

SYNTHESIS OF NEW HOMOLOGS OF HEXESTROL

KEIITI SISIDO, HITOSI NOZAKI, AND HIROSI KUYAMA

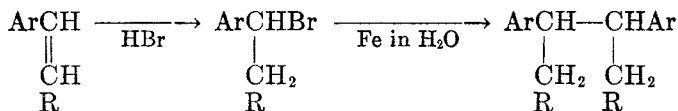
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In a previous paper (1) we have described an effective method for the preparation of hexestrol and its homologs involving the dehalogenation condensation of *p*-(α -halogenoalkyl)anisoles with iron powder in a water suspension. In this procedure, not only are the reagents, *i.e.* iron and water, easily obtainable, but also the operation is simple and does not require the use of anhydrous conditions while all of the other published methods do. According to Quelet (2), since α -halogenoalkylanisoles are relatively unstable in the absence of moisture, they easily decompose, when dry, with the elimination of hydrogen halide. Our method has, therefore, an advantage also in this point.

We have now found that the use of reduced iron instead of the ordinary iron powder gives better results in this dehalogenation.

Kharasch and Kleiman (3) have pointed out the accelerating action of ferric, nickelous, or especially cobaltous chloride in a similar condensation employing a Grignard reagent in anhydrous ether. Recently Wilds and McCormack (4) have made an extensive investigation of the condensation catalyzed by cobaltous chloride and ascribe the catalytic action of the chloride to finely divided cobalt powder formed in the reaction. In connection with this view, further investigations on the syntheses in aqueous and non-aqueous mediums with iron, nickel or cobalt prepared under different reduction conditions are now under way in collaboration with an inorganic laboratory of our Department.

The present paper comprises the syntheses of 2,3-bis-(*p*-hydroxy-*m*-tolyl)butane, 3,4-bis-(*m*,*p*-dihydroxyphenyl)hexane, 3,4-bis-(*p*-hydroxy-*o*-tolyl)hexane, 4,5-bis-(*p*-hydroxyphenyl)octane, 2,7-dimethyl-4,5-bis-(*p*-hydroxyphenyl)octane, 5,6-bis-(*p*-hydroxyphenyl)decane, and 6,7-bis-(*p*-hydroxyphenyl)dodecane. The reactions used in the preparations are, in general, as follows.



R = Alkyl; Ar = Aryl

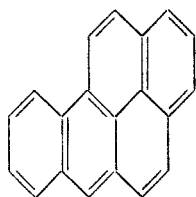
Although the synthesis of the diphenylhexatriacontane derivative (R = C₁₆H₃₃) was not successful, the reaction seems to be widely applicable to the preparation of derivatives of the α , α' -dialkylbibenzyl type with the exception of higher members.

The new compound, 2,3-bis-(*p*-hydroxy-*m*-tolyl)butane, now synthesized, corresponds to 2,3-bis-(*p*-hydroxy-*m*-tolyl)-2-butene, a new estrogen found by us (5). Since the pairs, hexestrol and diethylstilbestrol as well as 2,3-bis-(*p*-hydroxy-*o*-tolyl)butane (6) and 2,3-bis-(*p*-hydroxy-*o*-tolyl)-2-butene (5, 7) have an ac-

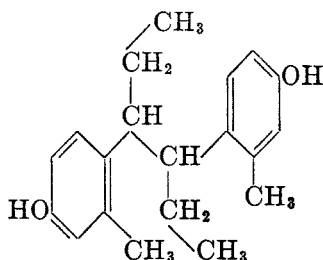
tivity of the same order, we anticipate its estrogenity although the *in vivo* test is not completed.

For the sake of comparison with 3,4-bis-(*p*-hydroxy-*m*-tolyl)hexane, an estrogen of high activity and low toxicity found by Niederl, Siconolfi, Bloom, and Van Meter (8), a new isomer, 3,4-bis-(*p*-hydroxy-*o*-tolyl)hexane, was prepared.

In the study of estrogenic substances having a 1,3-diarylpropane structure, Stuart, Shukis, Tallman, McCann, and Treves (9) have noted a structural resemblance of highly active benzestrol with the carcinogens, 9,10-dimethyl-1,2-benzanthracene and cholanthrene. It is interesting to prepare other phenolic substances with an open skeleton of a carcinogenic hydrocarbon. 3,4-Bis-(*p*-hydroxy-*o*-tolyl)hexane mentioned above is a symmetrical open model of 3,4-benzopyrene.



3, 4-Benzopyrene

3, 4-Bis-(*p*-hydroxy-*o*-tolyl)hexane

3,4-Bis-(*m*,*p*-dihydroxyphenyl)hexane was prepared already by Baker (10) in another way. This compound is an isomer of nordihydroguaiaretic acid (11) and activity also as an antioxidant of fatty oils is expected.

An attempt to synthesize genuine nordihydroguaiaretic acid from safrole hydrobromide (a compound with a bromine atom attached to the β -position from the atomatic ring) by means of this condensation reaction resulted in failure. Styrene dibromide, on treatment with iron in water, also did not give any condensation product other than styrene and styrene dimer. Funakubo and Ootuka (12) described a similar dehalogenation of α,β -dihalogeno- α -phenylpropane.

The biological testing of these compounds is being carried out in the laboratory of Prof. Kinoshita of Osaka University Medical School. The pharmacological results will be published elsewhere.

EXPERIMENTAL

Improved preparation of 3,4-di-p-anisylhexane (1). A solution of 40 g. of anethole (synthesized from *p*-bromoanisole and allyl bromide) in 200 cc. of toluene was saturated with dry hydrogen bromide under cooling with an ice-salt mixture. After washing with ice-cooled water the toluene solution was added dropwise with stirring to a suspension of 24 g. of reduced iron [ferrum reductum, P.J.V. (Fifth Pharmacopoeia of Japan) grade] in 240 cc. of hot water maintained at 80–98°. The addition required about fifteen minutes, during which the toluene was distilled from the reaction vessel. In the course of this the toluene solution contained in a dropping-funnel attached to the reaction flask was added directly with several pieces of crushed ice in order to prevent the decomposition of the halogeno compound

and to supply the water driven off with the toluene. The reaction mixture then was heated under a reflux condenser for an additional three hours at 95–98° and allowed to cool. The product was extracted with ether and the ether solution was washed with water, dried, and the solvent was evaporated. Recrystallization of the residue from methanol-ligroin afforded colorless plates, m.p. and mixed m.p. with *meso*-3,4-di-*p*-anisylhexane 144°; yield, 8.1 g. (20%).

The mother liquor was distilled *in vacuo* and 9 g. of a fraction b.p. 70–115° at 23 mm. and 17 g. of a fraction b.p. 180–200° at 6 mm. were obtained. The latter fraction, which seemed to consist of *racemic* dianisylhexane and possibly of anethole dimer etc., did not give any crystalline product when treated with methanol-ligroin. The lower-boiling fraction contained, according to the analysis by the method of McIlhiney (13), 85% of anethole. The purity of the starting anethole was, according to the same analysis, 99.5%. Allowing for recovered anethole the yield of hexestrol dimethyl ether was 25%.

When anethole hydrochloride was used instead of the hydrobromide in the present condensation, lower yields (14–15%, without considering the recovered material) were obtained.

2,3-Bis-(p-hydroxy-m-tolyl)butane.* A mixture of 10 g. of *p*-vinyl-*o*-methylanisole prepared by the method of Quelet (14), and 50 cc. of ligroin was saturated with hydrogen chloride at –8 to –10° and was treated with 5 g. of reduced iron powder and 60 cc. of water at about 100° for four hours as above. There was obtained 6 g. of a fraction b.p. 180–193° at 6 mm. together with 3 g. of a lower-boiling fraction which contained the starting material. Crystallization from methanol-ligroin afforded 1.5 g. of colorless crystalline *meso*-2,3-*bis*-(*p*-methoxy-*m*-tolyl)butane,* m.p. 124–125°.

Anal. Calc'd for C₂₀H₂₆O₂: C, 80.49; H, 8.78.

Found: C, 80.93; H, 8.40.

Demethylation with a Grignard reagent or with hydriodic acid in glacial acetic acid and recrystallization from benzene gave *meso*-2,3-*bis*-(*p*-hydroxy-*m*-tolyl)butane,* m.p. 174–174.5°, in large colorless crystals which changed soon to a white powder. Due perhaps to this property the analysis did not give satisfactory values. Bretschneider, de Jonge-Bretschneider, and Ajtai (6) reported a similar case.

The *diacetate** prepared with acetic anhydride and pyridine melted at 145–145.5° after recrystallizations from alcohol.

Anal. Calc'd for C₂₂H₂₈O₄: C, 74.55; H, 7.39.

Found: C, 74.80; H, 7.42.

3,4-Bis-(m,p-dihydroxyphenyl)hexane. A solution of 50 g. of isosafrole with a purity of 99.3% in 100 cc. of ligroin was saturated with hydrogen bromide and treated with 20 g. of iron powder in 200 cc. of water as above. The reaction product separated during the operation as white crystals. The reaction mixture was extracted with benzene and 12 g. of crystals was obtained. From the mother liquor there was obtained on distillation *in vacuo* 1 g. of a fraction b.p. 60–100° at 35–40 mm., 9 g. of a fraction b.p. 120–130° at 35–40 mm., and 13 g. of a fraction b.p. 210° at 3 mm. On analyses according to McIlhiney (13), the lower-boiling fractions contained 43.0 and 91.2%, respectively, of isosafrole. The last fraction gave on recrystallization from benzene-alcohol an additional 4 g. of the above mentioned crystals. Recrystallized from benzene-alcohol the combined crystals gave 12 g. of *meso*-3,4-*bis*-(*m,p*-methylenedioxyphenyl)hexane,* m.p. 174–175°.

Anal. Calc'd for C₂₀H₂₂O₄: C, 73.60; H, 6.79.

Found: C, 73.65; H, 6.74.

A mixture of 10 g. of 3,4-*bis*-(*m,p*-methylenedioxyphenyl)hexane, 45 g. of toluene, and 42 g. of phosphorus pentachloride was refluxed for three hours and the resulting 3,4-*bis*-(*m,p*-dichloromethylenedioxyphenyl)hexane* was decomposed with ice and a saturated sodium carbonate solution. From the toluene layer, after washing with water, drying, and evaporation, 6 g. of 3,4-*bis*-(*m,p*-carbonyldioxyphenyl)hexane* was obtained, which after recrystallization from toluene melted at 186–187°.

* Indicates a new compound.

Anal. Calc'd for $C_{20}H_{18}O_4$: C, 67.79; H, 5.12.

Found: C, 67.32; H, 5.05.

A mixture of 6 g. of the carbonyldioxy compound, 320 g. of methanol, and 100 cc. of conc'd hydrochloric acid was heated at 78° in an atmosphere of carbon dioxide for 2½ hours and evaporated *in vacuo*. When about two-thirds of the solvent was distilled off, the phenolic substance deposited in white fine crystals, which were filtered and dried on porous plate. Yield, 5 g. After recrystallization from 50% acetic acid the compound melted with decomposition at 230–235°. This melting point coincides with the one reported by Baker (10).

On acetylation and recrystallization from alcohol, the phenol gave the *tetraacetate*,* m.p. 167–167.5°. The same tetraacetate was prepared also directly from the methylenedioxy compound by the cleavage of the methylenedioxy ring with acetic anhydride. When 2 g. of the methylenedioxy compound and 6.5 g. of acetic anhydride were heated at 200° for fifteen hours in a sealed tube considerable carbonization took place, but 0.3 g. of the impure tetraacetate and 1 g. of unchanged material were obtained.

Anal. Calc'd for $C_{26}H_{30}O_8$: C, 66.37; H, 6.43.

Found: C, 66.08; H, 6.23.

Variations in the condensation procedure. In order to determine the best conditions for this dehalogenation reaction, we carried out the following three experiments employing isosafrole. In each case, 100 g. of isosafrole in 150 g. of toluene was saturated with hydrogen bromide at $-10 \pm 3^\circ$ and condensed by means of 40 g. of reduced iron powder in 400 cc. of water.

(a) A mixture of iron powder and water was heated to 100° and the hydrobromide solution was added slowly at such a rate that toluene distilled off completely from the reaction vessel. The addition required about one hour. There was obtained 35 g. of a lower-boiling fraction and 45 g. of a condensate fraction which gave 20 g. of the crude crystalline *meso* compound and a resinous residue.

(b) Into a mixture of iron powder and water heated to about 80–90° the hydrobromide solution was added in the course of twenty minutes regardless of the rate of distilling toluene. There was obtained 33 g. of a lower-boiling fraction and 53 g. of a condensate including 25 g. of the *meso* crystals.

(c) Iron powder, water, and the hydrobromide solution were mixed to an emulsion at room temperature and heated gradually until toluene was azeotropically distilled off. Twenty-five grams of a lower-boiling fraction and 50 g. of a condensate fraction were obtained. The latter gave 23 g. of the *meso* crystals.

Attempted synthesis of 2,5-bis-(m,p-methylenedioxyphenyl)hexane. Thirty grams of safrole hydrobromide, b.p. 130–140° at 8 mm., 15 g. of iron powder, and 150 cc. of water were heated to reflux under stirring for two hours, but only very small amount of a condensation product was obtained. Even when we used an active cobalt powder freshly reduced instead of iron, almost the same result was obtained.

*3,4-Bis-(p-hydroxy-o-tolyl)hexane.** *p*-Methoxy-*o*-methylpropionophenone was prepared from *m*-cresol methyl ether and propionyl chloride by the Friedel-Crafts reaction and reduced to the corresponding carbinol with sodium in isoamyl alcohol. The carbinol was dehydrated with potassium bisulfate to *o*-methylanethole. A solution of 10 g. of *o*-methylanethole in 60 cc. of ligroin or toluene was saturated with hydrogen bromide and treated with 7 g. of iron powder in 60 cc. of water as above. There was obtained 6 g. of a lower-boiling fraction and 3 g. of a condensation product which afforded on repeated recrystallizations from methanol large prisms of *meso*-3,4-bis-(*p*-methoxy-*o*-tolyl)hexane,* m.p. 129–130°, yield, 0.6 g.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26.

Found: C, 81.04; H, 9.27.

Demethylation with hydriodic acid and glacial acetic acid and recrystallizations from benzene yielded *meso*-3,4-bis-(*p*-hydroxy-*o*-tolyl)hexane, m.p. 218–219°.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78.

Found: C, 80.42; H, 8.45.

The *diacetate*,* recrystallized from ligroin formed needles melting at 153°.

Anal. Calc'd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91.

Found: C, 75.17; H, 8.02.

4,5-Bis-(p-hydroxyphenyl)octane (octestrol). Starting from anisole and *n*-butyryl chloride the corresponding arylalkene was obtained. Ten grams of this olefin gave, besides 4 g. of a lower-boiling fraction, 3.5 g. of a condensate which gave on recrystallization from methanol 1 g. of *meso*-4,5-bis-(*p*-methoxyphenyl)octane, m.p. 121–122°.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26.

Found: C, 80.71; H, 9.00.

On demethylation and recrystallization from benzene long needles of *meso*-4,5-bis-(*p*-hydroxyphenyl)octane, m.p. 166–167°, were obtained.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78.

Found: C, 80.27; H, 8.70.

The melting points of the hydroxy and the methoxy compounds coincide with those recorded by Dodds, Golberg, Grünfeld, Lawson, and Saffer (15).

The *diacetate*,* crystallized from ligroin, m.p. 167.5–168.5°.

Anal. Calc'd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91.

Found: C, 75.32; H, 7.96.

2,7-Dimethyl-4,5-bis-(p-hydroxyphenyl)octane.* Using 13 g. of the olefin derived from isovaleryl chloride as above, 3 g. of an oily reaction product and 7 g. of a lower-boiling fraction were obtained.

Since this oily mixture of *meso* and *racemic* compounds did not give any crystalline substance, it was demethylated as such and gave 0.5 g. of a hydroxyphenyl compound. On repeated recrystallizations from benzene, long colorless needles were obtained, which changed soon to white powder. The melting point was not sharp, 167–170°.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26.

Found: C, 80.59; H, 8.77.

The *diacetate** melted at 187–190°.

Anal. Calc'd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35.

Found: C, 75.84; H, 7.91.

5,6-Bis-(p-hydroxyphenyl)decane (decestrol).*Twelve grams of the olefin derived from *n*-valeryl chloride afforded 2.5 g. of an oily condensation product in addition to 7 g. of a lower-boiling fraction. On demethylation, 1 g. of crystalline *meso*-5,6-bis-(*p*-hydroxyphenyl)decane was obtained in long needles, m.p. 170–171° from benzene.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26.

Found: C, 80.56; H, 9.04.

The *diacetate*,* m.p. 128.5–129°.

Anal. Calc'd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35.

Found: C, 75.78; H, 7.99.

6,7-Bis-(p-hydroxyphenyl)dodecane.* Twenty grams of the corresponding olefin from caproic acid gave 10 g. of a lower-boiling fraction and 6 g. of an oily product which on demethylation yielded 2 g. of a crystalline phenolic compound. Repeated recrystallizations from benzene yielded hair-like crystals, m.p. 145–146°.

Anal. Calc'd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.66.

Found: C, 81.17; H, 9.39.

The *diacetate** formed fibrous brilliant crystals, m.p. 98–99°, from ligroin.

Anal. Calc'd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73.

Found: C, 76.19; H, 8.88.

Attempted synthesis of 18,19-bis-(p-hydroxyphenyl)hexatriacontane. Analytically pure *p*-methoxystearophenone, m.p. 78–79°, was reduced to the corresponding carbinol and dehydrated to the olefin, b.p. 170–180° at 0.015 mm. The toluene solution of this olefin was saturated with hydrogen bromide in the same manner. Treatment of the product with iron powder, however, failed to afford any distillable condensation product.

Reaction of styrene dibromide with iron. Twenty-five grams of styrene dibromide, 5.6 g.

of iron powder, and 64 cc. of water were heated to reflux under stirring for eight hours, and treated as usual. There was obtained 2.5 g. of a fraction, b.p. 50–57° at 20–30 mm. and 2.7 g. of the higher-boiling oily fraction, b.p. 110–120° at 5 mm. Bromination of the first fraction gave styrene dibromide, m.p. and mixed m.p. 72–73°. The higher-boiling fraction gave no crystalline substance and was negative in the Beilstein test. As it absorbed bromine, it was assumed to be a dimer of styrene. These results indicate the occurrence of an intramolecular dehalogenation (12) followed by polymerization.

SUMMARY

By the dehalogenation condensation of α -halogenoalkylanisoles with metallic iron powder in a water suspension, some homologs of hexestrol were prepared. This dehalogenation procedure seems to be applicable in general.

KYŌTO, JAPAN.

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