afforded *p*-mentha-2,4(8)-dien-10-ol (VIII) (0.5 g): bp 77.5–79° (0.6 mm); $n^{23}D$ 1.5312; λ_{max}^{EtOH} 245 mμ (ε 28,500); λ_{max}^{film} 3.05, 6.15 (weak), 6.25 (weak), 8.8, 10, 10.5, 12.35, 13.35, and 13.65 μ; τ_{CCl_4} 3.63 (double doublet, J = 10 cps, J' = 1.5 cps, 1 H), 4.36 (broad bands, doublet, J = 10 cps, 1 H), 5.9 (singlet, 2 H), 6.2 (broad singlet, 1 H), 8.2 (singlet, 3 H), 8.98 (doublet, J = 7 cps, 3 H), 7.2–8.8 (broad absorption, 5 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.14; H, 10.59.

***p*-Menth-4(8)-ene-3,9-diol (X).**—Lithium aluminum hydride (0.5 g) was added to a well-stirred solution of lactone VI (2 g) in ethyl ether (20 ml) at 0° under nitrogen. Stirring was maintained for 10 hr while the mixture was warmed slowly to room temperature. After the usual work-up procedure, a colorless, thick oil (1.8 g) was obtained which failed to crystallize from *n*-hexane after standing several days in the refrigerator. Features of the nmr spectrum of this compound pointed to structure of diol X: τ_{CCl_4} 5.3–6 (broad band), 8.25 (singlet), and 8.95 (doublet). Dinitrobenzoylation by the conventional procedure gave a thick brown oil (4.3 g) which upon repeated crystallization with acetone afforded a bis-3,5-dinitrobenzoate (0.3 g): mp 133–134.5°; τ_{CDCl_3} 0.95 (multiplet), 3.55 (broad band), 4.5 (doublet, J = 12 cps), 4.85 (doublet, J = 12 cps), 7.2–7.9 (broad band), 8.03 (singlet), 8.63 (doublet, J = 4 cps), 8.9 (doublet, J = 4 cps).

Anal. Calcd for $C_{24}H_{22}N_4O_{12}$: C, 51.61; H, 3.97; N, 10.03. Found: C, 51.44; H, 3.92; N, 9.79.

Keto Acid XI and Lactol XII.—A solution of lactone VI (3.6 g) in 25% methanolic potassium hydroxide (36 ml) was refluxed 2 hr under nitrogen atmosphere. The solution was diluted with water and extracted with ethyl ether. The aqueous layer was acidified with 6 *N* hydrochloric acid and extracted with ethyl ether to give after the usual treatment a yellow oil (3.4 g) which crystallized upon cooling. Methylation of this product with diazomethane ethyl ether solution and glpc analysis on a 20 ft × 0.375 in. 20% XF-1150 on Chromosorb W column at 190° revealed the presence of three main components in a 26:62:12 ratio. Recrystallization with benzene–hexane afforded a mixture of crystals, mp 85–105° (0.5 g), which, after three new recrystallizations, gave pure lactol XII (0.1 g): mp 123–124; λ_{max}^{KBr} 2.95, 5.73, 9.3, 10.5, 10.65, 12.05, 12.4, and 13.65 μ; τ_{CCl_4} 4.3 (broad singlet, 1 H), 8.8 (doublet, J = 6 cps, 3 H), 9.05 (doublet, J = 6 cps, 3 H), 7.2–8.6 (multiplet, 7 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.13; H, 9.01.

From the first mother liquors a new crop of crystals (0.6 g), mp 75–95°, was obtained, which by repeated crystallization from benzene–hexane afforded keto acid XI: mp 110–112°; λ_{max}^{KBr} 3–4.25 (broad), 5.9, 7.78, 7.85, 8.03, 8.15, 8.4, and 10.65 μ; τ_{CCl_4} 0.9 (broad absorption, 1 H), 8.8 (doublet, J = 7 cps, 3 H), 8.93 (doublet, J = 4 cps, 3 H); $\tau_{CCl_4-C_6H_6}$ 8.85 (doublet, J = 7 cps), 9.05 (doublet, J = 4 cps), 7.2–8.7 (broad absorption, 7 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.15; H, 8.47.

Glpc analysis of the methylated keto acid under the conditions described above gave a single band identified by peak enhancement as the major component (62%) of the original oil. On the other hand, application of the same method to lactol XII gave puzzling results not consistent with the spectral data. Under the conditions described, the methylated lactol exhibited two bands in a similar ratio which corresponded to the two major products of the starting mixture (26 and 62%).

Registry No.—IV, 16434-34-7; V, 16434-35-8; VI, 16434-36-9; VII, 16434-37-0; VIII, 16434-38-1; dinitrobenzoate of VIII, 16434-39-2; IX, 16452-31-6; dinitrobenzoate of IX, 16434-40-5; X, 16434-41-6; XI, 16434-42-7; XII, 16434-43-8; $C_{16}H_{26}NO_3Cl$, 16450-58-1.

Acknowledgments.—The author wishes to thank Professor J. Pascual for his encouragement and Drs. J. Castells and F. Serratosa for helpful discussions.

The Synthesis of 2- and 4-Fluoroestradiol[1]

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Received September 13, 1967

The 2- and 4-fluoro isomers of estradiol, which were of interest in the National Institutes of Health cancer program, have been synthesized by an unambiguous route *via* a Schiemann type of reaction from the respective amino precursors; the preparation of these as well as the consecutive steps is described below. A remarkably easy formation of a steroid nitrite ester and its decomposition to the corresponding ketone at low temperatures (15–25°) is reported. A striking difference in the intensities of the ultraviolet spectra enables a facile differentiation of the 2- from the 4-substituted series.

The synthesis of the 2- and 4-fluoroestradiol (2- and 4-fluoro-1,3,5(10)-estratriene-3,17β-diol, VIIa and b) was undertaken for the cancer program of the Cancer Chemotherapy National Service Center of the National Institutes of Health.[1,2] The 4-fluoro isomer had been prepared earlier by Neeman and Osawa[3] *via* a lengthy route starting with 19-nortestosterone. This route, however, was inapplicable to the preparation of the 2 isomer and for the 4 isomer the present route appears also to be the preferred one. Our initial attempts to introduce the fluorine by an unpublished procedure[4] requiring ultraviolet irradiation of the pertinent diazotized aminoestradiol 3-methyl ethers in a mixture of anhydrous hydrogen fluoride and dioxane in the presence of a copper powder catalyst were unsuccessful. The melting points reported in this procedure, which were the only physical data given, differed markedly (30–50°) from those found in this laboratory. On the other hand, our physical data for the 4 isomer agree fully with those reported by Neeman and Osawa.

We adopted the Schiemann reaction for the introduction of the fluorine into the aromatic ring., *i.e.*, thermal decomposition of the solid estrone 2- and 4-diazonium fluoroborate salts. For reasons explained below estrone was used as a starting material rather than estradiol and was nitrated with 1 equiv of nitric

(1) Supported by Contract No. PH-43-62-479, Cancer Chemotherapy National Service Center, National Institutes of Health, U. S. Public Health Service.

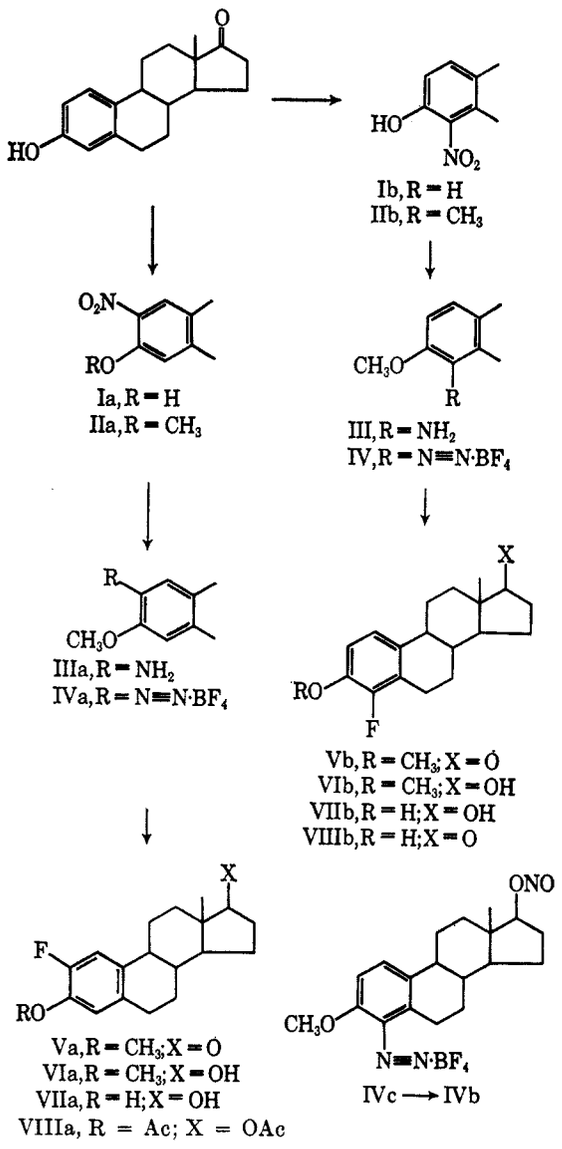
(2) Both 2- and 4-fluoroestradiol were found active in anti-implantation and estrogen tests (30 and 140% of estradiol, respectively) in the laboratories of Dr. J. R. Brooks and Dr. D. J. Patanelli of the Merck Institute for Therapeutic Research, Rahway, N. J. The uterotropic results were confirmed in the laboratories of the National Institutes of Health, Bethesda, Md., while at higher doses (*i.e.*, ten times) both epimers exhibited androgenic activities. With respect to cancer, no information has as yet been received by us from the National Institutes of Health.

(3) N. Neeman and Y. Osawa, *Tetrahedron Lett.*, **28**, 1987 (1963).

(4) This procedure was made available to us through the Cancer Chemotherapy National Service Center, Bethesda, Md. A mixture from this source was purified by thin layer chromatography and tested biologically by E. Hecker and G. Farthofer-Boeckh, *Biochem. Z.*, **338**, 1628 (1963).

acid, essentially as described by Werbin and Holoway.[5] The two isomers (Ia and b) were easily separated owing to the greater solubility of the 2-nitro isomer and obtained in about equal yield, 40% of the 4- and 37% of the 2-nitro isomer, which with dimethyl sulfate and dilute alkali[6] gave the methyl ethers (IIa and b) in 91 and 76% yield, respectively. Nuclear magnetic resonance spectra for these isomers showed two singlets at τ 2.17 and 3.18 in one case (IIa) and a pair of doublets at τ 2.55, 2.70 and 3.05, 3.20 (J = 9 cps) in the other (IIb), consistent with substitution of the 2 and the 4 positions, respectively. These assignments agree with those of Werbin and Holoway, which were arrived at by means of ultraviolet and infrared spectroscopy, as opposed to assignments by Niederl and Vogel[7] as well as Hillmann-Elies and coworkers.[8] Hydrogenation of the nitro isomers over Raney nickel gave good yields, 79% in each instance, of the two amino derivatives (IIIa and b) having physical properties similar to those reported by Kraychy, who prepared the same amines by another method.[6,9] They were diazotized in aqueous fluoroboric acid to yield the corresponding 2- or 4-diazonium fluoroborate (IVa and b) as solid yellow salts in 75 and 86% yield, respectively. Thermal decomposition of these salts at 130–135° under vacuum and in the presence of copper powder, serving both as catalyst and heat transfer agent, permitted isolation of the respective fluoro derivatives (Va and b) as sublimates, yielding 35% in both cases after chromatography. Reduction with sodium borohydride in tetrahydrofuran gave the respective 17β-carbinols (VIa and b) in nearly quantitative yields. Cleavage of the methyl ethers with pyridine hydrochloride yielded the desired 2- and the 4-fluoroestradiol (VIIa and b) in yields of 35 and 39%, respectively.[10] The 2 isomer was contaminated with a little estradiol, apparently formed during one of the latter steps, requiring separation *via* the diacetate (VIIIa). The previous assignment of structures to the nitro derivatives was confirmed by the proton magnetic resonance spectra of the fluoroestradiols. The appearance in the aromatic region of one spectrum (VIIa) of two doublets at τ 2.91, 3.13 and 3.24, 3.40 (J = 13 and 9.5 cps) indicated that the fluorine was located on carbon 2, since the pattern is characteristic for *ortho* and *meta* proton–fluorine coupling. The location of the fluorine at carbon 4 of the other isomer (VIIb) was arrived at by inference, the spectrum showing an aromatic multiplet centered at approximately τ 3.15. All other physical data were in accord with these structural assignments for the final products as well as the intermediates.

When initially estradiol was employed as the starting material, in a reaction sequence equivalent to the route described above, the diazotization reaction on the 4-aminoestradiol 3-methyl ether gave no solid fluoroborate salt but dark oils only. However, when a 1 mol excess of sodium nitrite was used, a yellow solid was rapidly formed. It was identified as the 17β-nitrite ester of the diazonium fluoroborate salt of estradiol methyl ether (IVc), the mode of formation and its behavior substantiating the structure. The product was very unstable and decomposed to the corresponding 17-ketone (IVb) on standing over several days at 20–



25° or at an accelerated rate at elevated temperatures. If left in the original reaction mixture, the product decomposed much faster; after stirring at 15–25° for 1 hr, the ketone was isolated directly, in yields of 60–85%. Heating under vacuum to 130° in the presence of copper powder gave the 4-fluoroestrone methyl ether (Vb), identical with the product obtained *via* the above-described route from estrone. The general utility of these reactions for preparative use are presently being looked into, particularly with a view toward a convenient way of preparing steroid nitrites and/or a mild method for oxidizing secondary alcohols, etc. Previously Coe and Doumani[11] prepared the *t*-butyl nitrite in the presence of aqueous sulfuric acid and decomposed it photochemically to acetone and nitro-

(5) H. Werbin and C. Holoway, *J. Biol. Chem.*, **223**, 651 (1956).

(6) S. Kraychy, *J. Amer. Chem. Soc.*, **81**, 1702 (1959); methanol was replaced with tetrahydrofuran as solvent.

(7) J. B. Niederl and H. J. Vogel, *ibid.*, **71**, 3566 (1949).

(8) E. A. Hillmann-Elies, G. Hillmann, and U. Schiedt, *Z. Naturforsch., B*, **8b**, 436 (1953).

(9) S. Kraychy and T. F. Gallagher, *J. Amer. Chem. Soc.*, **79**, 754 (1957); *J. Biol. Chem.*, **229**, 519 (1957).

(10) Reversal of the order of these two last steps gave a lesser over-all yield (20%); a small amount of 4-fluoroestrone (VIIIb) was thus prepared.

(11) C. S. Coe and T. F. Doumani, *J. Amer. Chem. Soc.*, **70**, 1516 (1948).

somethane. Barton and coworkers[12,13] prepared steroid nitrites with nitrosyl chloride in pyridine and subjected them to photolysis, causing rearrangements to the corresponding hydroxamic acids. They also briefly mentioned pyrolysis at high temperatures (160–300°?) of two steroid nitrites to a mixture of the corresponding ketones and alcohols; few experimental details and no yields were given.[14] In our case the ease of both the nitrite ester and the ketone formation was quite remarkable, the latter taking place at room temperature with or without isolation of the ester.[15] It is not yet clear if this facility is due to the particular conditions in the reaction mixture, such as an influence of the fluoroboric acid on the rate of decomposition, or due to some long-range effects from the diazonium fluoroborate group (over eight carbon atoms) or intermolecular phenomena, in either case interesting aspects.

It is noteworthy that in these series the ultraviolet absorption intensities of the 2-substituted steroids are considerably higher, mostly about two to four times, than those of the 4 isomers. This is true for all members of the two series, regardless of the electronic nature of the substituents, *i.e.*, whether they are electron-withdrawing or -donating groups. There are also minor variations in the wavelengths and some additional bands in the 2-substituted series, while in base the differences are largely eliminated. Table I illustrates

TABLE I
ULTRAVIOLET ABSORPTION INTENSITIES OF 2- AND 4-SUBSTITUTED ESTRONES AND ESTRADIOLS (IN METHANOL)

	4 substituted[a]	2 substituted[b]
I (NO_2)	ϵ_{275} 1700 (ϵ_{217} 11,000)	ϵ_{284} 6800 (ϵ_{216} 17,200)
I in base	ϵ_{288} 4480 (ϵ_{240} 15,400)	ϵ_{287} 5100 (ϵ_{233} 18,700)
II (NO_2)	ϵ_{275} 1525	ϵ_{275} 4400 (ϵ_{339} 3,070)
III (NH_2)	ϵ_{287} 2770	ϵ_{296} 4380 (ϵ_{237} 6,800)
V (F)	ϵ_{274} 1410	ϵ_{277} 2470
VI (F)	ϵ_{273} 1240	ϵ_{277} 2780
VII (F)	ϵ_{277} 1280	ϵ_{280} 2810
VII in base	ϵ_{290} 2300 (ϵ_{238} 9,700)	ϵ_{296} 3720 (ϵ_{237} 9,050)
VIII (F)	ϵ_{277} 1420 (ϵ_{217} 8,150)	

[a] b series. [b] a series.

this phenomenon and could serve to identify and distinguish between 2- and 4-substituted isomers of 1,3,5(10)-estratrienes.[16]

Experimental Section

Melting points were taken on a calibrated Thomas–Hoover Unimelt apparatus. Ultraviolet spectra were run on a Cary 11 spectrophotometer, infrared spectra on a Perkin-Elmer 421 grating spectrophotometer, and nuclear magnetic resonance spectra on a Varian A-60 spectrometer. Chemical shifts are reported in τ values relative to tetramethylsilane. Optical rotations were measured on a Zeiss precision polarimeter.

2-Nitroestrone (Ia) and 4-nitroestrone (Ib) were prepared essentially as described by Werbin and Holoway.[5] Nitration of estrone in acetic acid with 1 mol of concentrated nitric acid gave about equal amounts of each isomer, 37 and 40%, respectively. During the work-up the 4 isomer separated directly in nearly pure form whereas the more soluble 2 isomer was obtained from the mother liquors. Chromatography on alumina (Merck) with chloroform gave the pure 4 isomer (Ib), mp 274–280° (lit.[5,7] 270–280°, 258°), λ_{max}^{MeOH} 275 mμ (ϵ 1700) [lit.[5] 278 mμ (ϵ 1720)], and the pure 2 isomer (Ia), mp 179–183° (lit.[5,8] 183–184°, 155°), λ_{max}^{MeOH} 284 (ϵ 6800) and 216 mμ (ϵ 17,200) [lit.[5] 293 mμ (ϵ 8220)]. The infrared spectra were as expected for both isomers. Nuclear magnetic resonance data on the methylated derivatives below supported the structural assignments of Werbin and Holoway[5] and disagreed with those of Niederl and Vogel[7] and of Hillmann-Elies and coworkers.[8]

2- and 4-Nitroestrone Methyl Ether (IIa and b).—Methylation with dimethyl sulfate and dilute alkali in tetrahydrofuran in the usual manner[6] gave the 2- and 4-nitroestrone methyl ethers in 91 and 76% yields, respectively. The 2 isomer (IIa) showed mp 163–166° (lit.[6] 147°; 157–159°), λ_{max}^{MeOH} 275 (ϵ 4400) and 339 mμ (ϵ 3070) [lit.[6] 272.5 (ϵ 4510) and 336 mμ (ϵ 3130)]; the 4 isomer (IIb) showed mp 253–256° (lit.[6] 261–261.5°), λ_{max}^{MeOH} 275 mμ (ϵ 1525) [lit.[6] 275.5 mμ (ϵ 1570)]. The infrared spectra were as expected for both epimers.

The nuclear magnetic resonance spectra (in deuteriochloroform) of the two isomers showed in addition to the common features of peaks at τ 9.08 (18-CH_3) and 6.07 or 6.13 (CH_3O–) also two singlets at τ 2.17 and 3.18 in one case (IIa) and a pair of doublets at τ 2.55, 2.70 and 3.05, 3.20 in the other (IIb) (J = 9 cps), consistent with substitution of the 2 position and the 4 position, respectively.

2-Aminoestrone Methyl Ether (IIIa).—2-Nitroestrone methyl ether (IIa, 20 g) was hydrogenated in 2.4 l. of absolute ethanol over 9 g of Raney nickel (W-2) catalyst at 25° and an initial pressure of 40 psi, until the theoretical amount of hydrogen was absorbed. The catalyst was removed, the filtrate concentrated to dryness under vacuum and the residue recrystallized from methanol to yield 15 g (79%) of 2-aminoestrone methyl ether (IIIa), mp 170–173° (lit.[6] 172–174°). The product showed a single spot on a thin layer chromatogram (alumina–benzene), λ_{max}^{MeOH} 237 (ϵ 6800) and 296 mμ (ϵ 4380) [lit.[6] 239 (ϵ 6980) and 295.5 mμ (ϵ 4480)]. The infrared spectrum was consistent with the structure IIIa exhibiting bands at 3450, 3370 (N–H), 1725 (17-C=O), 1610, 1585, 1580 (Ph), 1260, 1280 cm^{-1} (OCH_3).

Estrone Methyl Ether 2-Diazonium Fluoroborate (IVa).—A suspension of 25 g of 2-aminoestrone methyl ether (IIIa) in a mixture of 100 ml of tetrahydrofuran, 20 ml of dioxane, and 125 ml of 48% aqueous fluoroboric acid was chilled to 0° to −5°. A solution of 12.5 g of sodium nitrite in 40 ml of cold water was added dropwise over 5 min to the vigorously stirred mixture while maintaining the above temperature. Stirring the slurry at 0 to 10° for 1 hr gave a reddish colored solution from which, upon dilution with 1.3 l. of cold water, the yellow diazonium fluoroborate salt precipitated. This was stirred for 1 hr at 0°, filtered off and washed with cold water, sucked as dry as possible, washed with ether, and dried under vacuum to yield 25 g (75%) of estrone methyl ether 2-diazonium fluoroborate (IVa), mp 160–165° dec. The infrared spectrum was consistent with the assigned structure IVa, exhibiting bands at 2230 (N≡N), 1735 (17-C=O), 1600, 1550, 1490 (Ph), 1280 (OCH_3), and 1050–1080 (br) cm^{-1} (BF_4).

Anal. Calcd for $C_{19}H_{23}O_2N_2BF_4$ (398.20): C, 57.40; H, 5.81; N, 7.03; F, 19.08. Found: C, 57.00; H, 5.70; N, 6.90; F, 18.60.[17]

2-Fluoroestrone Methyl Ether (Va).—A mixture of 17 g of estrone methyl ether 2-diazonium fluoroborate (IVa) and 17 g of copper powder (Martin Marietta Corp.) was spread in a thin layer in a sublimation apparatus (diameter of the pot, 13 cm). The diazonium salt was decomposed under vacuum (0.2 mm) by increasing the oil-bath temperature slowly to 130–135° over a

(12) C. H. Robinson, O. Gnoj, A. Mitchell, E. P. Oliveto, and D. H. R. Barton, *Tetrahedron*, **21**, 743 (1965); see also *J. Amer. Chem. Soc.*, **83**, 1771 (1961).

(13) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *ibid.*, **83**, 4076 (1961).

(14) After our article was first submitted a report by D. H. R. Barton, G. C. Ramsay, and D. Wege appeared in *J. Chem. Soc.*, 1915 (1967), describing the use of primary nitrites, prepared according to the method of Coe and Doumani,[11] in photolysis and pyrolysis reactions at 300 ± 10°. One steroidal nitrite was also converted at 132° in solution to the corresponding ketone and alcohol; no yields were given.

(15) This work was actually done in early 1965 and reported in the "Quarterly Progress Reports to the Cancer Chemotherapy National Service Center," Merck Sharp & Dohme Research Laboratories, Rahway, N. J., No. 30, 1965, p 11, and No. 31, 1965, p 12.

(16) This information was used advantageously in a forthcoming publication (*J. Org. Chem.*, in press) from this laboratory on the synthesis of 2- and 4-bromoestradiol suggesting that a previous preparation in the literature was impure or possibly not the desired isomers.

(17) The elemental analyses of this and the two following diazonium fluoroborates (IVb and c) are as good as can reasonably be expected for a direct precipitate that was not at all purified.

period of 1 hr, kept at this temperature for 2 hr, and finally increased to 170° for 3 hr. During this period some white solid and a red by-product sublimed onto the sides of the still. After cooling, the solids were dissolved in chloroform and filtered, and the filtrate was concentrated to dryness to yield 16 g of a dark amorphous solid. This material was stirred for 10 min in 125 ml of benzene and filtered to remove some tarry material; the filtrate was concentrated to dryness to yield 10 g of dark product. Chromatography on 300 g of acid-washed alumina (Merck) and elution with benzene yielded 4.5 g (35%) of 2-fluoroestrone methyl ether (Va), mp 125–128°, $[\alpha]^{25}D$ +69° (*c* 1, chloroform). Thin layer chromatography (alumina–benzene) showed a single spot; uv, λ_{max}^{MeOH} 277 mμ (ε 2470). The infrared spectrum was consistent with the structure Va showing bands at 1735 (17-C=O), 1610–1620, 1590–1510 (Ph), and 1270 cm^{-1} (OCH_3).

Anal. Calcd for $C_{19}H_{23}O_2F$ (302.39): C, 75.50; H, 7.65; F, 6.28. Found: C, 75.25; H, 7.70; F, 5.96.

2-Fluoroestradiol 3-Methyl Ether (VIa).—A solution of 11 g of 2-fluoroestrone methyl ether (Va) in 240 ml of tetrahydrofuran was chilled to 0–5° and treated with a solution of 4 g of sodium borohydride in 50 ml of cold methanol at 0–5° for 30 min. The solution was acidified by the cautious addition of 40 ml of cold 4 *N* hydrochloric acid, during which time the product precipitated. Most of the organic solvents were removed under vacuum on a water bath, 500 ml of water was added, and the mixture was stirred at 0–5° for 1 hr. The white 2-fluoroestradiol 3-methyl ether (VIa) was washed to neutrality with water and recrystallized from methanol to yield 10 g (90%), mp 84–86°, $[\alpha]^{25}D$ +61° (*c* 1, chloroform). A thin layer chromatogram (alumina–benzene) showed a single spot; uv, λ_{max}^{MeOH} 277 mμ (ε 2780). The infrared spectrum was consistent with the structure VIa, with bands at 3000–3650 (OH), 1580–1620, 1500 (Ph), and 1260 cm^{-1} (OCH_3).

Anal. Calcd for $C_{19}H_{25}O_2F$ (304.40): C, 75.01; H, 8.16; F, 6.24. Found: C, 74.80; H, 7.90; F, 5.93.

2-Fluoroestradiol (VIIa).—2-Fluoroestradiol 3-methyl ether (VIa, 10g) was mixed thoroughly with 100 g of pyridine hydrochloride in a glass vial and heated in a steel bomb to 180° for 4 hr. After cooling, the residue was treated with 0.1 *N* hydrochloric acid and extracted with ether, and the combined extracts were washed with 0.1 *N* hydrochloric acid and water. The ether layer was extracted four times with 250-ml portions of 1 *N* potassium hydroxide, the combined alkaline extracts were washed with ether and acidified with concentrated hydrochloric acid, and the organic material was extracted with chloroform. The combined extracts were washed to neutrality with water and concentrated to dryness under vacuum yielding 8 g of crude 2-fluoroestradiol. Recrystallization from methanol and treatment with charcoal gave 6.0 g of crystalline product, mp 170–173°. Phase solubility analysis and thin layer chromatograms on both alumina or silica gel (chloroform) showed a single component; however, two spots were visible on cellulose (ethylene glycol–benzene). The close physical similarities of the two components required their separation as the diacetates. Thus, 3.5 g of this material was treated with 14 ml of pyridine and 14 ml of acetic anhydride at 25° overnight. Addition of 500 ml of cold water, stirring for 2 hr, and washing with water yielded 4 g of diacetate, mp 95–105°. (A thin layer chromatogram showed the impurity to be the more polar estradiol diacetate.) This material was chromatographed on 120 g of silica gel (Baker); elution with benzene yielded 2.6 g (58%) of pure 2-fluoroestradiol 3,17-diacetate (VIIIa), mp 118–120°. A thin layer chromatogram (silica gel–benzene) now showed a single spot. The infrared spectrum (in Nujol) was consistent with the diacetate structure, as was a hydrolytic acetyl determination. The diacetate was hydrolyzed in 25 ml of methanol and 8 ml of water with a solution of 1.25 g of potassium hydroxide in 15 ml of methanol by stirring at 25° under nitrogen. The steroid dissolved within 5 min while the reaction mixture was stirred for 8 hr to ensure complete hydrolysis, then was neutralized with acetic acid and concentrated under vacuum on a water bath to remove most of the organic solvent. Water (50 ml) was added, the mixture was stirred at 0–5° for 1 hr, and the solids were washed with water to give 2.1 g of product. Sublimation at 180° (50 μ) gave 1.9 g (35%) of pure 2-fluoroestradiol (VIIa), mp 173–175°, $[\alpha]^{25}D$ +76° (*c* 1, methanol). A thin layer chromatogram (cellulose–ethylene glycol–benzene) showed a single spot; uv, λ_{max}^{MeOH} 280 mμ (ε 2810), in base 296 mμ (ε 3720) and 237 (9050). The infrared spectrum (in Nujol) exhibited bands at 3100, 3350–3400, 3550–3600 (OH), 1610, 1590, 1500 cm^{-1} (Ph). The nuclear magnetic resonance spectrum (in deuterioacetone) was consistent with the assigned structure VIIa, with peaks at τ 9.22 (18-CH_3), 6.30 (17-OH), and two doublets at 2.91, 3.13 and 3.24, 3.40 (*J* = 13 and 9.5 cps). The latter pattern is characteristic for *ortho* and *meta* proton–fluorine coupling respectively, indicating that the fluorine was located on carbon 2.

Anal. Calcd for $C_{18}H_{23}O_2F$ (290.38): C, 74.45; H, 7.98; F, 6.54. Found: C, 74.42; H, 8.08; F, 6.32.

4-Aminoestrone Methyl Ether (IIb).—4-Nitroestrone methyl ether (IIb, 20 g) was hydrogenated as described for the 2 isomer (IIIa) and the residue recrystallized from methanol, yielding 15 g (79%) of 4-aminoestrone methyl ether (IIIb), mp 173–175° (lit.[6] 188–191°). Thin layer chromatography (alumina–benzene) showed a single spot; uv, λ_{max}^{MeOH} 287 mμ (ε 2770) [lit.[6] 287.5 mμ (ε 2820)]. The infrared spectrum was consistent with the structure IIIb, with bands at 3400, 3450 (N–H), 1730 (17-C=O), 1600 (NH_2), and 1560, 1480 cm^{-1} (Ph).

Estrone Methyl Ether 4-Diazonium Fluoroborate (IVb).—A suspension of 20 g of 4-aminoestrone methyl ether (IIIb) in a mixture of 40 ml of dioxane and 80 ml of 48% aqueous fluoroboric acid was diazotized as described for the 2 isomer (IVa), yielding 23 g (86%) of estrone methyl ether 4-diazonium fluoroborate (IVb), mp 160–165° dec. The infrared spectrum was consistent with the structure IVb, with bands at 2230 (N≡N), 1735 (17-C=O), 1600, 1550, 1490 (Ph), 1280 (OCH_3) and 1050–1080 (br) cm^{-1} (BF_4).

Anal. Calcd for $C_{19}H_{23}O_2N_2BF_4$ (398.20): C, 57.40; H, 5.81; N, 7.03; F, 19.08. Found: C, 57.33; H, 5.81; N, 7.02; F, 18.50.[17]

4-Fluoroestrone Methyl Ether (Vb).—A mixture of 17 g of estrone methyl ether 4-diazonium fluoroborate (IVb) and 17 g of copper powder was treated in the same manner as the 2 isomer (Va), to yield 4.5 g (35%) of pure 4-fluoroestrone methyl ether (Vb), mp 160–163°, $[\alpha]^{25}D$ +132° (*c* 1, chloroform). Thin layer chromatography (alumina–benzene) showed a single spot, uv, λ_{max}^{MeOH} 274 mμ (ε 1410). The infrared spectrum was consistent with the structure Vb, with bands at 1730 (17-C=O), 1600–1620, 1590 (Ph), and 1280 cm^{-1} (OCH_3).

Anal. Calcd for $C_{19}H_{23}O_2F$ (302.39): C, 75.50; H, 7.65; F, 6.28. Found: C, 75.45; H, 7.87; F, 5.95.

4-Fluoroestradiol 3-Methyl Ether (VIb).—To a solution of 8 g of 4-fluoroestrone methyl ether (Vb) in 160 ml of tetrahydrofuran chilled to 0–5° was added 4 g of sodium borohydride dissolved in 50 ml of cold methanol, as described for the 2-fluoro isomer (VIa). The 4-fluoroestradiol 3-methyl ether (VIb) was recrystallized from methanol to yield 7.2 g (90%), mp 135–138°, $[\alpha]^{25}D$ +75° (*c* 1, chloroform). A thin layer chromatogram (alumina–benzene) showed a single spot; uv, λ_{max}^{MeOH} 273 mμ (ε 1240). The infrared spectrum was consistent with the structure VIb, with bands at 3600, 3450 (OH), 1600–1620, 1500 (Ph), and 1290 cm^{-1} (OCH_3).

Anal. Calcd for $C_{19}H_{25}O_2F$ (304.40): C, 75.01; H, 8.16; F, 6.24. Found: C, 74.83; H, 8.00; F, 5.95.

4-Fluoroestradiol (VIIb).—4-Fluoroestradiol 3-methyl ether (VIb, 8 g) was mixed with 80 g of pyridine hydrochloride and treated as described for the 2-fluoro isomer (VIIa), yielding 7 g of material. Recrystallization from methanol gave 3.0 g (39%) of pure 4-fluoroestradiol (VIIb), mp 189–191° (lit.[3] mp 190–191°), $[\alpha]^{25}D$ +70.8° (*c* 1, methanol). A thin layer chromatogram (alumina–chloroform) showed a single spot; uv, λ_{max}^{MeOH} 277 mμ (ε 1280) [lit.[3] 274 mμ (ε 1210)], in base 290 mμ (ε 2300) and 238 (9700) [lit.[3] 292 mμ (ε 2340)]. The infrared spectrum (in Nujol) showed bands at 3200–3500 (OH), 1610, 1580, 1490 cm^{-1} (Ph). The nuclear magnetic resonance spectrum (in deuterioacetone) was consistent with the assigned structure VIIb, with peaks at τ 9.23 (18-CH_3), 6.30 (17-OH), and an aromatic multiplet extending from 2.97 to 3.40, centered at approximately 3.15.

Anal. Calcd for $C_{18}H_{23}O_2F$ (290.38): C, 74.45; H, 7.98; F, 6.54; C, 74.50; H, 7.91; F, 6.54.

Estradiol 3-Methyl Ether 4-Diazonium Fluoroborate 17β-Nitrite Ester (IVc).—To a solution of 5 g of 4-aminoestradiol 3-methyl ether in a chilled mixture of 8 ml of dioxane and 8 ml of 48% aqueous fluoroboric acid was added dropwise 2.5 g of sodium nitrite in 3 ml of cold water over 5 min while maintaining the temperature at 0–5°. The yellow precipitate which formed was filtered off after stirring for 10 min at 0–5°, washed with cold water, sucked as dry as possible, and washed with ether. The product, weighing 5 g (67%), was shown to be the estradiol 3-methyl ether 4-diazonium fluoroborate 17β-nitrite ester (IVc),

as also suggested by its mode of formation and behavior. The infrared spectrum (in Nujol) was consistent with this structure, showing bands at 1650 (-ONO_2 or ONO), 2280 (N≡N), 1610, 1580, 1500 (Ph), 1020–1090 cm^{-1} (BF_4).

Anal. Calcd for $C_{19}H_{24}O_3N_3BF_4$ (429.22): C, 49.50; H, 5.22; N, 9.10; F, 16.45. Found: C, 50.54; H, 5.17; N, 9.47; F, 17.05.[17]

The product was very unstable and decomposed rapidly without melting at about 120°, giving off a brown gas, while standing at 20–25° for several days gave a pale yellow solid, identified as the estrone 3-methyl ether 4-diazonium fluoroborate (IVb). In experiments where the initial precipitate of the diazonium fluoroborate nitrite ester was left stirring in the original reaction mixture for 1 hr at 15–25°, good yields (60–85%) of the 17-ketone (IVb) were obtained directly.[18] This could be converted into the 4-fluoroestrone methyl ether (Vb), as described above in 33% yield.

4-Fluoroestrone (VIIIb).—4-Fluoroestrone methyl ether (Vb, 500 mg) was mixed thoroughly with 5 g of pyridine hydrochloride and treated as described for the 4-fluoroestradiol methyl ether (VIb), yielding 100 mg (21%) of 4-fluoroestrone (VIIIb), mp 223–225°, $[\alpha]^{25}D$ +144° (*c* 1, chloroform). A thin layer chromatogram (alumina–chloroform) showed a single spot; uv, λ_{max}^{MeOH} 277.5 mμ (ε 1420) and 217 (8150). The infrared spectrum (in Nujol) was consistent with the structure VIIIb, with bands at 3200–3500 (OH), 1610, 1580, 1490 (Ph), 1730 cm^{-1} (17-C=O).

Anal. Calcd for $C_{18}H_{21}O_2F$ (288.37): C, 75.00; H, 7.33; F, 6.59. Found: C, 74.90; H, 7.40; F, 6.50.

Registry No.—Ia, 5976-73-8; Ib, 5976-74-9; IIa, 16223-65-7; IIb, 14846-62-9; IIIa, 13010-22-5; IIIb, 13010-21-4; IVa, 16222-59-6; IVb, 15091-55-1; IVc, 16222-60-9; Va, 16205-28-0; Vb, 16205-29-1; VIa, 16205-30-4; VIb, 16205-31-5; VIIa, 16205-32-6; VIIb, 1881-37-4; VIIIa, 16205-34-8; VIIIb, 1881-36-3.

Acknowledgments.—The authors wish to thank Dr. Byron H. Arison for interpretation of the nuclear magnetic resonance spectra, Mr. Robert W. Walker for the infrared spectra, Mr. Richard N. Boos and his staff for the elemental analyses, and Mr. Alec Kalowsky for the ultraviolet data.

(18) NOTE ADDED IN PROOF.—Subsequently this procedure was improved upon by filtering off the nitrite ester (IVc) and re-treating it with the original volumes of dioxane and aqueous fluoroboric acid at about 20°. After the evolution of gas had subsided, the estrone 3-methyl ether 4-diazonium fluoroborate (IVb) crystallized from the cooled (0°) reddish solution in 90% yield. This high yield indicates that this reaction proceeds by a mechanism quite different from the one suggested by Barton and coworkers[12-14] or authors cited by Barton, for the thermal decomposition of nitrite esters. Their mechanism requires the formation of equal amounts of ketone and the corresponding carbinol *via* an over-all disproportionation reaction, whereas we found no such alcohol. It is hoped that this subject can be expanded upon

$$2R_2CHO\text{—}N{=}O \longrightarrow R_2C{=}O + R_2CHOH + 2NO$$

in a planned forthcoming publication on low temperature decomposition of nitrite esters.

Synthesis of Optically Active 1-C-Phenylglycerols and Their Derivatives[1a]

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Received January 3, 1968

Addition of phenylmetallic reagents to 1,2-*O*-isopropylidene-D-glyceraldehyde leading to the formation of optically pure D-*erythro*- and D-*threo*-1-*C*-phenylglycerol was investigated. Oxidation of the newly formed hydroxyl group in the addition products by Moffatt's reagent gave the expected ketone, which was reduced by $LiAlD_4$ to yield a pair of optically active diastereomers, 2,3-*O*-isopropylidene-D-*erythro*-1-*C*-phenylglycerol-1-d_1 and 2,3-*O*-isopropylidene-D-*threo*-1-*C*-phenylglycerol-1-d_1. The absolute configuration of the phenylglycerols and their derivatives was established by conversion into compounds of known configuration and supported by infrared and nuclear magnetic resonance (nmr) spectrometric studies. The complex nmr splitting patterns of the 1-*C*-phenylglycerols and their acyclic derivatives are interpretable by their resemblance to simple first-order splitting patterns.

Stereoselective addition of phenylmagnesium bromide to *aldehydro* and *keto* sugars and the determination of absolute configuration at the benzylic center was reported[2] recently. The steric difference between phenyllithium and phenylmagnesium bromide reagents was suggested as an explanation for the dramatic difference in diastereomeric product distribution, when these reagents added to *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldimine.[3] Addition of phenylmagnesium bromide to 2,3-di-*O*-benzoyl-D-glyceraldehyde was reported to yield a single optically active product, whose absolute configuration was not firmly established, but which was identified as "dibenzoyl-α-D-phenylglycerol" by the authors.[4] In this Article, we shall describe the synthesis of optically active 1-*C*-phenylglycerols; their derivatives, including some with a deuterium atom attached to the benzylic carbon; and the assignment of absolute configuration to these compounds.

When phenyllithium or phenylmagnesium bromide was allowed to react with 2,3-*O*-isopropylidene-D-glyceraldehyde,[5] the same pair of diastereomers, 2,3-*O*-isopropylidene-D-*threo*-1-*C*-phenylglycerol (**1**) and 2,3-*O*-isopropylidene-D-*erythro*-1-*C*-phenylglycerol (**4**), were obtained in good yield. Product analysis by glpc revealed that the phenyllithium addition gives almost the same diastereomeric distribution (62% *threo*, 38% *erythro*) as the phenylmagnesium bromide addition (58% *threo*, 42% *erythro*). The preponderant isomer in each case was the one predicted by Cram's rule of asymmetric induction.[6] Although the stereoselectivity of phenylmagnesium bromide reagent appears to be somewhat less than that observed for phenyllithium, no dramatic reversal of product distribution was noted in the course of this work, contrary to the reversal noted by Yoshimura, Ohgo, and Sato[3] for their work involving the addition of these two reagents to *N*-benzyl-2,3-*O*-

(1) (a) Presented at 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968, Abstracts, p C2. (b) National Science Foundation Undergraduate Research Program Participant, Grant No. GY-817.

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