Totally Synthetic Steroid Heterocycles. Part 7. (1). A Facile Approach to 16-Oxa-D-homoestrogens

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In search of biologically active modified steroids, novel 16-oxa-D-homoestrone and -D-homoestradiol 3-methyl ethers were synthesized from 16-oxa-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaen-17a-one. The straightforward synthesis involved stereoselective two-step reduction of the 8,14-diene system. The B/C stereoisomers were also derived from the estrapentaene. The stereostructures of these heterocyclic estrogens were determined on the basis of their spectral data.

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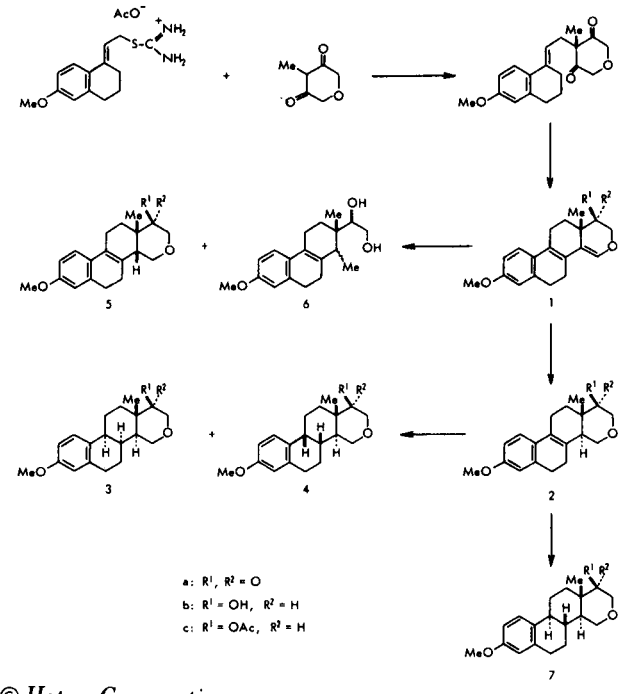
We recently achieved total synthesis of the novel and biologically interesting 16-thia-D-homoestrogens (2). In this communication, we wish to report a short and stereoselective synthesis of the 16-oxa analogues. The useful intermediates, 16-oxa-3-methoxy-D-homoestra-1,3,5(10),-8,14-pentaen-17a-one and -17aβ-ol (**1a** and **1b**) have already been prepared (70-80%) in a few steps from 2-methyl-5-oxacyclohexane-1,3-dione (3). It was hoped that these estrapentaenes, different from the thia analogues (4), would normally permit stepwise reduction of the 8,14-diene system.

Selective hydrogenation of the 14,15-double bond of **1a** could be accomplished by catalytically reducing over 5% palladium charcoal in ethanol-tetrahydrofuran (2:1). When the catalyst was used up to 30% on the substrate, the hydrogenation occurred fairly easily and completed within 60 minutes affording 16-oxa-3-methoxy-D-homoestra-1,3,5(10),8-tetraen-17a-one (**2a**) in nearly 90% yield. Homogeneity of the product indicated that the hydrogenation is highly stereoselective. However, the hydrogenation condition appeared to be crucial; other conditions led to extremely sluggish reaction or often over-reduction. An attempted hydrogenation of **1a** over 10% palladium charcoal (30% by weight, 2 hours) resulted in complete saturation of the 8,14-diene to give only isomeric D-homoestrones **3a** and **4a**, which were separated by chromatography (2.5:1). On the other hand, catalytic reduction of **1b** with 5% palladium charcoal under various conditions eventually led to a mixture of the dihydro and tetrahydro compounds that was difficult to separate. Thus, the pure 16-oxa-3-methoxy-D-homoestra-1,3,5(10),8-tetraen-17aβ-ol (**2b**) was obtained *via* hydride reduction of **2a**. Reduction using sodium bis-(2-methoxyethoxy)-aluminum hydride (SMEAH) gave **2b** in 95% yield. Acetylation furnished its acetate **2c**. Similarly, isomeric D-homoestradiols **3b** and **4b** and their acetates **3c** and **4c** were derived from **3a** and **4a**, respectively.

The above catalytic hydrogenation would be expected to proceed mainly from the less hindered α-side. The assigned 14α-configuration was supported by the well-known nmr observation (5) that the 13-methyl resonance of a C/D *trans* steroid (**2b**: δ 0.93) generally appears at higher field relative to the C/D *cis* isomer (**5b**: δ 1.05), as was the case for the corresponding thia steroids (6). The latter 14β-homoestratetraene **5b** resulted from sodium-ammonia reduction of **1b**, along with a ring-cleaved derivative **6** and other by-products. Convincing evidence for the *cis* C/D ring fusion of **5** came from the fact that the double bond reduction of **1b** to **5b** caused configurational conversion of the 17aβ-hydroxy group from the equatorial to the axial position, as shown by the spectral data of **5b** and its acetate **5c** in comparison with those of **1b** and **1c**.

Reduction of **2b** with lithium in liquid ammonia and aniline gave solely the expected 16-oxa-D-homoestradiol 3-methyl ether (**7b**) in 92% yield, which on acetylation yielded its acetate **7c**. When **2b** was treated with triethylsilane and trifluoroacetic acid in dichloromethane, the above *anti-trans* compound was again predominantly



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formed together with the possible *anti-cis* isomer. The minor product was identical with the foregoing **4b**. Finally, the major isomer **7b** was smoothly converted by oxidation with dipyridine chromium (VI) oxide (Collins reagent) (8) in dichloromethane to 16-oxa-D-homoestrone 3-methyl ether (**7a**) in 88% yield.

The B/C ring stereochemistry of isomeric homoestratrienes thus obtained was confirmed on the basis of nmr evidence as follows. In an octahydrophenanthrene system (ABC), Nagata, *et al.*, have previously reported the dependence of the chemical shift of the C_1-aromatic proton (steroid numbering) on the B/C configuraton, which is associated with steric interaction with the C_{11}-hydrogens (9). According to this theory, a large downfield shift for C_1-H (relative to C_4-H) should be expected in the spectra of the 8β,9β- and 8β,9α-isomers with more severe steric compression between relevant hydrogens, compared to the 8α,9α-isomer. The values ($\Delta\delta$ H_1-H_4) observed for ketones **3a** (0.43), **4a** (0.60) and **7a** (0.57), alcohols **3b** (0.43), **4b** (0.60) and **7b** (0.58) and acetates **3c** (0.43), **4c** (0.59) and **7c** (0.57) were all consistent with the above structural assignments.

EXPERIMENTAL

Melting points were determined on a calibrated Kofler hot-stage apparatus. Ir spectra were recorded on a JASCO-DS-403G spectrophotometer and unless otherwise stated, chloroform was used as solvent. Uv spectra were determined with a Hitachi 323 spectrophotometer in 95% ethanol. Nmr spectra were taken on a Varian T-60A spectrometer in deuteriochloroform using tetramethylsilane as internal standard. Mass spectra were determined using a Hitachi RMU-6 mass spectrometer at 70 eV. Preparative thin layer chromatography (preparative tlc) was carried out on 20 x 20 x 0.05 cm or 20 x 20 x 0.2 cm glass plates pre-coated with silica gel F-254 (type 60; Merck). Silica gel 60 (grain size 0.063-0.2 mm; Merck) was used for column chromatography. Usual workup means washing extracts with water and then brine, drying (sodium sulfate), filtration and evaporation *in vacuo*.

16-Oxa-3-methoxy-D-homoestra-1,3,5(10),8-tetraen-17a-one (**2a**).

A suspension of 160 mg. of 5% palladium charcoal in 45 ml. of ethanol was equilibrated in an atmosphere of hydrogen for 1.5 hours. A solution of 533 mg. (1.8 mmoles) of 16-oxa-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (**1a**) in 23 ml. of tetrahydrofuran was added and the mixture was stirred. After 45 minutes, uptake of 1 equivalent of hydrogen was realized and the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* to leave an oily residue which was purified through silica gel (2.5 g.) by eluting with benzene. The solvent was evaporated and the product was triturated with ether to give 448 mg. of **2a** as a crystalline solid, m.p. 111-112°. The mother liquor residue was further purified by preparative tlc [benzene-ethyl acetate (20:1) with double development] which separated 29 mg. of **2a** as a second crop, m.p. 108-111° and 18 mg. of **3a**. The latter compound was identical with its authentic sample prepared below. The total yield of **2a** was 88.8%. Recrystallization from ether afforded an analytical sample, m.p. 114-116°; ir: ν max 1721 (C=O), 1607, 1571 and 1502 cm^{-1} (styrene); uv: λ max 277 nm (ε 16,200); nmr: δ 1.24 (s, 3H, 13-Me), 3.79 (s, 3H, OMe), 6.6-7.3 (m, 3H, aromatic H); ms: m/e 298 (M^+).

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.53; H, 7.43.

16-Oxa-3-methoxy-D-homoestra-1,3,5(10),8-tetraen-17aβ-ol (**2b**).

To a stirred solution of 831 mg. (2.8 mmoles) of **2a** in 45 ml. of dry benzene was added 1.3 ml. (2.9 mmoles) of a 2.2 M solution of SMEAH in benzene at 5°. After 50 minutes, the reaction was quenched with ice-water. The aqueous layer separated was again extracted with ether-dichloromethane (3:1). The organic layers were combined and worked up as usual to leave a viscous syrup. Crystallization from ether-dichloromethane gave 695 mg. of **2b** as a crystalline solid, m.p. 122-125°. The mother liquor residue was subjected to preparative tlc [benzene-ethyl acetate (1:1) with double development] which furnished 98 mg. of a second drop. The total yield of **2b** was 94.8%. Recrystallization fron ether-dichloromethane afforded an analytical specimen, m.p. 127-128°; ir (dilute carbon tetrachloride): ν max 3633 cm^{-1} (free OH); uv: λ max 276 nm (ε, 16,400); nmr: δ 0.93 (s, 3H, 13-Me), 3.79 (s, 3H, OMe) and 6.5-7.3 (m, 3H, aromatic H).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.74; H, 8.06.

The acetate **2c**, prepared with acetic anhydride and pyridine in the usual way, was obtained as a crystalline solid. Recrystallization from ether-dichloromethane gave an analytical sample, m.p. 140-141°; ir: ν max 1732 (OAc), 1608, 1572 and 1503 cm^{-1} (styrene); nmr: δ 1.01 (s, 3H, 13-Me), 2.07 (s, 3H, OAc), 3.79 (s, 3H, OMe), 4.83 (q, 1H, J = 6, 10 Hz, 17a-H) and 6.6-7.4 (m, 3H, aromatic H).

16-Oxa-8α- and 16-Oxa-9β-D-homoestrone 3-Methyl Ethers (**3a** and **4a**).

A.

The pentaenone **1a** (200 mg., 0.67 mmole) in 30 ml. of ethanol-tetrahydrofuran (2:1) was hydrogenated on 60 mg. of 10% palladium charcoal. The reaction consumed 2 equivalents of hydrogen during 2 hours and stopped. The mixture was filtered, evaporated and the residue was purified through silica gel (4 g.) with benzene. The product was crystallized from ether-dichloromethane giving 105 mg. of **3a** as a crystalline solid, m.p. 139-142°. The mother liquor residue was further purified by preparative tlc [cyclohexane-ether (2:1) with double development], whereupon 27 mg. of **3a** and 53 mg. of **4a** were isolated as crystalline solids.

The total yields of **3a** and **4a** were 65.1 and 26.1%, respectively. Recrystallization from ether-dichloromethane provided both analytical samples. The major isomer **3a** had m.p. 140-143°; ir: ν max 1719 (C=O), 1611, 1585, 1578 and 1503 cm^{-1} (aromatic); nmr: δ 1.29 (s, 3H, 13-Me), 3.76 (s, 3H, OMe), 6.64 (bs, 1H, 4-H), 6.5-6.9 (m, 1H, 2-H) and 7.07 (d, 1H, J = 8 Hz, 1-H); ms: m/e 300 (M^+).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.91; H, 8.08.

The minor isomer **4a** had m.p. 138-140°; ir: ν max 1722 (C=O), 1610, 1575 and 1502 cm^{-1} (aromatic); nmr: δ 1.33 (s, 3H, 13-Me), 3.78 (s, 3H, OMe), 6.66 (bs, 1H, 4-H), 6.6-6.9 (m, 1H, 2-H) and 7.26 (d, 1H, J = 8 Hz, 1-H); ms: m/e 300 (M^+).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.79; H, 8.02.

B.

Similarly, 36 mg. of **2a** in 5 ml. of ethanol-tetrahydrofuran (2:1) was hydrogenated over 11 mg. of 10% palladium charcoal. Preparative tlc of the crude product afforded 12 mg. of **3a** and 9 mg. of **4a**, identical with their authentic samples.

16-Oxa-8α-D-homoestradiol 3-Methyl Ether (**3b**).

To a stirred solution of 60 mg. (0.2 mmole) of **3a** in 3 ml. of dry benzene was added 0.1 ml. (0.2 mmole) of a 2.2 *M* solution of SMEAH in benzene at 5-10°. The reaction was continued for 1 hour and then quenched with ice-water. The mixture was extracted with ether. Usual workup left a viscous syrup which was crystallized from ether to give 47 mg. of crystalline **3b**, m.p. 158-160°. Recrystallization from ether-dichloromethane afforded an analytical sample, m.p. 160-162°; ir (dilute carbon tetrachloride): ν max 3632 cm^{-1} (free OH); nmr: δ 1.05 (s, 3H, 13-Me), 3.76 (s, 3H, OMe), 6.60 (bs, 1H, 4-H), 6.5-6.9 (m, 1H, 2-H) and 7.03 (d, 1H, J = 8 Hz, 1-H).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.15; H, 8.62.

The acetate **3c** was obtained in the usual way and crystallized from ether-dichloromethane giving an analytical sample, m.p. 191-193°; ir: ν max 1750 sh, 1732 (OAc), 1610 and 1503 cm^{-1} (aromatic); nmr: δ 1.13 (s, 3H, 13-Me), 2.04 (s, 3H, OAc), 3.77 (s, 3H, OMe), 4.69 (q, 1H, J = 5.5, 10.5 Hz, 17a-H), 6.61 (bs, 1H, 4-H), 6.5-6.8 (m, 1H, 2-H) and 7.04 (d, 1H, J = 8 Hz, 1-H).

16-Oxa-9β-D-homoestradiol 3-Methyl Ether (**4b**).

As above, 44 mg. (0.15 mmole) of **4a** in 3 ml. of dry benzene was reduced with 0.07 ml. (0.15 mmole) of a 2.2 *M* SMEAH solution in benzene. The product was crystallized from ether-pentane as a crystalline solid, m.p. 128-130°; ir (dilute carbon tetrachloride): ν max 3634 cm^{-1} (free OH); nmr: δ 1.05 (s, 3H, 13-Me), 3.78 (s, 3H, OMe), 6.67 (bs, 1H, 4-H), 6.6-6.9 (m, 1H, 2-H) and 7.27 (d, 1H, J = 8 Hz, 1-H).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.23; H, 8.65.

The acetate **4c** obtained as a crystalline solid had m.p. 80-82° (ether-pentane); ir: ν max 1731 (OAc), 1610, 1574 and 1501 cm^{-1} (aromatic); nmr: δ 1.13 (s, 3H, 13-Me), 1.99 (s, 3H, OAc), 3.80 (s, 3H, OMe), 4.55 (q, 1H, J = 5.5, 10 Hz, 17a-H), 6.67 (bs, 1H, 4-H), 6.6-6.9 (m, 1H, 2-H) and 7.26 (d, 1H, J = 8 Hz, 1-H).

16-Oxa-3-methoxy-14β-D-homoestra-1,3,5(10),8-tetraen-17aβ-ol (**5b**) and 16-Oxa-3-methoxy-15,16-seco-14ξ-D-homoestra-1,3,5(10),-8-tetraen-17aβ-ol (**6**).

Sodium metal (272 mg., 11.8 mg.-atom) was added portionwise to a stirred solution of 235 mg. (0.79 mmole) of **1b** in 60 ml. of dry liquid ammonia and 8 ml. of dry tetrahydrofuran at -75°. After 20 minutes, the deep blue color of the mixture was discharged with ammonium chloride. The ammonia was evaporated and the residue was extracted with dichloromethane followed by usual workup. The crude product was subjected to preparative tlc [benzene-ethyl acetate (1:1) with double development] which afforded four fractions. The first fraction (17 mg.) contained tetrahydro derivatives showing m/e 302 (M^+) but could not be purified and not further be pursued. The fourth fraction (58 mg.) showing m/e 316 and 300 probably composed of an oxygenated dihydro derivative contaminated with a dihydro compound. This material, however, failed to be purified and remained unidentified. The second fraction (75 mg.) was obtained as a crystalline solid, m.p. 123-133°. Repeated recrystallization from ether-*n*-hexane gave 24 mg. of the pure material identified as **5b**, m.p. 139-141°; ir (dilute carbon tetrachloride): ν max 3583 cm^{-1} (bonded OH); uv: λ max 273.5 nm (ε, 16,200); nmr: δ 1.05 (s, 3H, 13-Me), 3.79 (s, 3H, OMe) and 6.6-7.3 (m, 3H, aromatic H); ms: m/e 300 (M^+).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.81; H, 8.02.

The acetate **5c** was obtained as a crystalline solid. Recrystallization from ether-dichloromethane provided an analytical specimen, m.p. 172.5-174°; ir: ν max 1727 (OAc), 1607, 1572 and 1501 cm^{-1} (styrene); nmr: δ 0.96 (s, 3H, 13-Me), 2.13 (s, 3H, OAc), 3.79 (s, 3H, OMe), 4.63 (t, 1H, J = 2 Hz, 17a-H) and 6.6-7.4 (m, 3H, aromatic H).

The third fraction (50 mg.) was triturated with ether-*n*-hexane giving a white solid, m.p. 132-136°. Recrystallization from ether afforded 36 mg. of the pure material identified as **6**, m.p. 141-143°; ir (dilute carbon tetrachloride): ν max 3640 (free OH) and 3593 cm^{-1} (bonded OH); uv: λ max 273 nm (ε, 14,200); nmr: δ 0.80 (s, 3H, 13-Me), 0.98 (d, 3H, J = 7 Hz, 14-Me), 3.78 (s, 3H, OMe) and 6.5-7.4 (m, 3H, aromatic H); ms: m/e 302 (M^+).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.17; H, 8.82.

The diacetate of **6** was obtained as a crystalline solid. Recrystallization from ether-*n*-hexane furnished an analytical sample, m.p. 95-96°; ir: ν max 1735 (OAc), 1608, 1573 and 1501 cm^{-1} (styrene); nmr: δ 0.97 (s, 3H, 13-Me), 1.05 (d, 3H, J = 7 Hz, 14-Me), 1.98 (s, 3H) and 2.08 (s, 3H) (OAc), 3.78 (s, 3H, OMe), 4.02 (q, 1H, J = 8, 12 Hz) and 4.47 (q, 1H, J = 3, 12 Hz) (CH_2OAc), 5.27 (q, 1H, J = 3, 8 Hz, CHOAc) and 6.6-7.3 (m, 3H, aromatic H).

16-Oxa-D-homoestradiol 3-Methyl Ether (**7b**).

A.

Lithium metal (32 mg., 4.6 mg.-atom) was added to a stirred solution of 90 mg. (0.3 mmole) of **2b** in 6 ml. of dry tetrahydrofuran and 23 ml. of dry liquid ammonia containing 2.3 ml. of aniline at -75°. After 15 minutes, ammonium chloride was added until the deep blue color disappeared. The ammonia was evaporated and the residue was extracted with dichloromethane-ether. Usual workup afforded a viscous oil which was purified by preparative tlc [benzene-ethyl acetate (2:1)] to give 84 mg. (92.4%) of **7b** as a crystalline solid, m.p. 151-153°. Recrystallization from ether afforded an analytical specimen, m.p. 157-159°; ir (dilute carbon tetrachloride): ν max 3633 cm^{-1} (free OH); nmr: δ 0.97 (s, 3H, 13-Me), 3.74 (s, 3H, OMe), 6.62 (bs, 1H, 4-H), 6.6-6.9 (m, 1H, 2-H) and 7.20 (d, 1H, J = 8 Hz, 1-H).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.17; H, 8.76.

The acetate **7c** was prepared in the usual way and crystallized from ether giving the pure material as a white solid, m.p. 166-169°; ir: ν max 1752 sh, 1731 (OAc), 1610, 1577 and 1502 cm^{-1} (aromatic); nmr: δ 1.05 (s, 3H, 13-Me), 2.06 (s, 3H, OAc), 3.78 (s, 3H, OMe), 4.76 (q, 1H, J = 6, 11 Hz, 17a-H), 6.64 (bs, 1H, 4-H), 6.6-6.9 (m, 1H, 2-H) and 7.21 (d, 1H, J = 8 Hz, 1-H).

Trifluoroacetic acid (0.05 ml.) was added to a stirred solution of 30 mg. (0.1 mmole) of **2b** in 2 ml. of dichloromethane containing 58 mg. (0.5 mmole) of triethylsilane. The mixture was allowed to stand for 18 hours, then poured into cold aqueous sodium bicarbonate and extracted with dichloromethane. The oily residue obtained after usual workup was dissolved in 1 ml. of dry tetrahydrofuran and treated with 2 mg. of lithium aluminum hydride for 10 minutes. The mixture was quenched with ice-water and extracted with ether-dichloromethane (3:1). Usual workup left a viscous oil which was purified by preparative tlc [benzene-ethyl acetate (2:1) with double development] affording 17 mg. (54.6%) of **7b** and 5 mg. (16.9%) of **4b**, identical with their authentic samples.

16-Oxa-D-homoestrone 3-Methyl Ether (**7a**).

To a stirred solution of 30 mg. (0.1 mmole) of **7b** in 4 ml. of dichloromethane was added 181 mg. (0.7 mmole) of Collins

reagent (8). The mixture was stirred at room temperature for 24 hours, then poured into cold dilute hydrochloric acid and extracted with ether-dichloromethane (3:1). Usual workup left an oily residue which was purified through a short column of silica gel with benzene. The product was crystallized from ether-pentane to yield 26 mg. (87.7%) of crystalline **7a**, m.p. 118-121°; ir: ν max 1717 (C=O), 1610, 1576 and 1502 cm^{-1} (aromatic); nmr: δ 1.27 (s, 3H, 13-Me), 3.78 (s, 3H, OMe), 6.65 (bs, 1H, 4-H), 6.5-6.9 (m, 1H, 2-H) and 7.22 (d, 1H, J = 8 Hz, 1-H).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.91; H, 8.12.

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