[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH AND THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CHICAGO]

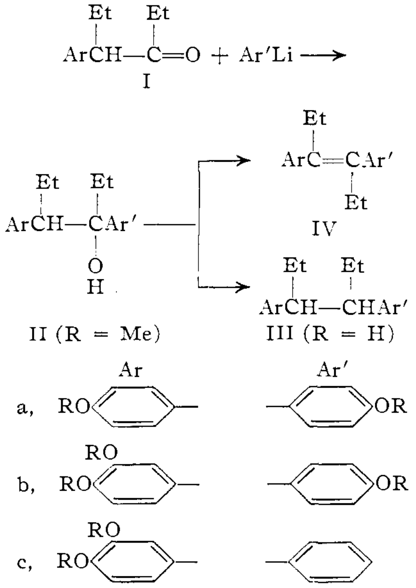
Hormone Analogs. III.[1] The Preparation of Hexestrol Analogs

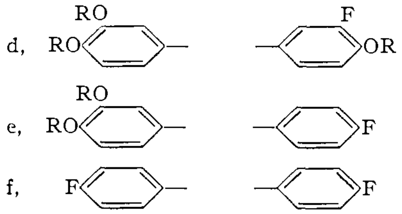
BY RICHARD J. PRATT AND ELWOOD V. JENSEN

RECEIVED APRIL 9, 1956

Catalytic hydrogenation over palladium black of the carbinol (IIa), prepared by the reaction of 4-*p*-anisylhexan-3-one and *p*-anisyllithium, takes place stereospecifically to yield hexestrol dimethyl ether. Similar reduction of a number of analogous carbinols followed by demethylation with hydriodic acid in the presence of red phosphorus furnished a series of hexestrol analogs in which the nature of one or both aryl groups is varied. The effect of nuclear substituents and of perchloric acid on the hydrogenolysis reaction is discussed.

In connection with a search for hormonally inactive compounds which are capable of inhibiting pituitary secretion or antagonizing the actions of sex hormones,[2] the preparation of certain analogs of stilbestrol was described recently[1] in which the nature of one or both of the aromatic rings was varied. This synthesis involves the conversion of the appropriate aromatic aldehyde to the corresponding arylhexanone (I) which, on treatment with an aryllithium reagent, gives a carbinol II. Dehydration of the latter substance followed by cleavage of the protecting methoxyl groups yields the stilbestrol analog IV. This procedure possesses two unfavorable features. First, the yield of the *trans*-stilbene compound on dehydration is always rather low (25–40%). Second, when applied to substances possessing a veratryl group (*e.g.*, IIb), the final demethylation step, namely, heating with dry methylmagnesium iodide,[3] was found to give products which rapidly turn black and from which no crystalline material could be isolated. This paper describes a process for the transformation of the intermediate carbinols II into the corresponding hexestrol derivatives III, a procedure which is free from both of the undesirable features of the previous method.





When an acetic acid solution of the carbinol IIa, obtained by the reaction of 4-*p*-anisylhexan-3-one with *p*-anisyllithium, is shaken with hydrogen in the presence of a palladium black catalyst there is a rapid uptake of hydrogen with reductive elimination of the benzyl-type[4] hydroxyl group. The reduction of this presumably erythro[1,5] carbinol takes place stereospecifically and apparently with retention of configuration to give in 73% yield hexestrol dimethyl ether possessing the *meso* configuration. In contrast to compounds of the stilbestrol series, demethylation of hexestrol dimethyl ether can be effected in high yield by heating with hydriodic acid.[6]

A similar process of hydrogenolysis and demethylation was applied to a number of other carbinols obtained in analogous fashion from the reaction of an arylhexanone with an aryllithium reagent. It was found that the hydrogenolysis of carbinols in which Ar' is anisyl (IIa and b) takes place rapidly in acetic acid solution whereas with the other carbinols, especially those in which Ar' possesses a fluorine substituent, it proceeds more slowly. Addition of a small amount of perchloric acid to the hydrogenation medium results in all cases in a significant increase in the rate of hydrogen uptake. However, the yield of *meso*-hexestrol derivative isolated usually was somewhat lower in the presence of perchloric acid than in its absence. Therefore, it would appear that perchloric acid should be added only when the rate of hydrogenolysis in its absence is too slow to be practical.

In contrast to demethylation by the Grignard reagent, the cleavage of methoxyl groups of veratryl residues by hydriodic acid in the presence of red phosphorus[7] was found to proceed smoothly to yield crystalline products. By this procedure, the hexestrol analogs (IIIb-f) were prepared without difficulty. The hormonal and antihormonal properties of these compounds are being investi-

---

(1) Paper II. R. L. Morgan, P. Tannhauser, R. J. Pratt, T. C. Myers and E. V. Jensen, THIS JOURNAL, **77**, 5658 (1955).

(2) T. C. Myers, R. J. Pratt, R. L. Morgan, J. O'Donnell and E. V. Jensen, *ibid.*, **77**, 5655 (1955).

(3) E. Späth, *Monatsh.*, **35**, 319 (1914).

(4) W. H. Hartung in "Organic Reactions," Vol. 7, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 263.

(5) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1952).

(6) S. Bernstein and E. S. Wallis, *ibid.*, **62**, 2871 (1940).

(7) T. H. Guerrero and V. Deulofeu, *Ber.*, **70**, 947 (1937).

gated in this laboratory by Dr. Charles Huggins, and the results will be reported separately.

Experimental[8]

Preparation of Arylhexanones (I).—The synthesis of 4-*p*-anisylhexan-3-one and 4-*p*-fluorophenylhexan-3-one was described previously.[2] 4-Veratrylhexan-3-one was prepared similarly using the nitropropane method adapted from the procedures of Shepard[9] and of Baker.[10] From the reaction of veratraldehyde (99 g., 0.6 mole), 1-nitropropane (89 g., 0.6 mole) and *n*-butylamine (6.0 ml., 0.06 mole for 15 days at 28° there was obtained 1-veratryl-2-nitrobutene-1, 92.5 g. (65%), m.p. 70–74°. The analytical sample, obtained on 3 recrystallizations from ethanol, melted at 79–80°.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.35; N, 5.91. Found: C, 61.07; H, 6.29; N, 5.62.

The foregoing product (92 g., 0.39 mole) was heated under reflux for two hours in a mixture of 400 ml. of water, 85 ml. of concentrated hydrochloric acid, 205 g. of iron filings (40 mesh) and 570 mg. of ferric chloride. Distillation of the reaction product gave crude 1-veratrylbutan-2-one, 67 g. (84%), b.p. 113–118° (0.04 mm.), $n^{22}D$ 1.5335. Redistillation through a Podbielniak whirling band column yielded the purified product, 44 g. (55%), b.p. 102–104° (0.03 mm.), $n^{23}D$ 1.5277.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.25; H, 7.75. Found: C, 69.11; H, 7.71.

The semicarbazone derivative of this ketone melted at 153–154° from methanol.

Anal. Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 59.23; H, 7.24; N, 15.90.

A stirred mixture of 1-veratrylbutan-2-one (42.5 g., 0.204 mole) and sodium methoxide (22 g., 0.41 mole) was treated at 0° with 30 ml. of ethyl iodide. After reaction was complete, another 30 ml. of ethyl iodide was added and the mixture heated under reflux for one hour. After cooling, 120 ml. of 20% acetic acid was added; the product was extracted with ether and distilled through a short column to yield 4-veratrylhexan-3-one, 40 g. (84%), b.p. 102.5–104.5 (0.05 mm.), $n^{25}D$ 1.5173.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.11; H, 8.53. Found: C, 70.75; H, 8.18.

The semicarbazone derivative melted at 138–139° from methanol.

Anal. Calcd. for $C_{15}H_{23}O_3N_3$: C, 61.41; H, 7.90; N, 14.33. Found: C, 61.70; H, 7.98; N, 14.14.

Hexestrol (IIIa). **Carbinol Preparation.**—An ethereal solution of *p*-bromoanisole (4.0 g., 0.02 mole) was added at room temperature to a stirred solution of *n*-butyllithium (0.02 mole) in 30 ml. of ether. After stirring for half an hour the mixture was cooled to −30° and a solution of 4-*p*-anisylhexan-3-one (2.06 g., 0.01 mole) in 50 ml. of dry ether was added. After stirring for half an hour at −15° the reaction mixture was warmed to 0° and poured into a beaker of crushed ice. The product was extracted with ether and the extract washed with water, dilute acetic acid, sodium bicarbonate solution and finally with saturated sodium chloride solution. The ether was evaporated and the residue was crystallized from ethanol to yield 3,4-bis-(*p*-anisyl)-hexan-3-ol (IIa), 2.46 g. (80%), m.p. 115.8–116.4° (reported[11] 117°).

Reduction.—A solution of the carbinol IIa (315 mg., 1.0 mmole) in 10 ml. of glacial acetic acid was stirred magnetically in an atmosphere of hydrogen in the presence of 150 mg. of palladium black catalyst. As the reaction proceeded the product began to separate from solution. The calculated amount of hydrogen was absorbed in 26 minutes, whereupon the mixture was warmed to effect solution of all organic material and filtered. Upon dilution of the filtrate with water there was obtained a white precipitate of hexestrol dimethyl ether, 216 mg. (73%), m.p. 139–141°. Two recrystallizations from acetone gave the analytically pure product, m.p. 143–144° (reported[12] 144–145°).

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.23; H, 8.78.

In another experiment 315 mg. of IIa in 12 ml. of acetic acid with 65 mg. of palladium black was hydrogenated in 34 minutes to yield 215 mg. (73%), of hexestrol dimethyl ether, m.p. 139–141.5°. When 0.1 ml. of 72% perchloric acid was added to a similar system, hydrogenation was complete in 20 minutes but the product, 213 mg., melted at 118–135° and required a crystallization from acetone to furnish 180 mg. (61%) of material, m.p. 138–142°.

When the reduction of 315 mg. of IIa in 20 ml. of acetic acid was carried out with 630 mg. of a 10% palladium on charcoal catalyst, hydrogen uptake was much slower than with palladium black. After 1.5 hours hydrogen uptake ceased. From the mixture there was isolated hexestrol dimethyl ether, 226 mg. (75%), m.p. 140–142° and 75 mg. of starting material, m.p. 116–118°, not depressed by admixture with IIa. In ethanol solution reduction of IIa using a palladized charcoal catalyst did not take place.

Demethylation.—A mixture of hexestrol dimethyl ether (149 mg., 0.50 mmole), acetic anhydride (2.0 ml.), 50% hydriodic acid (2.0 ml.) and red phosphorus (149 mg.) was heated under reflux for 30 minutes, after which 10 ml. of acetic acid was added and the hot solution filtered. The filtrate was diluted with water and the precipitated solid collected on a filter, washed with water and dried to yield hexestrol (IIIa), 125 mg. (93%), m.p. 180–183°. Recrystallization from a mixture of acetone and hexane yielded a purified product melting at 182–183° which did not depress the melting point of an authentic sample of hexestrol.

3-Hydroxyhexestrol (IIIb). **Carbinol Preparation.**—To a stirred solution of *p*-anisyllithium, prepared by the exchange reaction at room temperature of *n*-butyllithium (0.09 mole) and *p*-anisyl bromide (18.7 g., 0.10 mole) in 50 ml. of dry ether, there was added at −10° a solution 4-veratrylhexan-3-one (8.0 g., 0.034 mole) in 20 ml. of dry ether. The mixture was allowed to stand for 12 hours at 0–15° and then worked up as described for the preparation of IIa. The oily product was recrystallized from a mixture of hexane and acetone to yield 3-*p*-anisyl-4-veratrylhexan-3-ol (IIb), 1st crop 7.55 g., m.p. 125–127°, 2nd crop 1.02 g., m.p. 122–124°, total yield 74%. Recrystallization from hexane–acetone furnished the analytical sample, m.p. 126.5–127.5°.

Anal. Calcd. for $C_{21}H_{27}O_4$: C, 73.23; H, 8.19. Found: C, 73.45; H, 8.30.

Reduction.—Hydrogenation of the carbinol IIb (781 mg., 2.27 mmoles) in 20 ml. of acetic acid with 156 mg. of palladium black in the manner described for IIa was effected in 86 minutes to yield *meso*-3-*p*-anisyl-4-veratrylhexane, 559 mg. (75%), m.p. 98–101°, from hexane. Recrystallization from methanol furnished the analytical sample, m.p. 105.5–107°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.93; H, 8.59. Found: C, 76.95; H, 8.70.

A similar reduction of 1.0 g. of IIb in acetic acid with 150 mg. of palladium black was complete in 50 minutes to yield 760 mg. (80%) of the product melting at 102–104.5°. A reduction of 688 mg. of IIb with 138 mg. of palladium black in acetic acid in the presence of 0.1 ml. of 72% perchloric acid was completed in 39 minutes to give 438 mg. (67%), of 3-*p*-anisyl-4-veratrylhexane, m.p. 102–105°.

Demethylation.—A mixture of 3-*p*-anisyl-4-veratrylhexane (444 mg., 1.35 mmoles), acetic anhydride (6.0 ml.), 50% hydriodic acid (6.0 ml.) and red phosphorus (960 mg.) was heated under reflux for 30 minutes and the product isolated as described for IIIa. Thus was obtained 3-hydroxyhexestrol (IIIb), 372 mg. (96%), m.p. 180–182°. Recrystallization from benzene yielded the analytical sample, m.p. 181.5–183°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.75. Found: C, 75.31; H, 8.04.

---

[8] Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois. All reactions involving lithium reagents were carried out in an atmosphere of dry nitrogen. 2-Fluoro-4-bromoanisole was prepared by the bromination of 2-fluoroansiole (G. Schiemann, *et al.*, *J. prakt. Chem.*, **143**, 18 (1935)).

[9] E. R. Shepard, J. F. Noth, H. D. Porter and C. K. Simmons, THIS JOURNAL, **74**, 4611 (1952).

[10] B. R. Baker, *ibid.*, **65**, 1572 (1943). The authors regret having overlooked this prior work in the previous paper.

[11] E. C. Dodds, L. Goldberg, W. Lawson and R. Robinson, *Nature*, **141**, 247 (1938); F. v. Wessely, E. Kerschbaum, A. Kleedorfer, F. Prissinger and E. Zajic, *Monatsh.*, **73**, 127 (1940).

[12] A. M. Docken and M. A. Spielman, THIS JOURNAL, **62**, 2163 (1940).

3-Hydroxy-4′-desoxyhexestrol (*meso*-**3-Phenyl-4-*m,p*-dihydroxyphenylhexane, IIIc). Carbinol Preparation.**—To a stirred ethereal solution of phenyllithium (0.03 mole) held at 0° there was added during a period of 15 minutes a solution of 4-veratrylhexan-3-one (6.0 g., 0.025 mole) in 20 ml. of dry ether. After stirring at 0° for two hours the product was isolated in the manner described for IIa. The oily residue was crystallized from a mixture of hexane and ether to yield 3-phenyl-4-veratrylhexan-3-ol (IIc), 1st crop 4.75 g., m.p. 80–81.5°, 2nd crop, 0.65 g., m.p. 75–78°, total yield 68%. Recrystallization from hexane furnished the analytical sample, m.p. 81–82.5°.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.31; H, 8.42.

Reduction.—Hydrogenation of IIc (942 mg., 3.0 mmoles) in 20 ml. of acetic acid with 140 mg. of palladium black in the manner described for IIa was effected in 180 minutes. The oily product (900 mg.) was chromatographed on 30 g. of alumina (Merck acid washed) and the fraction (455 mg.) eluted with 1:1 pentane–benzene was recrystallized from hexane to yield *meso*-3-phenyl-4-veratrylhexane, 338 mg. (38%), m.p. 60–64°. Recrystallization of a portion of this product from hexane furnished the analytical sample, m.p. 62–63°.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.69; H, 9.02.

Further elution of the column with ether yielded 342 mg. of the starting carbinol, m.p. 80–81° not depressed by admixture with IIc.

In a similar experiment reduction of IIc (667 mg., 2.12 mmoles) in 15 ml. of acetic acid with 200 mg. of palladium black was effected in 110 minutes to give, on crystallization of the oily product from hexane, *meso*-3-phenyl-4-veratrylhexane, 1st crop 367 mg., m.p. 55–58°, 2nd crop 68 mg., m.p. 51–55°, total yield 70%. Hydrogenation of IIc (315 mg., 1.0 mmole) with 63 mg. of palladium in 12 ml. of acetic acid to which had been added 0.1 ml. of perchloric acid was complete in 26 minutes to yield the same product, 1st crop 111 mg., m.p. 58–61°, 2nd crop 95 mg., m.p. 55–59°, total yield 69%.

Demethylation.—The above phenylveratrylhexane (408 mg., 1.24 mmoles) was subjected to demethylation under the conditions described for hexestrol dimethyl ether. Recrystallization from benzene yielded 3-hydroxy-4′-desoxyhexestrol (IIIc), 298 mg. (80%), m.p. 167–169°. Further recrystallization from benzene furnished the analytical sample, m.p. 168.5–169.5°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.21. Found: C, 80.06; H, 8.50.

Similar demethylation of 319 mg. of the oily residues obtained from the mother liquors from the crystallization of the reduction product of IIc yielded 71 mg. of IIIc, m.p. 166–168.5°.

3-Hydroxy-3′-fluorohexestrol (IIId). **Carbinol Preparation.**—To a stirred ethereal solution of *m*-fluoro-*p*-anisyllithium, prepared from the exchange reaction at −50° of *n*-butyllithium (0.05 mole) and 2-fluoro-4-bromoanisole (6.15 g., 0.03 mole), there was added at −50° a solution of 4-veratrylhexan-3-one (6.0 g., 0.025 mole). The product was isolated as described for IIIa and crystallized from an ether–hexane mixture to yield 3-*m*-fluoro-*p*-methoxyphenyl-4-veratrylhexan-3-ol (IId), 1st crop 3.45 g., m.p. 121–124°, 2nd crop 0.91 g., m.p. 118.5–122.5°, 3rd crop 0.51 g., m.p. 118–122°, total yield 54%. Recrystallization from ether furnished the analytical sample, m.p. 127–128°.

Anal. Calcd. for $C_{21}H_{27}O_4F$: C, 69.59; H, 7.51. Found: C, 69.81; H, 7.70.

Reduction.—Hydrogenation of the carbinol IId (1.09 g., 3.0 mmoles) with 217 mg. of palladium black in 20 ml. of acetic acid with 0.1 ml. of perchloric acid was complete in 60 minutes. The oily product was chromatographed over 20 g. of alumina (Merck acid washed) and the material (611 mg.) eluted with pentane-benzene 8:1 was crystallized from hexane to yield *meso*-3-*m*-fluoro-*p*-methoxyphenyl-4-veratrylhexane, 472 mg. (49%), m.p. 87–90.5°. Recrystallization from hexane furnished the analytical sample, m.p. 88.5–90°.

Anal. Calcd. for $C_{21}H_{27}O_3F$: C, 72.80; H, 7.86. Found: C, 72.87; H, 8.02.

When the hydrogenation was carried out in acetic acid without perchloric acid, hydrogen uptake ceased after 11 minutes when less than half the expected amount of hydrogen had been absorbed. On addition of 0.01 ml. of perchloric acid, hydrogen uptake commenced again and was complete in 17 minutes more. Chromatography over alumina and elution with pentane gave a 54% yield of a product melting at 87–90°.

Demethylation.—The above fluoroanisylveratrylhexane (361 mg.) was subjected to demethylation with hydriodic acid and phosphorus under the conditions described for hexestrol dimethyl ether to give a practically quantitative yield of crude 3-hydroxy-3′-fluorohexestrol (IIId), m.p. 155–160°. Recrystallization from benzene furnished the analytically pure material, m.p. 164–165.5°.

Anal. Calcd. for $C_{18}H_{21}O_3F$: C, 71.03; H, 6.95. Found: C, 71.31; H, 7.08.

meso-**3-*p*-Fluorophenyl-4-*m,p*-dihydroxyphenylhexane** (**IIIe**). **Carbinol Preparation.**—Reaction of 4-veratrylhexan-3-one (6.0 g., 0.025 mole) with *p*-fluorophenyllithium, obtained from the exchange reaction at −40° of *n*-butyllithium (0.05 mole) with *p*-fluorophenyl bromide (10.5 g., 0.06 mole), was carried out at −10° in a manner similar to that described for IIa. Crystallization of the oily reaction product from hexane yielded 3-*p*-fluorophenyl-4-veratrylhexan-3-ol (IIe), 1st crop 5.22 g., m.p. 74–77°, 2nd crop 0.80 g., m.p. 77–80°, total yield 71%. Recrystallization from a hexane–ether mixture furnished the analytical sample, m.p. 87.5–88.5°.

Anal. Calcd. for $C_{20}H_{25}O_3F$: C, 72.26; H, 7.58. Found: C, 72.37; H, 7.71.

Reduction.—Hydrogenation of the above carbinol IIe (996 mg., 3.0 mmoles with 200 mg. of palladium black in acetic acid in the presence of 0.1 ml. of perchloric acid was complete in 45 minutes to give an oily product which was chromatographed over alumina. Elution with pentane gave 3-*p*-fluorophenyl-4-veratrylhexane, 282 mg. (30%), m.p. 63–65°. Recrystallization from hexane furnished the analytical sample, m.p. 64–65°.

Anal. Calcd. for $C_{22}H_{25}O_2F$: C, 75.91; H, 7.97. Found: C, 75.85; H, 7.97.

The oily material (612 mg.) obtained from the further elution of the chromatography column with pentane was demethylated with hydriodic acid as described below to yield a solid (400 mg.) which after one recrystallization from benzene gave IIIe, 150 mg., m.p. 160–162°. Thus, the total yield in the reduction of IIe was about 47%.

Demethylation.—The crystalline 3-*p*-fluorophenyl-4-veratrylhexane (116 mg., 0.37 mmole) was subjected to demethylation with hydriodic acid and phosphorus as described for hexestrol dimethyl ether to give *meso*-3-*p*-fluorophenyl-4-*m,p*-dihydroxyphenylhexane (IIIe), 103 mg. (97%), m.p. 159–161°. Three crystallizations from benzene furnished the analytical sample, m.p. 163.5–165°.

Anal. Calcd. for $C_{18}H_{21}O_2F$: C, 74.97; H, 7.35. Found: C, 75.14; H, 7.46.

meso-**3,4-Bis-(*p*-Fluorophenyl)-hexane** (IIIf).—The preparation of the carbinol IIf, m.p. 113–114°, has been described previously.[1] When this material (580 mg., 2.0 mmoles) was hydrogenated in acetic acid with 116 mg. of palladium black, hydrogen uptake ceased in 7 minutes when less than one-half the expected amount had been absorbed. Upon the addition of 0.1 ml. of perchloric acid, hydrogen uptake commenced again and was complete in 68 minutes. The oily reaction product was recrystallized from hexane to yield *meso*-3,4-bis-(*p*-fluorophenyl)-hexane (IIIf), 349 mg. (64%), m.p. 100–103°. Recrystallization from hexane furnished the analytical sample, m.p. 103–103.5°.

Anal. Calcd. for $C_{18}H_{20}F_2$: C, 78.80; H, 7.35. Found: C, 78.57; H, 7.25.

3-Hydroxystilbestrol Trimethyl Ether.—A mixture of 3-*p*-anisyl-4-veratrylhexan-3-ol (IIb) (1.5 g., 4.4 mmoles), concentrated hydrochloric acid (10 ml.), glacial acetic acid (25 ml.) and water (0.4 ml.) was heated under reflux for three hours. After pouring the cooled reaction mixture into crushed ice the product was extracted with ether and the extract washed with water, sodium bicarbonate solution and finally with saturated sodium chloride solution. After evaporation of the ether, the residue (1.24 g.) was chromatographed on 40 g. of alumina. In pentane–benzene, 8:1, there was eluted *trans*-3-*p*-anisyl-4-veratrylhexene-3 (3-hydroxystilbestrol trimethyl ether) 311 mg., m.p. 81–83°.

Further elution of the column with benzene gave 851 mg. of an oil which was subjected to another dehydration treatment followed by chromatography to yield an additional 125 mg. of product, m.p. 81–83°, bringing the total yield to 31%. Recrystallization from hexane furnished the analytical sample, m.p. 86–87.5°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.26; H, 8.03. Found: C, 76.65; H, 8.01.

In an attempt to obtain 3-hydroxystilbestrol (IVb), the above trimethyl ether was subjected to demethylation by heating to 190–200° with three molar equivalents of methylmagnesium iodide, in the manner described previously.[1] The crude product rapidly turned dark and no solid material could be isolated, either by crystallization or by chromatography on alumina.

CHICAGO 37, ILLINOIS

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Studies on Lignin and Related Products. XII.[1] The Synthesis of Lignin Model Compounds Related to Diethylstilbestrol[2]

BY IRWIN A. PEARL

RECEIVED MARCH 19, 1956

Pinacol reduction of propiovanillone yielded α,α'-diethylhydrovanilloin, and this pinacol in the presence of acid underwent rearrangement to the pinacolone 4,4-di-(4-hydroxy-3-methoxyphenyl)-3-hexanone. Sodium and butanol reduction of the pinacolone yielded the pinacolone alcohol 4,4-di-(4-hydroxy-3-methoxyphenyl)-3-hexanol, which was heated with aqueous sulfuric acid to yield the desired 3,3'-dimethoxydiethylstilbestrol by dehydration and retropinacolone rearrangement. 3,3'-Dimethoxydiethylstilbestrol may serve as an excellent intermediate for the preparation of 3,3'-dimethoxyhexestrol and 3,3'-dimethoxydienestrol.

A few years ago[3] the possibility of the presence in at least a part of the complex lignin structure of a linkage between the α-carbon atoms of two C_6–C_3 units was suggested. More recently, it was demonstrated that except for the compounds having carbon chains in the 5-position of the guaiacyl group, the compounds formed in alkaline cupric oxide oxidations of lignosulfonate materials actually could be prepared by similar oxidation of bis-vanillyl compounds such as vanillil (I) and its reduction products.[4] These bis-vanillyl compounds, unfortunately, contained only C_6–C and not the preferred C_6–C_3 groups. Therefore, it was desired to submit lignin model compounds containing C_6–C_3 groups to similar oxidation experiments to determine whether the β- and γ-carbon atoms of the C_6–C_3 groups would be removed. The recently published results of Vanderlinde and co-workers[5] in which 4,4'-dihydroxybenzil (II) and *p*-hydroxybenzoic acid were obtained as products of alkaline oxidation of diethylstilbestrol (III) proved that the β- and γ-carbon atoms were indeed removed by alkaline oxidation of such compounds. Furthermore, these results suggested that guaiacyl or syringyl analogs of diethylstilbestrol would be ideal model compounds for lignin oxidation studies. The present paper reports the synthesis of 3,3'-dimethoxydiethylstilbestrol (IV). This compound will be employed as a model compound for lignin and lignosulfonate oxidation studies.

Most syntheses of III comprise a series of reactions of alkoxyphenyl compounds in which the last step consists of the removal of the alkyl group to liberate the desired 4-hydroxyphenyl derivative. Because of the non-specificity of dealkylation of dialkyl ethers of *o*-dihydroxyphenyl compounds, similar syntheses with alkyl ethers of guaiacyl compounds yield mixtures which can be resolved only with great difficulty. Therefore, a search was made for a synthesis employing free phenolic compounds. After failure in attempts at adapting many well-known procedures for the synthesis of III to the use of free guaiacyl compounds, the elegant procedure of Adler, Gie and von Euler[6] was found to be applicable to these compounds for the synthesis of IV.

Propiovanillone (V), obtained by Fries rearrangement of guaiacol propionate or by oxidation of 1-(4-hydroxy-3-methoxyphenyl)-1-propanol was reduced with alkali and either sodium amalgam or sodium–lead alloy to yield the pinacol, α,α'-diethylhydrovanilloin (VI), which could be isolated in either its *meso*- or *dl*-form. The pinacol VI was rearranged with acid to the pinacolone, 4,4-di-(4-hydroxy-3-methoxyphenyl)-3-hexanone (VII), and this pinacolone was reduced with sodium and butanol to give the pinacolone alcohol, 4,4-di-(4-hydroxy-3-methoxyphenyl)-3-hexanol (VIII). Dehydration and retropinacolone rearrangement of the pinacolone alcohol (VIII) by means of aqueous sulfuric acid yielded the desired 3,3'-dimethoxydiethylstilbestrol (IV) as a mixture of *cis* and *trans* isomers which could not be crystallized. Acetylation of the mixture with acetic anhydride and pyridine gave crystalline 3,3'-dimethoxydiethylstilbestrol diacetate (IX). All phenolic compounds were characterized by acetates. IV may serve as an excellent intermediate for the preparation of two other possible lignin model compounds, namely, 3,3'-dimethoxyhexestrol (X) and 3,3'-dimethoxydienestrol (XI). All of these model compounds may have useful physiological properties.

---

[1] For paper XI of this series, see *Tappi*, **39**, 171 (1956).

[2] Presented before the Division of Organic Chemistry at the 129th Meeting of the American Chemical Society, Dallas, Texas, April 8 to 13, 1956.

[3] I. A. Pearl and E. E. Dickey, THIS JOURNAL, **74**, 614 (1952).

[4] I. A. Pearl and D. L. Beyer, *ibid.*, **76**, 2224 (1954).

[5] R. E. Vanderlinde, F. D. Vasington and W. W. Westerfeld, *ibid.*, **77**, 4176 (1955).

[6] E. Adler, G. J. Gie and H. von Euler, Swedish Patent 115,816 (Feb. 12, 1946); U. S. Patent 2,421,402 (June 3, 1947).