* 444 (M^+) and **6b** (30 mg, 57%), *m/z* 442 (M^+).

Reaction of Estradiol **1a** *with Benzeneselenenyl Bromide*.—To a solution of estradiol **1a** (272 mg, 1 mmol) in chloroform (10 ml) was added benzeneselenenyl bromide (472 mg, 2 mmol). The reaction mixture was stirred at room temperature for 3 h and then extracted with chloroform (2 × 20 ml). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by HPLC, elution with 70% MeOH in H_2O giving compound **4a**, R_t = 25 min, m.p. 190–192 °C (lit.,[9] 191–193 °C) (140 mg, 40%); compound **7a**, R_t = 31 min, m.p. 208–210 °C (lit.,[9] 206–208 °C) (80 mg, 220%); compound **8a**, R_t = 35 min, m.p. 215–218 °C (lit.[9] 225–226 °C) (20 mg, 5%). All three compounds exhibit identical HPLC mobilities as authentic products obtained *via* an established procedure.[9]

Reaction of Estrone **1b** *with Benzeneselenenyl Chloride and Silver Nitrate*.—To a solution of benzeneselenenyl chloride (19 mg, 0.1 mmol) and silver nitrate (17 mg, 0.1 mmol) in acetonitrile (10 ml) was added estrone **1b** (27 mg, 0.1 mmol). The mixture was stirred at room temperature for 3 h during which time the solution turned yellow. It was then diluted with water (20 ml) and extracted with chloroform (3 × 15 ml). Work-up as described above followed by HPLC purification using a gradient (30 min) of 40% acetonitrile in water to 100% acetonitrile—eluted the products which were characterized by comparison of their HPLC mobilities with those of authentic samples: compound **10** (5 mg, 15%) R_t 17 min, m.p. 265–272 °C (decomp.) (lit.,[12] 270–280 °C); compound **9** (25 mg, 79%) R_t 25 min, m.p. 180–183 °C (lit.,[12] 183.5–184 °C).

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