[Contribution from the Ben May Laboratory for Cancer Research and the Department of Biochemistry, University of Chicago]

Hormone Analogs. II. The Preparation of Stilbestrol Analogs[1,2]

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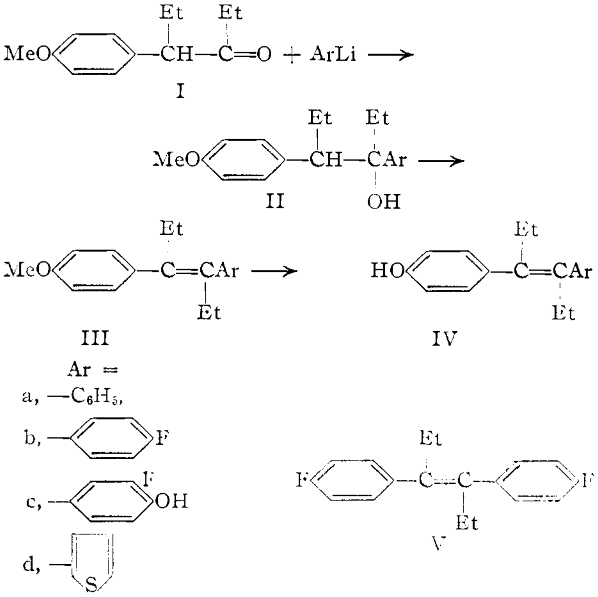
By reaction of 4-(*p*-anisyl)-hexan-3-one with the appropriate aryllithium compound followed by dehydration and demethylation, stilbestrol analogs have been prepared in which one hydroxyphenyl group is replaced by either a phenyl, *p*-fluorophenyl, *m*-fluoro-*p*-hydroxyphenyl or 2-thienyl group. In a similar fashion, 4-(*p*-fluorophenyl)-hexan-3-one has been converted to 4,4′-difluoro-α,α'-diethylstilbene.

This paper describes the preparation of certain analogs of the estrogenic hormone, stilbestrol, in which the nature of one or both aromatic rings has been varied. For compounds with one ring altered, 4-(*p*-anisyl)-hexan-3-one (I), prepared from anisaldehyde as described in the previous paper,[3] is treated with the appropriate aryllithium compound to form carbinol II. Dehydration of the latter substance yields the diethylstilbene derivative III which on demethylation gives the desired analog IV. In this way compounds were obtained in which one aromatic group of the stilbestrol molecule is replaced with the following groups: phenyl[4] (IVa), *p*-fluorophenyl (IVb), *m*-fluoro-*p*-hydroxyphenyl (IVc) and 2-thienyl[5] (IVd). A similar reaction sequence starting with 4-(*p*-fluorophenyl)-hexan-3-one[3] furnished an analog of stilbestrol with both aryl groups replaced by *p*-fluorophenyl groups V. The hormonal and anti-hormonal properties of these substances are being investigated by Dr. Charles Huggins, and the results of these studies will be reported separately.



The addition of aryllithium compounds to hindered ketones of the type I was found to proceed much more readily than that of aryl Grignard reagents which is accompanied by the side reaction of enolization. For example, the reaction of 4-anisylhexan-3-one (I) with excess *p*-fluorophenylmagnesium bromide gave only a 25% yield of the corresponding carbinol IIa with 49% of the starting ketone being recovered. With *p*-fluorophenyllithium, on the other hand, the desired carbinol was obtained in 68% yield. Therefore the lithium reagents were used for the preparation of the other carbinols described in this paper. With the exception of phenyllithium and thienyllithium, the aryllithium reagents were prepared by the exchange of *n*-butyllithium with the corresponding aryl bromide.[6] It was observed that optimum temperature for this exchange reaction depends markedly on the nature of the substituents on the aromatic ring. A comparison of the yields of substituted benzoic acids obtained under comparable conditions by carbonation of the reaction mixture (Table I) demonstrates that if electron-withdrawing groups, such as fluoro, are present in the aromatic ring, the successful preparation of the lithium derivative and its subsequent reaction with the ketone requires a low temperature. With an electron-donating substituent, such as *p*-methoxyl, the process proceeds more favorably at a higher reaction temperature. In the case when both a fluoro (*meta*) and methoxyl (*para*) substituent are present, a low reaction temperature is preferable.

Table I

Effect of Temperature on Exchange of *n*-Butyllithium with Aryl Bromides

Bromide	Yield of substituted benzoic acid, % 25°	−50°
p-Methoxyphenyl	>60	8
p-Fluorophenyl	0	42
m-Fluoro-*p*-methoxyphenyl	28	67

In every case the reaction of the lithium compound with the substituted hexanone I led predominantly to one of the two possible diastereoisomeric modifications of the resulting carbinol II. According to the generalization proposed by Cram,[7] the carbinols thus prepared should possess the

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(2) This investigation was supported in part by a grant from the American Cancer Society as recommended by the Committee on Growth of the National Research Council.

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

(4) Previously described by G. Brownlee, F. C. Copp, W. M. Duffin and I. M. Tonkin, *Biochem. J.*, **37**, 572 (1943).

(5) Prepared in non-crystalline form by W. R. Biggerstaff and O. L. Stafford, This Journal, **74**, 419 (1952).

(6) R. G. Jones and H. Gilman, "Organic Reactions," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 339.

(7) D. J. Cram and F. A. Abd Elhafez, This Journal, **74**, 5828 (1952).

erythro configuration. Such *erythro*-carbinols would be expected to yield predominantly the desired *trans*-stilbenes (III) directly when treated with reagents which effect dehydration by a *trans* mechanism. However, on heating either with hydrochloric acid in wet acetic acid, with *p*-toluenesulfonic acid or with iodine in boiling xylene, our carbinols formed both a solid and a liquid dehydration product of which the crystalline material (presumably the *trans*-stilbene) always was present in the smaller amount. Repeated treatment of the liquid isomer with the dehydration reagent often yielded an additional amount of the solid isomer. However the total yield of crystalline product was never high, and the dehydration reaction constitutes the only unsatisfactory step in the over-all procedure.

Similar difficulties in obtaining *trans*-stilbenes from carbinols of type II have been reported by other investigators who have recommended *p*-toluenesulfonic acid[8a] or iodine in boiling xylene[8b,c] as dehydration reagents which will catalyze the isomerization of the liquid dehydration product to the crystalline modification. In the present experiments, both *p*-toluenesulfonic acid and iodine in boiling xylene were found to be inferior to the hydrochloric acid reagent in yielding a solid product from the dehydration of the carbinols. In the special case of the thiophene compound, dehydration of the carbinol IId was accomplished readily by heating with oxalic acid[9] in aqueous ethanol, although here again both solid and liquid isomers were produced with the crystalline modification as the minor product. The stereochemistry of the formation and dehydration of carbinols of type II is being investigated further, and the results will be reported separately.

Demethylation to obtain the desired stilbestrol analog IV was effected in excellent yield by heating the *p*-methoxystilbene (III) at 200° with dry methylmagnesium iodide.[10] This procedure does not affect a fluorine substituent on an aromatic ring, whereas demethylation with potassium hydroxide in alcohol at 220°[8a] was found to cause replacement of the fluorine by a hydroxyl group.

Experimental[11]

4-Hydroxy-α,α'-diethyl-*trans*-stilbene (IVa). Carbinol Preparation.—To a stirred ethereal solution of phenyllithium prepared[6] from 11 g. (0.07 mole) of bromobenzene, there was added 10.3 g. (0.05 mole) of 4-(*p*-anisyl)-hexan-3-one[3] in 10 ml. of ether. After heating under reflux for 10 minutes the reaction mixture was cooled and poured into crushed ice and acidified. The ethereal extract was washed with water, sodium bicarbonate and saturated sodium chloride solution, and evaporated. The residual oil (14.2 g.) was crystallized from hexane to yield 3-phenyl-4-(*p*-anisyl)-hexan-3-ol (IIa), 8.7 g., 61%, m.p. 67–69°. Recrystallization from hexane and then from ethanol furnished the analytical sample, m.p. 67–68°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.78; H, 8.36.

Dehydration.—1.0 g. (3.5 mmoles) of the carbinol IIa was heated under reflux for 12 hours in 40 ml. of a mixture containing glacial acetic acid, concd. hydrochloric acid and water in a ratio by volume of 10:5:1. The cooled mixture was diluted with water and the product extracted with ether. After washing, drying and removal of the ether, the semisolid residue (849 mg.) was dissolved in hexane and chromatographed over 30 g. of alumina to yield, after two recrystallizations from ethanol, 157 mg. of 4-methoxy-α,α'-diethylstilbene (IIIa), m.p. 80.2–80.5°, reported[4] 79–80°. The residue (402 mg.) from the mother liquors was treated again with the acid reagent and worked up as before to yield an additional 106 mg. of IIIa, m.p. 79.1–79.8°. The total yield was 28%.

Demethylation.[10]—A mixture of 232 mg. (0.87 mmole) of IIIa and 1.09 mmoles of methylmagnesium iodide was heated to 200° for 30 minutes. The cooled mixture was treated with dilute sulfuric acid, the product extracted with pentane, washed, dried and recrystallized from hexane to yield 4-hydroxy-α,α'-diethyl-*trans*-stilbene (IVa), 1st crop, 122 mg., m.p. 124.2–124.6°; 2nd crop, 26 mg., m.p. 121.4–122°; reported[4] m.p. 125–127°, total yield 67%.

4-Hydroxy-4'-fluoro-α,α'-diethyl-*trans*-stilbene (IVb). Carbinol Preparation.—An ethereal solution of *p*-fluorobromobenzene[12] (5.5 g., 0.03 mole) was added to a stirred solution of 0.026 mole of *n*-butyllithium[6] held at −50° in a nitrogen atmosphere. After stirring for 45 minutes at −50°, the anisylhexanone (I, 2.0 g., 0.01 mole) in ether was added, and the reaction mixture was stirred for 40 minutes at −15°. The product was isolated in a manner similar to that described for IIa, to yield 3-(*p*-fluorophenyl)-4-(*p*-anisyl)-hexan-3-ol (IIb), 2.0 g., 68%; m.p. 95.8–96.5° from hexane. Recrystallization from 80% ethanol gave the analytical sample, m.p. 96.2–97.2°.

Anal. Calcd. for $C_{19}H_{23}O_2F$: C, 75.47, H, 7.67. Found: C, 75.22; H, 7.68.

Dehydration with Iodine.—A mixture of 5 g. (0.017 mole) of the carbinol IIb and 310 mg. of iodine in 80 ml. of dry xylene was distilled slowly for three hours until 60 ml. of distillate had been collected. An additional 100 mg. of iodine and 40 ml. of xylene were added and distillation continued for one hour. The residue was taken up in ether, washed with dilute sodium thiosulfate, water, and finally sodium chloride solution and dried. After removal of the ether, the residual oil was distilled *in vacuo*. The fraction (1.84 g.) boiling at 143–145° (0.9 mm.) was crystallized from ethanol, and the solid product (615 mg.) was purified by chromatography over alumina of activity III. Elution with hexane yielded 563 mg. of 4-methoxy-4'-fluoro-α,α'-diethyl-*trans*-stilbene (IIIb), m.p. 78–78.5° from ethanol. Chromatography of the residue from the original ethanol mother liquors yielded an additional 60 mg. of product bringing the total yield to 13%. Recrystallization from ethanol furnished the analytical sample, m.p. 78.4–78.9°.

Anal. Calcd. for $C_{19}H_{21}OF$: C, 80.25; H, 7.44. Found: C, 79.70; H, 7.49.

Dehydration with Hydrochloric–Acetic Acid.—Nine hundred six mg. (3.0 mmoles) of the carbinol IIb was treated with 40 ml. of the acid dehydration reagent as described for the case of IIa. The crude oily product was purified by chromatography over 20 g. of alumina. Elution with hexane furnished 709 mg. of a crystalline product which, on recrystallization from ethanol, gave 4-methoxy-4'-fluoro-α,α'-diethyl-*trans*-stilbene (IIIb), 266 mg., 31%, m.p. 78–78.5°.

Repeated treatment of the oily fractions of the above dehydration products with the acid mixture or with *p*-toluenesulfonic acid usually furnished small additional amounts of the crystalline stilbene IIIb. However dehydration of the carbinol IIb with thionyl chloride and pyridine or by heating with *p*-toluenesulfonic acid yielded only non-crystalline products.

Demethylation.—A mixture of 500 mg. (1.76 mmoles) of IIIb and 1.84 mmoles of methylmagnesium iodide was treated as described for IIIa. Two recrystallizations of the product from hexane yielded 4-hydroxy-4'-fluoro-α,α'-diethyl-*trans*-stilbene (IVb), 450 mg., 95%, m.p. 104.5–105°. Recrystallization from hexane gave the analytical sample as colorless needles, m.p. 108–109°. When the crystals were crushed to a powder, the m.p. was lowered to 105–106°.

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[8] (a) A. L. Wilds and W. R. Biggerstaff, THIS JOURNAL, **67**, 789 (1945); (b) R. Neher and K. Miescher, *Helv. Chim. Acta*, **29**, 449 (1946); (c) E. Rohrmann, U. S. Patent 2,346,049 (April 4, 1944).

[9] R. E. Miller and F. F. Nord, *J. Org. Chem.*, **15**, 89 (1950).

[10] E. Späth, *Monatsh.*, **35**, 319 (1914).

[11] Melting points are uncorrected. Microanalyses were carried out by Micro-Tech Laboratories and Mr. William Saschek. All reactions involving lithium and Grignard reagents were carried out in an atmosphere of dry nitrogen.

[12] Obtained from the Custom Chemical Laboratories, Chicago, Ill.

Anal. Calcd. for $C_{18}H_{19}OF$: C, 80.00; H, 7.08. Found: C, 80.05; H, 7.23.

3-Fluoro-4,4′-dihydroxy-α,α′-diethyl-*trans*-stilbene (IVc), Carbinol Preparation.—An ethereal solution of 2-fluoro-4-bromoanisole[13] (5.13 g., 0.025 mole) was added to a stirred ethereal solution of 0.02 mole of *n*-butyllithium held at −35°. After stirring for 0.5 hour at −25°, the anisylhexanone (I, 2.1 g., 0.01 mole) was added and the reaction mixture stirred at 0° for one hour and poured into crushed ice. The oily product, isolated as described for IIa, was heated to 75° at 0.01 mm. pressure to remove volatile compounds. The residue was washed with pentane and recrystallized from ethanol to yield 3-(*m*-fluoro-*p*-methoxyphenyl)-4-(*p*-anisyl)-hexan-3-ol (IIc); 1st crop, 2.00 g., m.p. 117–118°; 2nd crop, 0.52 g., m.p. 113–115°, total yield 76%. Recrystallization from ethanol gave the analytical sample, m.p. 117.5–118.5°.

Anal. Calcd. for $C_{20}H_{25}O_3F$: C, 72.26; H, 7.58. Found: C, 72.30; H, 7.58.

Dehydration.—1.27 g. (3.8 mmoles) of IIc was heated under reflux for 3 hours with 50 ml. of the acid dehydration mixture as described for IIa. In this case the crude reaction product (1.17 g.) solidified. Recrystallization from pentane gave 3-fluoro-4,4′-dimethoxy-α,α′-diethyl-*trans*-stilbene (IIIc), 346 mg., m.p. 103–104°. The residual oil from the mother liquor (760 mg.) was dissolved in pentane and chromatographed on 55 g. of alumina. The first fractions to be eluted in pentane yielded an additional 127 mg. of IIIc, m.p. 97–100°, to bring the total yield to 39%. Recrystallization from an equal mixture of ethanol and hexane gave the analytical sample, m.p. 107.4–107.9°.

Anal. Calcd. for $C_{20}H_{23}O_2F$: C, 76.40; H, 7.37. Found: C, 76.61; H, 7.57.

Demethylation.—One hundred fifty-five mg. (0.48 mmole) of IIIc was heated to 200° for 30 minutes with 1.4 mmoles of methylmagnesium iodide. The reaction mixture was taken up in 1 *N* sulfuric acid and the product extracted with chloroform, washed with water and dried. The crude brown product (146 mg.) was recrystallized from a 2:1 mixture of hexane and benzene, decolorized with Norit in ethanol and finally recrystallized again from hexane–benzene to give 3-fluoro-4,4′-dihydroxy-α,α′-diethyl-*trans*-stilbene (IVc), 121 mg., 87%, m.p. 139–139.2°.

Anal. Calcd. for $C_{18}H_{19}O_2F$: C, 75.50; H, 6.69. Found: C, 75.41; H, 6.82.

4-(*p*-Hydroxyphenyl)-3-(2-thienyl)-*trans*-hexene-3 (IVd). Carbinol Preparation.—An ethereal solution of freshly distilled thiophene (5.8 g., 0.07 mole) was added slowly to a stirred ethereal solution containing 0.04 mole of *n*-butyllithium held at −35°. After stirring for 30 minutes the mixture was warmed to −20° and 5.05 g. (0.024 mole) of the anisylhexanone (I) was added. After two hours the reaction mixture was poured into crushed ice and the product isolated in the manner previously described for the preparation of IIa except that the residual oil was heated to 80° in high vacuum to remove volatile materials, and then decolorized with Norit. Crystallization from hexane yielded 4-(*p*-anisyl)-3-(2-thienyl)-hexan-3-ol (IId), 4.2 g., 60%, m.p. 55–57°. Recrystallization from hexane furnished the analytical sample, m.p. 59.5–60.0°.

Anal. Calcd. for $C_{17}H_{22}O_2S$: C, 70.30; H, 7.64; S, 11.04. Found: C, 70.25; H, 7.57; S, 10.68.

In a similar experiment in which both the exchange reaction of *n*-butyllithium with thiophene[14] and the subsequent condensation with anisylhexanone were carried out at room temperature, the yield of IId, m.p. 58–60°, was 80%.

Dehydration.—A mixture of 2.03 g. (7.0 mmoles) of the carbinol IId and 3 g. of oxalic acid in 75 ml. of 65% ethanol was heated under reflux for 18 hours, whereupon a brown oil separated from solution. The reaction product was isolated as described for previous dehydrations and crystallized from hexane to give 4-(*p*-anisyl)-3-(2-thienyl)-*trans*-hexene-3 (IIId) 400 mg., 21%, m.p. 75–78°. Recrystallization from hexane furnished the analytical sample, m.p. 81–82°.

Anal. Calcd. for $C_{17}H_{20}OS$: C, 74.97; H, 7.40. Found: C, 74.67; H, 7.50.

Demethylation.—A mixture of 150 mg. (0.55 mmole) of IIId and 0.65 mmole of methylmagnesium iodide was heated at 200° for 15 minutes and the product isolated as described for IVa. The crude reaction product was recrystallized from a benzene–hexane mixture to yield 4-(*p*-hydroxyphenyl)-3-(2-thienyl)-*trans*-hexene-3 (IVd), 92 mg., 65%, m.p. 71–72°. Recrystallization from a mixture of benzene and pentane gave the analytical sample, m.p. 71–71.5°.[15]

Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.41; H, 7.02. Found: C, 74.74; H, 7.01.

4,4′-Difluoro-α,α′-diethyl-*trans*-stilbene (V). Carbinol Preparation.—To an ethereal solution of *p*-fluorophenyllithium, prepared as described previously from the reaction at −50° of *n*-butyllithium (0.21 mole) with *p*-fluorobromobenzene (42 g., 0.24 mole), there was added 4-(*p*-fluorophenyl)-hexan-3-one[3] (19.4 g., 0.10 mole) with stirring at −15°. The product was isolated in the manner described for IIa and recrystallized from hexane to yield 3,4-bis-(*p*-fluorophenyl)-hexan-3-ol, 23.0 g., 79%, m.p. 113–114°.

Dehydration.—1.00 g. (3.45 mmoles) of the above carbinol was treated with 40 ml. of the acid dehydration mixture as described for IIa. The crude oily product (936 mg.) was adsorbed on a column of 60 g. of alumina of activity II, eluted with pentane and recrystallized several times from acetonitrile to yield 4,4′-difluoro-α,α′-diethyl-*trans*-stilbene (V), 159 mg., 17%, m.p. 89.3–89.7°. Analytical samples were prepared by recrystallization (a) from acetonitrile, m.p. 90.1–90.6°, and (b) from ethanol, m.p. 91.6–92.0°. Repeated treatment of the residue from the mother liquors and oily chromatogram fractions with the acid dehydration mixture yielded an additional 65 mg. (6%), m.p. 89–90.3°.

Anal. Calcd. for $C_{18}H_{18}F_2$: C, 79.38; H, 6.66. Found: C, (a) 79.75; (b) 78.87; H, (a) 6.96, (b) 6.93.

Carbonation of Aryllithium Reagents.—A stirred ethereal solution of *n*-butyllithium was maintained at the desired temperature in an atmosphere of dry nitrogen while an excess of the aryl bromide was added. The reaction was allowed to proceed for one-half hour, whereupon a large excess of powdered Dry Ice was added. The product was shaken with water and ether, the aqueous layer acidified, and the precipitated acid washed and recrystallized, from aqueous ethanol. The yields given in Table I are based on the recrystallized acids possessing the following melting points: *p*-anisic 183–183.8°, reported[16] 184.2°; *p*-fluorobenzoic 183.5–184.1°, reported[17] 186°; *m*-fluoro-*p*-anisic 209–211°, reported[18] 208–210°.

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[13] B. p. 86–88° (0.7 mm.), $n^{25}D$ 1.5430, prepared by the bromination of *o*-fluoroanisole[12] according to G. Schiemann, W. Winkelmüller, E. Baesler, E. Ley, G. Wiehage and M. Seyhan, *J. prakt. Chem.*, **143**, 18 (1935).

[14] *Cf.* H. Gilman and D. A. Shirley, THIS JOURNAL, **71**, 1870 (1949).

[15] Subsequent samples of this product were obtained which melted at 72.6–73.2°.

[16] A. Oppenheim and S. Pfaff, *Ber.*, **8**, 890 (1875).

[17] G. Schiemann and W. Winkelmüller, "Organic Syntheses," Vol. 2, A. H. Blatt, Ed., J. Wiley and Sons, Inc., New York, N. Y., 1943, p. 299.

[18] J. English, Jr., J. F. Mead and C. Niemann, THIS JOURNAL, **62**, 350 (1940).