The Reactions of Estrogens with Benzeneseleninic Anhydride and Hexamethyldisilazane

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Reaction of estrone and 17-ethynylestradiol with benzeneseleninic anhydride and hexamethyldisilazane gave predominantly the respective 4-phenylselenoimines, together with smaller amounts of the corresponding 2-substituted derivatives. Reductive acetylation of these compounds gave high yields of the 4- and 2-acetamido-derivatives of 3-acetoxyestrone and 3,17-diacetoxy-17-ethylnylestradiol respectively. Under similar conditions 4-bromoestrone gave the 2-phenylselenoimine which was then converted into 2-acetamido-3-acetoxy-4-bromoestra-1,3,5(10)-trien-17-one. This on hydrogenolysis furnished 2-acetamido-3-acetoxyestra-1,3,5(10)-trien-17β-ol. A possible mechanistic rationalisation of these results is proposed.

SYNTHETIC and endogenous estrogens are hydroxylated in the 2- or 4-positions by mammals *in vivo*.[1,2] These catechol estrogens are important metabolites because of their physiological activity and potential toxicity.[2,3] The conventional synthetic route to these compounds involves the nitration of estrone, separation of the 1 : 1-mixture of 2- and 4-nitro-derivatives followed by reduction to the corresponding amino-phenols,[4] and conversion of these into the catechols, through quinone-imine intermediates.[5]

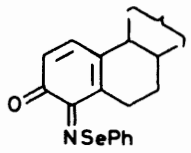
Recently it has been shown that the reaction of phenols with benzeneseleninic anhydride and hexamethyldisilazane provides a potentially useful synthesis of *o*-aminophenols.[6] We now find that the use of this reagent combination with estrone and derivatives provides a convenient and more regioselective synthetic route to aminoestrone derivatives than those previously available.

Reaction of estrone with benzeneseleninic anhydride in tetrahydrofuran, followed by the introduction of hexamethyldisilazane, resulted in a rapid reaction at room temperature to produce a mixture of the 4- and 2-phenylselenoimines, (1) and (2) respectively, which were separated by layer chromatography. The former compound (1), formed in 64% yield, was a relatively stable crystalline compound, but the latter compound (2), formed in only 12% yield, proved to be rather unstable. However, both gave satisfactory ^{1}H-n.m.r. spectra which unambiguously distinguished between them, since the 4-substituted isomer (1) showed an AB system for the 1- and 2-protons, δ 7.37 and 6.63 p.p.m. (J 10 Hz) whereas the 2-substituted isomer (2) showed the 1- and 4-protons as broad singlets δ 6.98 and 6.52 p.p.m. Reductive acetylation of compounds (1) and (2) gave the corresponding *o*-aminophenol diacetates (3) and (4) in yields of 83 and 69% respectively. Exactly parallel results were obtained with 17-ethynylestradiol where the 4- and 2-selenoimines (5) and (6) were obtained in 58 and 14% yields respectively, and these on reductive acetylation gave the corresponding aminophenol triacetates (7) and (8) in satisfactory yields.

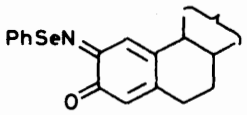
The above route probably provides the most efficient conversion yet achieved of estrone and 17-ethynylestradiol into their respective 4-acetamido-derivatives (3) and (7) respectively, but is clearly unsuitable for the synthesis of the corresponding 2-substituted derivatives (4) and (8). We therefore investigated the reaction of 4-bromoestrone, obtained from estrone in 83% yield by bromination of estrone with *N*-bromoacetamide,[7] with benzeneseleninic anhydride and hexamethyldisilazane. In this case the intermediate phenylselenoimine (9) was not characterised but converted directly into 2-acetamido-3-acetoxy-4-bromoestrone (10) by reductive acetylation. This product obtained in 76% yield, was then hydrogenolysed with concomitant reduction of the 17-carbonyl function to give 2-acetamido-3-acetoxyestra-1,3,5(10)-trien-17β-ol (11) in 94% yield. It should be noted that although this is probably the best route to 2-aminoestrone derivatives, an alternative potential route has been published.[8] In this, estrone is treated with tribenzenesulphenamide to give a mixture of the 2- and 4-phenylthioimines (12) and (13) in 51 and 28% yields respectively. However, the further conversion of these compounds into aminoestrones does not appear to have been reported.

It is interesting that the predominant product in the reaction of estrone with tribenzenesulphenamide is the 2-phenylthioimine, whereas with the benzeneseleninic anhydride–hexamethyldisilazane combination it is the 4-phenylselenoimine. The former reaction is thought to involve the dibenzenesulphenamido-radical, $(PhS)_2N\cdot$, as the reactive intermediate.[8] Although there appear to have been no mechanistic rationalisations of the products formed in the reactions of phenols with the reagent combination used in the present work, it has been suggested that reactions of phenols with benzeneseleninic anhydride as the sole reagent, leading to *ortho*-hydroxylated derivatives, proceed *via* Claisen-type [3,3]-sigmatropic rearrangement of an intermediate selenic ester (14) to the ketonic tautomer of the dihydric phenyl monoester (15).[9]

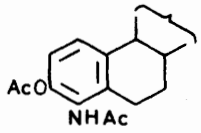
In the case of estrone, attempted reaction with benzeneseleninic anhydride, either alone or in the presence of sodium hydride at room temperature, followed by aqueous work-up, gave only unchanged steroid. Furthermore, we find that in the reaction with the anhydride–hexa-



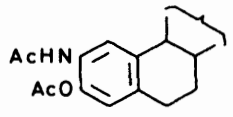
(1) and (5)



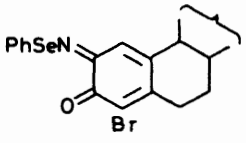
(2) and (6)



(3) and (7)



(4) and (8)



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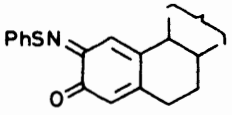

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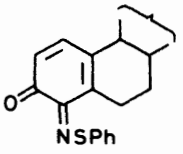

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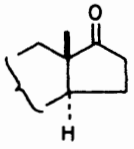
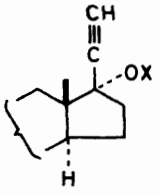
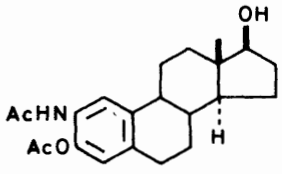


(1)–(4), (9), (10), (12), and (13)



(5) and (6) (X = H); (7) and (8) (X = Ac)



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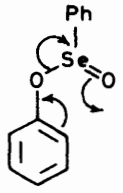

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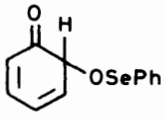
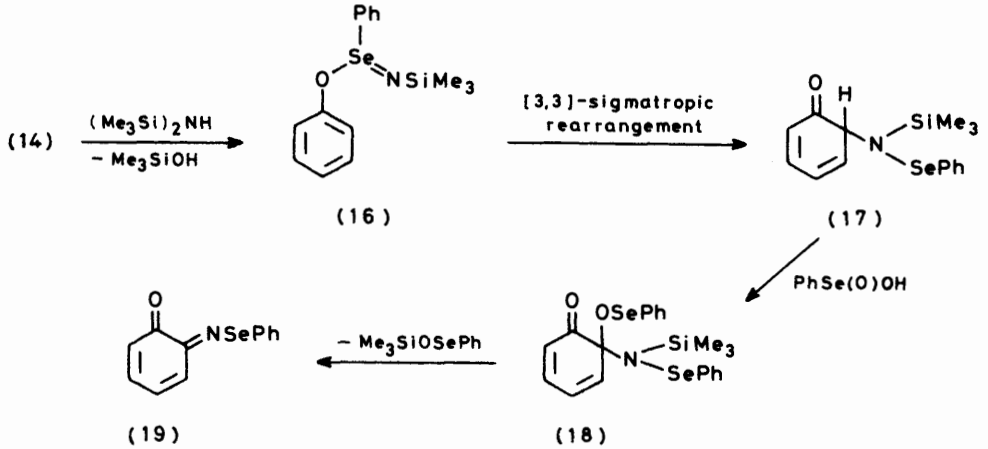


(15)

methyldisilazane combination the best yields of products are obtained by stirring the steroid in tetrahydrofuran with the anhydride for 30 min, before adding the amine, when the rapid formation of a deep red colour is indicative of reaction. On this basis we assume that the expected ester of type (14) is formed initially and this is converted into the imino-ester (16) on adding the amine. The Claisen-type rearrangement then proceeds rapidly leading to the product (17) and further oxidation of this, or the derived tautomeric phenol, might involve reaction



SCHEME

with benzeneseleninic acid giving a further intermediate (18) from which elimination of $Me_3SiOSePh$ would lead to the final product (19). These proposals are summarized in the Scheme.

Although there is no direct evidence for the intermediates proposed in this speculative Scheme it is interesting that Claisen Rearrangement of estrone allyl ether gives a preponderance of the 4-allyl derivative (3 parts) over the corresponding 2-allyl derivative (1 part),[10] proportions very similar to those observed in the present work.

EXPERIMENTAL

Except where otherwise stated, ^1H n.m.r. spectra were measured in deuteriochloroform with $SiMe_4$ as internal standard on a Perkin-Elmer R34 instrument operating at 220 MHz, u.v. spectra in ethanol on a Pye-Unicam SP8-100 instrument, and i.r. spectra in Nujol on a Perkin-Elmer 257 instrument. Mass spectra were determined with an AEI MS-12 instrument at 70 eV and accurate masses with an AEI MS-9 instrument. Preparative-layer chromatography was carried out with silica gel PF 254 (Merck), and m.p.s (uncorrected) with a Reichert hot-stage. Benzeneseleninic anhydride was supplied by Aldrich Chemical Co.

General Procedure for Conversion of Estrone and Derivatives into Phenylselenoimines.—The steroid (3.0 mmol) in tetrahydrofuran (15 ml) was stirred with benzeneseleninic anhydride (3.1 mmol) under nitrogen at room temperature for 30 min, after which hexamethyldisilazane (3.1 mmol) was added and stirring continued for a further 1 h. The deep red solution was then diluted with water (50 ml) the mixture extracted with chloroform (2 × 20 ml) and the combined extract repeatedly washed with water until the washings were neutral. After drying (Na_2SO_4) the chloroform solution was evaporated to give the phenylselenoimine as a deep red solid.

4-*Phenylselenoiminoestra*-1,5(10)-*diene*-3,17-*dione* (1) and 2-*Phenylselenoiminoestra*-1(10), 4-*diene*-3,17-*dione* (2).—The mixed product from the reaction of estrone (810 mg) under the above conditions was subjected to preparative-layer chromatography on silica with chloroform as developing solvent, with multiple elution. One principal component separated from ether as a red microcrystalline solid (840 mg, 64%) of 4-*phenylselenoiminoestra*-1,5(10)-*diene*-3,17-*dione* (1), m.p. 154—155 °C, $\nu_{max.}$ 1 740, 1 725, and 1 590 cm^{-1}; $\lambda_{max.}$ 228 (ε 44 000), 270 (27 000), 280 (5 400), 440 (9 800), and 480 (9 900) nm; δ_H 0.92 (3 H, s, 18-Me), 1.25—3.30 (15 H, m), 6.63 (1 H, d, *J* 10 Hz, 2-H], 7.37 [1 H, d, *J* 10 Hz, 1-H), and 7.35—7.9 (5 H, m) (Found: C, 65.8; H, 5.9; N, 3.4%; M^+, 440. $C_{24}H_{25}NO_2Se$ requires C, 65.7; H, 5.7; N, 3.2%; *M*, 440). The second component separated from ether as a red microcrystalline solid (160 mg, 12%) of 2-*phenylselenoiminoestra*-1(10),4-*diene*-3,17-*dione* (2), m.p. 135 °C, $\nu_{max.}$ 1 730, 1 715, and 1 580 cm^{-1}; $\lambda_{max.}$ 210 (ε 40 600), 230 (20 300), 430 (6 800), and 480 nm (6 850); δ_H 0.91 (3 H, s, 18-Me), 1.25—2.90 (15 H, m), 6.52 (1 H, bs), 6.98 (1 H, bs), and 7.30—7.85 (5 H, m).

17β-*Ethynyl*-17α-*hydroxy*-4-*phenylselenoiminoestra*-1,5(10)-*dien*-3-*one* (5) and 2-*Phenylselenoiminoestra*-1(10),4-*dien*-3-*one* (6).—The mixed product from the reaction of 17-ethynylestradiol (918 mg) under the above conditions was subjected to preparative-layer chromatography on silica with multiple elution using chloroform. The low R_F band gave a red powder (803 mg, 58%) of 17β-*ethylnyl*-17α-*hydroxy*-4-*phenylselenoiminoestra*-1(10),4-*dien*-3-*one* (5), m.p. 158—159 °C (decomp.) from ether, $\nu_{max.}$ 3 480, 3 240, 1 720, and 1 620 cm^{-1}; $\lambda_{max.}$ 228 (ε 24 800), 266 (4 700), 438 (8 700) and 480 nm (9 300); δ_H 0.92 (3 H, s, 18-Me), 1.25—2.4 (12 H, m) 2.64 (1 H, s, C≡CH), 2.84 (1 H, m, 9-H), 3.20 (2 H, m, 6-H), 6.62 (1 H, d, *J*, 10 Hz, 2-H), 7.38 [1 H, d, *J* 10 Hz, 1-H], and 7.38—7.85 (5 H, m) (Found: M^+, 465.124. $C_{26}H_{27}NO_2Se$ requires *M*, 465.121).

The high R_F band gave a red powder (199 mg, 14%) of 17β-*ethynyl*-17α-*hydroxy*-2-*phenylselenoiminoestra*-1(10),4-*dien*-3-*one* (6), m.p. 140—142 °C (decomp.) from ether, $\nu_{max.}$ 3 260, 1 730, and 1 715 cm^{-1}; $\lambda_{max.}$ 226 (ε 20 590), 266 (6 080), 430 (7 488), and 480 nm (6 552); δ_H 0.88 (3 H, s, 18-Me), 1.2—2.5 (12 H, m), 2.60 (1 H, s, C≡CH), 2.6—2.9 (3 H, m), 6.50 (1 H, bs, 4-H), 6.96 (1 H, bs, 1-H), and 7.1—7.9 (5 H, m) (Found: M^+ 465. $C_{26}H_{27}NO_2Se$ requires M^+, 465).

4-*Acetamido*-3-*acetoxyestrone* (3).—The 4-phenylselenoimine (1) (440 mg) in acetic anhydride (15 ml) was shaken vigorously with zinc dust (2 g) overnight and the mixture subsequently warmed to 45 °C for 3 h. After filtration the resultant solution was evaporated to dryness under reduced pressure and the residue subjected to layer chromatography on silica with chloroform–ethanol (97 : 3) as developing solvent. Thus obtained, 4-acetamido-3-acetoxyestrone (3) separated from ethyl acetate as prisms (310 mg, 83%), m.p. and mixed m.p. with an authentic sample 228—231 °C, $\nu_{max.}$ 1 760, 1 725, and 1 685 cm^{-1}; δ_H 0.88 (3 H, s, 18-Me), 2.16 (3 H, s, MeCON), 2.28 (3 H, s, $MeCO_2$), 6.62 (1 H, s, NH), 6.96 (1 H, d, *J* 10 Hz, 1- or 2-H), and 7.30 (1 H, d, *J* 10 Hz, 1- or 2-H) (Found: C, 71.4; H, 7.2; N, 4.0%; M^+, 369. Calc. for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4; N, 3.8%; *M*, 369).

2-*Acetamido*-3-*acetoxyestrone* (4).—Prepared by reductive acetylation of the 2-phenylselenoimine (2) (110 mg) as described above, 2-acetamido-3-acetoxyestrone (4) separated from ethyl acetate as prisms (63 mg, 69%), m.p. and mixed m.p. with an authentic sample 116—118 °C, $\nu_{max.}$ 3 280, 1 770, 1 730, and 1 680 cm^{-1}; δ_H (CD_2Cl_2) 0.89 (3 H, s, 18-Me), 2.12 (3 H, s, Me CO·N), 2.32 (3 H, s, Me CO_2), 6.87 (1 H, s, 1- or 4-H), 7.10 (1 H, s, NH), and 7.95 (1 H, s, 1- or 4-H) (Found: C, 71.4; H, 7.5; N, 3.8%; M^+, 369.195. Calc. for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4; N, 3.8%; *M*, 369.194).

4-*Acetamido*-3,17α-*diacetoxy*-17β-*ethynylestra*-1,3,5(10)-*triene* (7).—Prepared from the 4-phenylselenoimine (5) (90 mg) by reductive acetylation under the above conditions, compound (7) separated from ether–hexane as *prisms* (72 mg, 82%), m.p. 195—196 °C, $\nu_{max.}$ 3 270, 1 765, 1 740, and 1 700 cm^{-1}; δ_H 0.83 (3 H, s, 18-Me), 2.10 (3 H, s, MeCON), 2.27 (6 H, s, 3- and 17-MeCO·O), 2.67 (1 H, s, −C≡CH), 7.13 1 H (d, *J* 10 Hz, 1- or 2-H), and 7.45 (1 H, (d, *J* 10 Hz, 2- or 1-H) (Found: C, 69.2; H, 6.9; N, 3.0%; M^+, 437.218. $C_{26}H_{31}NO_5 \cdot H_2O$ requires C, 68.6; H, 7.3; N, 3.1%; *M*, 437.220).

2-*Acetamido*-3,17α-*diacetoxy*-17β-*ethynylestra*-1,3,5(10)-*triene* (8).—Prepared from the 2-phenylselenoimine (6) (50 mg) by reductive acetylation under the above conditions, compound (8) was obtained as a gum (33 mg, 67%), $\nu_{max.}$ 3 250, 1 760, 1 740, 1 690 cm^{-1}; δ_H 0.88 (3 H, s, 18-Me), 2.03 (3 H, s, MeCO·O), 2.12 (3 H, s, MeCO·N), 2.30 (3 H, s, MeCO·O–), 2.63 (1 H, s, C≡CH), 6.83 (1 H, s, 1- or 4-H), 7.06 (1 H, s, NH), and 7.95 (1 H, 1- or 4-H) (Found: M^+, 437.221. $C_{26}H_{31}NO_5$ requires *M*, 437.220).

4-*Bromoestrone*.—This was carried out by variant of a literature method [7] using *N*-bromoacetamide instead of *N*-

bromosuccinimide. Estrone (1.35 g) in absolute ethanol (150 ml) was treated with *N*-bromoacetamide (0.69 g) with stirring overnight at room temperature. 4-Bromoestrone which separated from the mixture was collected (0.82 g) and further amounts were obtained by concentration of the solution. The total product was recrystallised from ethanol to give prisms (1.48 g, 83%), m.p. 267 °C (lit.,[7] m.p. 264—265 °C), δ_H (CD_2Cl_2), 0.85 (3 H, s, 18-Me), 6.84 [1 H, d, *J* 10 Hz, 1- or 2-H], 7.19 (1 H, d, *J* 10 Hz, 1- or 2-H] (Found: C, 61.4; H, 6.0. Calc. for $C_{18}H_{21}BrO_2$: C, 61.8; H, 6.0%).

2-*Acetamido*-3-*acetoxy*-4-*bromoestra*-1,3,5(10)-*trien*-17-*one* (10).—Prepared from 4-bromoestrone (350 mg) with benzeneseleninic anhydride and hexamethyldisilazane by the general procedure described above, the crude 2-phenylselenoimine was then reductively acetylated as described above and the product purified by preparative-layer chromatography using 3% EtOH in CH_2Cl_2 as the developing solvent. Thus obtained, the *ketone* (10) separated from acetone in needle clusters (340 mg, 76%), m.p. 222 °C, $\nu_{max.}$ 1 760, 1 730, and 1 680 cm^{-1}; δ_H (CD_2Cl_2), 0.89 (3 H, s, 18-Me), 2.10 (3 H, s, MeCON), 2.30 (3 H, s, MeCO·O), 7.18 (1 H, s, NH), and 8.08 (1 H, s, 1-H) (Found: C, 58.8; H, 5.9; N, 3.0. $C_{22}H_{26}NO_4$ requires C, 58.9; H, 5.8; N, 3.1%).

2-*Acetamido*-3-*acetoxyestra*-1,3,5(10)-*trien*-17β-*ol* (11).—The bromo-derivative (10) (58 mg) in ethanol (1.5 ml) and triethylamine (1.5 ml) was shaken under hydrogen with 10% palladium–carbon (70 mg) until absorption of gas was complete (12 h). After filtration, the solvent was evaporated and the residue crystallised from acetone to give needles (45 mg, 94%) of the *trienol* (11), m.p. 269—271 °C, $\nu_{max.}$ 3 280br, 1 740, and 1 725 cm^{-1}; δ_H 0.91 (3 H, s, 18-Me), 2.21 (3 H, s, MeCO·N), 2.26 (3 H, s, MeCO·O), 6.77 (1 H, s, 1- or 4-H), 7.01 (1 H, s, 1- or 4-H), and 8.19 (1 H, s, NH) (Found: C, 71.3; H, 7.5; N, 3.9. $C_{22}H_{29}NO_4$ requires C, 71.1; H, 7.9; N, 3.8%.)

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