Synthesis of 6-Styryl-2-pyrones

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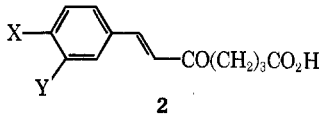
α-Pyrones containing variously oxygenated α′-styryl substituents are known natural products,[1] some of which have been synthesized.[2] We report simple syntheses of five such α-pyrones, three of which (**3a**, **3b**, and **3e**)[1a] proved to be identical with natural substances.[3]

$CH_3CO(CH_2)_3CO_2H$
1

Controlled, base-catalyzed condensations[4] of four aromatic aldehydes with 5-oxohexanoic acid (**1**) yielded 6-arylidene-5-oxohexanoic acids **2a–2d** whose treatment with acetic anhydride in the presence of sodium acetate afforded enol lactones. Dehydrogenation of the latter over palladium on charcoal gave the desired α-pyrones **3a–3d**.



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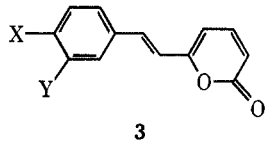

3

a, X = Y = H
b, X+Y = CH_2O_2
c, X = Y = MeO
d, X = $C_6H_5CH_2O$; Y = MeO
e, X = HO; Y = MeO

Since neither vanillin nor its *O*-acetyl or *O*-tetrahydropyranyl derivatives could be condensed with ketone **1** in the above manner, the α-pyrone **3e** related to vanillin was produced by acid-catalyzed debenzylation of **3d**.

Experimental Section[5]

6-Arylidene-5-oxohexanoic Acids (2a–2d).—The required aldehyde (1 equiv) was condensed with 5-oxohexanoic acid (1 equiv) in the presence of alcoholic NaOH solution (5% 2 equiv) by heating on a water bath (80°) for 20–30 min and a work-up according to Erlenmeyer.[4] Crystallization from an appropriate solvent afforded the desired product in 40–60% yield.

2a: light yellow crystals from EtOH; mp 114–116°; ir 3509–2638, 1715, 1661, 1618, 982 cm^{-1}; nmr δ 1.8–2.2 (m, 2, CH_2 at 3), 2.3–2.9 (m, 4, CH_2 at 2 and 4), 6.7 (d, 1, J = 16 Hz, HC=C), 7.2–7.7 (m, 6, HC=C and Ph), 10.0 (s, 1, COOH).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.27; H, 5.92.

2b: recrystallized from benzene as yellow crystals; mp 139–141°; nmr δ 5.98 (s, 2, CH_2O_2).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.82; H, 5.21.

2c: yellow crystals from benzene; mp 105–107°; nmr δ 3.92 (s, 6, 3′,4′-OCH_3).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.68; H, 6.72.

2d: yellow crystals from benzene; mp 129–131°; nmr δ 3.9 (s, 3, OCH_3), 5.2 (s, 2, $ArCH_2O$).

Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.09; H, 6.09.

6-Styryl-2-pyrones (3a–3e).—The above keto acids (**2a–2d**) were refluxed 6 hr in acetic anhydride containing a catalytic amount of fused sodium acetate. Removal of acetic anhydride and sodium acetate and recrystallization from a suitable solvent afforded the desired enol lactone. Some enol lactones were unstable on standing and were immediately dehydrogenated by refluxing (15 hr) in xylene containing a catalytic amount of Pd/C (10%). The product was directly chromatographed on a silica gel (E. Merck) column and eluted with $CHCl_3$. Recrystallization of the appropriate fraction from a suitable solvent afforded the desired α-pyrone. Synthetic **3a**, **3b**, **3c**, and **3e** had ir and nmr spectra identical with those of authentic samples[1a,3] and suffered no mixture melting point depression.

3a.—Keto acid **2a** (2.4 g) on enol-lactonization and recrystallization of the product from petroleum ether gave an enol lactone (1.9 g): yellow crystals; mp 108–110°; ir 1751, 1661, 1592, 971 cm^{-1}. Dehydrogenation of 0.35 g thereof and purification of the product as described above gave **3a** (0.15 g) as yellow crystals from petroleum ether: mp 113–114°; ir 1733, 1637, 1603, 972 cm^{-1}; nmr δ 6.1–6.3 (m, 2, pyronic), 6.60 (d, 1, J = 16 Hz, C=CH), 7.2–7.6 (m, 7, aromatic, pyronic and C=CH).

3b.—Similarly, keto acid **2b** (0.42 g) gave an enol lactone (0.3 g), yellow crystals from benzene, mp 131–133°, which on dehydrogenation, purification, and recrystallization of the product from benzene yielded **3b** (0.17 g) as yellow crystals: mp 173–174°; nmr δ 6.0 (s, 2, O_2CH_2).

3c.—Similarly the enol lactone (0.27 g, mp 92–95°) from the keto acid **2c** (0.31 g) furnished **3c** (0.15 g): yellow crystals from petroleum ether; mp 96–98°, nmr δ 3.93 (s, 6, OCH_3 at 3′ and 4′).

3d.—Enol lactone (2.0 g, mp 130–132°) from keto acid **2d** (2.5 g) afforded **3d** (1.2 g) as yellow crystals from EtOH: mp 131–133°; nmr δ 3.9 (s, 3, OCH_2Ar).

Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.56; H, 5.40.

3e.—α-Pyrone **3d** (1.2 g) was debenzylated with 48% HBr (0.1 ml) in AcOH (5 ml) by heating on a steam bath for 10 min. After neutralization with a saturated solution of sodium bicarbonate and extraction with chloroform, the crude product was purified as in the previous cases. The final product **3e** was obtained as yellow crystals (0.3 g) from benzene: mp 158–160°; ir 3360 cm^{-1} (OH); nmr δ 3.9 (s, 3, OCH_3), 5.9 (s, 1, OH).

Registry No.—**2a**, 28845-58-1; **2b**, 28845-59-2; **2c**, 28845-60-5; **2d**, 28845-61-6; **3a**, 1208-97-5; **3b**, 1219-50-7; **3c**, 28845-64-9; **3d**, 28845-65-0; **3e**, 1429-09-0.

(1) (a) O. R. Gottlieb, A. M. Bittencourt, W. B. Mors, and M. T. Magalhães, *Ann. Acad. Brasil Cienc.*, **36**, 29 (1964); (b) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, pp 82–134.

(2) J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 502 (1960); D. G. F. R. Kostermans, *Recl. Trav. Chim. Pays-Bas*, **70**, 79 (1951); L. P. Sorokina and L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1**, 73 (1964) [*Chem. Abstr.*, **60**, 9233 (1964)].

(3) The natural products were supplied kindly by Professor O. R. Gottlieb, Universidade Federal Rural do Rio de Janeiro.

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(5) Melting points are uncorrected. Infrared spectra were recorded as KBr pellets on a Perkin-Elmer Model 137 spectrometer. Nmr spectra were run in $CDCl_3$ on a Varian A-60D spectrometer. The petroleum ether used had a boiling point range of 80–100°.

Preparation and Nuclear Magnetic Resonance Spectra of 11-Oxygenated Estrogen Catechols[1]

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A distinctive feature of the nmr spectrum of 2-hydroxyestrone Ia is the two aromatic proton absorptions

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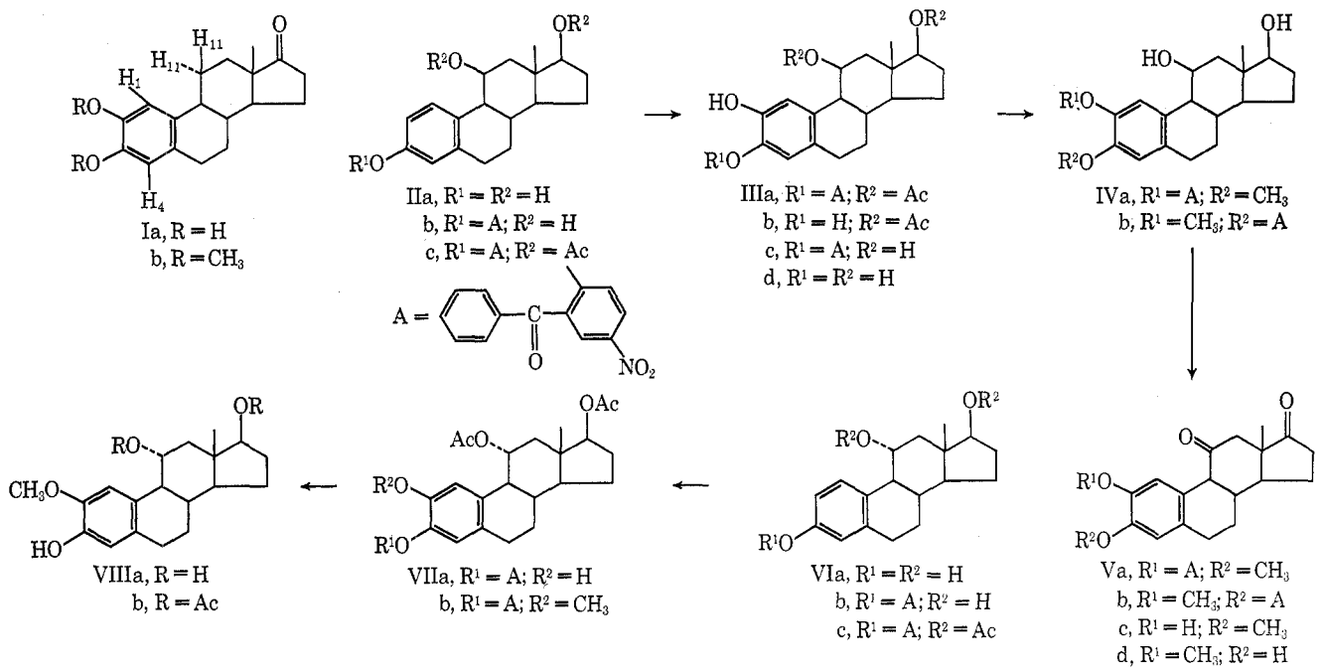
SCHEME I



in the downfield region. The H-1 and H-4 protons appear as singlets 12 Hz apart with that of H-1 being the downfield one.[3] Inspection of the spectra of the parent compound and of its various derivatives[4] revealed that the H-1 resonance was consistently of lower intensity and greater half-height width than that of the corresponding H-4 resonance. This difference persisted in the presence of identical substituents at C-2 and C-3, and its origin must therefore reside in long-range coupling with protons elsewhere in the molecule. The most likely candidates for this interaction are the benzylic[5] hydrogens at C-6 and C-9. One might infer that, contrary to the observed result, H-4 would have greater opportunity for benzylic coupling with the two protons at C-6 than H-1 with the single hydrogen at C-9. It is possible, however, that the conformationally rigid H-9 has an angular relationship to H-1 more favorable for coupling than that of the hydrogens on the flexible C-6 to H-4. To establish whether benzylic coupling was responsible for the broadening of the H-1 resonance, the benzylic hydrogens at C-6 and C-9 in 2,3-dimethoxyestrone Ib were exchanged for deuterium,[6] and the replacement was confirmed by the absence of benzylic proton resonance at δ 2.63 in the deuterated compound. The spectrum of the deuterated compound, however, still retained the full difference of 0.5 Hz between the half-height widths of the H-1 and H-4 bands which eliminated the benzylic protons as being responsible for this interaction. The proximity of the hydrogens on C-11 to the affected H-1 proton suggested these protons as the next logical candidates for long-range coupling with H-1. To investigate this possibility it was necessary to prepare the 11-oxygenated derivatives of 2-hydroxy estrogens and to obtain their nmr spectra. Furthermore, 2-hydroxylation is the major metabolic pathway of estradiol in man,[7] which together with the biological significance of 11-hydroxylation makes the preparation of compounds containing both these features of considerable interest.

The synthesis of 2,11-dihydroxy estrogens presents the choice of introducing the C-2 hydroxy group prior to that at C-11 or adding it to the preformed 11-hydroxy estrogen. For obvious reasons of starting material availability and synthetic ease we selected the latter sequence. Reductive aromatization[8] of 11β-hydroxyandrost-1,4-dien-3,17-dione by a modification of the published procedure[9] gave 11β-hydroxyestradiol IIa. The epimeric 11α-hydroxy compound was not available by this method since reductive aromatization in this instance results in ring C cleavage.[9] The method of Tsuda, *et al.*,[10] was, therefore, used to prepare 11α-hydroxyestradiol VIa.

The introduction of the C-2 hydroxy group in both epimeric 11-hydroxyestradiols was accomplished by an application of the procedures used in the original catechol estrogen synthesis.[11] Condensation with 2-chloro-5-nitrobenzophenone, cyclization, and oxidation of the resultant aromatic ether gave the 2-hydroxy compounds which were converted to the various derivatives as depicted in Scheme I. Smiles rearrangement of the intermediate catechol ether permitted the preparation of isomeric 2- and 3-monomethyl compounds, while oxidation of the protected intermediates led to the 11-keto derivatives.

Nmr Spectra.—Inspection of the aromatic resonances in the various compounds showed that the difference in the half-height widths between the H-1 and H-4 resonances was retained in all except the 11α-hydroxy

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(4) J. Fishman, M. Tomasz, and R. Lehman, *J. Org. Chem.*, **25**, 585 (1960).
(5) H. Rottendorf and S. Sternhell, *Tetrahedron Lett.*, 1289 (1963).
(6) H. Budzikewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Holden-Day, San Francisco, Calif., 1964, p 24; J. W. Chamberlin, Ph.D. Thesis, Stanford University, 1963.
(7) J. Fishman, *J. Clin. Endocrinol. Metab.*, **23**, 207 (1963).
(8) H. L. Dryden, G. M. Webber, and J. J. Wieczorek, *J. Amer. Chem. Soc.*, **86**, 742 (1964).
(9) J. S. Baran, *J. Med. Chem.*, **10**, 1188 (1967).
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and 11-keto derivatives. This clearly pointed to the 11α H as the proton responsible for the long-range coupling of H-1. That this was the case was confirmed by a double resonance experiment on the 11β-hydroxy derivative, where the H-1 and H-4 resonances had half-height widths of 2.8 and 2.0 Hz, respectively. Irradiation at δ 4.40, the absorption frequency of the 11α hydrogen, resulted in a disappearance of the inequality of H-1 and H-4 resonances with both now being 2 Hz wide at half-height. It should be emphasized that the difference in the height of H-1 and H-4 is not derived from a nuclear Overhauser effect[12,13] since in repeated integrations the areas of H-1 and H-4 resonances were equal. The steric relationship of the protons involved in this homobenzylic interaction permits some observations on its mechanism. In cases where unsaturation is present in the coupling path, a mechanism involving electron overlap is the preferred one.[14] In the present case the protons best situated for overlap of their σ bonds with the π electrons of the benzene ring are located at 9α and 11β positions. The fact that the 11α hydrogen, which is closest in space to H-1 (<3 Å)[15] but which is poorly situated for electron overlap is involved in the coupling, suggests that this interaction proceeds by a direct through-space mechanism.[16]

In view of the proximity of the two centers the effect of substitution at C-11 on the chemical shift of H-1 is of interest. Inspection of the chemical shift values of H-1 in the various structures listed in Table I reveals

TABLE I

CHEMICAL SHIFTS OF AROMATIC PROTONS IN 11-SUBSTITUTED 2,3-DIHYDROXYESTRATRIENES

C-11	H-1	H-4	ΔH-1	ΔH-4
<H, H	6.88	6.67		
<OAC, H	6.67	6.67	−0.21	0
<H, OAC	6.67	6.70	−0.11	+0.03
=O	6.60	6.64	−0.28	−0.03
<H[a], H	6.68	6.47		
<OH[a], H	6.77	6.53	+0.11	+0.06
<H[a], OH	7.58	6.43	−0.90	−0.1

[a] In DMSO-d_6; all others in $CDCl_3$.

that the 11α and 11β acetates produce only a small upfield shift with little difference between the epimers. The 11-ketone also results in a modest upfield shift suggesting the influence of its shielding cone although clearly not at its maximal zone. The 11α- and 11β-hydroxy derivatives in dimethyl sulfoxide both produce downfield shifts with that of 11α hydroxyl being ten times greater. This large deshielding is clearly the result not of the 11α-hydroxyl group itself but of the hydrogen-bonded dimethyl sulfoxide molecule. The geometry of the hydrogen-bonded hydroxy–dimethyl sulfoxide complex is speculative,[17] but clearly the orientation of the 11α-hydroxy group allows for greater proximity of the electropositive sulfur to H-1. This distance-related dimethyl sulfoxide effect may prove useful in other similar situations as an aid in structure determination.

(12) F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5250 (1965).
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(16) C. N. Banwell and N. Sheppard, *Discuss. Faraday Soc.*, **34**, 115 (1962).

Experimental Section[18]

Estra-1,3,5(10)-triene-3,11β,17β-triol 3-(2-Benzoyl-4-nitro)phenyl Ether (IIb).—To a solution of 0.42 g of estra-1,3,5(10)-triene-3,11β,17β-triol (IIa) and 0.05 g potassium hydroxide in 40 ml of 95% ethanol, 0.35 g of 2-chloro-5-nitrobenzophenone was added. The reaction mixture was refluxed for 48 hr. After concentration to one-half volume, the cooled mixture was poured into 1 *N* sodium hydroxide solution and extracted with chloroform. Removal of the solvent yielded 0.54 g of a yellow oil which was chromatographed on alumina. Elution with petroleum ether (bp 30–60°)–benzene (1:1) yielded 0.04 g of 2-ethoxy-5-nitrobenzophenone while benzene and chloroform–benzene (1:1) gave 0.42 g of estra-1,3,5(10)-triene-3,11β,17β-triol 3-(2-benzoyl-4-nitro)phenyl ether (IIb) which crystallized from methanol–water, mp 123–125°, $[\alpha]^{27}D$ +74.2°.

Anal. Calcd for $C_{31}H_{31}NO_6 \cdot H_2O$: C, 70.04; H, 6.26. Found: C, 69.85; H, 6.02.

The diacetate IIc, obtained with acetic anhydride in pyridine, crystallized from ether, mp 108–110°, $[\alpha]^{27}D$ +3.15°.

Anal. Calcd for $C_{35}H_{35}NO_8$: C, 70.33; H, 5.90. Found: C, 70.15; H, 5.85.

Estra-1,3,5(10)-triene-2,3,11β,17β-tetrol 3-(2-Benzoyl-4-nitro)phenyl Ether 11,17-Diacetate (IIIa).—To a solution of 0.33 g of the diacetate IIc in 1 ml of glacial acetic acid 1 ml of concentrated sulfuric acid was added slowly with cooling and stirring. The dark red solution was stored at room temperature for 30 min and then diluted with 3.5 ml of glacial acetic acid, and 1 ml of 30% hydrogen peroxide was added dropwise with stirring. After 5 min the color of the solution lightened and after standing for 30 min at room temperature it was poured into ice–water and the precipitate filtered off. After washing with 5% sodium bicarbonate solution and then water, the precipitate was dried and recrystallized from methanol–water to give 0.2 g of IIIa, mp 134–136°, $[\alpha]^{27}D$ +36.5°.

Anal. Calcd for $C_{35}H_{35}NO_9 \cdot {}^1/_2H_2O$: C, 67.41; H, 5.78. Found: C, 67.25; H, 5.78.

Estra-1,3,5(10)-triene-2,3,11β,17β-tetrol 11,17-Diacetate (IIIb).—A sample of IIIa (0.08 g) was refluxed for 2 hr in 10 ml of piperidine. The dark solution was diluted with benzene and washed with dilute sulfuric acid and then water. Evaporation of solvent and crystallization from methanol yielded 0.02 g of IIIb: mp 220–224°; $[\alpha]^{28}D$ +36.7°; nmr 1.11 (s, C-18 CH_3), 1.90 (s, 11β-CH_3CO), 5.77 (m, H-11α), and 6.63 (s, H-1,4).

Anal. Calcd for $C_{22}H_{28}O_6 \cdot CH_3OH$: C, 65.69; H, 7.67. Found: C, 65.63; H, 7.61.

Estra-1,3,5(10)-triene-2,3,11β,17β-tetrol 3-(2-Benzoyl-4-nitro)phenyl Ether (IIIc).—A solution of 0.1 g of IIIa in 20 ml of methanol containing 1 ml of concentrated sulfuric acid was refluxed for 15 hr. The solution was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate, dried, and evaporated to give material which crystallized from dilute methanol to give 0.07 g of IIIc, mp 212–214°, $[\alpha]^{27}D$ +79.6°.

Anal. Calcd for $C_{31}H_{31}NO_7 \cdot CH_3OH$: C, 68.43; H, 6.28. Found: C, 68.58; H, 6.22.

Estra-1,3,5(10)-triene-2,3,11β,17β-tetrol (IIId).—A solution of 80 mg of IIIb in 20 ml of tetrahydrofuran was stirred with 70 mg of $LiAlH_4$ for 4 hr. The reaction mixture was diluted with 20 ml of acetone and then acidified with dilute HCl. After extraction with ethyl acetate the organic layer was washed with sodium bicarbonate solution and then water, dried, and evaporated. The residue was crystallized from acetone–petroleum ether to give 24 mg of IIId: mp 231–232° with previous melting and solidification; nmr (DMSO) 0.89 (C-18 CH_3), 4.40 (H-11α),

(17) R. J. Oulette, D. L. Marks, and D. Miller, *J. Amer. Chem. Soc.*, **89**, 913 (1967).
(18) Rotations were carried out on chloroform unless otherwise specified. Melting points were obtained on a hot stage apparatus and are corrected. Nmr spectra were obtained on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. The chemical shifts are reported in δ (parts per million) and the couplings are given in hertz. The double resonance experiment was performed on a Varian V-6058A spin decoupler.

6.38 (H-4), and 6.63 (H-1). Irradiation at δ 4.40 reduced the H-1 and H-4 resonances to equal width at half-height.

Anal. Calcd for $C_{18}H_{24}O_4 \cdot H_2O$: C, 67.06; H, 8.13. Found: C, 67.42; H, 7.94.

Smiles Rearrangement and O-Methylation of IIIc.—A solution of 160 mg of IIIc in 10 ml of Claisen alkali was allowed to stand for 10 min, acidified, and extracted with chloroform to give a partially rearranged product. The rearranged mixture was dissolved in 10 ml of tetrahydrofuran and stored for 24 hr at 5° with excess ethereal diazomethane. Evaporation of excess reagent and solvent gave a material which upon preparative thin layer chromatography in cyclohexane–ethyl acetate (1:1) gave 60 mg of a more polar compound identified as estra-1,3,5(10)-triene-2,3,11β,17β-tetrol 2-(2-benzoyl-4-nitro)phenyl ether 3-methyl ether (IVa) [nmr 3.70 (s, 3-OCH_3), 4.73 (m, H-11α)] and 28 mg of a less polar material identified as the isomeric 2-methyl ether 3-(2-benzoyl-4-nitro)phenyl ether IVb [nmr 3.66 (s, 2-OCH_3), 4.55 (m, H-11α)]. Neither of the two compounds could be obtained crystalline.

2,3-Dihydroxyestra-1,3,5(10)-triene-11,17-dione 3-Methyl Ether (Vc).—To a solution of 30 mg of IVa in 10 ml of acetone Jones reagent was added dropwise until the orange-brown color persisted. The mixture was allowed to stand for 20 min at room temperature, poured into water, and extracted with chloroform. Following evaporation of the solvent, the noncrystalline product Va was homogenous according to thin layer chromatography in cyclohexane–ethyl acetate (1:1). A solution of the above oil in piperidine was refluxed for 2 hr and cooled, benzene was added, and the reaction mixture was washed well with 5% sulfuric acid. Drying and evaporation of solvent gave 8 mg of a semisolid Vc which crystallized from methanol: mp 135–140°; $[\alpha]_D$ +129.7°; nmr 0.93 (s, C-18 CH_3), 3.86 (s, 3-OCH_3), 6.57 (s, H-1), and 6.62 (s, H-4).

Anal. Calcd for $C_{19}H_{22}O_4 \cdot CH_3OH$: C, 69.34; H, 7.57. Found: C, 68.91; H, 6.98.

2,3-Dihydroxyestra-1,3,5(10)-triene-11,17-dione 2-Methyl Ether (Vd).—This isomer was prepared from 14 mg of IVb exactly as described above: mp 145–147°; $[\alpha]_D$ +123.1°; nmr 0.93 (s, C-18 CH_3), 3.78 (s, 2-OCH_3), 6.44 (s, H-1), and 6.70 (s, H-4).

Anal. Calcd for $C_{19}H_{22}O_4 \cdot CH_3OH$: C, 69.34; H, 7.57. Found: C, 68.86; H, 7.72.

Estra-1,3,5(10)-triene-3,11α,17β-triol 3-(2-Benzoyl-4-nitro)-phenyl Ether 11,17-Diacetate (VIc).—The diacetate VIc was prepared from VIa as described for IIc and gave a crystalline product from ether, mp 103–105°, $[\alpha]_D$ −66.0°.

Anal. Calcd for $C_{35}H_{35}O_8N$: C, 68.63; H, 7.51. Found: C, 68.48; H, 7.24.

Estra-1,3,5(10)-triene-2,3,11α,17β-tetrol 2-Methyl Ether 11α,-17β-Diacetate (VIIIb).—A 0.745-g sample of VIc was converted to the 2-hydroxy derivative VIIa which without purification was methylated with diazomethane to VIIb. The latter, upon cleavage with piperidine, afforded 0.23 g of VIIIb. The above reactions were carried out by procedures identical with those used in the 11β-hydroxy series. The isolated VIIIb crystallized from acetone–petroleum ether, mp 226–228°, $[\alpha]_D$ −101.7°.

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.42; H, 7.83.

Estra-1,3,5(10)-triene-2,3,11α,17β-tetrol 2-Methyl Ether (VIIIa).—A solution of 0.1 g of VIIIb in 20 ml of methanol containing 1 ml of concentrated sulfuric acid was refluxed for 15 hr. The solution was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate, dried, and evaporated to give the 0.06 g of VIIIa: crystallized from dilute methanol; mp 243–245°; $[\alpha]_D$ +25.8°; nmr 0.78 (s, C-18 CH_3), 3.85 (s, 2-OCH_3), 6.67 (s, H-4), and 7.76 (s, H-1).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.19; H, 7.98.

2,3-Dimethoxyestra-1,3,5(10)-trien-17-one-*6α,6β,9α-d*$_3$.—A solution of 50 mg of 2,3-dimethoxyestra-1,3,5(10)-trien-17-one (Ib) in 20 ml of ethyl acetate was shaken with deuterium over 100 mg of 10% palladized charcoal for 4 hr at room temperature and atmospheric pressure. Filtration of the catalyst and evaporation of solvent gave the trideuterio derivative of Ib. The nmr spectrum of the starting material Ib showed a three-proton multiplet at 2.63 representing the benzylic hydrogens, and 1-proton singlet at 6.83 and 6.63 with the former being 0.6 Hz wider at half-height. The deuterated product lacked the absorption at 2.63 but the resonances at 6.83 and 6.63 were unchanged in shape.

Registry No.—IIb, 28841-14-7; IIc, 28841-15-8; IIIa, 28897-65-6; IIIb, 28897-66-7; IIIc, 28897-67-8; IIId, 28897-68-9; IVa, 28897-69-0; IVb, 28841-16-9; Vc, 28897-70-3; Vd, 28897-71-4; VIc, 28897-72-5; VIIIa, 28897-73-6; VIIIb, 28897-74-7; 2,3-dimethoxyestra-1,3,5(10)-trien-17-one-*6α,6β,9α-d*$_3$, 28897-75-8.

New Approaches to the Preparation of Halogenated Methylenediphosphonates, Phosphonoacetates, and Malonates

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Three synthetic routes to tetraalkyl dihalomethylenediphosphonates have appeared in the literature. Low yields of tetraethyl dichloromethylenediphosphonate were obtained from the reaction of Cl_3CBr and $P(O-C_2H_5)_3$.[1] This is not a useful preparative method, however, as there are a number of products and separation is difficult. Reaction of molecular halogen with the sodium carbanion of tetraisopropyl methylenediphosphonate gave mixtures containing less than 50% of the dihalo derivative.[2] Again, separation problems render this method impractical for preparative purposes. Equation 1 describes the halogenation *via* hypohalite

$$2NaOX + H_2C(PO_3R_2)_2 \longrightarrow X_2C(PO_3R_2)_2 + 2NaOH \quad (1)$$
$$X = Cl, Br, I$$

reaction with tetraalkyl methylenediphosphonate.[2] Quantitative yields of $X_2C(PO_3R_2)_2$ are obtained when X = Cl or Br; when X = I, the product is somewhat unstable resulting in reduced yields.

Each of the above three methods could conceivably be modified to yield tetraalkyl monohalomethylenediphosphonates. Chloroform reacts with trialkyl phosphite in a complex manner; the intermediacy of $ClCH(PO_3R_2)_2$ has been postulated but never proven.[3] Direct halogenation and hypohalite halogenation have both been shown to yield at best mixtures of tetraalkyl monohalomethylenediphosphonate with the corresponding unhalogenated and dihalogenated derivatives.[2] These mixtures are exceedingly difficult to separate, rendering pure tetraalkyl monohalomethylenediphosphonates nearly inaccessible.[4]

Hata[5] has reported the preparation of monobromo derivatives of activated methylenes through the reaction of equimolar quantities of the corresponding di- and unhalogenated species. This method was not successful with diphosphonates. After extended heating (100°) of a mixture of tetraisopropyl dibromomethylenediphosphonate and tetraisopropyl methylenediphos-

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