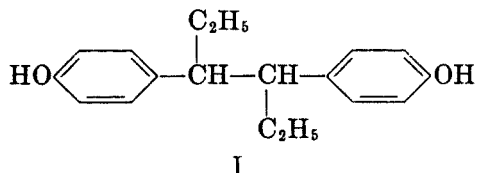# THE SYNTHESIS OF HEXESTROL THROUGH THE CATALYZED-GRIGNARD COUPLING OF ANETHOLE HYDROBROMIDE AND THE MECHANISM OF THE REACTION
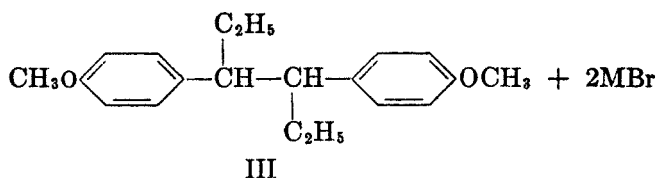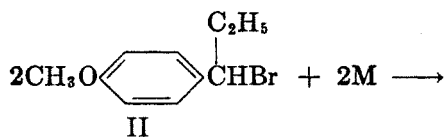
A. L. WILDS and WILLIAM B. MCCORMACK[1]

The first practical synthesis of the estrogen hexestrol (I),

I

discovered by Dodds, et al. (1), was reported in 1940 by Docken and Spielman (2) and independently by Peak and Short (3) and Bernstein and Wallis (4). This synthesis involved a Wurtz-type coupling of anethole hydrobromide (II) to hexestrol dimethyl ether (III):

II

III

The yield of the *meso* isomer of hexestrol dimethyl ether by this reaction was 15 to 20% using metals such as magnesium and sodium, and somewhat lower (6%) employing a Grignard reagent such as methylmagnesium iodide (5). In 1943 Kharasch and Kleiman (6) described an improved Grignard coupling procedure using phenylmagnesium bromide in the presence of catalytic amounts of cobaltous chloride, and reported yields as high as 42% of the *meso* ether III.

The coupling of benzyl halides to dibenzyls by the action of Grignard reagents in the presence of a catalyst (or "uncatalyzed") has been studied by many investigators, notably Spaeth (7), Job (8), Fuson (9) and more recently Vavon (10). The outstanding contribution of Kharasch and his co-workers (11) to this and related reactions of Grignard reagents has been to point out the effectiveness of cobaltous chloride in catalytic amounts and to investigate more fully the nature and scope of the reactions.

We have been interested in studying the catalyzed-Grignard synthesis of hexestrol in some detail and have investigated the effect of the Grignard reagent and a number of other factors on the yield of III. We have been unable to arrive at the yield reported by Kharasch and Kleiman with phenylmagnesium bromide, but have developed what we believe to be a more practical procedure using ethylmagnesium bromide, which has given consistent yields of 31–34% of the *meso* dimethyl ether III. Our experiments also have illuminated certain aspects of the mechanism of th's reaction.

In a series of runs under similar conditions, employing anethole hydrobromide and different Grignard reagents in the presence of five to seven mole per cent of cobaltous chloride, the highest yields (29–31%) of the *meso* ether III were obtained with the ethyl Grignard reagent, while with the phenyl, methyl, isopropyl, or *tert*-butyl reagents the yields were significantly lower (23–25%). The coupling reaction was poorer with anethole hydrochloride, giving 19–23% yields of III with ethyl-, isopropyl-, *tert*-butyl- or phenyl-magnesium bromide and only 12% with methylmagnesium bromide. Anethole hydriodide was not suitable for the reaction (2% yield) apparently due to polymerization of the anethole during addition of hydrogen iodide. In the hydrobromide series, then, the best yield obtained (31%) was considerably below the highest reported by Kharasch and Kleiman (42%) when five mole per cent of cobaltous chloride was used, but was comparable to their yields (27%) using fifteen mole per cent of catalyst.[2]

Next the effect of temperature was investigated. Since anethole hydrobromide and ethylmagnesium bromide proved to be the best combination, most of the subsequent work was carried out with these. Variations over the range −20° to 30° had a negligible effect on the yield of III; the yield was slightly higher at the higher temperatures. With phenylmagnesium bromide, however, there was a definite rise in yield with temperature reaching a maximum of 32% at 20°. At 30° the yield was considerably lower (17%). These results, particularly with the ethyl derivative, are in contrast with the statement of Kharasch and co-workers (11, 12) that a rise in temperature caused deterioration and deactivation of the catalyst.[3]
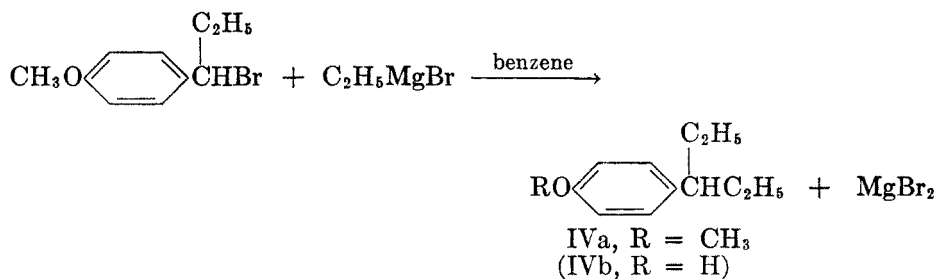
The use of a larger excess of Grignard reagent or more cobaltous chloride (five to fifty mole per cent with a constant excess of Grignard reagent) had no appreciable effect on the yield, nor did varying the time for addition of anethole hydrobromide from five to one hundred and ten minutes. The reaction, as judged by the evolution of gas, appeared to be complete in each case within one-half minute after the end of addition. The same yields were obtained whether ordinary commercial magnesium turnings were used to prepare the Grignard

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[2] In this connection it should be mentioned that, in our hands, this variation in the amount of catalyst did not affect the yield, nor did further addition of small amounts of catalyst after part of the anethole hydrobromide had been added.

[3] It would appear that Kharasch may have modified his views on this point, since recently (13) some cobaltous chloride-catalyzed reactions have been carried out at 100°, and indeed with better results than at lower temperatures. To be sure, these reactions were attributed to breakdown of the organo-cobalt intermediate to form radicals—perhaps a different mechanism from that operating here. See, however, footnote 7.

reagent or a very pure sample of sublimed magnesium; filtering the Grignard solution also failed to improve the yield. These results would appear to eliminate impurities in the magnesium as the explanation of the discrepancy between our yields and that of Kharasch and Kleiman.

In all of these runs ether was employed as the solvent. When this was replaced by benzene, none of the desired methyl ether III could be isolated and instead the major product was that of alkylation (IVa). In

$$CH_3O\!\!\left<\!\!\boxed{}\!\!\right>\!\!\overset{\overset{\displaystyle C_2H_5}{\displaystyle |}}{CHBr} + C_2H_5MgBr \xrightarrow{\text{benzene}}$$

$$RO\!\!\left<\!\!\boxed{}\!\!\right>\!\!\overset{\overset{\displaystyle C_2H_5}{\displaystyle |}}{CHC_2H_5} + MgBr_2$$

IVa, R = CH₃
(IVb, R = H)

di-*n*-butyl ether the yield of the *meso* ether III was only 5%. It seems possible that the ineffectiveness of the cobaltous chloride catalyst in benzene may be due to insolubility.

Thus, the most satisfactory procedure for preparing hexestrol dimethyl ether was found to be the coupling of anethole hydrobromide in the presence of ethylmagnesium bromide and cobaltous chloride.[4] Consistent yields of 31–34% of the *meso* isomer could be obtained over a fairly wide range of reaction conditions. Ethylmagnesium bromide was superior to phenylmagnesium bromide because of greater ease in isolating the product. With the phenyl reagent, a large amount of biphenyl is formed which interferes with crystallization of the product unless removed by steam distillation; with ethylmagnesium bromide the corresponding by-products are gases.

In order to gain further insight into the reaction the material remaining after crystallization of the *meso* ether III was fractionally distilled, giving two main fractions, b.p. 95–110° (8–12 mm.) and b.p. 160–180° (0.1–0.3 mm.). From the latter the racemic dimethyl ether (2) corresponding to III could be crystallized; the yield of this isomer was slightly less than that of the *meso* isomer, amounting to 25–30% for the runs using ethylmagnesium bromide and anethole hydrobromide (11–14% using anethole hydrochloride). The remainder of this fraction (5–8%), an oil which did not crystallize, probably contained some of the dimer isoanethole.

The lower-boiling fraction amounted to about 15% of the weight of the anethole used in the hydrobromide runs and 30% in the hydrochloride runs. By titration with bromine in carbon tetrachloride these fractions were found to

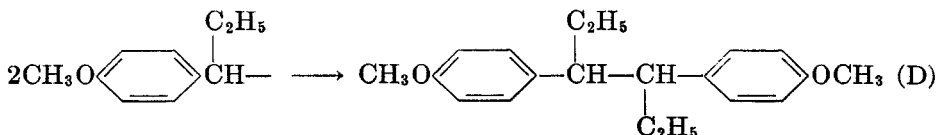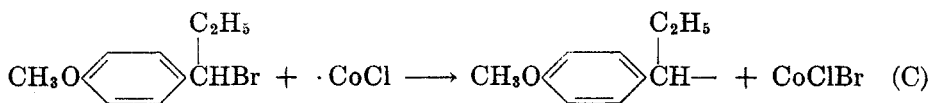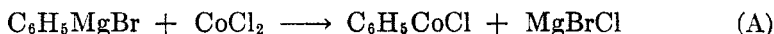[4] It was of interest to see if cobaltous chloride would increase the yield of the dimethyl ether III when the procedure of Docken and Spielman (2) was used, employing magnesium instead of a Grignard reagent. In the presence of seven mole per cent of cobaltous chloride the yields were increased from 15–20% to around 25%. This may indicate the formation of a Grignard reagent as an intermediate in this reaction (*cf.* Ref. 14).

contain about 27% and 10%, respectively, of unsaturated material, presumably anethole. Initially it was assumed that the saturated component of this fraction was the product of alkylation of the anethole hydrohalide with the ethyl Grignard reagent, and this was indeed the case with anethole hydrochloride. After demethylation, crystalline 3-(p-hydroxyphenyl)pentane (IVb) was isolated and identified by comparison with a synthetic sample. In the case of anethole hydrobromide, however, only a small amount of the alkylation product IVa was formed, and the main saturated component of this fraction was p-n-propylanisole; this was identified as the crystalline 3,5-dinitrobenzoate of p-n-propylphenol after demethylation and esterification. When the cobaltous chloride was omitted, the alkylation product was the major product, even with anethole hydrobromide; this constitutes a simple method of preparing 3-(p-anisyl)pentane (IVa) in 82% yield.[5]

The major factor responsible for the variations in yield of meso-hexestrol dimethyl ether (III) resulting from changes in the anethole hydrohalide (chloride or bromide) or in the Grignard reagent, seems to be the effect on the relative rates of the catalytic reaction and the alkylation reaction, for when the yield of III was lowered the amount of alkylation product (in Fraction 1) was increased. In the runs using anethole hydrochloride and ethylmagnesium bromide, the amount of this alkylation could be diminished, with an accompanying increase in the yield of III from 22 to 26% (a small but significant difference), by adding the Grignard reagent along with the anethole hydrochloride. Corresponding runs with anethole hydrobromide, however, resulted in no improvement, (indeed the yield was lower), in agreement with the finding that relatively little alkylation occurred with these reagents in the normal procedure.

MECHANISM OF THE REACTION

Kharasch and his co-workers (6, 11, 12, 15) have investigated a great many reactions with Grignard reagents in the presence of catalytic amounts of cobaltous chloride. The mechanism which they have proposed is as follows, applied to the coupling reaction of anethole hydrobromide in the presence of phenylmagnesium bromide:

$$C_6H_5MgBr + CoCl_2 \longrightarrow C_6H_5CoCl + MgBrCl \qquad (A)$$

$$2C_6H_5CoCl \longrightarrow C_6H_5C_6H_5 + 2 \cdot CoCl \qquad (B)$$

(C)

(D)

[5] The failure to obtain any of III was unexpected in view of the findings of Fuson (9) that benzyl halides are coupled to dibenzyls by Grignard reagents (also Ref. 5).

The reaction is believed to be a chain reaction involving free radicals with cobaltous subhalide postulated as the chain propagator.
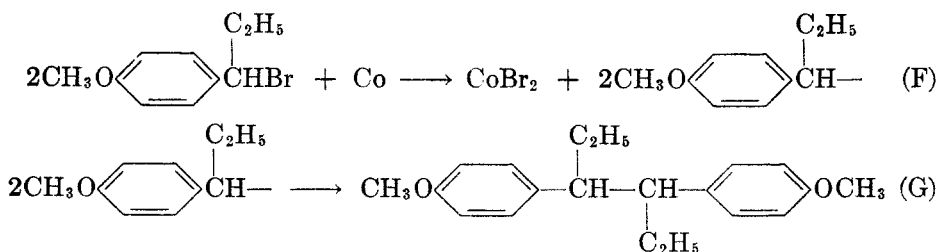
Several features of this mechanism seem to us to be inconsistent with the reaction as we have observed it. In the first place, all attempts to prepare organo-cobalt compounds as postulated in equation A have indicated these to be unstable compounds (16, 17, 18) decomposing at once to metallic cobalt and the coupling or disproportionation products of the organic group.[6] Secondly, there is no experimental evidence to indicate the stable existence of the cobaltous subhalide proposed as the reactive intermediate in equation B. To be sure, each of these might be postulated as possible intermediates in the reaction, but it seems certain that they would be very short-lived. Yet our observations indicate that the reaction of the Grignard reagent with cobaltous chloride can be carried out several hours before the addition of the anethole hydrobromide. Indeed some catalytic activity was retained by the Grignard-cobaltous chloride mixture after standing at room temperature for several days or even weeks. This seems incompatible with the above mechanism, since equations A and B should proceed in the absence of the anethole hydrobromide, and the reactive intermediates would decompose to give metallic cobalt. In addition, the organic product formed in reaction B presents a dilemma, for if the phenylcobaltous chloride intermediate decomposed to give the radical $\cdot$CoCl, it might be expected that the other product would be the phenyl radical. Yet, as pointed out by Kharasch and co-workers (11), phenyl radicals generated in solution by other methods do not combine to give biphenyl as in this reaction, but instead give a variety of products (by disproportionation, attack on the solvent, etc.). To avoid this dilemma, the breakdown in equation (B) must be considered to occur in some other manner, as yet obscure, not involving phenyl radicals.[7]

These facts and others which will be presented below can be reconciled, however, with a chain mechanism in which cobalt metal is the reactive intermediate. The cobalt formed by decomposition of the unstable organo-cobalt compound is in a very finely divided and reactive form and may be considered to effect a Wurtz-type of reaction with the anethole hydrobromide, very likely with the intermediate formation of the free radical from the halide:

$$2C_2H_5MgBr + CoCl_2 \longrightarrow MgBr_2 + MgCl_2 + [(C_2H_5)_2Co] \longrightarrow$$
$$C_2H_6 + C_2H_4 + Co \quad (E)$$
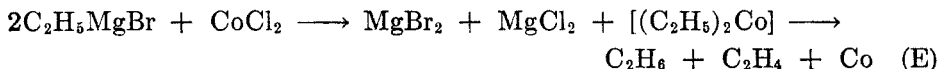
[6] However, starting with organozinc compounds Job and Reich (19) believed they obtained organo-cobalt derivatives.

[7] Recently Kharasch and Urry (13) have concluded that a similar breakdown with aliphatic Grignard reagents and cobaltous chloride does give rise to free alkyl radicals as intermediates. It seems to us, however, that the experimental evidence upon which this is based is still inconclusive, since radicals are believed to be formed from the alkyl halide also present; thus, reactions indicating their presence cannot be attributed to organo-metallic breakdown in the absence of additional evidence. Indeed the different proportion of products resulting from such "radicals" from the organo-metallic intermediates, compared with those generated from diacyl peroxides, suggests that they are too short-lived to be considered true radicals in solution. A definitive test for their existence would appear to be a reaction similar to those described by Kharasch and Urry but *in the absence* of alkyl halide and with a full equivalent of cobaltous chloride to carry the reaction to completion.

$$2CH_3O\text{—}C_6H_4\text{—}CHBr(C_2H_5) + Co \longrightarrow CoBr_2 + 2CH_3O\text{—}C_6H_4\text{—}CH(C_2H_5)\text{—} \quad (F)$$

$$2CH_3O\text{—}C_6H_4\text{—}CH(C_2H_5)\text{—} \longrightarrow CH_3O\text{—}C_6H_4\text{—}CH(C_2H_5)\text{—}CH(C_2H_5)\text{—}C_6H_4\text{—}OCH_3 \quad (G)$$

According to this mechanism the catalytic activity of the Grignard-cobaltous chloride mixture would be retained indefinitely, or as long as the cobalt metal remained in its active, finely divided form. Kharasch and Fields (11) observed differences in the stability of the catalyst prepared from aryl and alkyl Grignard reagents. They reported that a solution of phenylmagnesium bromide and cobaltous chloride retained about 50% of its catalytic activity after refluxing in ether solution for one and one-half hours, while the catalyst from methylmagnesium bromide was practically completely destroyed under these conditions. Their explanation of these results on the basis of varying stabilities of the aryl- and alkyl-cobalt intermediates hardly seems tenable, since neither type of organocobalt compound would be expected to survive such conditions. The results are explainable on the basis of the metallic cobalt mechanism, since Job and Reich (19) and Dupont and Piganiol (17) have reported that the colloidal cobalt prepared using an alkyl Grignard reagent is more easily flocculated than that from a phenyl Grignard reagent, which seems to stabilize the colloidal solution. With coagulation of the colloidal solution the reactivity of the cobalt was lost. In our own experiments we have found that the catalytic activity of the cobalt is not lost when the reaction is carried out at temperatures as high as 35°, provided an excess of Grignard reagent is present; this is doubtless due to the fact that the finely divided cobalt is continually regenerated in a chain reaction, thus preventing flocculation.

The products observed from the Grignard reagent in the cobaltous chloride-catalyzed reactions are those to be expected from decomposition of an unstable organo-metallic compound, viz, a diaryl from an aryl Grignard reagent (11), disproportionation products from higher alkyl Grignard reagents, (e.g. butene and butane from n-butylmagnesium bromide) (20), and principally methane from the methyl Grignard (13, 20), although the available evidence for alkyl organometallic compounds is scanty.

The reaction of finely divided cobalt metal with anethole hydrobromide (equations F and G) is analogous to the earlier procedures (2, 3, 4) where magnesium or sodium was used. It may be considered to lie at one extreme of reactions of the Wurtz type since the cobalt probably only removes the halogen to give a free radical and does not react further to give an organo-metallic intermediate at this stage. Kharasch and his co-workers have pointed out that the products obtained in this type of reaction are indicative of free radicals rather than unstable organo-metallic compounds, since dimers are formed only with a few special halides which would form the more stable radicals, while most of the others, including aryl halides, give disproportionation products.

In order to provide experimental confirmation for reactions F and G, runs were carried out in which the Grignard reagent was used up by reaction with an equivalent amount of cobaltous chloride. The resulting suspension of cobalt metal, which now could not be regenerated during the reaction, was found to give 8.5% of *meso*-hexestrol dimethyl ether when treated with anethole hydrobromide. Although this yield is lower than that obtained in the usual procedure, it can be attributed to a less favorable state of subdivision of the cobalt metal than when it is continually regenerated in the chain reaction. In support of this view, the yield of III was increased to 15% when the cobalt was first "recycled" to increase the state of subdivision of the metal by allowing it to react with an equivalent mixture of ethyl bromide and ethylmagnesium bromide *prior* to the addition of the anethole hydrobromide.[8]

The course of the reaction of anethole *dibromide* with ethylmagnesium bromide in the presence of catalytic amounts of cobaltous chloride might be considered to support the proposed new mechanism. If cobaltous subchloride were the reactive intermediate it might be expected to give to an appreciable extent a free radical similar to that postulated in equation (C) or (F), but containing a bromine atom, resulting in a significant amount of coupling to dimeric or polymeric products. If cobalt metal were the reactive intermediate, on the other hand, it would not be unexpected for simple debromination to occur, giving anethole. Actually anethole was obtained in this reaction in 92% yield.

It seems probable that the low-boiling by-products of the coupling reaction, anethole and *p-n*-propylanisole, result from some intermediate involved in the coupling reaction itself, rather than from an independent reaction, for the total amount of these by-products was remarkably constant throughout the variations in conditions, although there was considerable change in their ratio. They might be considered as arising from the free radical intermediate in equation (F), either by disproportionation or attack on the solvent.

This mechanism involving cobalt metal can be used satisfactorily to explain most of the other Grignard reactions catalyzed by cobaltous chloride, including the dimeric reduction of certain ketones to pinacols and related reactions (22).

EXPERIMENTAL[9]

Anethole hydrobromide. Through a solution of 100 g. of anethole (Eastman Kodak Co.)[10] in 400 cc. of 40–60° petroleum ether cooled in an ice–salt bath was passed dry hydrogen

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[8] It is difficult to rule out completely the cobaltous subchloride postulate, and we recognize that it is possible that after the cobalt metal has initiated the reaction, cobaltous subchloride might exist as a short-lived intermediate which could help continue the chain reaction. Indeed some of the products obtained with cobaltous chloride-catalyzed Grignard reagents are similar to those produced by the binary magnesium-magnesium iodide mixture of Gomberg and Bachmann (21), for which magnesious iodide has been suggested as the reactive component. Docken (5) has found that this binary mixture gives III in 11% yield. However, for the present reaction there is no direct evidence to support the cobaltous subhalide hypothesis or need for its postulation, since the concept of finely divided, reactive cobalt metal seems to be in good accord with the observed facts.

[9] All melting points are corrected.

[10] Redistillation of the anethole just prior to use had no appreciable effect upon the yields.

bromide gas at such a rate that the temperature remained below 0°. Near the end of the reaction the temperature fell to −20°; completeness of addition was ascertained by testing for unsaturation with a 5% solution of bromine in carbon tetrachloride. The petroleum ether was then removed under water pump pressure, employing a capillary tube attached to a calcium chloride tube to allow dry air to sweep through the liquid. The temperature fell to about −40° until most of the solvent was removed, and then rose to about −10°. The oily anethole hydrobromide was dissolved in anhydrous ether and used immediately.

Similarly anethole hydrochloride was prepared using dry hydrogen chloride, and anethole hydriodide with dry hydrogen iodide. In the latter case a considerable amount of viscous tar was formed, due to polymerization.

Cobaltous chloride. For most of the runs anhydrous cobaltous chloride was prepared by drying the hexahydrate in the oven, finally at 190° for about ten hours, then it was finely powdered and dried for several hours longer. The material gave a clear solution in water. The same results were obtained with this catalyst as with that prepared by the method of Kharasch (11) involving heating in a stream of dry hydrogen chloride.

Hexestrol dimethyl ether (best procedure—Run 22, Table I). Ethylmagnesium bromide was prepared in a 3-l., four-necked flask fitted with a reflux condenser, mercury-sealed Hershberg stirrer, dropping-funnel and thermometer, using 29 g., (1.19 mole) of magnesium turnings, 129 g. (1.17 mole) of ethyl bromide, and 1000 cc. of dry ether. The yield of Grignard reagent was 85%. Meanwhile anethole hydrobromide was prepared as described above from 100 g. (0.68 mole) of anethole.

To the stirred Grignard solution at room temperature was added 6.75 g. (0.052 mole) of anhydrous cobaltous chloride over a one-minute period. The system was then attached to a mineral oil trap and a solution of the anethole hydrobromide in 225 ml. of dry ether was added over a period of thirty minutes, with the temperature at 30–31°. The vigorous evolution of gas stopped within one-half minute after addition was complete and the temperature began to fall. (Tests in other runs showed the reaction to be complete at this point.)

The black mixture was poured onto ice and hydrochloric acid and extracted twice with ether, the extracts being thoroughly washed with 5% hydrochloric acid, water, saturated salt solution and dried over calcium chloride.[11] After removing the ether the residual yellow oil was dissolved in 250 cc. of methanol and allowed to crystallize in the refrigerator; 30.9 g. (31%) of *meso*-hexestrol dimethyl ether was obtained, m.p. 140–143°.[12]

The filtrate was concentrated and distilled under reduced pressure giving a first fraction of 14.5 g., b.p. 105–120° (12 mm.), n_D^{25} 1.5158, a second fraction of 38.2 g., b.p. 175–195° (0.6 mm.) and a third fraction of 7.8 g., b.p. 240–290° (1–2 mm.) with decomposition. The second fraction was dissolved in 100 cc. of methanol and allowed to stand for several days in the refrigerator, resulting in 27.4 g. (27%) of racemic hexestrol dimethyl ether, m.p. 53–56°. In some runs a small first crop of the *meso* isomer was obtained here.

meso-Hexestrol. A mixture of 30 g. of *meso*-hexestrol dimethyl ether (m.p. 143.5–144°), 500 cc. of acetic acid, and 200 cc. of 48% hydrobromic acid was refluxed for ten hours and then poured into 3 liters of water. After cooling, the solid was filtered, washed, and dried at 85°, giving 26.1 g. (96%) of hexestrol, m.p. 181–185°. Recrystallization from benzene gave 73% recovery of pure *meso*-hexestrol (dried at 80°) in the first crop, m.p. 186–187°, and an additional 23%, m.p. 182.5–185.5°.

Variations in the coupling reaction. In Table I are summarized runs in which various reagents or conditions were changed in the coupling reaction. When phenylmagnesium bromide was used, the reaction mixture was either steam distilled to remove biphenyl or the *meso* ether carefully crystallized from methanol and the biphenyl removed from the filtrate by distillation (around 90–140° at 8 mm.). The product of alkylation by the phenylmagnesium bromide appeared in Fraction 2 (b.p. 140–185° at 0.3 mm.) along with the racemic ether and anethole dimers. It could not be obtained crystalline.

Variation in the method of addition. A run was made in which 0.1 mole of ethylmagnesium

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[11] With sodium sulfate some of the product was removed by adsorption.

bromide solution was added at 30° simultaneously with 0.1 mole of anethole hydrochloride solution to a stirred suspension of the catalyst prepared by reducing 1 g. (0.0077 mole) of cobaltous chloride in 50 cc. of ether with 0.01 equivalent of the Grignard solution. The yield of *meso* ether was increased to 26% (m.p. 140–142°), that of racemic ether to 22% (m.p. 53–56°) and the amount of Fraction 1 was reduced to 2.1 g. However, this method of addition was not beneficial with anethole hydrobromide, the yield of *meso* ether being 22% and of racemic ether 16%.

Runs using equivalent amounts of cobaltous chloride and Grignard reagent. To an ether solution of 0.11 equivalent of ethylmagnesium bromide was added 15 g. (0.115 mole) of cobaltous chloride over a period of four minutes at 10°. After the addition, titration indicated the presence of 0.009 equivalent of basic material (which probably was due to the finely divided cobalt rather than Grignard reagent). A solution of 0.1 mole of anethole hydrobromide was added during ten minutes at 15–20°. After stirring for one hour the mixture was worked up as before to give a total of 1.28 g. (8.6%) of the *meso* ether (mainly 139–142° in m.p.). The yield was the same when cobaltous bromide was used.

When the cobaltous chloride (0.055 mole) was reduced by adding a mixture of 0.15 equivalent of ethylmagnesium bromide and 0.16 mole of ethyl bromide over a period of twenty minutes and "recycled" by addition of another 0.15 equivalent of Grignard reagent and 0.03 mole of ethyl bromide (titration showed presence of only 0.009 equivalent of basic material at this point) before adding the anethole hydrobromide (0.1 mole), the yield of *meso* ether was increased to 15%.

Retention of catalyst activity on standing. The yield was unaffected (32%) in a run by the usual procedure, when the Grignard-cobaltous chloride mixture was allowed to stand at room temperature for four hours before adding the anethole hydrobromide. Qualitative experiments to test for retention of catalytic activity were also made using ethylmagnesium bromide (0.15 equivalent) and 0.0077 mole of cobaltous chloride, followed by addition of 0.01 mole of ethyl bromide to give some "recycling." The activity was checked periodically by treating an aliquot with 0.01 mole of ethyl bromide and determining the amount of gas evolved. The catalytic activity decreased slowly over the first two days as the cobalt became less finely divided and settled out of suspension; considerable activity was left after nine days and some even after standing for sixteen days at room temperature.

Runs using magnesium (Docken–Spielman procedure). To a mixture of 5 g. (0.21 mole) of magnesium, 200 cc. of ether, and a few crystals of iodine was added 1 g. of cobaltous chloride and the solution cooled in an ice-salt bath to −10°. A small amount of the ether solution of anethole hydrobromide was added, and as there was no apparent reaction, 1 ml. of ethyl bromide was added and the temperature raised to 8° until some erosion of the magnesium was observed, then the remainder of the anethole hydrobromide (0.1 mole) was added at −10° over a forty-minute period. The mixture was stirred for one and one-half hours at 0°, three hours at 10–15°, four hours at room temperature and one hour at reflux, then worked up as before. The total yield of *meso*-hexestrol dimethyl ether was 25% (m.p. 140.5–142°) with 24% of the racemic ether. In another run using 0.25 g. of cobaltous chloride and no ethyl bromide, starting the addition at 0°, then continuing at −5° after the reaction began, the yield of meso ether was 22% with 20% of racemic ether.[12]

Investigation of Fraction 1. The low-boiling fraction from ethylmagnesium bromide runs with anethole hydrochloride was demethylated by heating 5.06 g. (b.p. 95–110° at 10 mm., n_D^{25} 1.5089, containing an estimated 11% of anethole) with 125 cc. of acetic acid and 25 cc. of 48% hydrobromic acid for eleven hours. After dilution and extraction with ether the phenol was distilled, giving 1.9 g. of clear liquid, b.p. 122–125° (12 mm.) which solidified. After several recrystallizations from petroleum ether (40–60°) the m.p. of the solid was 75.5–76°, and was not depressed when mixed with a synthetic sample of 3-(*p*-hydroxyphenyl)pentane, m.p. 76.5–77°.

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[12] With larger runs (330 g. of anethole) for which the amount of solvent was proportionately about one-half that described here, the yields of the *meso* ether dropped to 19.5–23.5%.

TABLE I
Conditions and Yields of Products

RUN NO.	ANETHOLE Moles Used	ANETHOLE Halide Used	GRIGNARD REAGENT Halide Used	GRIGNARD REAGENT Moles of Reagent[a]	MOLE % CoCl₃	TEMP., °C	TIME OF ADDN. MINS.	MESO ETHER[f] %	RACEMIC ETHER[g] %	FRACTION 1 g.	FRACTION 1 n_D^{25}	FRACTION 1 % anethole[b]	TOTAL WEIGHT FRACTION 2 G.	RESIDUE G.
1	.34	Cl	CH₃Br	(0.70)	4.5	0–5[c]	150	12	7	23.8	1.5374	44	10.5	5.5
2	.34	Cl	C₂H₅Br	(0.70)	4.5	0–5[c]	25	22	11	15.0	1.5070	}11	15.4	4.8
3	.34	Cl	C₂H₅Br	(0.70)	4.5	−5–0	20	21	14	16.2	1.5095		15.3	4.8
4	.34	Cl	i-C₃H₇Br	(0.70)	4.5	−5–0	55	23	15	15.1	1.5110	14	16.3	4.3
5	.34	Cl	t-C₄H₉Cl	(0.70)	4.5	−5–0	50	15	6	19.2	1.5065	}4	10.8	6.4
6	.34	Cl	t-C₄H₉Br	(0.70)	4.5	−5–0	80	21	9	16.3	1.5053		14.2	4.8
7	.34	Cl	C₆H₅Br	(0.70)	4.5	−5–0	55	19	7	[d]	—	—	21.1[d]	8.8
8	.10	Br	CH₃Br[e]	0.17	7.7	0	15	25	20	3.1	1.5420	72	5.4	0.85
9	.34	Br	C₂H₅Br	(0.70)	4.5	0	110	31	24	6.9	1.5228	(37)	18.8	5.6
10	.34	Br	C₂H₅Br[f]	(0.70)	4.5	0	120	28	27	7.7	1.5347	(58)	17.6	6.6
11	.10	Br	C₂H₅Br	(0.20)	7.7	0	70	31	27	1.5	1.5281	(46)	5.6	1.6
12	.10	Br	C₂H₅Br	0.18	7.7	0	5½	30	25	2.0	1.5241	(39)	5.4	1.4
13	.10	Br	C₂H₅Br	0.16[g]	7.7	0	20	30	25[f]	2.0	1.5273	(44)	5.9	1.6
14	.10	Br	C₂H₅Br	0.14	7.7	0	26	31	30	1.8	1.5214	36	5.8	1.5
15	.10	Br	C₂H₅Br	0.15	7.7	0	28	31	29	1.8	1.5161	26	5.9	1.5
16	.10	Br	C₂H₅Br	0.14	7.7	0	35	32	29	1.7	1.5272	(44)	5.8	1.2
17	.10	Br	C₂H₅Br	0.34	7.7	0	30	31	25	1.6	1.5193	(31)	5.8	1.7
18	.10	Br	C₂H₅Br	0.12[h]	7.7	30	11	34	25	1.9	1.5198	31	4.9	1.4
19	.10	Br	C₂H₅Br	0.13[i]	7.7	30	11	32	26	2.2	1.5197	28	5.6	1.0
20	.10	Br	C₂H₅Br	(0.20)[j]	20	30	20	30	21	1.9	1.5177	21	4.9	1.0
21	.10	Br	C₂H₅Br	0.24[k]	50	30	10	30	24	2.0	1.5099	13	5.7	1.0
22	.68	I[l]	C₂H₅Br	1.00	7.7	30	28	31	27	14.5	1.5158	27	38.2	9.4
23	.10	Br	C₂H₅Br	0.13	none[m]	0	8	none	none	0.5	1.5368	47	10.3	3.2
24	.10	Br	C₂H₅Br	0.14	7.7	0	22	none	none	14.7[m]	1.4988	trace	—	0.1
25	.10	Br	C₂H₅Br	0.19[n]	7.7	5	20	2.5[f]	6[i]	12.7[n]	1.4989	0.3	—	0.5
26	.10	Br	C₂H₅Br	0.14[o]	7.7	30–40	8	5.4[f]	6[i]	8.0	1.5018	10	2.6	0.9
27	.10	Br	C₂H₅I	0.14	7.7	−5–0	20	31	26	1.9	1.5246	36	5.4	1.6
28	.10	Br	C₂H₅I	0.14	7.7	30	11	32	27	1.9	1.5146	20	5.3	1.8
29	.34	Br	i-C₃H₇Br	(0.70)	4.5	0	60	25	23	11.0	1.5112	13	16.9	5.4
30	.10	Br	t-C₄H₉Br	0.15	7.7	0	20	23	19	5.2	1.5094	10	4.8	0.6
31	.10	Br	C₆H₅Br	0.14	7.7	20	20	32	1.3[i]	5.5	1.5629[p]	0	2.6	1.2
32	.10	Br	C₆H₅Br	0.14	7.7	10	12	29[i]	16	2.0	1.5650[p]	0	5.7	1.7
33	.10	Br	C₆H₅Br	0.14[q]	7.7	0	17	25	17	2.4	1.5642[p]	0	5.3	1.3
34	.10	Br	C₆H₅Br	0.15[g]	7.7	30–35	22	29[i]	4	9.1	1.5620[p]	0	2.5	1.7
35	.34	Br	C₆H₅Br	(0.70)	4.5	0	68	24	6	20.2	—	—	8.0	6.7

a Determined by titration except for those values in parentheses which are moles of magnesium and halide employed.

b Determined by titration with a standard solution of bromine in carbon tetrachloride, expressing the unsaturation as % anethole; values in parentheses were estimated from the refractive index assuming a linear relationship for mixtures of anethole and p-n-propylanisole.

c Estimated temperature.

d Most of the biphenyl was removed by steam distillation, but a small amount was obtained on distillation; total weight 43.5 g. Fraction 2, b.p.150–185° (0.1 mm.) appeared to contain some of the alkylation product corresponding to Fraction 1 of other runs.

e In this run the gas evolution during the anethole hydrobromide addition was followed, total volume 2160 cc. corresponding to 85% of theory, after correction to standard conditions.

f The anethole hydrobromide was prepared in toluene solution at −55° according to the method of Kharasch and Kleiman and kept at −80° during the addition.

g In this run pure sublimed magnesium was used to prepare the Grignard reagent in 95% yield. In some runs commercial magnesium turnings from the Dow Chemical Co. were used, the yield of Grignard reagent being about 77%, and in others an intermediate grade, giving 85% yields of Grignard reagent. Each of these gave similar yields of meso-hexestrol dimethyl ether.

h The Grignard reagent was filtered through glass wool immediately after preparation.

i The Grignard reagent was allowed to settle overnight and the clear supernatant solution was filtered through glass wool.

j After addition of the cobaltous chloride, 0.03 mole of ethyl bromide was added to give some "recycling" of the catalyst before adding the anethole.

k No"recycling" used here, see j; the volume of gas corresponded to 105% of the theoretical.

l There was much apparent polymerization of the anethole during addition of the hydrogen iodide.

m This was a "blank" run, the usual procedure being followed except that no cobaltous chloride was employed. The product (Fraction 1) corresponded to an 83% yield of the alkylation product IVa.

n The ether of the Grignard solution was replaced by benzene before addition of the cobaltous chloride. The product (Fraction 1) corresponded to a 71% yield of the alkylation product IVa.

o The Grignard reagent was prepared in di-n-butyl ether.

p See description of these fractions elsewhere in the experimental section.

q The Grignard solution was filtered through glass wool before using.

r Yield based in most cases on material melting over about a 1° range near 140–144°.

s Yield based in most cases on material melting over a 1–2.5° range in the region of 52–56.5°.

t Product was low melting.

The combined Fraction 1 from several of the anethole hydrobromide runs with ethylmagnesium bromide (n_D^{25} 1.5276, estimated to contain about 45% of anethole) was fractionally distilled through a 20-cm. Vigreux column, giving the following results:

FRACTION	B.P. °C AT 20 MM.	WT.	n_D^{25}	% ANETHOLE
A	104–108	1.8 g.	1.5052	10
B	108–109	4.5	1.5104	15
C	109–110	2.5	1.5103	16
D	118–119	5.4	1.5344	59
E	119–120	3.4	1.5421	69
F	120–130	1.1	1.5439	63
G	residue	2.3	1.55	

Demethylation of 3.8 g. of Fraction B with hydrobromic-acetic acids and distillation of the phenol gave 2.4 g., b.p. 110–115° (9 mm.). Since this did not crystallize even after redistillation, 0.5 g. was converted to the 3,5-dinitrobenzoate in pyridine solution and fractionally crystallized; 0.33 g. of the 3,5-dinitrobenzoate of p-n-propylphenol, m.p. 117.5–118.5° was obtained from ethanol. Further recrystallization gave the m.p. 119–119.5°, not depressed by mixing with the authentic sample prepared below.

Demethylation of 3.1 g. of fraction D gave 0.91 g. of phenolic distillate, b.p. 78–118° (8 mm.); 0.5 g. of this was converted to the 3,5-dinitrobenzoate and fractionally crystallized from ethanol. From the least soluble fraction was obtained a small amount of the derivative of p-n-propylphenol, m.p. 116.5–117.5° (mixed m.p. not depressed) while from the more soluble portion was obtained the derivative of 3-(p-hydroxyphenyl)pentane, m.p. 113.5–115° (mixed m.p. unchanged, but depressed below 100° by the derivative of p-n-propylphenol).

Investigation of Fraction 2 and residues. After removal of the racemic ether from the anethole hydrobromide-ethylmagnesium bromide runs the remainder of Fraction 2 was an oil which could not be further crystallized. Distillation gave fractions b.p. 155–175° (0.2 mm.) and 175–205° (0.2 mm.) which, judging from bromine titrations, may have contained 45% and 80%, respectively, of anethole dimer (isoanethole).

Distillation of the combined residues gave material boiling with decomposition in the range 230–260° (0.6 mm.) which corresponded approximately in molecular weight to a trimer (found mol. wt. 392 using boiling carbon tetrachloride; calc'd for a trimer 444).

Debromination of anethole dibromide. To the stirred mixture of ethylmagnesium bromide (from 0.16 mole of magnesium) and 1 g. of cobaltous chloride was added a solution of anethole dibromide (prepared from 8.5 g. of anethole and 2.95 ml. of bromine in 100 ml. of ether) at 30° over a period of thirty minutes. A vigorous evolution of gas occurred. After hydrolysis, extraction and distillation, 7.8 g. (92%) of anethole was obtained, b.p. 117.5–120° (19 mm.), n_D^{21} 1.5569.

3-(o-Methoxyphenyl)-2-pentene. The Grignard solution from 0.3 mole each of magnesium and ethyl bromide in 250 ml. of ether was slowly treated with 20.2 g. (0.12 mole) of anisoyl chloride in 100 ml. of ether and the mixture was refluxed for six hours. After hydrolyzing and isolating the product, it was distilled with a few crystals of iodine to give 16.4 g. (79%) of the olefin, b.p. 127–132° (19 mm.), n_D^{22} 1.5350. Fractional distillation through a 20-cm. Vigreux column gave material of b.p. 128.5–130° (19 mm.), n_D^{22} 1.5310 [reported (23), b.p. 129–130° at 17 mm., n_D^{21} 1.5395].

3-(p-Methoxyphenyl)pentane. Hydrogenation of 5.7 g. of the pentene was carried out in 50 cc. of absolute alcohol using 0.6 g. of palladium-on-barium sulfate catalyst (24) and thirty pounds pressure, and the process was repeated a second time. The product, 3.6 g. (63%), b.p. 110–112° (10 mm.), n_D^{25} 1.4980, was now saturated to bromine in carbon tetrachloride solution.

This compound was easily prepared in 83% yield by alkylation of anethole hydrobromide with ethylmagnesium bromide in the *absence* of cobaltous chloride (see Table I run **24**); b.p. 118-122° (23 mm.), n_D^{25} 1.4988.

3-(p-Hydroxyphenyl)pentane. Demethylation of 2.3 g. of the methyl ether with acetic-hydrobromic acids gave 1.9 g. (90%) of solid upon dilution, m.p. 75.5-76.5°. Recrystallization from petroleum ether raised the m.p. of the phenol to 76.5-77° [reported (25), 79.5-80°].

The *3,5-dinitrobenzoate*, after recrystallization from ethanol, melted at 117-117.5°.

Anal. Calc'd for $C_{18}H_{18}N_2O_6$: C, 60.3; H, 5.1.

Found: C, 60.5; H, 5.1.

p-n-Propylphenol. Anethole (5.8 g.) was hydrogenated using palladium-on-barium sulfate catalyst (24), and the product was shaken with potassium permanganate before distillation, yielding 3.9 g. of *p-n*-propylanisole, b.p. 212.5° (740 mm.), n_D^{25} 1.5024 [reported b.p. 213.5-214.5° at 760 mm. (26), n_D^{20} 1.5040 (27)].

Demethylation of 2.14 g. gave after distillation 1.53 g. of the phenol, b.p. 109-110° (8 mm.), m.p. 16-20°. The *3,5-dinitrobenzoate*, after recrystallization from ethanol, melted at 120-120.5°.

Anal. Calc'd for $C_{16}H_{14}N_2O_6$: C, 58.2; H, 4.3.

Found: C, 58.2, 58.4; H, 4.0, 4.4.

SUMMARY

A detailed investigation has been made of the synthesis of *meso*-hexestrol dimethyl ether from anethole hydrobromide by the cobaltous chloride-catalyzed Grignard procedure. The best yields (31-34%) were obtained using ethylmagnesium bromide.

On the basis of new experimental evidence and previous work on the instability of organo-cobalt compounds, a somewhat different mechanism from that of Kharasch is proposed for cobaltous chloride-catalyzed Grignard reactions. This new mechanism involves the reduction of cobaltous chloride to finely divided cobalt metal as the reactive intermediate in the chain reaction.

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