1-(*p*-Hydroxyphenyl)-2-phenyl-4-(*m*-methoxyphenyl)-1-butanol (26).—A solution of 2.0 g of 1-(*p*-hydroxyphenyl)-2-phenyl-4-(*m*-methoxyphenyl)-1-butanone in 50 ml of THF was added to 1.0 g of LAH in 10 ml of THF over 10 min. Following 2 hr of stirring at room temperature the mixture was cooled in ice and 50 ml each of saturated NH_4Cl and H_2O were added. The inorganic gel was removed by filtration through Supercel. The organic layer was diluted with Et_2O, washed with H_2O and brine, and taken to dryness. The residual solid was recrystallized twice from C_6H_6 to give 1.01 g of the carbinol, mp 100–103° (50% yield). *Anal.* ($C_{23}H_{24}O_3$) C, H.

***trans*-1-(*p*-Hydroxyphenyl)-2-phenyl-6-methoxy-1,2,3,4-tetrahydronaphthalene.**—A solution of 6.35 g of the carbinol and 3.80 g of *p*-TsOH in 250 ml of C_6H_6 was heated for 2 hr under a Dean–Stark trap. It was then allowed to cool and worked up in the usual way ($NaHCO_3$). The residue was chromatographed over silica gel (elution with CH_2Cl_2). Those fractions which were similar to tlc were combined and chromatographed over Florisil (elution with 5% Me_2CO). Those fractions which crystallized on trituration with Et_2O were combined and recrystallized. There was obtained 3.32 g of the tetralin as its Et_2O solvate; nmr: doublet (1 H) δ 4.05 (J = 10 cps).

2,N-Pyrrolidinoethoxy Ethers.—To a solution of 1.46 g of the phenol in 9 ml of DMF and 50 ml of C_6H_6 there was added 0.19 g of 56% NaH in mineral oil and, after effervescence had ceased (20 min), 1.19 g of a 1:1 mixture of PhMe and N-(β-chloroethyl)-pyrrolidine. The mixture was heated at reflux overnight, allowed to cool, and diluted with an equal volume of Et_2O. The organic solution was washed with H_2O and brine and taken to dryness. The residual gum was dissolved in Et_2O, and extracted with 2.5 *N* HCl. These aqueous extracts were combined and extracted in turn with CH_2Cl_2. The solid which remained when this last solution was taken to dryness was recrystallized.

Glyceryl Ethers. To a solution of 2.0 g of the phenol in 40 ml of MeOH was added 1.5 ml of 4.65 *N* NaOMe in MeOH followed after 10 min by 0.73 g of 1-chloro-2,3-propanediol. Following 18 hr of heating under reflux the mixture was taken to dryness. The residue was worked up in the usual way and chromatographed on Florisil. Elution with 10% Me_2CO gave recovered phenol. The product was obtained on elution with 50% Me_2CO.

3-Deoxy-16-haloestra-1,3,5(10)-trienes

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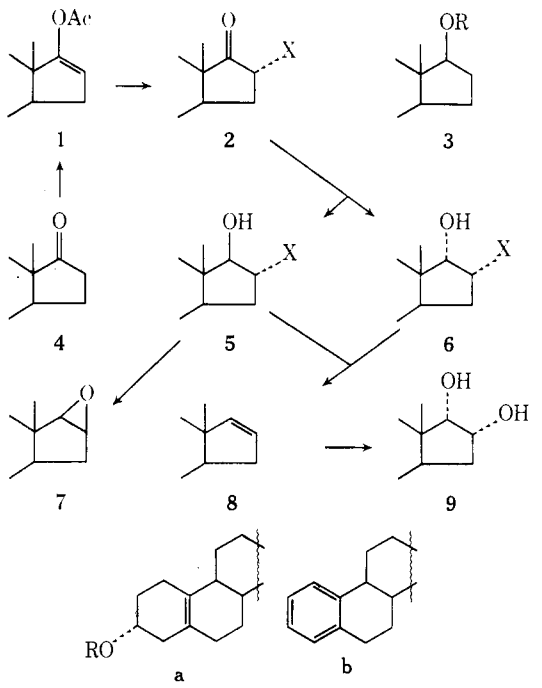
Formation of 3-deoxyestratriene derivative **2b** occurs as a side product in the preparation of 16-halo-19-norandrostanes **2a**. An efficient alternate route to these materials proceeds through halogenation of the enol acetate **1b**. Both the halo ketones **2b** and their derivative alcohols exhibit interesting lipodiatic properties.

The potentially valuable lipodiatic[1] (lipid-shifting) properties of the 16-haloestrone derivatives[2] in prevention of atherosclerosis gave impetus to a program of synthesizing both androstane[3] and 19-norandrostane analogs. Although the biological activities of the target compounds were not outstanding, a pharmacologically potent by-product arose in the synthesis of the norandrostanes. The identification of this compound and the preparation of related compounds form the subject of the present communication.

Synthesis of the 16-halo-19-norandrostanes was initiated by treatment of the 3α-hydroxy ketone **4a**[4] with isopropenyl acetate. The resultant enol diacetate **1a** was chlorinated under neutral conditions to provide chiefly the 16-chloro ketone **2a** (see Scheme I). A similar reaction of enol diacetate **1a** with Br_2 provided the analogous bromo ketone **2a**. The α configuration of the halogen atoms in these compounds is postulated on the basis of the α-face attack demonstrated in other steroidal C-17 enol acetates.[2] Treatment of the chloro ketone **2a** with LAH produced a mixture of the epimeric 17-alcohols (**5a**, **6a**). The first of the pair eluted from a chromatographic column is assigned the 17α-(pseudo axial) configuration **5a**[5] (see also the proof below for **5b**).

Acid-catalyzed hydrolysis of the 3-acetate group of **2a** (X = Br, Cl) proceeded efficiently without causing the halogen loss seen with use of base.[2b] When the

SCHEME I



R = H, $COCH_3$; X = Cl, Br, I

total chlorination product of enol diacetate **1a** was subjected to acid hydrolysis, a monooxygenated material was isolated in *ca.* 10% yield. Low-intensity uv maxima at 266 and 273 mμ, a strong ir band at 13.4 μ (characteristic of four adjacent aromatic protons),[6] and

(1) A. H. Goldkamp, W. H. Hoehn, R. A. Mikulec, E. F. Nutting, and D. L. Cook, *J. Med. Chem.*, **8**, 409 (1965).

(2) (a) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958); (b) G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961).

(3) W. F. Johns, U. S. Patent 2,911,418 (1959).

(4) W. F. Johns, *J. Org. Chem.*, **29**, 1490 (1964).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 14.

(6) A. S. Dreiding, W. J. Pummer, and A. J. Tomasewski, *J. Am. Chem. Soc.*, **75**, 3159 (1953).

nmr signals near 430 Hz showed clearly that the product had a 3-deoxy aromatic A ring. The nature of the D ring was clear from spectral and elemental analyses, thus indicating the unknown to be the deoxyestrone derivative **2b** (X = Cl). A more vigorous acid hydrolysis caused epimerization to occur, yielding the spectrally similar 16β-chloro ketone. The corresponding 16α-bromoestratriene **2b** was also produced by a mild acid-catalyzed hydrolysis of the entire enol acetate bromination product.

A plausible route for aromatization of the 3α-hydroxyestr-5(10)-ene system would involve initial ionic addition of halogen to the 5(10) double bond. Support for this hypothesis was obtained by neutral chlorination (or bromination) of monolefinic diacetate **3a**[7] followed by acid hydrolysis, yielding 20% of the expected estra-1,3,5(10)-trien-17β-ol (**3b**). An alternate aromatization mechanism would entail acid-catalyzed dehydration of the homoallylic 3-hydroxyl to a diene followed by autoxidation; this possibility was ruled out by demonstrating the stability of starting alcohol **4a** to acid. Free-radical halogenation allylic to the 5(10) double bond could also occur, as shown by N-bromosuccinimide treatment of **3a**. Subsequent steps (dehydrohalogenation, dehydration) leading to an aromatic A ring *via* acidic treatment[8] failed, however. Only the first of the suggested mechanisms is in accord with the observed results. The exact pathway followed during the reaction remains somewhat obscure, however, because of the low yield of **3b** obtained.

Additional quantities of the halo ketones in the aromatic series were prepared directly from deoxyestrone. The enol acetate of this compound was chlorinated under neutral conditions.[9a] The compound isolated in high yield was identical with that obtained as a by-product in preparation of the chloro ketone **1b**, confirming both the gross structure and stereochemistry of the latter. An alternate synthesis of this material was effected by lithium chloride displacement of 16β-mesyloxyestra-1,3,5(10)-trien-17-one.[9b] Also, both the bromo and iodo ketones **2b** were prepared from the enol acetate **1b** by direct halogenation.

LAH reduction of both the bromo ketone and chloro ketone afforded 1:2 mixtures of 17α:17β alcohols in accord with the results obtained in the 3-oxygenated series.[2b] To support the stereochemistry of the 17-hydroxy groups suggested by the relative points of elution from silica gel,[5] the β-oxide **7** was prepared from the *trans*-bromohydrin **5b** by treatment with base, and the 17α-alcohol **6b** (X = H) from the *cis*-bromohydrin **6b** by treatment with Raney Ni. The latter compound was identical with an authentic sample prepared by Li NH_3 reduction of the 3-diethyl phosphate ester of 17α-estradiol. In addition, Zn treatment of the bromohydrin mixture (**5b**, **6b**) afforded the amorphous 16(17)-olefin which was characterized by OsO_4-catalyzed hydroxylation to the *cis*-glycol **9b**.

(7) J. A. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955). The reversal in assigned configurations at C-3 from that given by Hartman is discussed in ref 4 and also by S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, 1517 (1963).

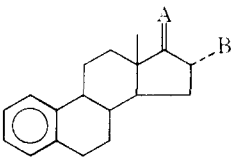
(8) Base-catalyzed dehydrohalogenation has successfully been used to effect this transformation in 6-keto derivatives: see A. Bowers and O. Halpern, U. S. Patent 3,201,428 (1965); *Chem. Abstr.*, **63**, 11964*h* (1965).

(9) (a) W. F. Johns, U. S. Patent 2,928,847 (1960). (b) The starting material, 16β-hydroxyestra-1,3,5(10)-trien-17-one, was prepared by the same general method reported by T. Nambara, M. Numazawa, and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **16**, 863 (1968).

Pharmacology.—Although it was initially surprising that steroids lacking a 3-oxygen function would possess any biological activity, the literature[1,10] soon showed other 3-deoxy steroids to be effective in several pharmacological assays. The 3-deoxyestratrienes exhibited biological activity chiefly in the lipodiatic estrogenic[1] area as was true of the analogous 3-methoxyestratrienes.[2] The generally lower estrogenicity of these compounds (see Table I) as compared to their 3-methoxy analogs led to a higher lipodiatic/estrogenic ratio for the deoxy derivatives, *e.g.*, the 3-methoxy analog of the chloro ketone **2b** had a lipodiatic/estrogenic ratio of 90/0.8 and the 3-methoxychlorohydrin analog of **6b**, 60/0.1, whereas the corresponding ratios for the deoxy compounds were 45/0.25 and 70/0.1.

TABLE I

LIPODIATIC AND ESTROGENIC ACTIVITIES OF 16α-SUBSTITUTED ESTRA-1,3,5(10)-TRIENES



	Lipodiatic/estrogenic ratio[a]			
	B			
A	H	Cl	Br	I
=O (**2b**)	130/10	45/0.25	45/>1	60/2
β-OH (**5b**)	120/10	150/>3	90/10	
α-OH (**6b**)	160/0.3	70/0.1	30/0.1	
16β,17-Oxide (**7b**)				60/0.3

[a] The first figure is the relative lowering of the plasma cholesterol–phospholipid ratio in cholesterol-fed cockerels, estrone = 100; see ref 1 for details of the bioassays. The second figure is the relative estrogenic potency as determined in the mouse uterine assay, estrone = 100; see ref 1.

Experimental Section[11]

3α,17-Diacetoxyestra-5(10),16-diene (1a).—A solution of 24 g of 3α-hydroxyestr-5(10)-en-17-one (**4a**)[4] in 400 ml of isopropenyl acetate containing 4.0 g of *p*-toluenesulfonic acid (TSA) was distilled to half-volume over a 20-hr period. The solution was cooled and diluted with Et_2O and aqueous $NaHCO_3$. The product was extracted with Et_2O; the extract was washed with additional aqueous $NaHCO_3$ and with H_2O, dried ($MgSO_4$), and concentrated to dryness.[12] The crude semicrystalline product was decolorized by dissolving it in hexane and passing it through a short column of 80 g of Florex. Concentration of the hexane eluate gave 17.0 g of the enol diacetate **1a**, mp 125–127°, which was recrystallized from Et_2O–MeOH to give a pure sample: mp 128–130°; ir 5.69, 5.75 μ; $[\alpha]D$ +163°. *Anal.* ($C_{22}H_{30}O_4$) C, H.

3α-Acetoxy-16α-chlorestr-5(10)-en-17-one (2a) (Procedure A).—A solution of 2.02 g of the enol acetate **1a** in 60 ml of CCl_4 at 10° was stirred vigorously with 3 g of anhydrous K_2CO_3. To this mixture was added 10.0 ml of an 0.68 *M* solution of Cl_2 in CCl_4. The mixture was then poured into aqueous $Na_2S_2O_3$ and the product was extracted with $CHCl_3$. Crystallization of the product from Me_2CO–hexane yielded 0.45 g of chloro ketone **2a**, mp 208–218°, ir 5.78 μ. *Anal.* ($C_{20}H_{27}ClO_3$) C, H.

(10) A. Kasal, V. Cerny, and F. Sorm, *Collect. Czech. Chem. Commun.*, **30**, 472 (1965), presents a list of several papers describing 3-deoxy steroids.

(11) We wish to thank Dr. R. T. Dillon and staff for the spectra and analyses reported here. Ir spectra were run on KBr disks; rotations were determined in $CHCl_3$ 1% solutions and uv spectra in MeOH. Melting points are uncorrected.

(12) This general work-up was used throughout the experimental work described.

16α-Chloroestr-5(10)-ene-3α,17α-diol (6a) (Procedure B).—A solution of 3.30 g of chloroacetate **2a** in 80 ml of THF was added to a slurry of 2.0 g of LAH in 800 ml of Et_2O with stirring over a 10-min period. After 5 min more, the mixture was cautiously diluted with H_2O and then with dilute HCl. The product was extracted with Et_2O and chromatographed on 200 g of silica gel. Fractions eluted with 10% EtOAc–C_6H_6 yielded first 1.48 g of crude chlorodiol **6a** which was crystallized from Me_2CO–hexane to afford 0.26 g of the pure material: mp 178–180°; ir 2.79, 2.98, and 3.12 μ; $[\alpha]D$ +147°. *Anal.* ($C_{18}H_{27}ClO_2$) C, H.

The remainder of chlorohydrin fractions were a mixture of 17α- and 17β-hydroxy derivatives.

3α-Hydroxy-16α-chlorestr-5(10)-en-17-one (2a).—The acetate **2a** (0.42 g) dissolved slowly in 100 ml of MeOH and 5 ml of concentrated HCl at room temperature. After 18 hr the solution was diluted with H_2O and the resulting precipitate was collected. Recrystallization from Me_2CO–hexane gave 0.20 g of pure 3-hydroxychloro ketone **2a**: mp 126–127°; ir 2.85, 3.06, 5.75 μ. *Anal.* ($C_{18}H_{23}ClO_2$) C, H.

In a subsequent run, 7 g of mother liquors of hydroxychloro ketone **2a** were chromatographed on 450 g of silica. Fractions eluted with C_6H_6 were combined (1.3 g, *ca.* 8% of the total product) and crystallized from Me_2CO–hexane to give 0.95 g of the 16-chloro ketone **2b**, mp 153–156°, identical spectrally with the material prepared below.

With more vigorous acidic treatment a new component was formed, being eluted shortly after 16-chloro ketone **2b**. The material was crystallized from CH_2Cl_2–MeOH to give pure 16β-chlorestra-1,3,5(10)-trien-17-one, mp 130–131°, ir 5.71 μ, $[\alpha]D$ +81°. *Anal.* ($C_{18}H_{21}ClO$) C, H.

3α-Acetoxy-16α-bromoestr-5(10)-en-17-one (2a).—Br_2 in CCl_4 (19 ml, 2.1 moles) was added dropwise over 10 min to a stirred mixture of 7.12 g of enol diacetate **1a** and 20 g of anhydrous K_2CO_3 in 200 ml of CCl_4 at 5°. The solution was then diluted with aqueous $Na_2S_2O_3$ and the product was extracted with CH_2Cl_2. The crude product was dissolved in 100 ml of Me_2CO containing 15 g of KI and the mixture was stirred at room temperature for 0.5 hr. The solution was decolorized with aqueous $Na_2S_2O_3$ and the product was extracted with CH_2Cl_2. The crude crystalline residue (5.1 g) was recrystallized from CH_2Cl_2–Me_2CO to yield 4.05 g of the bromide, mp 193–200°, 5.72 μ, $[\alpha]D$ +194°. *Anal.* ($C_{20}H_{27}BrO_3$) C, H.

16α-Bromo-3α-hydroxyestr-5(10)-en-17-one (2a).—A mixture of 3.95 g of bromo acetate **2a** in 0.8 l. of MeOH and 1.30 g of TSA was stirred at room temperature for 2 days. The solution was diluted with H_2O and the product was extracted with C_6H_6. The product was twice crystallized from Et_2O to yield 0.85 g of bromo alcohol **2a**: mp 88–90°; ir 2.99, 5.72 μ. *Anal.* ($C_{18}H_{25}BrO_2$) C, H.

Chromatography of the mother liquor yielded, on elution with C_6H_6, crude fractions (0.30 g) which were crystallized from MeOH to yield 0.13 g of bromo ketone **2b**, identical with the material prepared below.

Estra-1,3,5(10)-trien-17β-ol from 3,17β-Diacetoxyestr-5(10)-ene (3a).—A solution of 1.0 g of 3α,17β-diacetoxyestr-5(10)-ene (**3a**)[7] in 50 ml of CCl_4 was treated with Cl_2 as in procedure A. The noncrystalline product (1.24 g) was taken up in 80 ml of MeOH and 10 ml of concentrated HCl. The solution was allowed to stand at room temperature for 18 hr and diluted with H_2O, and the product was extracted with C_6H_6. Chromatography of the resulting amorphous product (0.7 g) on silica gel gave 0.15 g (20%) of semicrystalline material (eluted with 3% EtOAc–C_6H_6) which was recrystallized from aqueous MeOH to give pure estra-1,3,5(10)-trien-17β-ol, identical spectrally with an authentic sample.[1,13] A similar reaction was effected with Br_2 instead of Cl_2.

Passage of O_2 through a solution of estr-5(10)-ene-3α,17β-diol **3a** in refluxing MeOH containing concentrated HCl afforded no perceptible 3-deoxyestratriene. Also, diacetate **3a** reacted readily in refluxing CCl_4 with N-bromosuccinimide, but again, none of the desired aromatic A-ring matrial was found after acid treatment of the brominated product.

17-Acetoxyestra-1,3,5(10),16-tetraene (1b).—Deoxyestrone (**4b**, 3 g) was treated with isopropenyl acetate as described for the preparation of **1a**. The crude product, after purification on Florex, was crystallized from pentane to yield 0.70 g of enol acetate **1b**, mp 109–111°, ir 5.65 μ. *Anal.* ($C_{20}H_{24}O_2$) C, H.

Normally the entire crude product was used directly, to avoid the unnecessary losses involved in recrystallization.

16α-Chloroestra-1,3,5(10)-trien-17-one (2b).—Enol acetate **1b** (11.6 g) was treated in CCl_4 with Cl_2 as in procedure A. The crude product was crystallized twice from CH_2Cl_2–MeOH to yield 8.40 g of chloro ketone **2b**: mp 163–164°; ir 5.66, 13.40 μ; λ_{max} 266 mμ (ε 480), 273 (480); nmr 57 (18-CH_3), 265, 269, 273 (16β-H), 427 and 431 (ArH) Hz;[14] $[\alpha]D$ +168°. *Anal.* ($C_{18}H_{21}ClO$) C, H.

16β-Methanesulfonyloxyestra-1,3,5(10)-trien-17-one.—$MeSO_2Cl$ (0.2 ml) was added to 0.34 of 16β-hydroxyestra-1,3,5(10)-trien-17-one[9] in 20 ml of C_5H_5N at 5°. The reaction was allowed to proceed at ambient temperature for 18 hr. The solution was poured into iced aqueous $KHCO_3$ and the product was isolated by C_6H_6 extraction. Crystallization from Me_2CO–hexane gave 0.33 g of the mesylate, mp 169–170°, ir 5.70 μ. *Anal.* ($C_{19}H_{24}O_4S$) H; C: calcd, 65.50; found, 66.00.

Treatment of 0.96 g of the mesylate in 100 ml of DMF containing 6 g of LiCl at room temperature for 23 hr followed by C_6H_6 extraction and chromatography on silica gel led to isolation of 0.42 g of chloro ketone **2b**, mp 158–164°, identical in the ir with the compound described above.

16α-Chloroestra-1,3,5(10)-trien-17β-ol (5b) and 16α-Chloroestra-1,3,5(10)-trien-17α-ol (6b).—A solution of 1.00 g of chloro ketone **2b** in 15 ml of THF was reduced as in procedure B. The product was chromatographed on 50 g of Florex. The material (0.36 g) eluted with 5% EtOAc–C_6H_6 was crystallized from CH_2Cl_2 to yield 255 mg of pure chloro alcohol **6b**, mp 179–180°, ir 2.79 μ, $[\alpha]D$ +67°. *Anal.* ($C_{18}H_{23}ClO$) C, H.

Elution of the column with 20% EtOAc–C_6H_6 gave 0.78 g of crude material, crystallized from hexane to yield 0.42 g of pure chloro alcohol **5b**, mp 114–115°, ir 2.81 μ, $[\alpha]$ +79°. *Anal.* ($C_{18}H_{23}ClO$) C, H.

16α-Bromoestra-1,3,5(10)-trien-17-one (2b).—Titration of a stirred solution of 2.96 g of enol acetate **1b** in 60 ml of CCl_4 at 5° containing 10 g of suspended K_2CO_3 with a 2 *N* solution of Br_2 in CCl_4 was followed by dilution of the mixture with aqueous $Na_2S_2O_3$. The product, isolated by extraction with $CHCl_3$, was crystallized from Me_2CO–MeOH to yield 2.89 g of material, mp 158–163°. Recrystallization from MeOH gave the pure bromo ketone, mp 159–164°, ir 5.73 μ, $[\alpha]D$ +126°. *Anal.* ($C_{18}H_{21}BrO$) C, H.

16α-Bromoestra-1,3,5(10)-trien-17β-ol (5b) and 16α-Bromoestra-1,3,5(10)-trien-17α-ol (6b).—A solution of 2.33 g of bromo ketone **2b** in 25 ml of THF was reduced as in procedure B. The product, chromatographed on Florex, afforded crude fractions (0.75 g) crystallized from hexane to give 0.56 g of bromo alcohol **6b**, mp 168–169°, ir 2.83 μ, $[\alpha]D$ +77°. *Anal.* ($C_{18}H_{23}BrO$) C, H. Further elution of the column with 20% EtOAc–C_6H_6 gave 1.53 g of crude material, crystallized from hexane to yield 0.85 g of pure bromo alcohol **5b**, mp 100–101°, ir 2.97 μ, $[\alpha]D$ +77°. *Anal.* ($C_{18}H_{23}BrO$) C, H.

16β,17-Oxidoestra-1,3,5(10)-triene (7b).—A solution of *trans*-bromohydrin **5b** (0.70 g) and 3 g of KOH in 75 ml of MeOH was boiled for 16 hr, then cooled and diluted with H_2O. The product was extracted with C_6H_6 and chromatographed on 40 g of silica gel. Elution with 90% C_6H_6 yielded 0.34 g of crude material, crystallized from MeOH to yield 0.29 g of pure oxide **7b**, mp 112–113°; no carbonyl or hydroxyl absorption was seen in the ir. *Anal.* ($C_{18}H_{22}O$) C, H.

17α-Hydroxyestra-1,3,5(10)-triene.—Raney Ni (*ca.* 8 ml) was washed consecutively twice with 0.5% aqueous AcOH and 0.5% AcOH–EtOH and five times with EtOH; it was then added to 1.0 g of the *cis*-bromohydrin **6b** in 40 ml of EtOH containing 0.5 ml of AcOH. The mixture was stirred at room temperature for 0.5 hr, boiled for 1.5 hr, and filtered. The filtrate was concentrated to dryness, and the residue was dissolved in CH_2Cl_2 and filtered. The product was crystallized from CH_2Cl_2–Me_2CO to yield 0.50 g of 17α-hydroxyestratriene, mp 170–173°, ir 3.02 μ, $[\alpha]D$ +57°. The spectra were clearly different from the 17β epimer; tlc also indicated the difference as well as the purity of the α isomer. *Anal.* ($C_{18}H_{24}O$) C, H.

An authentic sample of the α-alcohol was prepared by Li–NH_3 reduction of the diethyl phosphate ester of 17α-estradiol, using the Goldkamp procedure.[1]

Estra-1,3,5(10)-triene-16α,17α-diol (9b).—The crude bromohydrin (1.40 g of **5b**, **6b**) dissolved in 40 ml of AcOH was boiled

(13) We wish to thank Dr. A. H. Goldkamp, of these laboratories, for this sample as well as for several helpful discussions.

(14) The nmr spectra were determined in $CDCl_3$ solution on a Model A-60 spectrometer, Varian Associates, Inc., at 60 Mc (TMS, $\Delta\nu$ = 0 Hz).

with 2 g of Zn dust. After 0.5 hr, an additional 7 g of Zn dust was added and the heating continued for 4 hr more. The mixture was filtered and the filtrate was diluted with H_2O. The product was extracted with C_6H_6 and chromatographed on Al_2O_3. The material eluted with hexane was essentially pure estra-1,3,5(10),16-tetraene (**8**) although it could not be induced to crystallize. A solution of 0.50 g of this material in 100 ml of Et_2O was treated with 0.50 g of OsO_4. After 18 hr at room temperature the mixture was diluted with 100 ml of EtOH and a solution of 1.0 g of $Na_2S_2O_3$ in 20 ml of H_2O. The mixture was heated at reflux for 1 hr and then filtered, using hot EtOH to wash the insoluble material. The filtrate was concentrated to dryness, diluted with H_2O, and extracted with C_6H_6. The resulting material (0.45 g), chromatographed on silica, was largely eluted with EtOAc. Crystallization of the eluates from Me_2CO-hexane gave 0.18 g of diol **9b**, mp 113–115°, ir 2.94 μ, $[\alpha]D$ +46°. *Anal.* ($C_{18}H_{24}O_2$) C, H.

16α-Iodoestra-1,3,5(10)-trien-17-one (2b).—Enol acetate **1b** (1.48 g) in 50 ml of AcOH containing 0.90 g of $Hg(OAc)_2$ was added to a stirred solution of 1.30 g of I_2 in 200 ml of AcOH. After 10 min the solution was poured into excess aqueous KI and extracted with C_6H_6. The extract was washed with aqueous $Na_2S_2O_3$, H_2O, and aqueous $KHCO_3$. The product obtained on concentration of the solvent was crystallized from CH_2Cl_2–MeOH to yield 0.70 g of pure iodo ketone **2b**, mp 190–193°, ir 5.76 μ, $[\alpha]D$ +85°. *Anal.* ($C_{18}H_{21}IO$) C, H.

Acknowledgment.—The author wishes to thank Dr. George P. Mueller for encouragement and advice during the course of this work. Also to be acknowledged are Drs. D. L. Cook and R. A. Edgren for the biological evaluations presented.

Biologically Oriented Organic Sulfur Chemistry. III. Formation of Mercaptals, Mercaptoles, an Orthothioformate, and Thiazolidines for the Latentiation of Thiols[1a-c]

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Mercaptals, mercaptoles, an orthothioformate, and thiazolidines are described. They were formed by the reaction of 2-aminoethanethiol hydrochloride with carbonyl compounds, several of which are reactive enough to form isolable hydrates. Most of the products had little or no activity as antiradiation drugs. D-5,5-dimethylthiazolidine-4-carboxylic acid did not reduce either the titer of rheumatoid factor *in vitro* or the skin-tensile strength of rats *in vivo*. The structural types mentioned thus seem less promising than α-hydroxy sulfides described previously for latentiating biologically active thiols, perhaps because of their greater stability *in vivo*.

The previous paper in this series[1a] reported that hemimercaptals, which can be derived from aldehydes sufficiently reactive to form isolable hydrates, afford a promising means of latentiating a typical radioprotective thiol (2-aminoethanethiol hydrochloride, **1**). The term "latentiation" simply is a convenient one for referring to the conversion of a biologically active compound to some derivative which will produce either the parent or a suitably active moiety of it *in vivo*.[1a] In order to explore the generality of this type of latentiation, it was important to learn whether formation of a mercaptal, a mercaptole, an orthothioformate, or a thiazolidine might be exploited similarly. Thiazolidines have been tested as antiradiation drugs; although many were inactive, some were active.[2] To the best of our knowledge, no reports have been published on antiradiation activity of the other types of structures.

Aldehydes or ketones usually react with thiols in the presence of acid catalyst to give mercaptals or mercaptoles, respectively (eq 1),[3] and with aminothiols in the absence of excess acid to give thiazolidines (eq 2).[3c,d,4] This paper describes derivatives of each kind.

$$2\ Cl^- H_3N^+(CH_2)_2SH + RR'CO \overset{H^+}{\rightleftharpoons} RR'C[S(CH_2)_2NH_3^+\ Cl^-]_2 + H_2O \quad (1)$$

(1)

2, R = R′ = H
3, R = H; R′ = CO_2H
4, R = H; R′ = $Cl^- H_3N^+(CH_2)_2S$
5, R = R′ = CH_3
6, R = H; R′ = C_6H_5
7, R = R′ = CO_2Et

$$1 + RR'CO \xrightarrow{-H_2O} \text{(thiazolidine)} \quad (2)$$

(2)

8, R = H; R′ = CCl_3
9, free base of **8**
10, R = R′ = CH
11, R = H; R′ = C_6H_5CO
12, RR′ = (indolinone)

Carbonyl compounds which are sufficiently reactive to form isolable hydrates, on the other hand, may give

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