Regioselective Synthesis of 2-Chloromercurio-estradiol and -estrone Derivatives: A Novel Approach to A-Ring Substituted Estrogens

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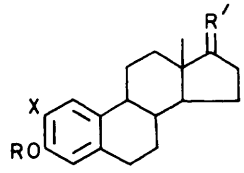
The following derivatives of estradiol and estrone, 3-methoxyestra-1,3,5(10)-trien-17β-yl acetate (3a), 3-methoxyestra-1,3,5(10)-trien-17-one (3b), estra-1,3,5(10)-triene-3,17β-diyl diacetate (1f), and 3-acetoxyestra-1,3,5(10)-trien-17-one (1g), can be regioselectively mercuriated at the less hindered position 2. The 2-mercurio derivative (4a), prepared from (3a), can be used as the starting material for the synthesis of some 2-substituted estrogens, such as 2-halogeno- and 2-hydroxy-estrogens. Additionally, the 2-chloromercurio-4-bromo derivative (5c) can be obtained from 4-bromo-3-methoxyestra-1,3,5(10)-trien-17β-yl acetate (2f), whereas from 3-methoxyestra-1,3,5(10)-triene-2,17β-diyl diacetate (3g) the 4-chloromercurio derivative (5d) can also be obtained. An explanation of the regioselectivity shown by some electrophiles towards the aromatic A-ring of estrogens is presented.

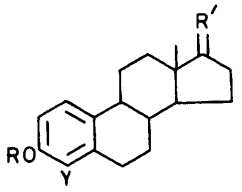
The hydroxylation of the aromatic ring in estrogens is well recognized as the most significant path in the oxidative metabolism of these compounds in man.[1] The two *ortho* positions in the phenolic ring of such steroids can both be hydroxylated, and from estradiol [estra-1,3,5(10)-triene-3,17β-diol] (1a) and estrone [3-hydroxyestra-1,3,5(10)-trien-17-one] (1b), 2- and 4-hydroxyestrogens (catechol estrogens) (1c), (1d), (2a), and (2b) can be formed. However, although 4-catechol estrogens have also been discovered more recently, in rats and in man,[2] it seems that 2-catechol estrogens in particular may be regarded as key compounds for subsequent biological reactions of estrogens such as methylation or binding to peptides or proteins.[1] Recently, we started a project aimed at the synthesis of 2- and 4-substituted estrogens in order to evaluate their biological activity, and we report here the results of some novel methods of functionalization of the A-ring in estrogens.

The synthesis of 2- and 4-substituted estrogens can be accomplished by classical electrophilic substitutions, but these procedures generally lead to equimolar amounts of the two *ortho* isomers.[3] As a consequence, tedious separation problems are encountered which are often solved by preferential crystallization or chromatographic resolution of the mixture. Generally, the 4-substituted steroid is the less soluble isomer and can in many instances be filtered off from the final crude mixture, but purification of the 2-isomer can cause more problems.



(1)

a; R = X = H, R′ = H, OH
b; R = X = H, R′ = O
c; R = H, R′ = H, OH, X = OH
d; R = H, R′ = O, X = OH
e; R = H, R′ = H, OH, X = I
f; R = Ac, R′ = H, OAc, X = H
g; R = Ac, R′ = O, X = H
h; R = Ac, R′ = H, OAc, X = I
i; R = Ac, R′ = H, OAc, X = OAc

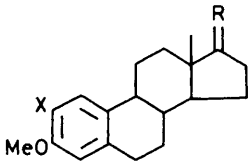


(2)

a; R = H, R′ = H, OH, Y = OH
b; R = H, R′ = O, Y = OH
c; R = H, R′ = H, OH, Y = HgOAc
d; R = H, R′ = H, OH, Y = I
e; R = H, R′ = H, OH, Y = Br
f; R = Me, R′ = H, OAc, Y = Br

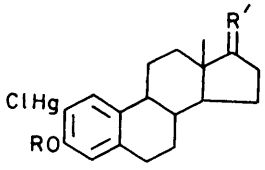
Results and Discussion

2-*Chloromercurioestrogens*.—When we started our work, the mercuriation of the A-ring of an estrogen was an intriguing reaction, since it had been reported that treatment of estradiol (1a) with $Hg(OAc)_2$ in acetic acid afforded the 4-acetoxymercurioestradiol (2c),[4] whereas reaction of (1a) with $Hg(OAc)_2$ and iodine in acetic acid afforded a mixture of the 2- and 4-iodoestradiols (1e) and (2d).[5] Since we had noticed that the reaction of compound (1a) in acetic acid with $Hg(OAc)_2$ afforded a mixture of the possible acetylated compounds, we decided to continue our investigation of 3-methoxyestra-1,3,5(10)-trien-17β-yl acetate (3a) using a different solvent. In dry acetonitrile, compound (3a) reacted with excess of $Hg(OAc)_2$ [5 moles of salt per mole of (3a)] and after treatment of the reaction mixture with saturated aqueous NaCl the 2-chloromercurio derivative (4a) was obtained in good yield (80% after column chromatography).[6] The regioselectivity of the reaction was unequivocally established by ^1H n.m.r. analysis, since two singlets at δ 6.65 and 7.15 (aromatic protons at C-4 and C-1, respectively) were present in the spectrum. The 2-chloromercurio derivative (4a) was a crystalline compound, which could be stored without any precaution. The 17β-acetoxy group could be hydrolysed with aqueous sodium carbonate in methanol without affecting the mercurio group, whereas treatment with acids (dilute HCl in



(3)

a; R = H, OAc, X = H
b; R = O, X = H
c; R = H, OAc, X = Br
d; R = H, OAc, X = I
e; R = H, OAc, X = Cl
f; R = H, OAc, X = OH
g; R = H, OAc, X = OAc



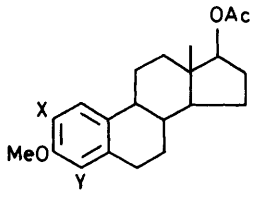
(4)

a; R = Me, R′ = H, OAc
b; R = Me, R′ = O
c; R = Ac, R′ = H, OAc
d; R = Ac, R′ = O

methanol or warm acetic acid) led to replacement of the chloromercurio group with hydrogen and compound (3a) was recovered in good yield.

When the mercuriation was performed on 3-methoxyestra-1,3,5(10)-trien-17-one (3b), yields were as good as for the estradiol derivative (3a) [85% of isolated 2-chloromercuriated estrone (4b)]. Therefore, no substantial difference was noticed on replacing the 17β-acetoxy function with a ketone.

Although both compounds (4a) and (4b) could be used as starting material for further manipulations, the presence of the methyl ether at position 3 might cause some problem, since the hydrolysis of an ether always requires forcing conditions.[7] We therefore investigated the possibility of introducing a mercuriated function into a substrate with a different protecting group at C-3 from the methyl ether in (3a). However, the protecting group at position 3 in the steroid was one of the critical factors for the introduction of the mercuriated function. In fact, both estradiol 3,17β-diacetate (1f) and estrone 3-acetate (1g) reacted slowly with a great excess of $Hg(OAc)_2$ (15 moles per mole of steroid, 6 days reflux) with acceptable yields (40—50%) of isolated product. In spite of the unexceptional yields, the easy removal of the acetyl groups from the molecules of the estrogens made the two 2-chloromercurio derivatives (4c) and (4d) attractive for further transformations. Moreover, we were able to improve the yields of the above reaction and shorten the reaction times by taking advantage of the procedure indicated by Kirk [8] who very recently described an easy synthesis of 4-hydroxyestradiol (2a) from estradiol (1a) in which the catalysis of perchloric acid apparently both accelerated the mercuriation and directed it toward position 4. We have used the perchloric acid catalysis in the preparation of the 2-chloromercurio derivatives (4c) and (4d) from the diacetate (1f) and the acetate (1g) and found the reaction to be most successful in acetonitrile.* By this procedure the yields were good (80—85%) and the reduced excess of $Hg(OAc)_2$ (8 molar excess, 4 days) led to a cleaner reaction than in absence of perchloric



(5)

a; X = Y = Br
b; X = Y = Cl
c; X = HgCl, Y = Br
d; X = OAc, Y = HgCl

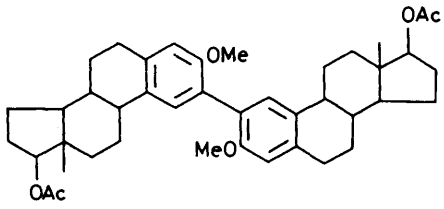
acid. Furthermore, the bulk of the salts was diminished and and easier work-up could be performed. The difference in orientation of the mercuriation in our case with respect to the results of Kirk [8] probably depends on the protection of position 3. Having thus obtained the 2-chloromercuriated estrogens, we explored their potential use for the preparation of A-ring substituted estrogens.

2-Halogenoestrogens.—Reaction of the 2-chloromercurio derivative (4a) with solutions of bromine and iodine in chloroform at room temperature quantitatively afforded the 2-bromo- (3c) and 2-iodo-estrogens (3d). The reaction was complete within a few minutes and could be monitored through the formation of mercuric salts which precipitated from the organic phase. Use of excess of bromine led to the formation of increasing amounts of the 2,4-dibromo derivative (5a), as could be ascertained by ^1H n.m.r. spectroscopy. In fact, whereas in the spectra of compounds (3c) and (3d) the resonances of the hydrogens at C-4 and C-1 were at δ 6.55 and 7.05, and 6.55 and 7.70, respectively, there was only a singlet at δ 7.40 in the ^1H n.m.r. spectrum of compound (5a). Iodination of the 2-chloromercurio derivative (4c) proceeded equally well and a good yield of the 2-iodoestrogen (1h) was obtained after crystallization (82%). The preparation of compound (1h) allowed an easy preparation of 2-iodoestradiol (1e) which could be quantitatively obtained by hydrolysis of the diacetate (1h) with potassium carbonate in methanol–water.

The preparation of the 2-chloroestrogen (3e) with *N*-chlorosuccinimide has already been described,[6] but further examination of this reaction showed also the partial formation of the 2,4-dichloro derivative (5b). In order to explore the reactivity of the 2-chloromercurio derivative (4a) toward other chlorinating agents, we treated (4a) with gaseous Cl_2. Only carefully controlled conditions of reaction afforded the 2-chloro compound (3e) in moderate yield (50%) after column chromatography. Excess of chlorine invariably afforded a mixture of several products, from which the 2,4-dichloroestrogen (5b) could be obtained as the main product, although in low yields.

2-Hydroxyestrogens.—A 2-mercurioestrogen could be a useful starting material for the preparation of 2,3-catechol estrogen itself and we approached this problem by applying the hydroxylation procedure developed by Hill and Whitesides for aliphatic mercurials.[9] By this method an alkylmercuric halide was treated with $NaBH_4$ and molecular oxygen in dimethylformamide and an alcohol was obtained. In our hands the procedure proved unsuccessful and no

* In acetic acid we found partial deacetylation of the 17β-acetoxy moiety.



(6)

2-hydroxy derivative was obtained by reaction of the 2-mercurio derivative (4a) in the above conditions. In one attempt at reproducing the hydroxylation procedure we were able to isolate in fair yield (38%) a dimer of estradiol, namely 17,17′-diacetoxy-3,3′-dimethoxy-2,2′-biestra-1,3,5(10)-trienyl (6). The dimeric structure was inferred by analysis of its ^{1}H n.m.r. spectrum, which showed two singlets at δ 6.75 and 7.35, and from the fact that the elemental analysis was practically the same as that of (3a). The mass spectrum of compound (6) confirmed its structure, since a molecular ion at *m/z* 654 was present together with *m/z* 328 [$(M^+/2) + 1$]. Also the metal–metal exchange of (4a) with $Pb(OAc)_4$ in acetic acid or acetonitrile showed no positive result, in contrast with the analogous successful reaction reported for 4-acetoxymercurioestradiol (2c).[8] In our experimental conditions, the main product of the above reaction was the estradiol derivative (3a) (70—80%) and for this reason we turned our attention to the hydroboration–oxidation method which converts simple aryl mercuric derivatives into the corresponding phenols.[10]

We have already reported in a preliminary communication this successful result [11] and describe here in more detail the overall sequence of reactions and the experimental procedure. Treatment of the chloromercurio compound (4a) with a solution of diborane in tetrahydrofuran afforded the putative intermediate organoboron derivative which was not isolated, but directly oxidized to compound (3f). We used neutral H_2O_2 for this step, since the catechol-like system formed after the reaction should be unstable in alkaline conditions.[1] The purification of the 2-hydroxyestrogen (3f) was not attempted and it was directly acetylated at room temperature to afford (3g), which was purified by column chromatography, using as the stationary phase ascorbic acid impregnated silica gel.[12] In the absence of ascorbic acid, column chromatographic purification of the diacetate (3g) gave only poor yields of the desired product. From estradiol (1a) one could obtain an average yield of 45—50% of isolated, pure diacetate (3g), which was treated with pyridinium hydrochloride to give the corresponding 3-hydroxy derivative. This compound was immediately acetylated and purified by ascorbic acid impregnated silica gel column chromatography and the pure triacetate (1i) was obtained in 75% yield from (3g). The triacetate (1i) is the most suitable derivative of 2-hydroxyestradiol and can be stored without any appreciable decomposition at −20 °C. The required 2-hydroxyestradiol (1c) may be prepared just prior to use by acidic hydrolysis in the presence of ascorbic acid as described.[12]

Mercuriation of 2- *and* 4-*Substituted Estrogens*.—It was clear from the reported results on the mercuriation of estrogens that the protection of the 3-hydroxy group was a critical factor for the regioselectivity of the electrophilic substitution. In fact, mercuriation of unprotected estradiol (1a) in acetic acid afforded the 4-acetoxymercurio derivative (2c),[4,8] whereas in acetonitrile the 3-methoxyestrogen (3a) afforded exclusively the 2-regioisomer (4a). Protection of the 3-hydroxy group as the acetate slowed down the reaction, but did not change the regioselectivity of the reaction. With this in mind we attempted the mercuriation of some 2- and 4-substituted estrogens. We felt that a 4-substituted steroid could be a better substrate than a 2-substituted one, since position 2 is more accessible than 4. This proved to be the case in the two examples that we have examined. We had prepared 4-bromoestradiol (2e) by reaction of estradiol (1a) with 2,4,4′,6-tetrabromocyclohexa-2,5-dienone and separation of the two 2- and 4-isomers formed.[3c] We treated compound (2e) with mercuric acetate in acetonitrile, but again mainly acetylation of positions 3 and 17 occurred. The mixture of acetates formed did not undergo mercuriation even after addition of catalytic amounts of perchloric acid. We therefore prepared the 3-methyl ether of (2e), protected position 17 as the acetate, and then treated (2f) with $Hg(OAc)_2$ in acetonitrile. Catalytic amounts of perchloric acid accelerated the reaction and lowered the excess of mercuric salt needed, and the 4-bromo-2-chloromercurioestrogen (5c) was obtained in 53% yield after column chromatography.

As expected the mercuriation at position 4 of the 2-substituted estrogen was more difficult and we could achieve only partial substitution at C-4 with long reaction times and acid catalysis. The 2-acetoxyestrogen (3g) was mercuriated in 24 h reflux, and after purification (silica gel chromatography) moderate yields of the 4-chloromercurio compound (5d) were obtained (25%).

Conclusions

From our results on the chloromercuriation of estrogens it is evident that a regioselective attack on ring A of estrogen is possible and that the less hindered position 2 is more accessible than the corresponding position 4. The bulkiness of the electrophilic reagent plays an essential role in determining the regioselectivity of the substitution. These results cannot be obtained with classical reagents for nitration or bromination,[3b,c] but efficient preparations of 2-substituted estrogens can be realized with $Hg(OAc)_2$, boron trifluoride–diethyl-ether–acetic anhydride adduct,[12,13] *N*-nitropyrazole or silver nitrate–boron trifluoride,[14] or iodine–copper(II) acetate.[15] As far as position 3 is concerned, the nature of the protecting group seems to affect the rate of the reaction, but no influence has been detected with regard to the regioselectivity.

Experimental

All m.p.s are uncorrected. I.r. spectra were recorded for solutions in chloroform or for Nujol mulls. ^{1}H N.m.r. spectra were recorded on a Varian XL-100 spectrometer in [^{2}H]-chloroform solutions unless otherwise stated with Me_4Si as internal standard. Mass spectra were recorded on a Varian 112 S mass spectrometer (direct inlet). The progress of all reactions and column chromatographies (silica 230—400 mesh) was monitored by t.l.c. on E. Merck silica gel HF_{254} plates visualized by spraying with 5 or 10% ethanolic phosphomolybdic acid followed by heating.

2-*Chloromercurio*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (4a).—To a solution of 3-methoxyestra-1,3,5(10)-trien-17β-yl acetate [16] (3a) (3 g, 9 mmol) in dry acetonitrile (300 ml) was added $Hg(OAc)_2$ in portions (1.95 g, 6 mmol) with stirring. The temperature was raised to 80 °C and three additions of $Hg(OAc)_2$ (1.95 g) were made every 3 h. After 12 h the reaction was almost complete and a saturated aqueous solution of NaCl (300 ml) was added to the final reaction mixture. Stirring was continued for 0.5 h at 0—5 °C and the products were then extracted with chloroform (3 × 200). Evaporation of the solvent left a residue (5 g) which was purified by silica gel column chromatography (240 g). The

fractions eluted with hexane–ethyl acetate (8 : 2) contained the *mercurio derivative* (4a) (4.36 g, 85%), m.p. 205—207 °C (from dichloromethane–hexane); $[\alpha]_D^{21}$ 42°; $\nu_{max.}$ 1 720, 1 580, and 1 260 cm^{-1}; δ 0.75 (s, 3 H, 18-CH_3), 2.05 (s, 3 H, $COCH_3$), 3.75 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), 6.65 (s, 1 H, 4-H), and 7.15 (s, 1 H, 1-H) (Found: C, 44.6; H, 4.7. $C_{21}H_{27}ClHgO_3$ requires C, 44.83; H, 4.80%).

2-*Chloromercurio*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* (4b).—To a solution of 3-methoxyestra-1,3,5(10)-trien-17-one (3b) (0.257 g, 0.9 mmol) in dry acetonitrile (25 ml) was added, with stirring, $Hg(OAc)_2$ (0.344 g). The temperature was raised to 80 °C and two more additions of the same amount of $Hg(OAc)_2$ were effected within 24 h. At the end of this time, the temperature was lowered to ambient conditions, and a saturated solution of NaCl (30 ml) was added and the whole reaction mixture stirred (0.5 h). The products were extracted with chloroform (3 × 20 ml) and, after evaporation of the solvents, purified on a silica gel column (25 g). The fractions eluted with hexane–ethyl acetate (8 : 2) were collected and the *mercurioketone* (4b) (0.428 g, 85%) was obtained, m.p. 221—223 °C (decomp.) (from dichloromethane–hexane); $[\alpha]_D^{21}$ 102°; $\nu_{max.}$ 1 715, 1 580, 1 470, and 1 450 cm^{-1}; δ 0.90 (s, 3 H, 18-CH_3), 3.75 (s, 3 H, OCH_3), 6.65 (s, 1 H, 4-H), and 7.20 (s, 1 H, 1-H) (Found: C, 43.8; H, 4.4. $C_{19}H_{23}ClHgO_2$ requires C, 44.01; H, 4.44%).

2-*Chloromercurioestra*-1,3,5(10)-*triene*-3,17β-*diyl Diacetate* (4c).—(*a*) *Without addition of* $HClO_4$. Estradiol diacetate (1f) was prepared in 95% yield by acetylation of the estradiol (1a) in pyridine and acetic anhydride at room temperature; m.p. 123—125 °C (from methanol) (lit.,[17] 123—125 °C).

To a solution of the diacetate (1f) (0.5 g, 1.4 mmol) in dry acetonitrile (300 ml) was added $Hg(OAc)_2$ (0.537 g) with stirring. The temperature was raised to 80 °C and portions (0.57 g) of $Hg(OAc)_2$ were added at intervals of 12 h. After 6 days a saturated solution of NaCl (300 ml) was added and the reaction mixture stirred for 0.5 h; then the insoluble material was filtered off on Celite and the filtrate extracted with chloroform (5 × 150 ml). After evaporation under reduced pressure, the crude mixture (0.593 g) was purified by column chromatography (silica gel, 48 g). The fractions eluted with hexane–ethyl acetate (8 : 2) contained pure diacetate (4c) (0.331 g, 40%).

(*b*) *With* $HClO_4$ *as catalyst*. To estradiol diacetate (1f) (0.712 g) in dry acetonitrile (400 ml) were added a few drops of 9.2M-$HClO_4$ and $Hg(OAc)_2$ (0.638 g) and the temperature was raised to 80 °C. Portions (0.638 g) of $Hg(OAc)_2$ were added during 4 days at intervals of 12 h and the solution was then brought to ambient temperature. Usual work-up with NaCl solution and column chromatography allowed the isolation of pure *diacetate* (4c) (0.73 g, 62%); m.p. 221—223 °C (from dichloromethane–pentane); $[\alpha]_D^{21}$ 40°; $\nu_{max.}$ 1 750, 1 710, and 1 100 cm^{-1}; δ 0.85 (s, 3 H, 18-CH_3), 2.05 (s, 3 H, acetyl), 2.30 (s, 3 H, acetyl), 4.75 (m, 1 H, 17α-H), 6.95 (s, 1 H, 4-H), and 7.50 (s, 1 H, 1-H) (Found: C, 44.6; H, 4.7. $C_{22}H_{27}ClHgO_4$ requires C, 44.67; H, 4.57%).

2-*Bromo*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (3c).—A solution of bromine in chloroform was prepared with bromine (1 ml, 19.3 mmol) in chloroform (10 ml) and 0.41 ml of the solution (0.72 mmol) was added dropwise to a solution of compound (4a) (0.4 g, 0.71 mmol) in chloroform (4 ml) at room temperature. As soon as the bromine was added its colour disappeared and a pink precipitate was formed immediately; this was filtered off by suction. Evaporation of the solvent left a residue of the *bromoacetate* (3c) (0.274 g, 95%), m.p. 161—163 °C (from dichloromethane–heptane); $[\alpha]_D^{21}$ 51°; δ 0.75 (s, 3 H, 18-CH_3), 1.95 (s, 3 H, CH_3CO), 3.61 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), 6.55 (s, 1 H, 4-H), and 7.05 (s, 1 H, 1-H) (Found: C, 62.7; H, 6.5. $C_{21}H_{27}BrO_3$ requires C, 61.91; H, 6.63%).

When the reaction was carried out with excess of bromine a 2,4-dibromo derivative was obtained as shown by its ^1H n.m.r. spectrum; δ 0.75 (s, 3 H, 18-CH_3), 2.0 (s, 3 H, CH_3CO), 3.75 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), and 7.40 (s, 1 H, 1-H).

2-*Iodo*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (3d).—Iodine (0.096 g, 0.38 mmol) was added to a solution of compound (4a) (0.2 g, 0.36 mmol) in chloroform (5 ml) with stirring at room temperature. As soon as the colour had disappeared, a red precipitate of mercuric salt was formed and filtered off. The organic solution was washed with aqueous sodium thiosulphate, dried (Na_2SO_4) and evaporated, to leave the *iodoacetate* (3d) (0.156 g, 97%), m.p. 128—129 °C (from dichloromethane–heptane); $[\alpha]_D^{21}$ 52°; $\nu_{max.}$ 1 710 and 1 170 cm^{-1}; δ 0.75 (s, 3 H, 18-CH_3), 2.05 (s, 3 H, $COCH_3$), 3.85 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), 6.55 (s, 1 H, 4-H), and 7.70 (s, 1 H, 1-H) (Found: C, 55.4; H, 5.8. $C_{21}H_{27}IO_3$ requires C, 55.50; H, 5.94%).

2-*Iodoestra*-1,3,5(10)-*triene*-3,17β-*diyl Diacetate* (1h).—The procedure was the same as for (3d), a solution of the 2-chloromercurio derivative (4c) (0.3 g, 0.5 mmol) in chloroform (10 ml) being treated with iodine (0.13 g, 0.5 mmol) to give the *iododiacetate* (1h) (82%, 0.198 g); m.p. 158—160 °C (decomp.) (from dichloromethane–hexane); $\nu_{max.}$ 1 750, 1 710, and 1 170 cm^{-1}; δ 0.80 (s, 3 H, 18-CH_3), 2.0 (s, 3 H, $COCH_3$), 2.30 (s, 3 H, $COCH_3$), 4.70 (m, 1 H, 17α-H), 6.80 (s, 1 H, 4-H), and 7.70 (s, 1 H, 1-H) (Found: C, 54.4; H, 5.7. $C_{22}H_{27}IO_4$ requires C, 54.77; H, 5.60%).

2-*Iodoestra*-1,3,5(10)-*triene*-3,17β-*diol* (1e).—The hydrolysis of (1h) was accomplished by treating a solution of (1h) (0.048 g, 0.1 mmol) in methanol (5 ml) with potassium carbonate (0.138 g, 1 mmol) and a few drops of water at room temperature for 3 days. The product was filtered off and washed with chloroform and methanol. Crystallization of (1e) from hot ethanol afforded pure product (40 mg); m.p. 174—176 °C (decomp.) [lit.,[5] 176—178 °C (decomp.)]; δ 0.65 (s, 3 H, 18-CH_3), 4.70 (m, 1 H, 17α-H), 6.60 (s, 1 H, 4-H), and 7.50 (s, 1 H, 1-H) (Found: C, 54.5; H, 5.9. Calc. for $C_{18}H_{23}IO_2$: C, 54.27; H, 5.77%).

2-*Chloro*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*yl Acetate* (3e).—A saturated solution (0.5 ml) of chlorine in chloroform was diluted with chloroform (1.5 ml). To a solution of the mercurio compound (4a) (0.3 g, 0.53 mmol) in chloroform (15 ml) was added 0.5 ml of the above solution of chlorine at 0 °C and, after 5 min, the reaction was terminated by addition of a saturated aqueous solution of sodium thiosulphate and the chloroform layer separated. After drying (Na_2SO_4) and evaporation of the solvent, the crude, complex reaction mixture was purified on a silica gel column (20 g). The fractions eluted with hexane–ethyl acetate (95 : 5) contained the desired product (3e) (0.086 g, 44.8%), m.p. 157—159 °C (from dichloromethane–hexane); δ 0.90 (s, 3 H, 18-CH_3), 2.00 (s, 3 H, $COCH_3$), 3.85 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), 6.65 (s, 1 H, 4-H), and 7.25 (s, 1 H, 1-H) (Found: C, 69.4; H, 7.6. $C_{21}H_{27}ClO_3$ requires C, 69.61; H, 7.46%).

2,4-*Dichloro*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (5b).—To a solution of compound (4a) (0.3 g, 0.53 mmol) in chloroform (3 ml) was added a saturated solution (0.5 ml) of chlorine in chloroform at room temperature (0.5 h). After filtration, the solution was evaporated under a stream of

nitrogen and the residue (0.283 g) was purified on a silica gel column (30 g). The fractions eluted with hexane–ethyl acetate (95 : 5) were collected and pure dichloro compound (5b) was obtained (0.045 g, 15%); δ 0.90 (s, 3 H, 18-CH_3), 2.10 (s, 3 H, $COCH_3$), 3.85 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), and 7.40 (s, 1 H, 1-H).

17,17′-*Diacetoxy*-3,3′-*dimethoxy*-2,2′-*biestra*-1,3,5(10)-*trienyl* (6).—Oxygen was bubbled into a solution of sodium borohydride (0.9 g, 0.024 mol) in the minimum amount of anhydrous dimethylformamide (15 min). A solution of (4a) (1 g, 1.8 mmol) in dimethylformamide (5 ml) was added to the above solution with stirring (1 h). After filtration of the precipitate, water was added to the solution of dimethylformamide and the products were extracted with ethyl acetate (3 × 20 ml), dried (Na_2SO_4) and the solvent evaporated to give a residue (0.6 g) which was purified by chromatography on a silica gel column. The fractions eluted with benzene–ethyl acetate (8 : 2) contained the *dimer* (6) (0.45 g, 38%); δ 0.75 (s, 3 H, 18-CH_3), 2.05 (s, 3 H, $COCH_3$), 3.75 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), 6.75 (s, 1 H, 4-H), and 7.35 (s, 1 H, 1-H); *m/z* 654 (M^+) and 328 [(M^+/2) + 1] (Found: C, 77.3; H, 8.3. $C_{42}H_{54}O_6$ requires C, 77.06; H, 8.26%).

3-*Methoxyestra*-1,3,5(10)-*triene*-2,17β-*diyl Diacetate* (3g).—A solution of 1M-diborane in tetrahydrofuran (18 ml) was added dropwise to compound (4a) (0.6 g, 1.07 mmol) at 0 °C with stirring under nitrogen (30 min). The crude reaction mixture was then added dropwise to a flask containing 30% hydrogen peroxide (1.5 ml) and stirred at room temperature (5 min). Water was added and the solution extracted with diethyl ether (3 × 15 ml), dried and the solvents evaporated to give a crude residue (0.528 g); this was directly acetylated at room temperature with pyridine (3 ml) and acetic anhydride (1 ml) (48 h). After a conventional work-up, the product was purified by column chromatography on silica gel impregnated with ascorbic acid.[12] Fractions eluted with hexane–ethyl acetate (9 : 1) were collected and the *diacetate* (3g) was recovered (0.34 g, 83%); m.p. 130—132 °C (from dichloromethane–hexane); δ 0.90 (s, 3 H, 18-CH_3), 2.05 (s, 3 H, $COCH_3$), 2.35 (s, 3 H, $COCH_3$), 3.80 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), 6.75 (s, 1 H, 4-H), and 6.90 (s, 1 H, 1-H); *m/z* 386 (M^+) (Found: C, 71.3; H, 7.7. $C_{23}H_{30}O_5$ requires C, 71.50; H, 7.77%).

Estra-1,3,5(10)-*triene*-2,3,17β-*triyl Triacetate* (1i).—The cleavage of the ether function in (3g) was performed essentially as described.[18] Freshly prepared pyridinium hydrochloride (0.8 g) and compound (3g) (0.25 g, 0.65 mmol) were mixed together and heated at 220 °C (1 h). After the solution had been cooled to room temperature, a saturated aqueous solution of ascorbic acid was added (10 ml) and the product was extracted with chloroform (3 × 15 ml). The residue (0.3 g) was acetylated at room temperature (48 h) and the crude mixture after a conventional work-up was purified by silica gel (30 g) impregnated with ascorbic acid. The fractions eluted with hexane–ethyl acetate (8 : 2) were collected and pure triacetate (1i) was obtained (0.2 g, 75%); m.p. and chemicophysical data are in agreement with reported values.[19]

4-*Bromo*-2-*chloromercurio*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*yl Acetate* (5c).—To a solution of 4-bromoestradiol [3c] (0.3 g, 0.85 mmol) in dry acetone (10 ml) were added methyl iodide (0.2 ml, 3.2 mmol) and potassium carbonate (1g). The mixture was refluxed until the starting material had completely reacted (5 h), and then cooled to room temperature, filtered and the solvent evaporated; the 3-methyl ether was then directly acetylated [pyridine (1 ml) and acetic anhydride (0.6 ml)]. The solution was left at room temperature for 12 h and, after usual work-up, compound (2f) was recovered (0.29 g, 85%).

To a refluxing solution of (2f) (0.12 g, 0.29 mmol) prepared as above in dry acetonitrile (10 ml), $Hg(OAc)_2$ was added in portions (0.18 g) every 5 h. After eight additions of the salt, the mixture was refluxed for an additional 7 h, then cooled to room temperature and treated with excess of a saturated solution of NaCl (0.5 h). The products were extracted with chloroform (4 × 20 ml) and the crude products were purified by column chromatography; the fractions eluted with hexane–ethyl acetate (9 : 1) afforded pure *acetate* (5c) (0.1 g, 53%), m.p. 245—247 °C (from dichloromethane–hexane); $[\alpha]_D^{21}$ 37°; δ 0.80 (s, 3 H, 18-CH_3), 2.05 (s, 3 H, $COCH_3$), 3.85 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), and 7.30 (s, 1 H, 1-H) (Found: C, 39.7; H, 4.1. $C_{21}H_{26}BrClHgO_3$ requires C, 39.31; H, 4.05%).

4-*Chloromercurio*-3-*methoxyestra*-1,3,5(10)-*triene*-2,17β-*diyl Diacetate* (5d).—To a solution of compound (3g) (0.167 g, 0.43 mmol) in dry acetonitrile (15 ml) were added a few drops of 9.2M-$HClO_4$ and $Hg(OAc)_2$ (0.273 g, 0.86 mmol). The solution was refluxed for 2 days, and eight portions (0.273 g) of $Hg(OAc)_2$ were added in this time. After being cooled to room temperature, the mixture was quenched with an excess of saturated NaCl solution (10 ml) (0.5 h). The organic layer was separated and the aqueous solution extracted with chloroform (4 × 15 ml). The combined organic solutions were dried (Na_2SO_4) and evaporated. The crude residue (0.2 g) was purified by column chromatography and the fractions eluted with hexane–ethyl acetate (8 : 2) to afford the *diacetate* (5d) (0.067 g, 25%), m.p. 129—130 °C (from dichloromethane–hexane); $[\alpha]_D^{21}$ 7°; δ 0.80 (s, 3 H, 18-CH_3), 2.05 (s, 3 H, $COCH_3$), 2.30 (s, 3 H, $COCH_3$), 3.85 (s, 3 H, OCH_3), 4.70 (m, 1 H, 17α-H), and 7.05 (s, 1 H, 1-H) (Found: C, 44.3; H, 4.4. $C_{23}H_{29}ClHgO_5$ requires C, 44.51; H, 4.67%).

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References

1 P. Ball and R. Knuppen, *Acta Endocrinol. Suppl. 32*, 1980, **93**, 1.
2 P. Ball, M. Haupt, and R. Knuppen, *Acta Endocrinol.*, 1978, **87**, 1.
3 (*a*) H. Werbin and C. Holoway, *J. Biol. Chem.*, 1956, **223**, 651; (*b*) T. Utne, R. B. Jobson, and R. D. Babson, *J. Org. Chem.*, 1968, **33**, 2469; (*c*) V. N. Zontova, V. M. Rzheznikov, and K. K. Pivnitsky, *Steroids*, 1975, **25**, 827; (*d*) H. Hamacher, *Arzneim. Forsch. (Drug Res.)*, 1979, **29**, 463.
4 C. C. Chin and J. C. Warren, *J. Biol. Chem.*, 1968, **243**, 5056.
5 F. Sweet, T. B. Patrick, and J. M. Mudd, *J. Org. Chem.*, 1979, **44**, 2296.
6 E. Santaniello and P. Ferraboschi, *J. Chem. Soc., Chem. Commun.*, 1981, 217.
7 J. F. W. McOmie, 'Protective Groups in Organic Chemistry,' Plenum Press, London, 1973, p. 145.
8 D. N. Kirk and C. J. Slade, *J. Chem. Soc., Chem. Commun.*, 1982, 563.
9 C. L. Hill and G. M. Whitesides, *J. Am. Chem. Soc.*, 1974, **96**, 870.
10 S. W. Breuer, M. J. Leatham, and F. G. Thorpe, *Chem. Commun.*, 1971, 1475.
11 E. Santaniello, A. Fiecchi, and P. Ferraboschi, *J. Chem. Soc., Chem. Commun.*, 1982, 1157.
12 H. P. Gelbke and R. Knuppen, *J. Chromatogr.*, 1972, **71**, 465.

13 K. Figge, *Fette, Seifen, Anstrichm.*, 1972, **74**, 9.
14 E. Santaniello, M. Ravasi, and P. Ferraboschi, *J. Org. Chem.*, 1983, **48**, 739.
15 C. A. Horiuchi and J. Y. Satoh, *J. Chem. Soc., Chem. Commun.*, 1982, 671.
16 Y. Urusibara and T. Nitta, *Bull. Chem. Soc. Jpn.*, 1941, **16**, 179.
17 E. Hecker and E. Walk, *Chem. Ber.*, 1960, **93**, 2928.
18 J. Fishman, M. Tomasz, and R. Lehman, *J. Org. Chem.*, 1960, **25**, 585.
19 M. L. Mihailovic, J. Forsek, and L. Lorenc, *Tetrahedron*, 1977, **33**, 235.

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