Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.64. Found: C, 56.80; H, 7.48; N, 16.10.

2-(2-Pyrrolemethyl)-1-nitrocyclohexane [Id, $R_1 = R_2 = -(CH_2)_5-$].—Condensation of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 43.5 g. (0.36 mole) of nitrocyclohexane in the usual manner gave 9.3 g. (25%) of the title compound, b.p. 129–131° (0.4 mm.).

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.40; H, 7.74; N, 13.45. Found: C, 62.95; H, 7.78; N, 13.70.

Ethyl 2-Nitro-2-(2-pyrrolemethyl)propionate (Ie, $R_1 = CH_3$; R_2 = Carbethoxy).—Condensation of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 53 g. (0.36 mole) of ethyl 2-nitropropionate furnished 9.6 g. (23%) of product, b.p. 110–112° (0.3 mm.). This substance decomposed too rapidly for analysis and immediately was reduced to the amine.

1-(2-Pyrrole)-2-aminobutane (IIa).—A solution of 15 g. (0.9 mole) of Ia in 150 ml. of absolute ethanol was refluxed for 0.5 hr. with some Raney nickel, filtered, and reduced in a Parr hydrogenator with 0.2 g. of platinum oxide until hydrogen uptake ceased (when the Raney nickel treatment was omitted, the reduction did not proceed). After removal of solvent, the product was purified through the hydrochloride, regenerated by treatment with base, and distilled to yield 6.8 g. (70%), b.p. 81–82° (0.8 mm.).

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.70; H, 10.10; N, 19.85.

1-(2-Pyrrole)-2-aminopropane (IIb).—Catalytic reduction of Ib in the same manner gave a 55% yield of IIb, b.p. 80–81° (1 mm.), which decomposed too rapidly for analysis; acetyl derivative, m.p. 93–93.5°; phenylthiourea derivative, m.p. 149–150°. The product was characterized as the acid succinate, m.p. 73–74°.

Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.52; H, 7.49; N, 11.57. Found: C, 54.11; H, 7.68; N, 11.52.

2-(2-Pyrrolemethyl)-2-aminopropane (IIc).—Prepared from Ic in 73% yield, b.p. 79–79.5°, it decomposed too rapidly to permit analysis. It was characterized as the phenylthiourea derivative, m.p. 125.5–126.5°, and analyzed as the acid succinate, m.p. 145–146°.

Anal. Calcd. for $C_{12}H_{20}N_2O_4$: C, 56.24; H, 7.87; N, 10.93. Found: C, 56.25; H, 7.89; N, 10.90.

Ethyl 2-(2-pyrrolemethyl)-2-aminopropionate (IIe).—This substance, m.p. 72.5–73.5°, was obtained in 58% yield by catalytic reduction of Ie.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.20; H, 8.00; N, 14.56.

2-(Isopropylaminoethylidene)pyrrole (IIIa).—To a solution of 20.2 g. (0.31 mole) of pyrrole in 150 ml. of acetic acid kept below 15° was added, in an atmosphere of nitrogen, 19.5 g. (0.33 mole) of isopropylamine and then over 1 hr. an ice-cold solution of 14 g. (0.32 mole) of acetaldehyde in 60 ml. of benzene. Stirring was continued for 3 hr. and the flask stored in a refrigerator for 3 days. The contents were poured into 500 ml. of ice water and 50 ml. of ether. The ether layer was separated and washed with sodium bisulfate. The combined aqueous layers were washed with ether and brought to pH 7 with 30% sodium hydroxide solution at a temperature not exceeding 20°. The material which precipitated was filtered and the filtrate made basic. The product was extracted with one 100-ml. and two 30-ml. portions of cyclohexane and the extract chilled in a Dry Ice–acetone bath. There precipitated 24 g. (52%) of IIIa, m.p. 49–51°. Sublimation furnished the analytical sample, m.p. 58–58.5°, whose picrate melted at 163–165° dec.

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.00; H, 10.59; N, 18.42. Found: C, 70.85; H, 10.38; N, 18.55.

2-(2-Pyrrole)propionamide (IV).—A solution of 9.0 g. (0.06 mole) of IIIa and 11.7 g. of potassium cyanide in 900 ml. of 80% ethanol was refluxed with stirring for 130 hr. until the evolution of isopropylamine had ceased, concentrated to 70 ml. on the water pump, and extracted thoroughly with methylene chloride. The organic extracts were washed, dried, and evaporated; yield of amide was 2.5 g. (32%), m.p. 120.5–121°, after recrystallization from benzene and vacuum sublimation.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.62; H, 7.49; N, 19.88.

The aqueous layer was acidified and extracted with methylene chloride. Purification of the acidic gum, presumably 2-(2-pyrrole)propionic acid, 4 g., by crystallization was unsuccessful; distillation resulted in decomposition.

Preparation of Lactam V.—A solution of 4.5 g. (0.03 mole) of 2-isopropylaminoethylidene pyrrole and 3 g. (0.014 mole) of diethyl acetamidomalonate in 50 ml. of xylene was heated at 90–95° with stirring for 55 hr. About 75% of the theoretical amount of isopropylamine was evolved. Cooling resulted in precipitation of 2.7 g. (51%) of lactam V, which was recrystallized from aqueous ethanol, m.p. 155–155.5°.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10, N, 10.60. Found: C, 58.75; H, 6.24; N, 10.35.

2-Isopropylaminobenzylidene Pyrrole (IIIb).—To a solution of 7 g. (0.115 mole) of pyrrole in 75 ml. of benzene was added in a nitrogen atmosphere, with cooling and stirring, 25 ml. of acetic acid followed by 15 g. (0.105 mole) of benzylideneisopropylamine in 75 ml. of benzene. The reaction vessel was stored in the refrigerator overnight and the product worked up in the usual manner. It solidified on cooling, yielding 11.5 g. (58%), m.p. 50.5–51.5°, after crystallization from cycloheptane and vacuum sublimation.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.46; N, 13.06. Found: C, 78.61; H, 8.50; N, 13.10.

When 10 g. (0.105 mole) of 2,5-dimethylpyrrole was substituted in the above preparation, Mannich base VIb was obtained in 60% yield, m.p. 91–92°, after crystallization from cycloheptane and sublimation.

Anal. Calcd. for $C_{16}H_{22}N_2$: C, 79.29; H, 9.14; N, 11.55. Found: C, 79.03; H, 9.14; N, 11.85.

Diethyl Phenyl-3-(2,5-dimethylpyrrole)methyl-α-acetamidomalonate (VIII).—Reaction of 2.2 g. of VIb with 2.1 g. (0.01 mole) of diethyl acetamidomalonate in boiling toluene for 18 hr. followed by removal of toluene furnished 2.0 g. (60%) of crude VIII, m.p. 179–182°. Two recrystallizations from ethanol raised the melting point to 191.5–192.5°.

Anal. Calcd. for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 65.66; H, 6.96; N, 7.35.

3-(Isopropylaminoethylidene)-2,5-dimethylpyrrole (VIa).—To a solution of 47.5 g. (0.5 mole) of 2,5-dimethylpyrrole in 60 ml. of acetic acid and 100 ml. of toluene–hexane (2:1) kept at 0–10° was added dropwise with stirring 43 g. (0.5 mole) of ethylideneisopropylamine. The temperature was then lowered to −10° which caused precipitation of the acetate of the Mannich base. This was filtered, washed with toluene, dissolved in water, and made basic. There was precipitated 45 g. (50%) of VIa which was sublimed *in vacuo*, m.p. 98–99°. The picrate melted at 138–140°.

Anal. Calcd. for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.17; H, 11.18; N, 15.41.

2-[3-(2,5-Dimethylpyrrole)]propionitrile.—Reaction of 6.4 g. of VIa with 5 g. of potassium cyanide in aqueous ethanol, until the theoretical volume of isopropylamine had evolved, yielded in the neutral fraction 1 g. of the nitrile, b.p. 112–113° (0.6 mm.), nitrile band at 2250 $mm.^{-1}$.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.80; H, 8.01; N, 18.58.

The acid fraction furnished 1.5 g. of the corresponding acid, m.p. 96–98°. Sublimation raised the melting point to 99.5–100.5°. The substance exhibited the usual air sensitivity of pyrrole acetic acids.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 65.04; H, 7.98; N, 8.22.

The Synthesis of C-15 β-Substituted Estra-1,3,5(10)-trienes. II[1]

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Received July 1, 1963

In part I of the titled paper[1] certain chemical properties of the Δ^{15}-17-one moiety of 3-methoxyestra-

(1) Part I, E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64 (1964).

TABLE I

MOLECULAR ROTATION ANALYSIS

Compound	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$
Estrone[3-hydroxyestra-1,3,5(10)-trien-17-one]	+165°[a]	+446°	
15β-Benzyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one	+55°	+207°	−239°
3,15β-Dihydroxyestra-1,3,5(10)-trien-17-one	+174° (pyridine)	+498°	+ 52°
3-Hydroxy-15β-methoxyestra-1,3,5(10)-trien-17-one	+97°	+291°	−155°
15β-Allyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one	+37°	+121°	−325°
15β-(2′-Dimethylamino)ethoxy-3-hydroxyestra-1,3,5(10)-trien-17-one	+61°	+218°	−228°
15β-(2′-Diethylamino)ethoxy-3-hydroxyestra-1,3,5(10)-trien-17-one	+57°	+220°	−226°
15β-Cyano-3-hydroxyestra-1,3,5(10)-trien-17-one	+79° (pyridine)	+233°	−213°
β-Estradiol(estra-1,3,5(10)-trien-3,17β-diol)[a]	+81° (ethanol)[b]	+218°	
15β-Methoxy-estra-1,3,5(10)-trien-3,17β-diol	+27° (pyridine)	+103°	−115°
15β-Cyano-estra-1,3,5(10)-trien-3,17β-diol	±0° (pyridine)	±0°	−218°

[a] V. Deulofeu and J. Ferrari, *Z. Physiol. Chem.*, **226**, 192 (1934). [b] B. Whitman, O. Wintersteiner, and E. Schwenk, *J. Biol. Chem.*, **118**, 789 (1937).

1,3,5(10),15-tetraen-17-one were described. We wish to record in this note the application of these findings to 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**), thus providing a number of novel estrone and β-estradiol intermediates and derivatives.

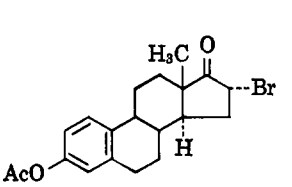
3-Hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**) was synthesized according to the sequence described for the 3-methyl ether.[1] Ketalization of 3-acetoxy-16α-bromoestra-1,3,5(10)-trien-17-one (**1**)[2] in toluene–ethylene glycol with *p*-toluenesulfonic acid over a period of 44 hr. gave a 69% yield of 16α-bromo-17-ethylenedioxyestra-1,3,5(10)-trien-3-ol (**2**). Dehydrobromination of the latter with potassium *t*-butoxide in toluene gave 17-ethylenedioxyestra-1,3,5(10),15-tetraen-3-ol (**3**). Mild acid hydrolysis afforded the desired intermediate, 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**).

Compound **4** on treatment with *p*-toluenesulfonic acid in refluxing benzene afforded a mixture, separated by partition chromatography, which consisted of 3-hydroxyestra-1,3,5(10),14-tetraen-17-one (**5**, 50% yield, ν_{max} 1730 and 1612 cm.$^{-1}$) and 3-hydroxy-14β-estra-1,3,5(10),15-tetraen-17-one (**6**, 19% yield, ν_{max} 1690 and 1620 cm.$^{-1}$, λ_{max} 222 and 280 mμ, ε 15,500 and 2550, respectively).

Treatment of the 14α-Δ^{15}-17-one (**4**) with potassium hydroxide in aqueous methanol resulted in a quantitative yield of 3-hydroxy-15β-methoxyestra-1,3,5(10)-trien-17-one (**7a**). The corresponding 15β-hydroxy derivative (**7c**) was obtained by hydrogenolysis of 15β-benzyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (**7b**), in turn prepared from **4** by reaction with benzyl alcohol and potassium hydroxide. Similarly from **4**, the following were prepared by the addition of the appropriate nucleophile: 15β-allyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (**7d**), 3-hydroxy-15β-(2′-dimethylamino)ethoxyestra-1,3,5(10)-trien-17-one (**7e**), 3-hydroxy-15β-(2′-diethylamino)ethoxyestra-1,3,5(10)-trien-17-one (**7f**), and 15β-cyano-3-hydroxyestra-1,3,5(10)-trien-17-one (**7g**).

In addition, 15β-methoxyestra-1,3,5(10)-trien-3,17β-diol (**8a**) and 15β-cyanoestra-1,3,5(10)-triene-3,17β-diol (**8b**) were prepared by sodium borohydride reduction of the 17-ones, **7a** and **7g**, respectively.

In Table I, the new C-15 substituted estrogens described herein have been submitted to molecular rotational analysis. The solvent effect in several instances has been disregarded with reservation. Generally, with the exception of 3,15β-dihydroxyestra-1,3,5(10)-trien-17-one (**7c**), it can be seen that the compounds conform with the anticipated negative shift in molecular rotation for a C-15 β-substituent.[1] It is believed that the rotational difference of **7c** is exceptional due probably to a solvent effect.



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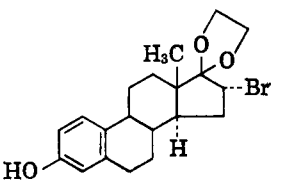

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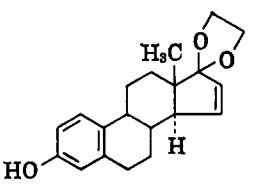

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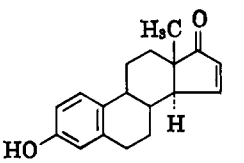

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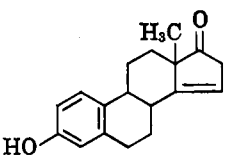

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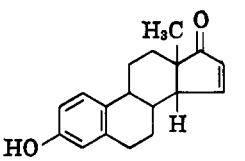

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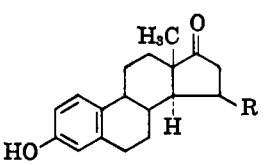
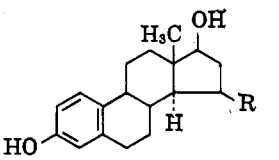


7a, R = OCH_3
b, R = $OCH_2C_6H_5$
c, R = OH
d, R = $OCH_2CH=CH_2$
e, R = $OCH_2CH_2N(CH_3)_2$
f, R = $OCH_2CH_2N(C_2H_5)_2$
g, R = CN



8a, R = OCH_3
b, R = CN

(2) W. S. Johnson and W. F. Johns [*J. Am. Chem. Soc.*, **79**, 2005 (1957)] have reported that a preliminary study of this ketalization was undertaken but was not studied further due to complications resulting from partial solvolysis of the acetoxy group.

Experimental

Melting points are uncorrected. The optical rotations are for chloroform solutions at 25° unless noted otherwise. The infrared absorption spectra were determined in potassium bromide disks, and the ultraviolet absorption spectra were determined in methanol. Petroleum ether refers to the fraction, b.p. 60–70°.

The authors are indebted to William Fulmor and associates for the infrared, ultraviolet, and optical rotation data. We wish also to thank Louis M. Brancone and associates for the analyses.

16α-Bromo-17-ethylenedioxyestra-1,3,5(10)-trien-3-ol (2).—A solution of 16α-bromoestrone acetate (**1**, 1.2 g.)[2] and *p*-toluenesulfonic acid monohydrate (0.220 g.) in toluene (60 ml.) and ethylene glycol (5 ml.) was distilled slowly through a Vigreux column for 44 hr. (total distillate, 45 ml.). The reaction mixture was cooled, neutralized with saturated sodium bicarbonate solution, and extracted with ethyl acetate. Evaporation, and crystallization of the residue from methanol gave 0.825 g. of **2**, m.p. 234–236°. A sample for analysis was recrystallized twice from the same solvent, m.p. 246–247° dec.; $[\alpha]_D$ +20°; ν_{max} 3500 and 1624 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{25}O_3Br$ (393.32): C, 61.06; H, 6.41; Br, 20.31. Found: C, 61.03; H, 6.71; Br, 20.34.

17-Ethylenedioxyestra-1,3,5(10),15-tetraen-3-ol (3).—A solution of potassium (0.4 g.) in *t*-butyl alcohol (20 ml.) was evaporated. Xylene (20 ml.) was added, and the evaporation was repeated. A solution of 16α-bromo-17-ethylenedioxyestra-1,3,5(10)-trien-3-ol (**2**, 0.600 g.) in xylene (40 ml.) was added to the potassium *t*-butoxide, and the mixture was refluxed under nitrogen for 18 hr. The mixture was cooled and extracted with ether. Evaporation gave 0.275 g. of a semisolid which was crystallized from methanol, 0.130 g., m.p. 215–219°. Two additional recrystallizations from acetone–petroleum ether gave the analytical sample, m.p. 218–220°; $[\alpha]_D$ −87°; ν_{max} 3395 and 1616 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}O_3$ (312.39): C, 76.89; H, 7.74. Found: C, 77.20; H, 8.11.

3-Hydroxyestra-1,3,5(10),15-tetraen-17-one (4).—A solution of 17-ethylenedioxyestra-1,3,5(10),15-tetraen-3-ol (**3**, 1.0 g.) and *p*-toluenesulfonic acid monohydrate (0.060 g.) in 85% aqueous acetone (82 ml.) was stirred at room temperature for 1.5 hr. The solution was extracted with ether (350 ml.), and the residue obtained upon evaporation was crystallized from methanol to give 0.475 g. of **4**, m.p. 249–251°. A sample for analysis was recrystallized once from ethanol and once from chloroform–methanol, m.p. 250–252°; λ_{max} 222 and 280 mμ (ε 13,700 and 2350); $[\alpha]_D$ −65°; ν_{max} 3380, 1690, and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2$ (268.34): C, 80.56; H, 7.51. Found: C, 80.38; H, 7.63.

Acid-Catalyzed Isomerization of 3-Hydroxyestra-1,3,5(10),15-tetraen-17-one (4).—To a suspension of **4** (1.04 g.) in benzene (100 ml.) was added *p*-toluenesulfonic acid monohydrate (0.700 g.). The steroid completely dissolved upon warming the mixture, and the resulting solution was refluxed for 15 min. The solution was extracted with benzene which on evaporation gave 1.0 g. of a crystalline solid. The latter was subjected to partition chromatography on Celite 545[3] with an *n*-heptane–methanol solvent system. Holdback volumes 3.0 to 5.2, on evaporation, gave 3-hydroxyestra-1,3,5(10),14-tetraen-17-one (**5**, 0.500 g.), m.p. 185–189°. Crystallization once from acetone–petroleum ether and once from ether–petroleum ether gave the analytical sample, m.p. 188–191°; λ_{max} 222 and 280 mμ (ε 8600 and 2260); $[\alpha]_D$ +294°; ν_{max} 3420, 1730, and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2$ (268.34): C, 80.56; H, 7.51. Found: C, 80.00; H, 7.52.

Evaporation of the eluate corresponding to holdback volumes 5.5 to 7.0 gave 3-hydroxy-14β-estra-1,3,5(10),15-tetraen-17-one (**6**, 0.190 g.), m.p. 205–210°. A sample for analysis was recrystallized twice from acetone–petroleum ether and had m.p. 222–224°; λ_{max} 222 and 280 mμ (ε 15,500 and 2550); $[\alpha]_D$ +475°; ν_{max} 3240, 1690, and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_2$ (268.34): C, 80.56; H, 7.51. Found: C, 80.06; H, 7.79.

3-Hydroxy-15β-methoxyestra-1,3,5(10)-trien-17-one (7a).—A solution of 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**, 0.450 g.) in methanol–tetrahydrofuran (55 ml., 10:1) was treated with 5% aqueous sodium hydroxide (1.2 ml.). The resulting solution was stirred for 0.5 hr., diluted with water, and the product was collected by filtration to give 0.450 g. of **7a**, m.p. 223–227°. Two crystallizations from acetone–petroleum ether gave the analytical sample, m.p. 224–226°; λ_{max} 222 and 278 mμ (ε 8300 and 2100); $[\alpha]_D$ +97°; ν_{max} 3400, 1732, and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_3$ (300.38): C, 75.97; H, 8.05; OCH_3, 4.99. Found: C, 75.41; H, 8.08; OCH_3, 4.88.

15β-Benzyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (7b).—A solution containing 3-hydroxyestra-1,3,5(10),15-tetraen-17-one (**4**, 1.0 g.) and powdered potassium hydroxide (0.600 g.) in benzyl alcohol (20 ml.) was stirred at room temperature for 4 hr. The reaction mixture was treated with ethyl acetate, filtered, steam distilled, and then extracted with ethyl acetate. Evaporation, and crystallization of the crude product from benzene afforded 0.480 g., m.p. 124–127°. A sample for analysis was recrystallized from acetone–benzene and had m.p. 125–128°; λ_{max} 222 and 282 mμ (ε 7600 and 1900); $[\alpha]_D$ +55°; ν_{max} 3390, 1730, 1615, and 734 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{28}O_3$ (376.47): C, 79.75; H, 7.50. Found: C, 79.92; H, 7.37.

3,15β-Dihydroxyestra-1,3,5(10)-trien-17-one (7c).—A solution of 15β-benzyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (**7b**, 0.300 g.) in acetic acid (4 ml.) containing 10% palladium–charcoal catalyst (0.100 g.) was hydrogenated for 4 hr. at room temperature and atmospheric pressure. The product was extracted with ethyl acetate, and the residue obtained on evaporation was recrystallized three times from acetone–petroleum ether to give the analytical sample, m.p. 224–227°; λ_{max} 222 and 280 mμ (ε 7200 and 2000); $[\alpha]_D$ +174° (pyridine); ν_{max} 3450, 3280, 1722, and 1628 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{22}O_3$ (286.36): C, 75.49; H, 7.74. Found: C, 75.36; H, 7.92.

15β-Allyloxy-3-hydroxyestra-1,3,5(10)-trien-17-one (7d).—A solution of **4** (1.0 g.) in allyl alcohol (50 ml.) containing 5% aqueous sodium hydroxide (2 ml.) was stirred at room temperature for 50 min. The solution was neutralized with acetic acid, and extracted with benzene. The residue obtained on evaporation was crystallized from methanol–water to yield 0.710 g. of **7d**, m.p. 165–168°. Further recrystallization did not alter the melting point; λ_{max} 222 and 282 mμ (ε 10,200 and 2800); $[\alpha]_D$ +37°; ν_{max} 3440, 1735, and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}O_3$ (326.42): C, 77.27; H, 8.03. Found: C, 76.77; H, 8.40.

3-Hydroxy-15β-(2′-dimethylamino)ethoxyestra-1,3,5(10)-trien-17-one (7e).—A solution containing **4** (0.300 g.) and 5% aqueous sodium hydroxide (1 ml.) in 2-dimethylaminoethanol (20 ml.) was stirred under a nitrogen atmosphere for 2 hr. at room temperature. Water was added, followed by several drops of acetic acid to give a solid which was collected by filtration, 0.22 g., m.p. 180–184°. Two crystallizations from acetone–petroleum ether gave **7e**, m.p. 185–187° $[\alpha]_D$ +61°.

Anal. Calcd. for $C_{22}H_{31}O_3N$ (357.48): C, 73.91; H, 8.74; N, 3.92. Found: C, 73.51; H, 8.63; N, 4.06.

3-Hydroxy-15β-(2′-diethylamino)ethoxyestra-1,3,5(10)-trien-17-one (7f).—A solution of **4** (0.600 g.) and 5% aqueous sodium hydroxide (2 ml.) in 2-diethylaminoethanol (15 ml.) was stirred at room temperature under a nitrogen atmosphere for 3 hr. The mixture was diluted with water and extracted with ethyl acetate. Evaporation gave an oil (0.6 g.) which by infrared analysis was shown to be a mixture of starting material and desired product. The oil was then subjected to partition chromatography on Celite 545[3] with a *n*-heptane–methanol solvent system. Holdback volume 9.5–10 on evaporation gave 70 mg. of **7b**, m.p. 131–134°. A sample recrystallized from acetone–petroleum ether for analysis had m.p. 131–134°, $[\alpha]_D$ +57°.

Anal. Calcd. for $C_{24}H_{35}O_3N$ (385.53): C, 74.96; H, 9.15; N, 3.63. Found: C, 74.84; H, 9.22; N, 3.66.

15β-Cyano-3-hydroxyestra-1,3,5(10)-trien-17-one (7g).—Treatment of **4** (0.250 g.) with sodium cyanide in refluxing aqueous tetrahydrofuran as described[1] afforded 0.180 g., m.p. 260–65°. Two recrystallizations from methanol gave the analytical sample, m.p. 274–276°; λ_{max} 222 and 280 mμ (ε 8300 and 2100); $[\alpha]_D$ +79° (pyridine); ν_{max} 3390, 2230, 1732, and 1628 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{21}O_2N$ (295.37): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.04; H, 7.24; N, 4.74.

15β-Methoxyestra-1,3,5(10)-triene-3,17β-diol (8a).—A solution of 3-hydroxy-15β-methoxyestra-1,3,5(10)-trien-17-one (**7a**, 0.200 g.) and sodium borohydride (0.200 g.) in methanol (20 ml.) was stirred at room temperature for 1 hr. Water was added,

(3) Celite 545 is a trade-mark of the Johns-Manville Corp. for a grade of diatomaceous earth. That used for partition chromatography was washed with 6 *N* hydrochloric acid, water, and methanol, and was then dried to constant weight.

and the product was extracted with chloroform. Evaporation gave an oil which gave crystals from acetone–petroleum ether, 0.160 g., m.p. 85–95° (containing acetone of crystallization by infrared analysis). Two recrystallizations from ether–benzene gave the analytical sample, m.p. 128–130°, containing 1 mole of benzene of crystallization; λ_{max} 222 and 280 mμ (ε 7600 and 2280); $[\alpha]_D$ +27° (pyridine); ν_{max} 3420, 1620, and 678 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_3 \cdot C_6H_6$ (382.54): C, 78.49; H, 8.96; OCH_3, 3.88. Found: C, 78.19; H, 8.72; OCH_3, 3.82.

15β-Cyanoestra-1,3,5(10)-trien-3,17β-diol (8b).—A solution of 15β-cyanoestra-1,3,5(10)-trien-3-ol-17-one (**7g**, 0.280 g.) and sodium borohydride (0.2 g.) in methanol–tetrahydrofuran (7:1, 40 ml.) was stirred at room temperature for 2 hr. Water was added and the product was collected by filtration to give 0.245 g., m.p. 280–282°. A sample for analysis was recrystallized twice from methanol, m.p. 284–286°; λ_{max} 222 and 280 mμ (ε 7500 and 2200); $[\alpha]_D$ ±0° (pyridine); ν_{max} 3460, 2250, and 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{23}O_2N$ (297.38): C, 76.73; H, 7.80; N, 4.71. Found: C, 76.43; H, 7.96; N, 4.84.

4-Cyanoformyl-1-methylpyridinium Iodide Oxime and Derivatives

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Received May 31, 1963

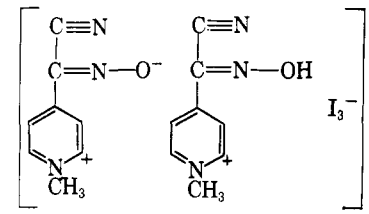
We wish to report on the synthesis of 4-cyanoformyl-1-methylpyridinium iodide oxime (I) and its derivatives, compounds which are more stable to light and oxygen than previously reported pyridinium oximes.

The synthesis of I was accomplished easily by the methylation of 4-pyridylglyoxylonitrile oxime. The glyoxylonitrile oxime was prepared either by isonitrosation of 4-pyridineacetonitrile or by reaction of potassium cyanide with isonicotinohydroxamic chloride.[3]

It was found that I with sodium ethoxide in ethanol or with concentrated ammonium hydroxide gave 4-cyanoformyl-1-methylpyridinium oximate (II). This conjugate base is soluble in water and slightly soluble generally in organic solvents.

4-Cyanoformyl-1-methylpyridinium cadmium triiodide oxime (III) was prepared from I and cadmium iodide in methanol. It was interesting to find that the residue obtained by evaporating the reaction mixture was *soluble* in ethyl ether. This important property may allow future investigations to be performed in other than a hydroxylic solvent.

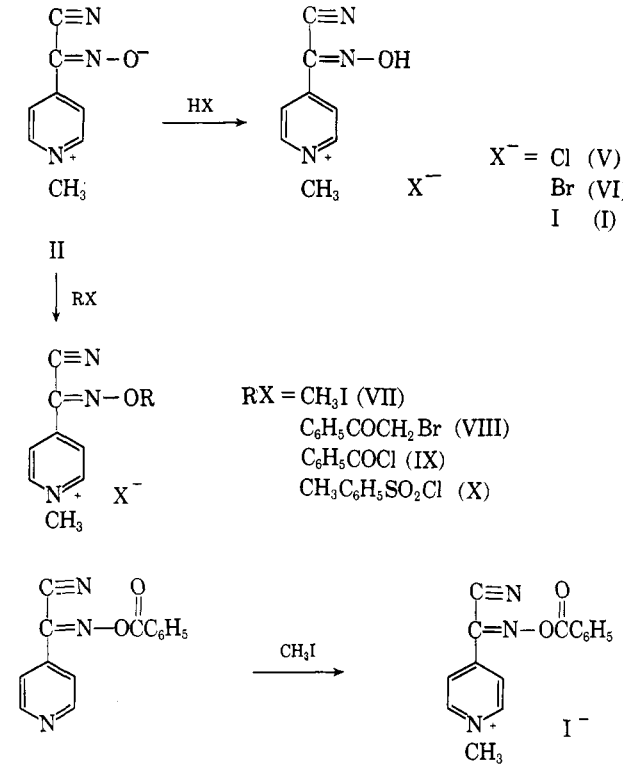
In previous experiences we found that quaternary heterocyclic aldoximes and ketoximes are not stable on exposure to intense ultraviolet light. Pyridinium aldoximates are especially sensitive to both oxygen and light.[4] Comparatively, aqueous solutions of I or II are stable to light and no precautions are needed in handling II in air. A 2% aqueous solution of I stored in quartz tubes for 7 months at 40° under intense ultraviolet light gave a solid which, on the basis of elemental analysis and a comparison of its infrared absorption spectrum to that of an authentic sample, was identified as the triiodide complex IV.



IV

The same complex was isolated when toluene was used in conjunction with methanol (methanol alone is a good solvent for recrystallizing I) in a recrystallization of I. The facile oxidation of iodide undoubtedly reflects a strong association of iodide with the pyridinium ring. It was shown that pyridinium iodide charge-transfer transitions involve an electron transfer to the pyridinium ring.[5] Toluene which is less polar than methanol probably allows a greater contribution of charge-transfer character. Consequently, the iodide should be more prone to radical formation and this would explain the oxidation. Multifold reactivity of tri(*p*-nitrophenyl)methyl derivatives was discussed similarly *vs.* solvent polarity by Kosower.[6] Appropriate light wave length also should promote radical formation.

The reaction of II with hydrochloric, hydrobromic, and hydroiodic acids gave 4-cyanoformyl-1-methylpyridinium chloride (V), bromide (VI), and iodide (I) oximes, respectively. When purifying I we found it more convenient to add hydrogen iodide to II rather than recrystallize crude I a number of times. (This is because of the iodide oxidation.)



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(2) Battelle Memorial Institute.
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(6) E. M. Kosower, *ibid.*, **80**, 3267 (1958).