

THE SYNTHESSES OF METHOXY DERIVATIVES
OF HEXESTROL

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OF HEXESTROL

By

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TABLE OF CONTENTS

	Page
Introduction	1
Historical Background	2
Preliminary Discussion	6
Experimental	
Preparation of:	
Veratric Aldehyde	8
Veratroin	9
Veratril	9
Piperoin	10
Desoxypiperoin	10
Isoeugenol Methyl Ether	11
Isoeugenol Methyl Ether Hydrochloride	11
3,4-Bis(3,4-dimethoxyphenyl)hexane	12
Isoeugenol Methyl Ether Hydrobromide	13
Discussion	16
Summary	18
Bibliography	19
Autobiography	20

INTRODUCTION

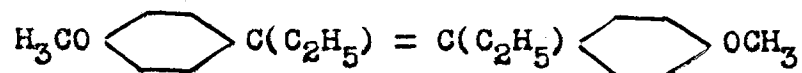
It is known that the dimethyl ether of hexestrol is an active estrogen in the domestic fowl (4). It was thought that the introduction of more methoxy groups, or of methylenedioxy groups, into the hexestrol molecule might increase the estrogenic activity in the chicken.

The purpose of this investigation was the synthesis of methoxy and methylenedioxy derivatives of hexestrol for testing as estrogens.

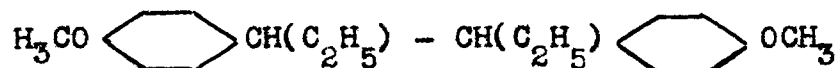
HISTORICAL BACKGROUND

The discovery of the estrogenic activity of stilbestrol in 1938 by Dodds, Goldberg, Lawson, and Robertson (3) provided an impetus that resulted in a very great amount of work being done by many investigators in an effort to synthesize compounds of similar structure having an equal or greater biological activity. This work has been thoroughly reviewed by Solmsen (5) who attempted a correlation of chemical structure and physiological activity for the synthetic estrogens.

Jaap (4) found the dimethyl ether of stilbestrol



to be a more active estrogen for oral administration in the domestic fowl than stilbestrol, and the dimethyl ether of hexestrol



to have a similar higher potency than hexestrol when orally administered to the fowl.

The foregoing observations are the direct opposite to those noted on rats and mice, in which the dimethyl ethers have a markedly lower activity than either stilbestrol or hexestrol.

Jaap (4) further found that of 17 estrogenic or potentially estrogenic substances tested, the dimethyl ether of hexestrol had the highest potency when orally administered to the domes-

tic fowl. The test for estrogenic activity used in these studies was the increase in oviduct weight by the seventeenth day after hatching.

Considerable interest has been shown in the possibility of administering synthetic estrogens to poultry for the purpose of increasing weight at market time.

Although extensive variations of the basic stilbestrol and hexestrol structures have been studied, there has been little or no work published on the biological effect of polyalkoxy substituents on the aromatic nucleus.

It was decided to study various methods of synthesizing 3,4-bis(3,4-dimethoxyphenyl)hexane and 3,4-bis(3,4-methylenedioxyphenyl)hexane, with the ultimate view of investigating the potency of these compounds.

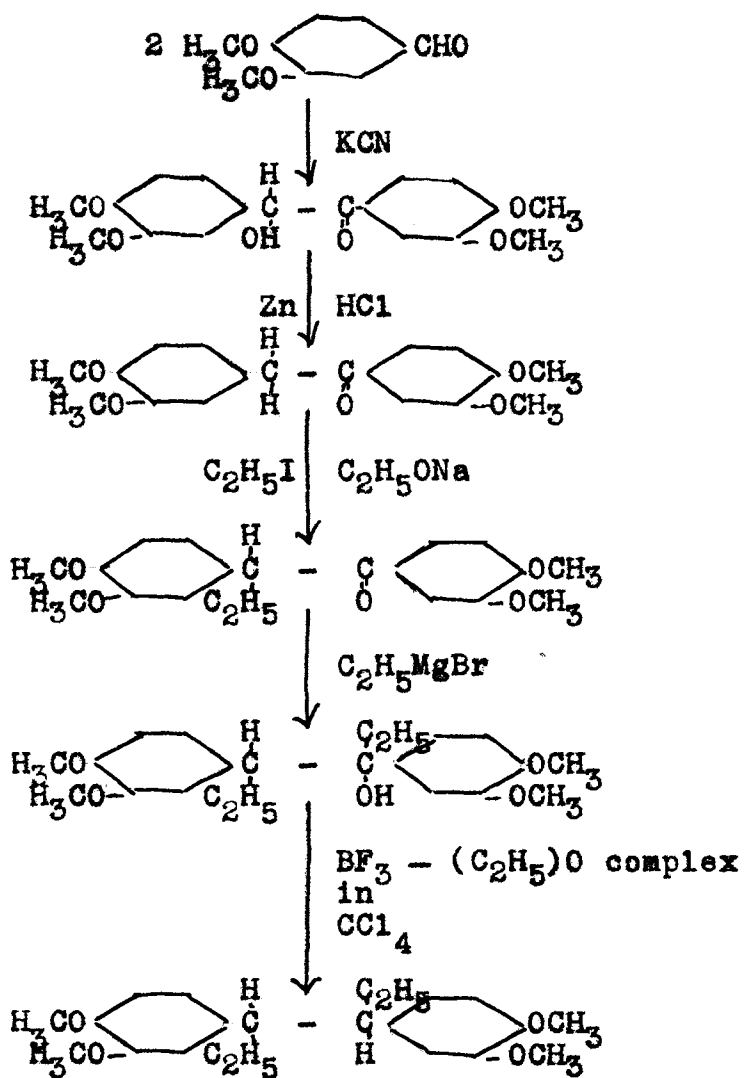
In 1938, Dodds (3) published the first synthesis of stilbestrol via desoxyanisoin. Desoxyanisoin was ethylated with ethyl iodide to α -ethyl desoxyanisoin. The latter was treated with ethyl Grignard solution and the reaction product dehydrated to give 3,4-bis(4-methoxyphenyl)-3-hexene. The sequence of reactions that appears in Table I is largely adopted from Dodd's original synthesis.

Wilds and McCormack (7) described a synthesis of hexestrol by coupling of two molecules of anethole hydrobromide (p-(α -chloro-n-propyl)anisole) by means of ethylmagnesium bromide, catalyzed by cobalt. The best yield of meso hexestrol dimethyl ether was 31%. They obtained this compound in 22% yield by the Wurtz-type condensation of anethole hydrobromide

effected by magnesium metal, catalyzed by cobalt.

A British patent (1) for a Wurtz-type reaction of an active metal such as magnesium with halides mentions the production of 3,3',4,4'-tetrahydroxy- α,β -diethylstilbene as an example, along with its hexestrol analog, but gives no information concerning its biological activity.

TABLE I



PRELIMINARY DISCUSSION

It was originally planned to attempt to follow the more or less classical route to such compounds, starting with the benzoin type condensation (3) as illustrated in Table I. This offered the advantage of using vanillin, a relatively cheap and available compound, as a starting material.

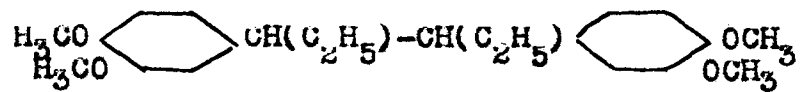
However, it was found possible to get only a very small yield of veratril by oxidation of veratroin (6), and since this step occurred early in the synthetic scheme, it nullified any chance for success via this route.

A similar scheme starting with piperonal was attempted and only a small yield of desoxypiperoin was achieved. It was decided that the accumulation of oxygen on the ring in compounds of this type make them too susceptible to oxidation and other side reactions to make the projected multi-step synthesis practicable.

It was next attempted to use the cobalt-catalyzed Grignard condensation described by Wilds and McCormack (7), as this offered the possibility of a three-step synthesis starting with isoeugenol. In a series of runs only very small yields were obtained by this method.

Finally a Wilds and McCormack modification of the original method of Docken and Spielman (2) was tried and a 13% yield of the desired product was obtained. This method consisted essentially of a cobalt-catalyzed Wurtz condensation of the hydro-

bromide of isoeugenol methyl ether.



EXPERIMENTAL

Veratric Aldehyde

A mixture of 91 g. (0.60 mole) of vanillin and 225 ml. of boiling water was placed in a 2-liter, three-neck flask equipped with a reflux condenser, liquid-sealed stirrer, and a dropping funnel. The mixture was heated on a steam bath and treated with 180 ml. of boiling 20% sodium hydroxide solution.

Heating was continued and 71 ml. (94.5 g.) of dimethyl sulfate was added through the dropping funnel over a period of 35 minutes. The solution was then heated for 45 minutes with continued stirring, after which time an additional 15 ml. of dimethyl sulfate was added at the same rate as for the first portion. After ten minutes of heating, the reaction mixture was made alkaline with 60 ml. of the same sodium hydroxide solution and then 30 ml. of dimethyl sulfate was added slowly. Thirty milliliters of the sodium hydroxide solution was added and then an additional 15 ml. of dimethyl sulfate. The total dimethyl sulfate added was 1.35 moles (172.5 g.).

The reaction mixture was made strongly alkaline with sodium hydroxide, heated for 20 minutes, and cooled rapidly in an ice bath with continued stirring. The reaction mixture was extracted with three 150 ml. portions of ether, the ether extract was dried over calcium chloride, and the ether removed by distillation. A light yellow oil remained which, on cooling

and scratching, crystallized into white crystals. The yield was 71.0 g. (71.3% of theoretical). The melting point obtained was 44-44.5° uncorr.; the melting point reported in the literature is 43-44.5°.

Veratroin

Five grams of veratric aldehyde (0.03 mole), one gram of potassium cyanide, 12 ml. of ethyl alcohol, and 5 ml. of water were refluxed in a 200-ml., round-bottom flask for two hours. The reaction mixture was diluted with 100 ml. of ice water while being stirred. A yellow oily phase was obtained along with a small amount of yellow crystals. The yellow crystals, removed by filtration, gradually darkened and became an oil. The filtrate was extracted with three 25-ml. portions of ether. The combined ether extracts were washed with water, dried over calcium chloride, and the ether removed by distillation. A yellow oil remained which was presumed to be veratroin. The yield was 2.5 g. (50% of theoretical).

Veratril

A mixture of 2.5 g. of veratroin (0.0075 mole) and 50 ml. of water was refluxed in a 200-ml., round-bottom flask. Fehling solution was added dropwise through the condenser to the boiling solution until the Fehling solution was no longer decolorized on addition. The reaction mixture was diluted with 100 ml. of cold water and filtered; the residue was extracted with hot carbon tetrachloride and filtered. Yellow crystals of veratril crystallized from the carbon tetrachloride solution on stand-

ing. The yield was 0.10 g. (4% of theoretical). The melting point obtained was 224° uncorr. The melting point reported in the literature is 223° .

Piperoin

Ten grams (0.066 mole) of piperonal, 3 g. potassium cyanide, and 50 ml. of 50% ethyl alcohol were refluxed for three hours in a 200-ml., round-bottom flask. The reaction mixture was cooled and the liquid decanted, leaving a yellow solid. The crude piperoin was recrystallized from ethyl alcohol and then from methyl alcohol. The crystals were air-dried. The yield was 4.0 g. (40% of theoretical). The melting point obtained was 119° uncorr. The melting point reported in the literature is 120° .

Note: When a 20-g. batch of piperonal was treated in exactly the same fashion, only a 20% yield could be obtained.

Desoxypiperoin

Four grams of piperoin (0.0133 mole), 4 g. of granulated tin, and 20 ml. of ethyl alcohol were placed in a 200-ml., round-bottom flask and refluxed over a steam bath. Seven and three-tenths milliliters of concentrated hydrochloric acid containing a trace of copper sulfate was added and refluxed for $2\frac{3}{4}$ hours. Five milliliters of ethyl alcohol and 2 ml. more of the copper-containing, concentrated hydrochloric acid were then added and refluxing was continued for an additional $1\frac{1}{2}$ hours. On cooling, the product crystallized out, and was recrystallized from ethanol. The yield was 0.5 g. (12.5% of

theoretical). The melting point obtained was 113° uncorr.; the melting point in the literature is 114° .

Isoeugenol Methyl Ether (4-Propenylveratrole)

A solution of 10 g. (0.25 mole) of sodium hydroxide in 200 ml. of water was placed in a one-liter, three-neck flask equipped with a mercury-sealed stirrer, a condenser, and a dropping funnel. The solution was warmed on a steam bath and 41 g. (0.25 mole) of isoeugenol was added while stirring.

Twenty-three and one-half milliliters (0.25 mole) of dimethyl sulfate that had previously been washed with water was added dropwise while the solution was warmed and stirred. The addition time was 40 minutes, and heating and stirring were continued for an additional hour.

The oil which had formed was separated from the reaction mixture and washed with water. The oil was then distilled under reduced pressure and the portion boiling at $108-115^{\circ}$ at 10 mm. pressure was retained. This oil was found to be insoluble in sodium hydroxide solution. The yield of isoeugenol methyl ether was 20 g. (45% of theoretical). The boiling point obtained was 263° uncorr.; the boiling point reported in the literature is 263° .

Isoeugenol Methyl Ether Hydrochloride (4-(α -Chloro-n-propyl)veratrole)

In a three-neck, 200-ml. flask equipped with a liquid-sealed stirrer and gas inlet and outlet tubes was placed 10 g. (0.056 mole) of isoeugenol methyl ether dissolved in 50 ml. of petroleum ether (boiling $30-60^{\circ}$) previously dried over calcium

chloride. The solution was chilled to -10° and treated with hydrogen bromide gas for one hour with stirring. At the end of this time the solution gave a negative test for unsaturation with a 5% solution of bromine in carbon tetrachloride.

The petroleum ether was removed at reduced pressure, a calcium chloride drying tube being used to draw air through the solution. The residual oil was taken up in anhydrous ether and used immediately.

3,4-Bis(3,4-dimethoxyphenyl)hexane

Run I

Ethylmagnesium bromide was prepared in a dry, 500-ml., three-neck flask equipped with a liquid-sealed stirrer, a dropping funnel and a reflux condenser from 2.43 g. (0.1 gram-atom) of magnesium, 10.7 g. (0.098 mole) of ethyl bromide, and 80 ml. of ether dried over sodium.

To the stirred Grignard solution at room temperature was added 0.58 g. (0.0046 mole) of anhydrous cobaltous chloride over a period of one minute. The condenser was then connected to a mineral-oil trap and a dry ether solution of hydrochloride of isoeugenol methyl ether which had previously been prepared from 10 g. (0.056 mole) of isoeugenol methyl ether was added over a period of 30 minutes. Stirring was continued during the addition and the temperature was maintained at $30-32^{\circ}$.

The black reaction mixture was poured into an ice-hydrochloric acid mixture and extracted twice with ether. The combined ether extracts were successively washed with 5% hydro-

chloric acid, water, and saturated salt solution, and dried over calcium chloride. The ether was removed by distillation under reduced pressure and the residual oil was taken up in 12 ml. of methanol and allowed to crystallize in the refrigerator for two days. The yield was 0.20 g. (2.0% of theoretical). The melting point of the crude material was 112.5-114°. After recrystallization from methanol, the melting point obtained was 135.5-136°.

Analysis: C, 73.23%; H, 8.51%; $C_{22}H_{30}O_4$ requires C, 73.74%; H, 8.38%.

Isoeugenol Methyl Ether Hydrobromide (4-(α -Bromo-n-propyl)
veratrole)

The hydrobromide of isoeugenol methyl ether was prepared like the hydrochloride. The hydrogen bromide was generated by dropping bromine into boiling tetralin in a 100-ml. distilling flask and washing the gas formed with excess tetralin.

3,4-Bis(3,4-dimethoxyphenyl)hexane

Run II

This run was similar to Run I with the exception that instead of the hydrochloride, the hydrobromide derived from 10 g. (0.056 mole) of isoeugenol methyl ether was used. The yield was 0.24 g. (2.4% of theoretical). The crude product melted at 112.5-114° uncorr. After recrystallization from methanol the product melted at 135.5-136° uncorr.

Analysis: C, 73.27%; H, 8.51%; $C_{22}H_{30}O_4$ requires C, 73.74%; H, 8.38%.

3,4-Bis(3,4-dimethoxyphenyl)hexaneRun III

Isoeugenol methyl ether hydrobromide was prepared from 10.68 g. (0.06 mole) of isoeugenol methyl ether.

Three grams (0.12 gram-atom) of magnesium and 120 ml. of anhydrous ether were placed in a 500-ml., three-neck flask equipped with a mercury-sealed stirrer, a thermometer, and a reflux condenser to which was attached a dropping funnel. A few crystals of iodine and 0.6 g. (0.0046 mole) of anhydrous cobaltous chloride were added and the solution was cooled to -10° in an ice-salt bath.

A small amount of the dry ether solution of the isoeugenol methyl ether hydrobromide was added, followed by 1.5 ml. of ethyl bromide. The temperature was raised to 10° with stirring until some erosion of the magnesium was noted. The reaction mixture was then chilled back to -10° while the remainder of the ether solution of isoeugenol methyl ether hydrobromide was added over a 30-minute period with continued stirring. After addition was complete, the reaction mixture was stirred for one hour at -10° , three hours at 10 to 15° , four hours at room temperature, and one hour at reflux temperature.

The reaction mixture was then poured into an ice-hydrochloric acid mixture and extracted twice with ether. The combined ether extracts were then washed successively with a 5% hydrochloric acid solution, water, and a saturated salt solution, then dried over calcium chloride. The ether was

removed by distillation under reduced pressure and the residual oil was taken up in 10 ml. of methanol. The solution was set aside in the refrigerator for two days to crystallize. The crystals were filtered and dried in air. The yield was 1.4 g. (13% of theoretical). The melting point obtained was 78-82° uncorr. The melting point obtained after recrystallization from methanol was 82-83° uncorr.

Analysis: C, 73.87%; H, 8.34%; $C_{22}H_{30}O_4$ requires C, 73.74%; H, 8.38%.

DISCUSSION

At the present time, no really satisfactory method has been devised for the preparation of analogs of hexestrol and stilbestrol having polyhydroxy or polyalkoxy aromatic substituents.

The route through the benzoin-type condensation seems impractical because the instability of the intermediates makes it difficult for them to withstand the rigors of such a multi-step synthesis. Very poor yields of both desoxy-piperoin and veratril were obtained. In the case of veratril, the difficulty of working up the reaction mixture may also have been a contributing factor toward the poor yield. Since these low yields occurred early in the proposed synthetic sequence, this method of approach had to be abandoned. The cause of the low yields may have been the great ease of oxidation of the intermediates.

The cobalt-catalyzed Grignard condensation which gave Wilds and McCormack (7) a 31% yield of mesohexestrol dimethyl ether, does not seem at all satisfactory as a method for preparing the compounds considered herein. Yields of only 2 to 2.4% of what is believed to be the meso isomer of 3,4-bis(3,4-dimethoxyphenyl)hexane were obtained.

Of the methods tried, the cobalt-catalyzed Wurtz reaction seems the only one of practical use, and even here the 13% yield of crude product is hardly satisfactory. Docken and Spielman (2) obtained a 15% yield of mesohexestrol dimethyl

ether, without using the cobalt catalyst, and Wilds and McCormack (7) report a 22% yield of the same compound when cobalt is used.

Two isomeric forms of 3,4-bis(3,4-dimethoxyphenyl)hexane were obtained in this study. The higher-melting isomer (135.5-136°) was obtained as a product of the Grignard condensation while the lower-melting isomer (82-83°) was a product of the Wurtz reaction. On the basis of an analogy with the melting points of the hexestrol dimethyl ethers (the meso form melts at 140-143° and the racemic form at 53-56°) it is believed that the Grignard product (melting point 135.5-136°) is the meso form, while the Wurtz product (melting point 82-83°) is the racemic form.

A possible method of synthesis of these compounds that might profitably be investigated is that of the pyrolysis or refluxing of substituted trithiobenzaldehydes in the presence of metal. A 25% yield of 3,3',4,4'-tetramethoxystilbene has been obtained (8) by the pyrolysis of trithioveratraldehyde intimately mixed with copper powder.

A suggested synthesis would be the refluxing of 3,4-dimethoxypropiophenone in the presence of Raney nickel in xylene. An 18% yield of α,α' -dimethylstilbene has been obtained (1-a) from thioacetophenone by this method.

SUMMARY

Two isomeric forms of 3,4-bis(3,4-dimethoxyphenyl)-hexane have been prepared for the first time. The form which is believed to be the meso form melts at 135.5-136°, while what is believed to be the racemic form melts at 82-83°.

Analyses:

Meso form	C, 73.27%; H, 8.51%
Racemic form	C, 73.87%; H, 8.34%
$C_{22}H_{30}O_4$	C, 73.74%; H, 8.38%

Of the various methods of preparation for these compounds investigated, the cobalt-catalyzed Wurtz reaction was found to be the best for preparing the racemic isomer, giving a 13% yield. The meso isomer was prepared in 2.4% yield by the Grignard condensation method.

The racemic form will be tested for estrogenic activity in the domestic fowl.

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AUTOBIOGRAPHY

Harold Lyons was born in New York City, March 27, 1919. In 1935 he entered the City College of New York. He was employed as a chemist by the Climax Rubber Company from 1937 to 1941, while continuing his studies at the City College of New York through the medium of evening classes.

In 1941 he went on active duty with the United States Navy and was returned to inactive duty in 1945 with the rank of Lieutenant. Mr. Lyons was awarded the Bachelor of Science degree by the City College of New York in 1945. From 1945 to 1948 he was employed as a research chemist by the Huberoid Company, meanwhile attending evening graduate courses at the Newark College of Engineering and the Stevens Institute of Technology. He resigned from the Huberoid Company to accept an appointment as a Graduate Fellow at Oklahoma Agricultural and Mechanical College, where he entered the Graduate School in September, 1948.

Typist: Larmer S. Tippit