salting-out (with subsequent extraction of the product with methanol for the removal of ammonium bromide) gave about the same yield. The dye II was a very dark purple powder which did not melt or decompose at temperatures up to 340°. It rapidly imparted a purple color to water, but was insoluble in the organic solvents that were tested. Analytical samples, dried at about 95° at 5 mm., had the composition of the trihydrate. In a dialysis experiment it behaved exactly as did I.

Anal. Calcd. for $C_{32}H_{28}O_{21}N_6B_2S_4Na_4$: C, 35.79; H, 2.61; B, 2.02: Found: C, 35.76; H, 2.89; B, 1.77.

Coupling with β-Naphthol.[12]—The tetrazonium solution prepared, as described above, from 0.5 g. of benzidine-2,2′-diboronic acid was added with stirring to a cold solution of 0.54 g. of β-naphthol and 5 g. of sodium carbonate in 18 ml. of 5% aqueous sodium hydroxide. The mixture was stirred in the ice-bath for two hours and then added with stirring to 30 ml. of 5% hydrochloric acid. The mixture was diluted with 25 ml. of ethanol and filtered hot. The red solid was dissolved in the minimum amount of Cellosolve (less than 5 ml.) and the solution was diluted with 5 ml. of ethanol and filtered hot. Water was added to the filtrate until the precipitation of the dye was complete, and the mixture was boiled to coagulate the solid. The solid was collected and dried at 95° at 5 mm. About 0.2 g. of a bright red powder, easily soluble in Cellosolve, less soluble in ethanol and insoluble in water, was obtained; it decomposed at about 240°.

Anal. Calcd. for $C_{32}H_{24}O_6N_4B_2$: C, 66.01; H, 4.13; N, 9.63. Found: C, 65.99; H, 4.21; N, 9.75.

Coupling with Acetoacetanilide.—The coupling procedure was a modification of that described by Linstead and Wang.[13] The tetrazonium solution prepared from 0.64 g. of the benzidine dihydrochloride was added over a period of fifteen minutes to a stirred mixture of 0.64 g. of acetoacetanilide, 1 g. of sodium acetate and 50 ml. of 1% aqueous sodium hydroxide. The resulting mixture was stirred in an ice-bath overnight. The solid was separated by filtration and recrystallized three times from dilute ethanol. The bright yellow solid contained boron. It was insoluble in water or aqueous sodium carbonate, but soluble in 5% aqueous sodium hydroxide. It decomposed sharply at 174–175° to give a black residue which melted at 270–280°.

Anal. Calcd. for $C_{32}H_{30}N_6O_8B_2$: C, 59.29; H, 4.63; N, 12.97. Found: C, 58.87; H, 4.70; N, 12.96.

Summary

Analogs of Trypan Blue and Evans Blue have been prepared by the coupling of tetrazotized benzidine-2,2′-diboronic acid with 1-amino-8-naphthol-3,6-disulfonic acid (H acid) and with 1-amino-naphthol-5,7-disulfonic acid (Chicago acid), respectively. The dyes so obtained have the expected boron contents. Boron-containing dyes also have been prepared by coupling the benzidinediboronic acid with β-naphthol and with acetoacetanilide.

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[12] The authors are indebted to Dr. Stanley M. Parmerter for the first experiments on this reaction.

[13] Linstead and Wang, *J. Chem. Soc.*, 807 (1937).

URBANA, ILLINOIS RECEIVED AUGUST 18, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Preparation of Synthetic Estrogens. I. The Synthesis of Diethylstilbestrol through the Pinacol–Pinacolone Compounds

BY KEIITI SISIDO AND HITOSI NOZAKI

Wessely[1] and others[2] have described synthetic approaches to the estrogenic diethylstilbestrol involving the use of the pinacol–pinacolone and retropinacolone rearrangements. We have carried out further investigations on this approach and have been able to improve several of the steps involved. The synthesis is outlined in the flow sheet.

Model experiments on the reduction of acetophenone and *p*-methoxyacetophenone to the pinacols using the method of Newman[3] gave the pinacols as a stereoisomeric mixture in 73 and 80% yields, respectively. With *p*-methoxypropiophenone (I) the yield of crystalline pinacol (II) was considerably lower, but after rearrangement of the crude pinacol the pinacolone (III) was obtained in 54% yield from the propiophenone (I). After reduction to carbinol (IV) and rearrangement with dilute sulfuric acid, only a small amount of crystalline product was obtained. However, heating the oily mixture with iodine in chloroform[1] effected isomerization and permitted the isolation of the dimethyl ether of diethylstilbestrol (V) in about 14% over-all yield from *p*-methoxypropiophenone (I). By further development of these procedures the yields can probably be improved.

By similar procedures starting with acetophenone we have prepared 2,3-diphenyl-2-butene in 30% over-all yield and 2,3-dianisyl-2-butene from *p*-methoxyacetophenone in 32% over-all yield.

According to a Swedish patent,[4] not accessible to us yet, diethylstilbestrol is said to be obtained from *p*-hydroxypropiophenone in an almost identical way. We have noticed in our model experiments with *p*-hydroxyacetophenone as well as with *p*-acetoxyacetophenone that the existence of free hydroxyl or acetoxyl groups hinders the smooth reaction of the pinacolic reduction.

Experimental[5]

(I) Pinacolic Reduction

2,3-Diphenyl-2,3-butanediol.—To a solution of 30 g. of acetophenone in 300 cc. of absolute alcohol and 200 cc. of dry, thiophene-free benzene were added 12 g. of alu-

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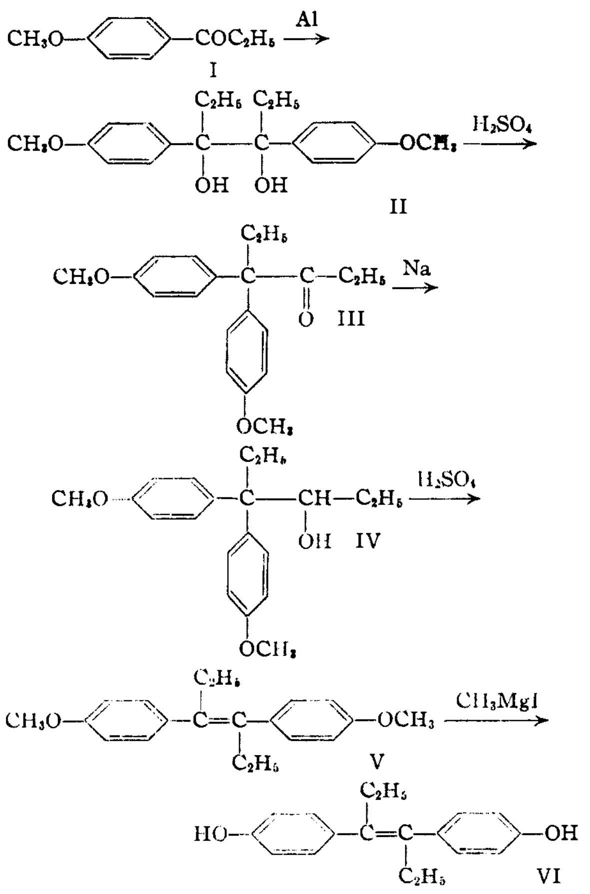
[1] Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940).

[2] For a review of these and other syntheses of diethylstilbestrol see Solmssen, *Chem. Rev.*, **37**, 481 (1945).

[3] Newman, THIS JOURNAL, **62**, 1683 (1940).

[4] Adler, Gie and von Euler, Swedish Patent No. 115,816, Feb. 12, 1946; *C. A.*, **41**, 486 (1947).

[5] Microanalyses by Miss Yasuko Meizyô of our Laboratory.



minum foil and 0.5 g. of mercuric chloride. On slight heating, a violent reaction ensued and the contents began to boil. When the reaction had subsided somewhat, the mixture was heated on a water-bath. After six hours of refluxing, the reaction product was poured over crushed ice acidified with hydrochloric acid. The top layer was separated and the bottom one extracted with benzene. The two benzene layers were combined, washed with a sodium chloride solution and dried. When the solvent was distilled off, the residue crystallized on cooling; there was obtained 22 g. of crude pinacol melting at 85–107°, which on recrystallizations from benzene–ligroin melted at 122°.

2,3-Dianisyl-2,3-butanediol.[6]—Forty grams of *p*-methoxyacetophenone[7] was subjected to the pinacolic reduction as above and the crude pinacol, m. p. 145–152°, was obtained with a yield of 32.5 g. Repeated recrystallizations from ethyl acetate gave colorless prisms melting at 159–160°. The same diol prepared by Price and Mueller[6] melted at 168–169°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.19; H, 7.66.

3,4-Dianisyl-3,4-hexanediol[1] (II).—Ten grams of *p*-methoxypropiophenone (I) was reduced in the same manner as mentioned above. As this pinacol is not easily soluble in cold benzene, the reaction product was added with 100 cc. of water and refluxed on a water-bath during an hour with stirring. The benzene layer was separated and the bottom one extracted with hot benzene. The combined benzene solution was washed with warm water and distilled without drying. The residue was crystallized from ligroin, yield 4 g., m. p. 186–190°. On repeated recrystallizations from ethyl acetate, the product formed colorless small prisms, m. p. 192–194°.

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H. 7.93. Found: C, 72.31; H, 8.38.

(II) Pinacolone Rearrangement

2,2-Diphenyl-3-butanone.—To a solution of 100 cc. of concentrated sulfuric acid in 100 cc. of water was added 22 g. of 2,3-diphenyl-2,3-butanediol. The mixture was refluxed for one and a half hours under stirring, poured into iced water and extracted with ether. When the extract was distilled under reduced pressure after removing the solvent, there was obtained 13 g. of ketone, m. p. 40°, which value accorded with that of the literature.

When 30 g. of acetophenone was subjected to the pinacolic reduction, and the crude product was immediately, without separating the pinacol, treated with dilute sulfuric acid, 15 g. of the ketone, m. p. 40°, was obtained.

2,2-Dianisyl-3-butanone.[6]—Thirty-two grams of crude 2,3-dianisyl-2,3-butanediol was treated in the same manner as above, and the product was recrystallized from ethyl acetate–petroleum ether; yield was 25 g., m. p. 69–70°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.07; H, 7.09.

3,3-Dianisyl-4-hexanone (III).—From 4 g. of crude crystalline 3,4-dianisyl-3,4-hexanediol 2.3 g. of the ketone in yellowish viscous oil, b. p. 215–225° at 3 mm. was obtained.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.25; H, 7.79.

For the preparation of this ketone, it is rather profitable to treat the crude product of the pinacolic reduction, without separating the crystals of the pinacol. Thus, from 21 g. of *p*-methoxypropiophenone 11.3 g. of the ketonic oil, b. p. 224–228° at 6 mm., was obtained.

Attempts to prepare a crystalline semicarbazone or oxime of this pinacolone were unsuccessful.

(III) Reduction and Retropinacolone Rearrangement

2,3-Diphenyl-2-butene.—A mixture of 50 cc. of xylene and 10 g. of metallic sodium was heated to 140° and 10 g. of crude 2,2-diphenyl-3-butanone was added. Under violent stirring, 110 cc. of absolute alcohol was run in at such a rate that the boiling of the mixture was uniform. To the reaction product isolated in the usual way a mixture of 50 cc. of concentrated sulfuric acid and 50 cc. of water was added. After one and a half hours of heating on a boiling water-bath the content was poured over crushed ice and extracted with ether. When the product was recrystallized from alcohol, there was obtained 5.6 g. of colorless prisms, m. p. 104° in accord with the literature.

2,3-Dianisyl-2-butene.[8]—From 13 g. of 2,2-dianisyl-3-butanone, 6 g. of the product, m. p. 126–128°, was obtained.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.37; H, 7.88.

3,4-Dianisyl-3-hexene (V).—When 10 g. of oily 3,3-dianisyl-4-hexanone (IV) was reduced and the product was dehydrated as above, 1.3 g. of the crude crystals was obtained. The mother liquor was distilled *in vacuo*, and the fraction, boiling at 182–190° at 5 mm., weighing 6.5 g., was treated with 0.7 g. of iodine in 150 cc. of chloroform.[1] When this iodine treatment was repeated, there was obtained in total 2.8 g. of the hexene derivative. Recrystallization from petroleum ether gave colorless plates, m. p. 123–124°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.08; H, 8.01. Found: C, 80.69; H, 7.83.

(IV) Demethylation[9]

2,3-bis-(*p*-Hydroxyphenyl)-2-butene.[8]—To the Grignard reagent from 2 g. of magnesium and 12 g. of methyl

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[6] Price and Mueller, THIS JOURNAL, **66**, 634 (1944), prepared the same diol by electrolytic reduction.

[7] Noller and Adams, *ibid.*, **46**, 1889 (1924).

[8] Dodds, *et al.*, *Proc. Roy. Soc.* (*London*), **B127**, 140 (1939); **B132**, 83 (1944).

[9] Kuwada and Sasagawa, *J. Pharm. Soc. Japan*, **60**, 27 (1940); U. S. Patent 2,252,696, August 19, 1941. *Cf.* Späth, *Monatsh.*, **35**, 319 (1914).

iodide was added a solution of 2 g. of 2,3-dianisyl-2-butene in 30 cc. of ether, the solvent was removed and the residue heated in an oil-bath to about 170° for forty minutes. Upon working up in the usual way, there was obtained colorless prisms, m. p. 194–196°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.93; H, 6.71. Found: C, 80.25; H, 7.08.

3,4-bis-(*p*-Hydroxyphenyl)-3-hexene (VI).—Demethylation of 2.0 g. of crude 3,4-dianisyl-3-hexene (V) gave 0.8 g. of pure diethylstilbestrol, m. p. 167–169°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.92; H, 7.07.

Summary

1. The Newman method of pinacolic reduction was applied to acetophenone, *p*-methoxyacetophenone and *p*-methoxypropiophenone. There were obtained excellent yields of the corresponding pinacols.

2. 2,3-Diphenyl-2-butene, 2,3-bis-(*p*-hydroxyphenyl)-2-butene and 3,4-bis-(*p*-hydroxyphenyl)-3-hexene were synthesized from these pinacols, improving the previous procedures.

KYÔTO, JAPAN RECEIVED MARCH 24, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

The Preparation of Synthetic Estrogens. II. The Synthesis of Hexestrol and its Homologs

BY KEIITI SISIDO AND HITOSI NOZAKI

One of the most important synthetic routes to hexestrol and related compounds involves the condensation of two molecules of *p*-α-bromopropylanisole (or the chloro derivative) with elimination of halogen. Magnesium, sodium, a Grignard reagent in the presence of cobaltous chloride, and other reagents have been used to effect the condensation.[1] All of these require the use of anhydrous conditions. According to Quelet[2] the α-halogenoalkylanisoles are more stable in the presence of moisture and accordingly a method which would not require the absence of water might have some advantages.

It is of interest that metallic iron powder is capable to act as a dehalogenating agent in the presence of water. Ogata, Turuta and Oda[3] have treated benzyl chloride, benzal chloride as well as benzo trichloride with iron powder in a large amount of hot water and obtained bibenzyl, stilbene and μ,μ'-dichlorostilbene, respectively. Model experiments on this condensation of α-chloroethylbenzene as well as of *p*-(α-chloroethyl)-anisole gave 2,3-diphenylbutane and 2,3-dianisylbutane, respectively, in 5–15% yields. With anethole hydrochloride[4] or hydrobromide the yield of the *meso* form of 3,4-dianisylhexane was 10 or 15%, respectively. It is to be pointed out that the recovered anethole was not subtracted in this calculation, as its purity was not determined. Demethylation of this product by heating with a Grignard reagent[5] gave hexestrol in good yield and in very pure state.

Although the yields realized from the present modification are not always superior to others, this method is believed to possess some merits in the simplicity and in the easy treatment, etc. The possibility of improving the yield by the use of very fine powder of iron or reduced iron in this condensation has been opened for a further research, which is now under way in our Laboratory.

Bretschneider and others[6] have prepared a metamer of hexestrol, 2,3-bis-(*p*-hydroxy-*o*-tolyl)-butane, and discovered that its estrogenic potency is of the same order as that of diethylstilbestrol or hexestrol. We have now prepared the same compound by means of our method from the hydrochloride of *p*-vinyl-*m*-methylanisole synthesized from *m*-cresol methyl ether.[7]

Experimental[8]

2,3-Diphenylbutane.—To a suspension of 12 g. of ordinary iron powder in 140 cc. of water heated at 95–98° was added with stirring 30 g. of α-chlorothylbenzene during ten minutes. The mixture was stirred for an additional three hours at the same temperature. The reaction product was extracted with benzene and the extract was fractionated. At 145–155° and 13 mm. came over 9.3 g. of colorless oil which solidified slowly. Repeated recrystallizations from alcohol yielded 3.6 g. of *meso*-2,3-diphenylbutane, m. p. and mixed m. p. 125.5°.

2,3-Dianisylbutane.—Dry hydrogen chloride was passed into a solution of 10 g. of *p*-vinylanisole containing about 10% of *o*-isomer[2,7] in 45 cc. of ligroin cooled in ice–salt mixture. The reaction solution was washed with ice-cooled water and subjected immediately to the condensation process. To a suspension of 4.2 g. of iron powder in 50 cc. of water the ligroin solution of the chloroethylanisole was added slowly with stirring at 85°. This required about thirty minutes, during which time the ligroin was removed from the vessel through a downward condenser. In the course of this, the ligroin solution contained in the dropping funnel was cooled with several pieces of crushed ice added directly in order to prevent the decomposition of the

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[1] For a review of these and other syntheses of hexestrol see Solmssen, *Chem. Rev.*, **37**, 481 (1945).

[2] Quelet, *Compt. rend.*, **202**, 956 (1936).

[3] Ogata, Turuta and Oda, *Bull. Inst. Phys. Chem. Research* (*Tôkyô*), **21**, 616 (1942) (in Japanese).

[4] Orndorff and Morton, *Am. Chem. J.*, **23**, 194 (1900). *Cf.* the fact that even the uniformity and the structure of the hydrochloride are not certain because of its unstableness.

[5] Kuwada and Sasagawa, *J. Pharm. Soc. Japan*, **60**, 27 (1940). *Cf.* U. S. Patent 2,252,696, August 19, 1941, and Späth, *Monatsh.*, **35**, 319 (1914).

[6] Bretschneider, de Jonge-Bretschneider and Ajtai, *Ber.*, **74** 571 (1941).

[7] Quelet, *Bull. soc. chim.*, **7**, 196 (1940).

[8] Microanalyses by Misses Yasuko Meizyô and Kenko Ogawa of our Laboratory.