Toxicity data in mice with six daily intraperitoneal injections show that **7** killed two of three mice at 2.5 mg/kg, **1** killed three of three mice at 2.5 mg/kg, and **6** killed three of three mice at 5 mg/kg. These are, thus, fairly toxic compunds, considerably more so than the corresponding aziridineacetyl derivatives.[8]

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## A Synthesis of 11β-Hydroxyestrone and Related 16- and 17-Hydroxyestratrienes

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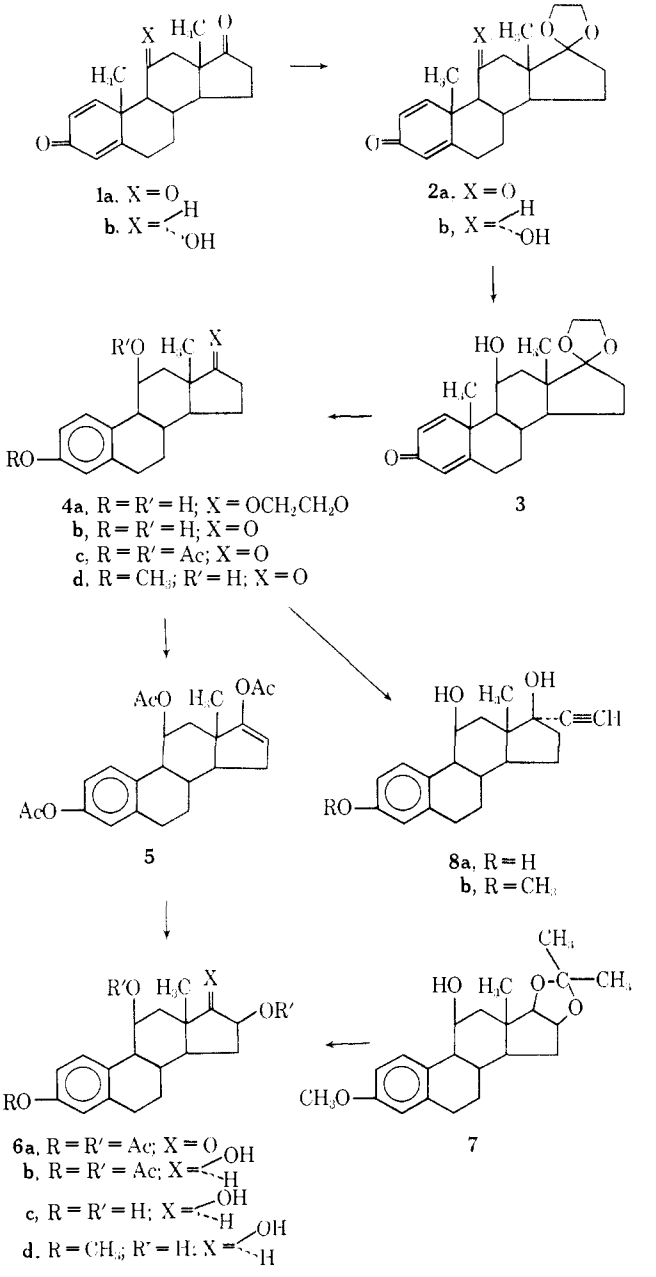
3,11-Dihydroxyestra-1,3,5(10)-trienes have been previously obtained from steroidal 11-oxygenated 1,4-dien-3-ones by pyrolysis in low yield.[1] A new and convenient synthesis of 11β-hydroxyestrone (**4b**) from androsta-1,4-diene-3,17-dione (**1a**) is now reported. The availability of 11β-hydroxyestrone made it suitable for conversion to derivatives which may be of biological interest, among them the 16- and 17-hydroxylated estratrienes.[2]

The recent discovery of the reductive aromatization of steroidal 1,4-dien-3-ones[3] was applied to the 11-hydroxydienones **2b** and **3**. When **1a** or **1b** was refluxed with *p*-toluenesulfonic acid and ethylene glycol in benzene, **2a** and **2b** were obtained, respectively. Selective reduction of the C-11 ketone **2a** with lithium tri-*t*-butoxyaluminum hydride yielded **3**. Reductive aromatization of **3** with loss of the angular methyl group to **4a** proceeded in yields up to 72%. Hydrolysis of **4a** gave **4b**. In contrast to the reductive aromatization of **3**, the 11α-hydroxydienone **2b** was reduced to a product in which the rupture of the bond between carbon atoms 9 and 10 had probably occurred. Evidence for this conclusion was obtained from the nmr spectrum of the crude product which exhibited peaks for a methyl group and three hydrogens on a benzene ring.

When **4b** was heated with acetic anhydride and pyridine, the diacetate **4c** was obtained which upon treatment with *p*-toluenesulfonic acid and isopropenyl acetate yielded **5**. The enol acetate **5** was converted with lead tetraacetate in acetic acid to a mixture of 16-acetoxy 17-ketones in which the 16β isomer **6a** was preponderant.[4] Reduction of **6a** with lithium tri-*t*-butoxyaluminum hydride followed by hydrolysis with aqueous potassium hydroxide gave **6c**. Evidence for the *cis* configuration of the 16,17-glycol **6c** was furnished when it was monomethylated to **6d** which then was converted to the acetonide derivative **7**. Ethynylation of **4b** and **4d** with lithium acetylide–ethylenediamine complex in dimethyl sulfoxide yielded the 11β-hydroxyethynylestradiol **8a** and its 3-methyl ether **8b**, respectively.

**Biology.**—Compounds **6c** and **8a** had 0.05 and 5% the activity of estrone, respectively, when administered by injection in the mouse uterine growth assay.[5] Compound **8a** produced no decidual cell formation[6] in the immature female rabbit when treated by injection at 10 mg/day.[7]

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(7) The author is indebted to Dr. E. F. Nutting and Mr. R. Bergstrom of the Division of Biological Research, G. D. Searle & Co., for the biological data reported herein.

## Experimental Section[8]

**17-Ethylenedioxyandrosta-1,4-diene-3,11-dione (2a).**—A mixture of 2.3 g of **1a** (Upjohn Co.), 200 mg of *p*-toluenesulfonic acid hydrate, 1.5 ml of ethylene glycol, and 200 ml of benzene was refluxed using a Dean–Stark trap for 2 hr, then cooled, washed with aqueous $Na_2CO_3$ solution, dried ($MgSO_4$), and distilled to dryness. Tituration of the residue with ether yielded 1.75 g of crude product, mp 216–218°. Crystallization of the crude product from $CH_2Cl_2$ and MeOH gave an analytical sample, mp 212–214°, $[\alpha]D$ +144°.

*Anal.* Cacd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.39; H, 7.72.

**17-Ethylenedioxy-11α-hydroxyandrosta-1,4-dien-3-one (2b).**—When 41 g of **1b** was converted to **2b** in the manner described for the preparation of **2a**, 45 g of crude product, mp 230–235°, was obtained. Recrystallization of the crude product from acetone and hexane gave an analytical sample mp 238–240°, $[\alpha]D$ −8.5°.

*Anal.* Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.49; H, 8.28.

**17-Ethylenedioxy-11β-hydroxyandrosta-1,4-dien-3-one (3).**—A solution of 500 mg of **2a** and 1 g of lithium tri-*t*-butoxyaluminum hydride in 20 ml of THF was stirred for 1 day. To the solution was then added successively, with vigorous stirring, 20 ml of THF, 10 ml of ether, 0.1 ml of $H_2O$, 0.1 ml of 20% aqueous NaOH solution, and 0.5 ml of $H_2O$. After 10 min the alumina was separated by filtration and washed with $CHCl_3$. The filtrate was stirred with 1 g of $MgSO_4$, filtered, and distilled to dryness. The residue when triturated with ether yielded 300 mg of crude product. Crystallization of the crude product from acetone and hexane gave an analytical sample, mp 203–204°, $\lambda_{max}$ 2.90 μ, $\lambda_{max}$ 237 mμ (ε 14,050), $[\alpha]D$ +43°.

*Anal.* Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.44; H, 8.31.

**17-Ethylenedioxyestra-1,3,5(10)-triene-3,11β-diol (4a).**—To a mixture of 41.8 g of Li dispersion in wax (30%), 125 g of biphenyl, 68.5 g of diphenylmethane, and 1200 ml of THF was added with vigorous stirring at reflux over a period of 35 min, a hot solution of 100 g of **3** in 850 ml of THF. The solution was refluxed an additional 10 min, and then 35 ml of MeOH was added very slowly and carefully. Then 80 ml of $H_2O$ was added slowly and carefully followed by another 400 ml of $H_2O$. The THF was removed from the mixture by distillation *in vacuo*. The mixture was cooled and extracted with 800 ml of benzene–hexane (3:1). The organic layer was extracted with four 200-ml portions of 5% aqueous KOH. The combined aqueous extract was washed with 300 ml of hexane and then added dropwise with vigorous stirring to a slurry of 200 ml of AcOH, 200 ml of $H_2O$, and 200 ml of ice. The temperature of the aqueous mixture was maintained at 10° by the addition of ice. The crystalline precipitate was collected by filtration, washed with $H_2O$, and dried *in vacuo*. The crude product weighed 49–86 g and melted at 105–110°. Crystallization of the crude product from acetone and hexane yielded 37.5–69 g (39–72%) of **4a**, mp 185–191°. Recrystallization of the crude product from acetone and hexane gave an analytical sample: mp 192–193°; $\lambda_{max}$ 280 mμ (ε 1915); $\lambda_{max}$ 2.74, 2.96, 6.21, and 6.31 μ; nmr peaks at 67.5 (C-13 methyl), 234 (C-17 ethylenedioxy), and 285 (multiplet, C-11 hydrogen) cps.

*Anal.* Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.54; H, 7.99.

When 9.0 g of **2b** was reduced according to the procedure described for the preparation of **4a** using proportionate amounts of reagents, the amorphous product, obtained during the acidification of the phenol salt with AcOH, was extracted into $CHCl_3$. The $CHCl_3$ solution was washed with aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and distilled to dryness. The residue, an amorphous product, exhibited maxima at 2.74, 2.95, and 6.19 μ in its infrared spectrum, and peaks at 51 (C-13 methyl), 130 (methyl on aromatic ring), 233 (17-ethylenedioxy), and 394–420 (multiplets, three hydrogens, C-1, -2, and -4 hydrogens on aromatic ring) cps.

**3,11β-Hydroxyestra-1,3,5(10)-trien-17-one (4b) and 11β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (4d).**—To a hot solution of 10 g of **4a** in 100 ml of MeOH was added 50 ml of 0.4 *M* HCl. After 15 min the mixture was concentrated by distillation and then diluted with 100 ml of $H_2O$. The precipitate was collected by filtration and dried. The crude 11β-hydroxyestrone weighed 9.0 g; mp 253–256° (lit.[1] mp 254–257°); $\lambda_{max}$ (KBr) 2.81, 2.90, 3.05, 5.76, 6.16, and 6.29 μ; $\lambda_{max}$ 280 mμ (ε 1730).

When **4b** was methylated according to the procedure described for the preparation of **6d**, a 90% yield of **4d**, mp 168–169° (lit.[1] mp 169–170°), was obtained.

**3,11β-Diacetoxyestra-1,3,5(10)-trien-17-one (4c).**—Ten grams of crude **4b** was acylated with pyridine and $Ac_2O$ at 100° for 2 hr to yield 10 g of crude diacetate, mp 148–162°. Crystallization from MeOH and $CH_2Cl_2$ gave an analytical sample: mp 162–163°; $[\alpha]D$ −18°; nmr peaks, 11.5, 136.5 (acetate bands), and 350–360 (multiplet, C-11 hydrogen) cps.

*Anal.* Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.56; H, 7.03.

**3,11β,17-Triacetoxyestra-1,3,5(10),16-tetraene (5).**—A solution of 10 g of **4c**, 500 mg of *p*-toluenesulfonic acid hydrate, and 1 l. of isopropenyl acetate was concentrated by distillation to 200 ml over a period of 8 hr. The reaction solution was diluted with 500 ml of isopropenyl acetate, distilled until another 400 ml of distillate was collected, neutralized with 1 ml of pyridine, and and then distilled to dryness *in vacuo*. The residue was extracted with benzene. The benzene solution was washed with $H_2O$, dried ($MgSO_4$), and distilled to dryness *in vacuo*. The residue was purified by column chromatography on 700 g of silica gel (Davison 60–200 mesh) in benzene. Elution of the column with benzene–EtOAc (19:1) yielded 6.4 g of crude crystalline enol acetate. Crystallization of the crude product from ether and hexane gave an analytical sample, mp 180–181° (lit. mp 180°).

*Anal.* Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 70.02; H, 7.03.

**3,11β,16β-Triacetoxyestra-1,3,5(10)-trien-17-one (6a).**—A mixture of 3.5 g of **5**, 4.25 g of lead tetraacetate, and 35 ml of AcOH was stirred for 2.5 hr. Then 0.5 g of $Pb(OAc)_4$ was added to the mixture and it was stirred another 1 hr. The reaction mixture was diluted with 175 ml of $CHCl_3$, washed (two 75-ml portions of aqueous 5% sodium thiosulfate, four 300-ml portions of $H_2O$, saturated aqueous $NaHCO_3$), then dried ($MgSO_4$), and distilled to dryness. The crude product when recrystallized from ether and hexane gave 2.0 g of **6a**: mp 203–207°; $\lambda_{max}$ 5.65, 5.73, and 6.20 mμ; nmr peaks at 112, 128, and 136 (acetate bands) cps.

*Anal.* Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.49; H, 6.69.

Tlc on silica gel G (Brinkmann Instruments), eluted with benzene–EtOAc (6:1), and the nmr spectrum of the crude product (minor C-18 methyl peak at 62 cps) indicated that only a very minor amount of the 16α-acetoxy isomer was produced.

**3,11β,16β-Triacetoxyestra-1,3,5(10)-trien-17β-ol (6b) and 3,11β,16β,17β-Tetrahydroxyestra-1,3,5(10)-triene (6c).**—A solution of 1.0 g of **6a**, 2 g of lithium tri-*t*-butoxyaluminum hydride, and 50 ml of THF was stirred for 1 hr and then poured with stirring into a mixture of 100 g of ice, 100 ml of $H_2O$, and 15 ml of AcOH. The mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed (three 200-ml portions of $H_2O$, saturated aqueous $NaHCO_3$), then dried ($MgSO_4$), and distilled to dryness. The residue was dissolved in ether. When the ether was removed by evaporation, a crystalline product remained: mp 113–114°; $\lambda_{max}$ 2.75 and 5.75 (broad) λ; nmr peaks at 60 (C-13 methyl), 111.5, 126, and 135 (acetate bands) cps.

The crude alcohol **6b** was dissolved in 20 ml of MeOH, diluted with a solution of 4 g of KOH in 25 ml of MeOH and 20 ml of $H_2O$, and warmed on the steam bath for 2 hr under $N_2$. The solution was concentrated to 30 ml and then acidified to about pH 1 with 4 *M* HCl solution. The crude, crystalline product was collected by filtration, washed with $H_2O$, and, when dried, weighed 0.85 g. Crystallization of the crude product from MeOH gave 640 mg of pure **6c**: mp 279–280° (lit. mp 370°); $[\alpha]D$ +19° (MeOH); $\lambda_{max}$ (KBr) 2.91, 3.06, 6.18, and 6.32 μ.

*Anal.* Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.13; H, 7.91.

**3-Methoxyestra-1,3,5(10)-triene-11β,16β,17β-triol (6d).**—A mixture of 2.25 g of **6c**, 9 g of $K_2CO_3$, 10 ml of MeI, and 50 ml of MeOH was refluxed for 2 hr, cooled, diluted with water, concentrated by distillation *in vacuo* until the MeOH was removed, and

(8) The author wishes to thank Dr. R. T. Dillon and staff for the analyses, spectra, and rotations, and Dr. E. G. Daskalakis and staff for the chromatography reported. The infrared spectra and rotations (1% solution) at 25° were determined in $CHCl_3$. The nmr spectra were determined in $CDCl_3$ on a Varian Model A-60 spectrometer at 60 Mc with $Me_4Si$ as an internal standard. The melting points are corrected. The ultraviolet spectra were determined in MeOH.

extracted with $CHCl_3$. When the $CHCl_3$ solution was dried ($MgSO_4$) and distilled to dryness, it yielded 2.25 g of crystalline product. Recrystallization from acetone and hexane gave an analytical sample, mp 172°, nmr peak at 65 (C-13 methyl) cps.

*Anal.* Calcd for $C_{19}H_{28}O_4$: C, 71.67; H, 8.23. Found: C, 71.47; H, 8.12.

**3-Methoxyestra-1,3,5(10)-triene-11β,16β,17β-triol 16,17-Acetonide (7).**—A solution of 50 mg of **6d** and 5 mg of *p*-toluenesulfonic acid in 10 ml of acetone was refluxed for several minutes, cooled, neutralized with pyridine, and evaporated to dryness. The crystalline residue was triturated with MeOH and collected by filtration. Recrystallization of the crude product from $Et_2O$ and hexane gave an analytical sample: mp 184–186°; nmr peaks at 66.5, 80, and 90 (3 methyl groups) cps.

*Anal.* Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.48; H, 8.33.

**17α-Ethynylestra-1,3,5(10)-triene-3,11β,17β-triol (8a).**—To a mixture of 17 g of lithium acetylide—ethylenediamine complex in 100 ml of DMSO at 25° was added with stirring a solution of 8 g of **4b** in 150 ml of DMSO. The mixture was stirred for 2 hr and then added with vigorous stirring to a mixture of 200 g of ice and 1 l. of cold $H_2O$. The solution was diluted with $H_2O$ to 2 l. and then adjusted to about pH 7 with 4 *M* HCl. The crude product was collected by filtration, washed with $H_2O$, and dried *in vacuo* at 60°. It weighed 6.3 g and melted at 265–272°. Crystallization of the crude product from MeOH–$CH_2Cl_2$ gave an analytical sample: mp 279–281° (lit.[9] mp 294°); $[\alpha]D$ +111.5 (pyridine); $\lambda_{max}$ (KBr) 2.83, 2.99, 3.01, 6.15, and 6.29 μ.

*Anal.* Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.70; H, 7.78.

**3-Methoxy-17α-ethynylestra-1,3,5(10)-trien-11β-ol (8b).**—When 3 g of **4d** was ethynylated according to the procedure described for the preparation of **8a**, 2.75 g of crude product, mp 172–175°, was obtained. Recrystallization from acetone and hexane gave an analytical sample: mp 176–177°; $[\alpha]D$ +79°; $\lambda_{max}$ 2.77, 3.03, and 6.22 μ.

*Anal.* Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.24; H, 7.92.

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## Insect Sex Attractants. VII. 5,9-Tridecadien-1-ol Acetates[1]

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The stereochemical configuration of insect attractants often determines their activity. For example, the sex attractant of the silkworm moth, *Bombyx mori* L., is the *trans, cis* isomer of 10,12-hexadecadien-1-ol; the other three isomers are much less active.[2-6] When the sex attractant of the pink bollworm moth was elucidated as 10-propyl-*trans*-5,9-tridecadien-1-ol acetate by Jones, *et al.*,[7] we decided to prepare analogs to evaluate attractancy and structure–activity relationships.[8]

The method used to prepare the 5,9-tridecadienyl acetates is shown in Chart I. The tetrahydropyranyl

CHART I

$RO(CH_2)_4C{\equiv}CH$ (**1**) + $Br(CH_2)_2CH{=}CH(CH_2)_2CH_3$ (**2a**, *cis*; **b**, *trans*) ⟶

$RO(CH_2)_4C{\equiv}C(CH_2)_2CH{=}CH(CH_2)_2CH_3$ (**3a**, *cis*; **b**, *trans*) ⟶

$RO(CH_2)_4CH{=}CH(CH_2)_2CH{=}CH(CH_2)_2CH_3$ (**4a**, *cis*-5, *cis*-9; **b**, *cis*-5, *trans*-9; **c**, *trans*-5, *cis*-9; **d**, *trans*-5, *trans*-9)

$CH_3CO_2(CH_2)_4CH{=}CH(CH_2)_2CH{=}CH(CH_2)_2CH_3$ (**5a**, *cis*-5, *cis*-9; **b**, *cis*-5, *trans*-9; **c**, *trans*-5, *cis*-9; **d**, *trans*-5, *trans*-9)

R = 2-tetrahydropyranyl

ether of 5-hexyn-1-ol was alkylated with the *cis* or *trans* isomer of 1-bromo-3-heptene (**2**) in dioxane by using lithium amide. Reduction of the isomers (**3**) in sodium–liquid ammonia or by hydrogenation over poisoned Pd–$CaCO_3$ yielded the tetrahydropyranyl ethers of 5,9-tridecadien-1-ol (**4**). Prolonged refluxing of these ethers with acetic acid–acetyl chloride cleaved the tetrahydropyran group to form the desired 5,9-tridecadienyl acetates (**5**).

The 5,9-tridecadienyl acetates were colorless liquids with similar infrared spectra, except that intensities varied for the *trans* peak at 960 $cm^{-1}$ and the *cis* peak at 720 $cm^{-1}$. Since each isomer contained certain amounts of the three remaining isomers as impurities, the *trans* content of each acetate was determined by infrared spectroscopy,[9] using elaidyl acetate as a standard. The results obtained are shown in Table I.

**Attractancy Tests.**—The acetates **5** were evaluated as attractants for male and female Mexican fruit flies, *Anastrepha ludens* (Lowe); Mediterranean fruit flies, *Ceratitis capitata* (Wiedemann); oriental fruit flies, *Dacus dorsalis* (Hendel); melon flies, *D. cucurbitae* Coquillet; male fall armyworms, *Spodoptera frugiperda* (J. E. Smith); codling moths, *Carpocapsa pomonella* L.; gypsy moths, *Porthetria dispar* L.; cabbage loopers, *Trichoplusia ni* (Hübner); and pink bollworm moths. The *cis*-5,*cis*-9 and *trans*-5,*cis*-9 acetates were attractive to fall armyworms in the laboratory and the *cis*-5, *trans*-9 acetate caused copulatory behavior in male cabbage looper moths. All other test results were negative.

### Experimental Section[10]

**2-(5-Hexynyloxy)tetrahydropyran (1).**—Dihydropyran (25.2 g, 0.30 mole) was added to 24.5 g (0.25 mole) of 5-hexyn-1-ol and 5 drops of concentrated HCl, with stirring. The solution was cooled to keep the temperature below 40° and then stirred at room temperature for 3 hr. Excess $Na_2CO_3$ was added to the

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(9) A.O.C.S. Tentative Method ed 11-61.

(10) Infrared spectra were obtained with a Perkin-Elmer 521 spectrophotometer. Gas chromatographic analyses were performed on a F and M Model 500 gas chromatograph with a flame ionization detector by using a column of 5% Carbowax 20M on 60–80 mesh base-washed Chromosorb W (60.9 × 0.03 cm). An approximate flow rate of 75 ml of $N_2$/min was maintained. Company and trade names are given for identification purposes only and do not constitute endorsement by the U. S. Department of Agriculture.