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Registry No. 1a, 3234-51-3; **1b**, 17343-73-6; **1c**, 41848-90-2; **1d**, 63262-97-5; **1e**, 39647-01-3; **1f**, 2415-79-4; **1g**, 1196-95-8; **1h**, 823-69-8; **2i**, 7436-90-0; **2j**, 39247-28-4; **2k**, 77295-77-3; diethyl phosphite, 762-04-9; *trans*-1-bromo-2-phenylcyclopropane, 32523-77-6; *cis*-1-bromo-2-phenylcyclopropane, 32523-76-5; *trans*-1-bromo-2-phenyl-2-methylcyclopropane, 72722-52-2; *cis*-1-bromo-2-phenyl-2-methylcyclopropane, 72722-55-5; *trans*-1-bromo-2-hexylcyclopropane, 34780-91-1; *cis*-1-bromo-2-hexylcyclopropane, 34780-90-0; *trans*-1-bromo-2-cyano-2-methylcyclopropane, 78004-14-5; *cis*-1-bromo-2-cyano-2-methylcyclopropane, 78004-15-6; methyl *trans*-2-bromo-1-methylcyclopropanecarboxylate, 58683-50-4; methyl *cis*-2-bromo-1-methylcyclopropanecarboxylate, 58683-51-5; (1α,6α,7β)-7-bromobicyclo[4.1.0]heptane, 1121-40-0; (1α,6α,7α)-7-bromobicyclo[4.1.0]-heptane, 1121-41-1; (1α,8α,9β)-9-bromobicyclo[6.1.0]nonane, 1551-95-7; (1α,8α,9α)-9-bromobicyclo[6.1.0]nonane, 1551-94-6; (*E*)-β-bromostyrene, 588-72-7; (*Z*)-β-bromostyrene, 588-73-8; (*E*)-1-bromonon-1-ene, 53434-75-6; (*Z*)-1-bromonon-1-ene, 39924-58-8; (*E*,X)-1-bromo-4-phenyl-3-methyl-1,3-butadiene, 78004-16-7.

Thio Analogues of Catechol Estrogens[1]

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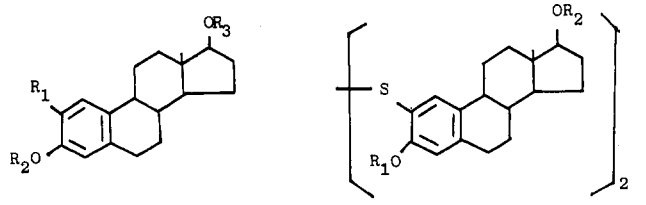
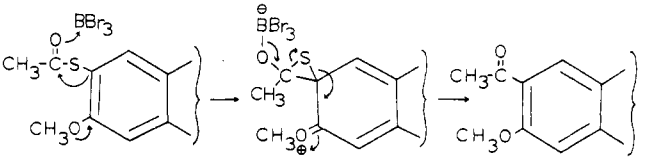
Catechol estrogens which contain a phenolic hydroxyl group at the C-2 position in addition to that originally present at C-3 are the dominant metabolites of estradiol in man and other mammalian species.[3,4] The principal catechol estrogen, 2-hydroxyestrone (2,3-dihydroxyestra-1,3,5(10)-trien-17-one), exhibits no conventional uterotropic activity[5] but does exert effects at the CNS or pituitary level.[6] A neuroendocrine role for the catechol estrogens is supported by their in situ formation in the brain and pituitary[7,8] and their action at these sites may be mediated by their biochemical interrelationships with the biogenic catecholamines. Thus, the catechol estrogens are excellent competitive inhibitors of the catechol *O*-methyltransferase mediated O-methylation of the catecholamines,[9] and they also have been demonstrated to inhibit tyrosine hydroxylase,[10] the rate-limiting enzyme of catecholamine biosynthesis. In order to probe the significance of these interactions, we sought to prepare derivatives of the catechol estrogens which would exhibit exaggerated effects on either one or both of these enzyme systems. In addition, these substances were desirable because of their potential as inhibitors of the brain estrogen-2-hydroxylase and hence as probes of the biological contribution of the catechol estrogens formed in the CNS.

Chart I



1. R_1 = H, R_2 = CH_3, R_3 = Ac
2. R_1 = SO_2Cl, R_2 = CH_3, R_3 = Ac
3. R_1 = SH, R_2 = CH_3, R_3 = H
4. R_1 = SAc, R_2 = CH_3, R_3 = Ac
5. R_1 = R_3 = Ac, R_2 = H
6. R_1 = CH_3, R_2 = H
7. R_1 = R_2 = H
8. R_1 = R_2 = Ac
9. R_1 = SAc, R_2 = R_3 = Ac

Scheme I



The initial structures to which we directed our synthetic efforts were those in which one or both of the phenolic groups of the catechol estrogen were replaced by thiol functions. The thiol derivatives were selected on the basis of a number of considerations including the recent report that a dopamine structure in which the meta phenolic group was replaced by a thiol function was an effective irreversible inhibitor of COMT.[11] A starting point in our synthesis of thiol derivatives of catechol estrogens was provided by the report that the electrophilic addition of chlorosulfonic acid to 17β-acetoxy-3-methoxyestra-1,3,5-(10)-triene (**1**, Chart I) results in the regioselective formation of the 2-chlorosulfonyl derivative which can be transformed to the 2-thiol by reduction with metal hydrides.[12,13] Utilizing the described procedure, we prepared 17β-acetoxy-2-(chlorosulfonyl)-3-methoxyestra-1,3,5(10)-triene (**2**), which was then reduced with lithium aluminum hydride ($LiAlH_4$) to yield the corresponding 2-thio derivative **3**. The material gave a positive response to Ellman's reagent, and it exhibited the signals for the C-1 and C-4 protons at 7.18 and 6.57 ppm, respectively, in the nuclear magnetic resonance (NMR) spectrum. Attempts at O-demethylation of **3** to provide the desired 2-mercapto-3-hydroxy product failed despite the use of O-demethylating reagents such as BBr_3 and 48% HBr in acetic acid, yielding only complex mixtures. With the expectation that protection of the thiol group would yield better results, the thiol derivative **3** was acetylated to provide the diacetate **4**, which was then subjected to O-demethylation with boron tribromide. This reaction also failed to yield the desired mercaptophenol. The product isolated contained no sulfur and was identified as 2-acetylestra-1,3,5(10)-triene-3,17β-diol 17-acetate (**5**) by means of its NMR spectrum as well

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as by comparison with an authentic sample.[14] We have not been able to find an analogy to this transformation, but the expulsion of sulfur could be postulated to proceed by the mechanism depicted in Scheme I, followed by O-demethylation, leading to the products.

Protection of the thiol function was then sought in the form of the oxidized disulfide dimer. The methoxy thiol **3** was converted by means of alkaline hydrogen peroxide to the disulfide **6**, whose structure followed from the shift in the C-1 and C-4 proton resonances in the NMR spectrum and the absence of a reaction with the Ellman's reagent. O-Demethylation of **6** with boron tribromide in anhydrous methylene chloride proceeded cleanly to yield bis(3,17β-dihydroxyestra-1,3,5(10)-trien-2-yl) disulfide (**7**) in a good yield. The structure of **7** was supported by its NMR spectrum in which the two singlets due to the C-1 and the C-4 proton signals appeared at 7.18 and at 6.68 ppm respectively, while the three-proton singlet representing the methyl protons of the C-3 methoxy group was now absent. The structure of **7** was confirmed by converting it to the 3,17-diacetate **8** and by regeneration of the parent methyl ether **6** with dimethyl sulfate.

Reductive cleavage of the disulfide bond in **7** to provide the desired thiol was attempted by using $LiAlH_4$, but the reaction resulted only in unchanged starting material, although under the same conditions the O-methylated derivative **6** was smoothly converted to the thiol **3**. The 2-mercapto-3-hydroxy derivative was eventually formed upon reaction of the disulfide **7** with dithiothreitol in dimethylformamide, but the rapid regeneration of the disulfide bond interfered with the isolation and purification of the thiol product. Its formation was, however, documented by its isolation in a derivative form upon acetylation of the crude product of the dithiothreitol reaction. This reaction gave two compounds in a ratio of 5:1 which were separable by preparative TLC. The minor product was identified as the 3,17-diacetate of the disulfide **8**. The major product exhibited three proton singlets at 2.03, 2.25, and 2.38 ppm, attributable to the acetyl groups at C-17, C-3, and C-2, respectively, indicating a 2-(acetylthio)estra-1,3,5(10)-triene-3,17β-diol diacetate (**9**) structure for this material. Attempts at hydrolysis of the acetate even under nitrogen in the presence of ascorbic acid resulted in either partial or total conversion to the disulfide **7**. The sensitivity to oxidation of the 2-mercapto-3-hydroxy compound is in contrast to the stability of the corresponding 3-methyl ether and is presumably a reflection of the greater electronegativity of the phenolic group and its activation of the ortho thiol function to oxidative attack. The exceptional lability of the desired structure precluded its direct use in biological studies, but considerable information regarding its activity could be obtained by the use of the disulfide precursor under reductive condition under which the desired compound was transiently generated. The results of the biological studies will be reported elsewhere.

Experimental Section

Melting points were taken on a micro-hot-stage apparatus and are uncorrected. Optical rotations were measured, unless otherwise stated, in $CHCl_3$. Infrared (IR) spectra were run on a Perkin-Elmer Model 23B infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Thompson Packard TPV-60T spectrometer at 60 MHz with tetramethylsilane as an internal standard. The abbreviations used are as follows: s = singlet, t = triplet. Analyses were performed by the Microanalytical Service at The Rockefeller University.

3-Methoxy-2-mercaptoestra-1,3,5(10)-trien-17β-ol (3). To a stirred suspension of lithium aluminum hydride (2.5 g) in anhydrous tetrahydrofuran (18 mL) was added a solution of 3 g of 17β-acetoxy-2-(chlorosulfonyl)-3-methoxyestra-1,3,5(10)-triene (**2**)[13] in anhydrous tetrahydrofuran (72 mL), dropwise at 0 °C. The mixture was refluxed for 5 h. After the mixture was cooled in a water bath, aqueous ethyl acetate was added dropwise to decompose the excess reagent, and 20% Rochelle salt solution was then added. The reaction was extracted with ethyl acetate, which was then washed with water, dried over anhydrous sodium sulfate, and evaporated. Recrystallization from methanol gave **3** (2 g) as colorless leaflets: mp 188–192 °C (lit.[12] mp 178–181 °C); NMR ($CDCl_3$ solution) δ 0.76 (3 H, S, 18-CH_3), 3.73 (1 H, t, J = 8 Hz, 17α-H), 3.83 (3 H, s, OCH_3), 6.57 (1 H, s, C_4H), 7.18 (1 H, s, C_1H).

2-(Acetylthio)-3-methoxyestra-1,3,5(10)-trien-17β-ol Acetate (4). Acetylation of **3** (25 mg) in the usual manner with pyridine (1 mL)–acetic anhydride (0.5 mL) and recrystallization from methanol gave **4** (30 mg) as colorless plates: mp 149–152 °C; $[\alpha]_D$ +52.7° (c 0.11); NMR ($CDCl_3$ solution) δ 0.83 (3 H, s, 18-CH_3), 2.06 (3 H, s, 17-OAc), 2.33 (3 H, s, 3-OAc), 2.52 (3 H, s, 2-SAc), 4.67 (1 H, t, J = 8 Hz, 17α-H); 6.80 (1 H, s, C_4H), 7.33 (1 H, s, C_1H). Anal. Calcd for $C_{23}H_{30}O_4S$: C, 72.34; H, 7.59. Found: C, 72.25; H, 7.59.

O-Demethylation of 4. To a stirred solution of boron tribromide (0.05 mL) in anhydrous methylene chloride (1 mL) was added a solution of **4** (50 mg) in anhydrous methylene chloride (1 mL) dropwise at -80 °C. The mixture was stirred for 24 h at room temperature after which water was carefully added to decompose the excess reagent. The reaction was extracted with ether, which was then washed with 5% sodium bicarbonate solution and water, dried over anhydrous sodium sulfate, and evaporated. The crude product was purified by preparative TLC with ethyl acetate–cyclohexane (1:3) as the developing solvent. Recrystallization of the eluate from methanol gave 22 mg of 2-acetylestra-1,3,5(10)-triene-3,17β-diol 17-acetate (**5**) as colorless leaflets: mp 202–204 °C; NMR ($CDCl_3$ solution) δ 0.84 (3 H, s, 18-CH_3), 2.05 (3 H, s, 17-OAc), 2.58 (3 H, s, 2-Ac), 4.67 (1 H, t, J = 8 Hz, 17α-H), 6.62 (1 H, s, C_4H), 7.54 (1 H, s, C_1H). Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.96; H, 7.97. The IR spectra of **5** and the authentic sample donated by Professor T. Nambara were identical in every respect.

Bis(17β-hydroxy-3-methoxyestra-1,3,5(10)-trien-2-yl) Disulfide (6). To a solution of **3** (100 mg) in 0.25% potassium hydroxide–methanol was added 30% hydrogen peroxide (0.025 mL) at room temperature. The precipitate formed was collected by filtration and was washed well with water. Recrystallization from methanol gave **6** (94 mg) as colorless needles: mp 196–197 °C; $[\alpha]_D$ +100° (c 0.2); NMR ($CDCl_3$ solution) δ 0.74 (3 H, s, 18-CH_3), 3.77 (3 H, s, OCH_3), 3.72 (1 H, t, J = 8 Hz, 17α-H), 6.53 (1 H, s, C_4H), 7.57 (1 H, s, C_1H). Anal. Calcd for $(C_{19}H_{25}O_2S)_2 \cdot 0.25H_2O$: C, 71.88; H, 7.95. Found: C, 71.37; H, 7.98.

Bis(3,17β-dihydroxyestra-1,3,5(10)-trien-2-yl) Disulfide (7). Demethylation of **6** (700 mg) was carried out by the same procedure as described for **4**. The crude product was chromatographed on a silica gel column. Elution with ethyl acetate–cyclohexane (1:1) and recrystallization from methanol gave **7** (150 mg) as a slightly orange amorphous powder: mp 228–231 °C; $[\alpha]_D$ +46.7° (c 0.06, MeOH); NMR ($CDCl_3$–CD_3OD (3:1) solution) δ 0.80 (3 H, s, 18-CH_3), 3.70 (1 H, t, J = 8 Hz, 17α-H), 6.68 (1 H, s, C_4H), 7.18 (1 H, s, C_1H). Anal. Calcd for $(C_{18}H_{23}O_2S)_2 \cdot H_2O$: C, 69.19; H, 7.76. Found: C, 68.86; H, 7.89.

Bis(3,17β-diacetoxyestra-1,3,5(10)-trien-2-yl) Disulfide (8). Acetylation of **7** (134 mg) was carried out with acetic anhydride and pyridine in the usual manner. The crude product was purified by chromatography on silica gel. Elution with ethyl acetate–cyclohexane (30:100) and recrystallization from acetone–*n*-hexane gave **8** (150 mg) as colorless needles: mp 169–171 °C; $[\alpha]_D$ -66.1° (c 0.18); NMR ($CDCl_3$ solution) δ 0.80 (3 H, s, 18-CH_3), 2.04 (3 H, s, 17-OAc), 2.23 (3 H, s, 3-OAc), 4.67 (3 H, t, J = 8 Hz, 17α-H), 6.74 (1 H, s, C_4H), 7.44 (1 H, s, C_1H). Anal. Calcd for $(C_{22}H_{27}O_4S)_2$: C, 68.19; H, 7.02. Found: C, 68.25; H, 7.17.

O-Methylation of 7. To a solution of **7** (5 mg) in methanol (1 mL) were added dimethyl sulfate (0.1 mL) and 30% potassium hydroxide (0.1 mL), and the mixture was refluxed for 3 h. After

(14) We thank Professor T. Nambara of The Tohoku University for the sample of 2-acetylestra-1,3,5(10)-triene-3,17β-diol 17-acetate.

cooling, water (5 mL) was added followed by extraction with ethyl acetate, which was then washed with water, dried over anhydrous sodium sulfate, and evaporated. The crude product was purified by preparative TLC with ethyl acetate–cyclohexane (1:1) as the developing solvent. Recrystallization from methanol gave **6** (2 mg) as colorless needles (mp 195–197 °C) identical with the authentic material.

2-(Acetylthio)estra-1,3,5(10)-triene-3,17β-diol Diacetate (9). To a solution of **7** (66 mg) in *N,N*-dimethylformamide (0.5 mL) was added dithiothreitol (100 mg). The mixture was allowed to stand at room temperature overnight. Water was added, and the crystalline product was collected by filtration and washed well with water (50 mL) containing some β-mercaptoethanol. Attempts at recrystallization resulted in the regeneration of **7**; therefore, after being dried under vacuum, the crude product was acetylated with acetic anhydride (0.5 mL) and pyridine (1 mL) in the usual manner. The acetylated material was separated by preparative TLC with ethyl acetate–*n*-hexane (1:3) as the developing solvent into two components. Recrystallization of the less polar fraction from methanol gave **9** (25 mg) as colorless leaflets: mp 139–140 °C; $[\alpha]_D$ +61.4° (*c* 0.7); NMR ($CDCl_3$ solution) δ 0.82 (3 H, s, 18-CH_3), 2.03 (3 H, s, 17-OAc), 2.25 (3 H, s, 3-OAc), 2.38 (3 H, s, 2-SAc), 4.67 (1 H, t, J = 8 Hz, 17α-H), 6.88 (1 H, s, C_4H), 7.33 (1 H, s, C_1H). Anal. Calcd for $C_{24}H_{30}O_5S$: C, 66.95; H, 7.02. Found: C, 67.04; H, 7.02.

Recrystallization of the more polar fraction from acetone–*n*-hexane gave **8** (5 mg) as colorless needles. This product was identical in every respect with that obtained by acetylation of the starting material.

Registry No. **2**, 24513-97-1; **3**, 21147-95-5; **4**, 26788-49-8; **5**, 26362-44-7; **6**, 26788-39-6; **7**, 78109-21-4; **8**, 78109-22-5; **9**, 78109-23-6.

Synthesis of Geometrical Isomers of β-Arylamidoacrylic Esters[1]

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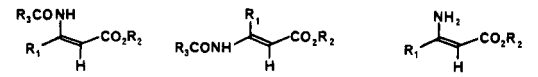
In connection with some studies on the metabolism of β-amino acids, we required several of the β-arylamidoacrylic esters (**1a–d**). Structures of this type had previously been prepared by acylation of the corresponding β-aminoacrylic esters.[2] The acylation, when carried out in a solvent mixture of pyridine and ether, was reported to yield only the *Z* isomers analogous to **1a–d**, in addition to some C-acylated byproducts. We report that under some conditions, the *E* isomers (**2a–d**) are also obtained as byproducts and are in some cases actually the major products of the reaction.



1 2 3

a R_1 = Me, R_2 = Et, R_3 = Ph
b R_1 = *i*-Pr, R_2 = Et, R_3 = Ph
c R_1 = Me, R_2 = Me, R_3 = (o-CO_2Me)Ph
d R_1 = *i*-Pr, R_2 = Et, R_3 = (o-CO_2Me)Ph

a R_1 = Me, R_2 = Me
b R_1 = Me, R_2 = Et
c R_1 = *i*-Pr, R_2 = Et

The starting β-aminoacrylic esters (**3a,b**) were obtained commercially; **3c** was prepared by treatment of ethyl isobutyrylacetate with ammonia.[3] In all cases, the β-aminoacrylic esters appeared from their ^1H NMR spectra to be single stereoisomers, presumably the *Z* isomers. Each showed in the NMR ($CDCl_3$) a single vinyl proton signal (**3a**, δ 4.50; **3b**, δ 4.49; **3c**, δ 4.56). The NH_2 proton signals in $CDCl_3$ were practically invisible but appeared in Me_2SO-d_6 solution as *two* broad bands ($W_{1/2}$ = ~20–30 Hz) at ca. δ 6.8–7.0 and ca. δ 7.6–7.7, consistent with the presence of two separate NH protons as would be expected for the *Z* isomers, **3**.

Treatment of **3a–c** with benzoyl chloride or *o*-(carbomethoxy)benzoyl chloride[4] in a mixture of pyridine and $CHCl_3$ at reflux (condition A, Table I) gave only the *Z* amides (**1a–d**), accompanied by minor unidentified byproducts (probably C-acylation products[2]). Products **1a–d** exhibited vinyl proton signals (in $CDCl_3$) in the range of δ 4.95–5.20 and prominent NH proton broadened singlets in the range of δ 11.40–12.10. However, when the acylation reactions were run in the same reagent mixture at 25 °C in the dark (condition B, Table I), each of the crude products contained a new compound having a characteristic singlet near δ 7.0. These products, isolated by preparative TLC, were identified as the *E* isomers **2a–d** primarily on the basis of their NMR spectra. These showed the expected peaks for ester grouping, alkyl side chain, and *N*-acyl function very similar to the corresponding peaks in the spectra of **1a–d**. However, the upfield vinyl proton signals of **1a–d** were replaced by 1 H singlets at substantially lower field (δ 6.78–7.07), consistent with their location proximate to the NH group.[5] Also the NH signals of **2a–d** in $CDCl_3$ were either invisible or barely detectable as an extremely broad band, e.g., in **2b** ca. δ 7.9 ($W_{1/2}$ = ~50 Hz); in Me_2SO-d_6 solution, the NH signal was clearly visible at δ 10.04 (for **2c**).

In support of the assigned structure of **2c**, hydrogenation of either **2c** or **1c** (Wilkinson's catalyst, in the dark) gave methyl 3-[*o*-(carbomethoxy)benzamido]butyrate (**4a**), which upon heating at 150 °C was converted in high yield into methyl 3-phthalimidobutyrate (**5a**).[6] Similar reduction of **1c** with D_2 in EtOD gave **4b**, which on heating gave **5b**, showing (among other bands) a broadened singlet for a single C-2 hydrogen at δ 3.13. In contrast, **2c** was converted with D_2 in EtOD to **4c**, which on heating gave **5c**, δ 2.80. Unlabeled **5a** shows for the C-2 and C-3 hydrogens a well-resolved ABX pattern, δ_A = 2.78, δ_B = 3.13, δ_X = 4.84. These facts establish that the hydrogenations proceeded stereospecifically without prior $E \rightleftarrows Z$ isomerization of the double bonds.

However, irradiation of **2c** in $CHCl_3$ plus a trace of Br_2 with a sunlamp[7] caused quantitative isomerization to **1c** in 30 min. Crude reaction mixtures containing the *E*

(1) This work was supported by Grant GM 25919 from the National Institute of General Medical Sciences.

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(6) Our original reason for preparing *o*-(carbomethoxy)benzamides such as **1c** or **1d** was to use these as a hydrogenatable intermediate in the preparation of labeled β-amino acids, which could be directly converted into the phthalimido derivative without the intermediacy of the free β-amino acid.

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