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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

## Factors Determining the Course and Mechanism of Grignard Reactions. VI. A New Synthesis of Hexestrol Dimethyl Ether (3,4-Dianisylhexane)

BY M. S. KHARASCH AND MORTON KLEIMAN<sup>1</sup>

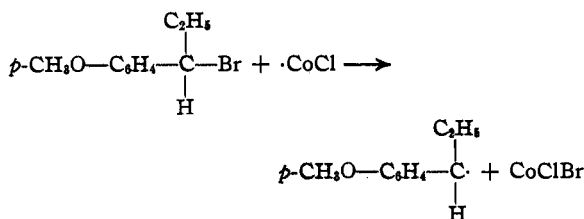
### Introduction

Hexestrol was first isolated from the demethylation products of anethole. Bioassays of the principal product, anol, indicated that the material contained a powerful estrogenic impurity [3,4-*bis*-(*p*-hydroxyphenyl)-hexane]. The name hexestrol, proposed for this compound, is now commonly used.

The earlier methods for the synthesis of hexestrol involve the use of intermediates which are difficult to prepare; the yields, moreover, are poor.<sup>2</sup> Better results (7 to 20% over-all yields) are claimed for the coupling action of metals on anethole hydrobromide.<sup>2,3</sup>

**Reaction of Anethole Hydrobromide with Grignard Reagents in the Presence of Cobaltous Chloride.**—Previous work in this Laboratory<sup>4</sup> has indicated that cobaltous chloride reacts with Grignard reagents to yield a cobalt subhalide (CoCl) which reduces many organic halides to organic free radicals. Hence, it was assumed that a chain reaction might take place when anethole hydrobromide is treated with a Grignard reagent, (*e. g.*, phenyl- or methyl-

magnesium bromide) in the presence of cobaltous chloride. One step in this chain is the reaction



The dimerization of these free radicals was anticipated because it has already been demonstrated<sup>5</sup> that weakly electronegative radicals have a strong tendency to dimerize.

When a well-cooled ether-toluene solution of anethole hydrobromide was added slowly to a cooled solution of phenylmagnesium bromide in ether containing cobaltous chloride (5 mole per cent.), a vigorous reaction took place. The reaction mixture yielded 42% of hexestrol dimethyl ether (m. p. 142°). The yield was somewhat lower when methylmagnesium bromide was used. Ferrous chloride and nickelous chloride are also catalysts for the desired reaction, but are not as effective as cobaltous chloride. Chromic, manganous, cupric and cuprous chlorides are totally ineffective.

### Experimental

The methylmagnesium bromide was prepared as follows. Seventy-five grams of pure magnesium was covered

(1) The authors wish to express their appreciation to E. I. du Pont de Nemours & Company, Wilmington, Delaware, for support which made this work possible.

(2) For a literature review dealing with this subject, see Docken and Spielman, *THIS JOURNAL*, **62**, 2163 (1940).

(3) Short, British Patent 523,320; *Chem. and Ind.*, **59**, 703 (1940); Bernstein and Wallis, *THIS JOURNAL*, **62**, 2871 (1940); Girard and Sandulesco, French Patent 855,879 (May 22, 1940).

(4) For earlier references, see Kharasch and Fields, *THIS JOURNAL*, **68**, 2316 (1941).

(5) Kharasch and Sayles, unpublished work.

with one liter of pure, dry ether and methyl bromide gas was passed into the mixture. Reaction set in after a short time. The methyl bromide was introduced at a rate sufficient to keep the ether gently refluxing, and, at the end of two hours, more ether was added to replace that lost by evaporation. When the magnesium was all dissolved, stirring and refluxing were continued for ten minutes; then the mixture was allowed to stand for twenty-four hours. The solution of the Grignard reagent was next filtered through a plug of glass wool into a dark bottle fitted with a siphon and a calcium chloride tube. Samples of 4 to 5 ml. of the Grignard reagent were used for analysis by titration. The proper aliquots were withdrawn for each reaction.

The phenylmagnesium bromide was similarly prepared from 48 g. of pure magnesium, one liter of dry ether, and 300 g. of phenyl bromide.

**Preparation of Anethole Hydrobromide.**—Fourteen and eight-tenths grams of anethole (0.1 mole) was diluted with two and one-half times its volume of dry toluene and cooled to  $-80^{\circ}$  while dry hydrogen bromide (8.1 g., 0.1 mole) was passed into the solution. This solution was next allowed to warm up to  $0^{\circ}$  while a stream of dry carbon dioxide was bubbled through it to displace unreacted hydrogen bromide. Finally, the solution was degassed at  $0^{\circ}$  by evacuation of the reaction vessel. The solution of anethole hydrobromide thus obtained was diluted with an equal volume of absolute ether, immediately cooled again to  $-80^{\circ}$ , and kept at that temperature. For the subsequent reactions, it was siphoned directly into the Grignard reagent mixture.<sup>6</sup>

**Apparatus for the Grignard Reactions.**—The apparatus consisted of a 500-cc. four-necked, round-bottom flask equipped with a mercury-sealed stirrer, a reflux condenser fitted with a calcium chloride tube, an adapter for addition of the catalyst, and a siphon tube through which the anethole hydrobromide was added.

**Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of Cobaltous Chloride (5 mole per cent.).**—To 65 cc. of 2.3 *M* ethereal phenylmagnesium bromide solution (0.15 mole) cooled in a bath at  $-20$  to  $-10^{\circ}$  and vigorously stirred, was added 1.0 g. of anhydrous cobaltous chloride (5 mole per cent.). The mixture became brownish-black. Anethole hydrobromide solution (0.1 mole) was next added in small portions over a period of one-half hour. During this time the reaction mixture was maintained at  $-20$  to  $-10^{\circ}$ . It was then allowed to warm to room temperature, and stirring was continued for a few hours.

At the end of this time, the reaction mixture was poured onto a mixture of 300 g. of ice and 10 cc. of concentrated hydrochloric acid. After separation of the organic layer, the aqueous solution was extracted twice with benzene. The organic extracts were combined and dried with calcium chloride. The solvents were removed by distillation, and the residue (a greenish-black oil which solidified on cooling) was crystallized twice from methyl alcohol. The yield was 6.1 g. (41%) of hexestrol dimethyl ether which melted sharply at  $142^{\circ}$ . No depression in melting point was

(6) It was found that the desired product is best obtained by adding the anethole hydrobromide solution to the Grignard reagent, rather than by the reverse order of addition

observed when this compound was mixed with an authentic sample of hexestrol dimethyl ether.

The residue from the reaction mixture yielded 6.0 g. of biphenyl, m. p.  $68-69^{\circ}$ , and some high-boiling material. The amount of biphenyl obtained corresponds very nearly to a 40% conversion of the Grignard reagent to biphenyl.

**Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of Cobaltous Chloride (15 mole per cent.).**—The above reaction was repeated using 15 mole per cent. cobaltous chloride. One-third of this chloride was added at the beginning of the reaction; the remainder was added in small portions continuously during the addition of the anethole hydrobromide solution. The reaction mixture was worked up in the manner already described; the yield of hexestrol dimethyl ether was 4.0 g. (27%).

**Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of Nickelous Chloride (5 mole per cent.).**—The procedure in carrying out this reaction was the same as that described above. One gram (5 mole per cent.) of anhydrous nickelous chloride used as a catalyst was added gradually during the course of the reaction. The yield of hexestrol dimethyl ether was 2.1 g. (14%).

**Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of Ferric Chloride (5 mole per cent.).**—The procedure in this reaction was the same as that described above. The catalyst, 0.8 g. of anhydrous ferric chloride (5 mole per cent.), was all added at the beginning of the reaction because of the tendency of ferric chloride to become sticky in the presence of ether vapor. The yield of hexestrol dimethyl ether was 4.3 g. (29%).

**Reaction of Anethole Hydrobromide with Phenylmagnesium Bromide in the Presence of other Metal Halides.**—Attempts were made to obtain hexestrol dimethyl ether by reaction of anethole hydrobromide with phenylmagnesium bromide in the manner described above; in each instance 5 mole per cent. of one of the following metal halides was used as a catalyst: chromic chloride, manganous chloride and cupric chloride. No hexestrol dimethyl ether was found among any of the reaction products.

**Reaction of Anethole Hydrobromide with Methylmagnesium Bromide in the Presence of Cobaltous Chloride (15 mole per cent.).**—The reaction was carried out in the usual manner. One-third of the catalyst was added at the beginning of the reaction, the remainder in small portions at intervals during the addition of the anethole hydrobromide solution. The yield of hexestrol dimethyl ether was 4.0 g. (27%).

### Summary

1. Hexestrol dimethyl ether has been prepared from anethole hydrobromide and Grignard reagents in the presence of a halide of cobalt, nickel or iron.

2. A mechanism to account for the catalytic effect of these metallic halides on the reaction of anethole hydrobromide with Grignard reagents is suggested.

3. The halides of chromium, manganese and

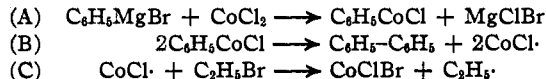
copper were found to be ineffective as catalysts in the synthesis of hexestrol dimethyl ether from anethole hydrobromide and Grignard reagents. CHICAGO, ILLINOIS RECEIVED JULY 31, 1942

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## Factors Determining the Course and Mechanism of Grignard Reactions. VII. Analysis of Gases Formed During the Reaction of Phenylmagnesium Bromide with Organic Halides in the Presence of Cobaltous Halides

BY M. S. KHARASCH, DANIEL W. LEWIS AND W. B. REYNOLDS

The catalytic effect of small quantities of certain metallic halides upon the reaction of Grignard reagents with organic halides has been previously reported from this Laboratory.<sup>1</sup> In most cases, the normal coupling is not increased; instead, there is initiated a chain reaction, at one stage of which the metal in the catalyst appears in an active sub-valence state. This active "subhalide" is then reoxidized by the organic halide; an organic free radical is thus produced. The series of reactions involved is illustrated below for the cobaltous chloride catalyzed reaction of phenylmagnesium bromide with ethyl bromide.



Since the gases evolved in this and similar reactions have not yet been quantitatively examined, it seemed desirable to undertake such a study in order further to elucidate the mechanism of these reactions. Accordingly, the reactions of phenylmagnesium bromide with methyl bromide, ethyl bromide, propyl bromide, *n*-butyl bromide and tertiary butyl chloride in the presence and absence of cobaltous chloride were studied.

**Analyses of Gases Formed.**—The reactions were carried out in a 500-ml. three-neck flask equipped with ground-glass joints. The center joint was fitted with a mercury-seal stirrer; one of the side joints carried an efficient Friedrichs condenser; the other side joint carried a wide, straight, adapter-shaped dropping funnel fitted with an auxiliary nitrogen inlet tube extending slightly into the flask. After the set-up had been thoroughly dried, it was filled with dry nitrogen (oxygen-free), and the Grignard reagent was introduced. The flask was cooled by surrounding it with an ice-pack. Anhydrous cobaltous chloride (5 mole per cent.) was next added. Nitrogen gas was then passed into the flask for three to five minutes; then the nitrogen inlet tube was closed. The alkyl halide

was next added slowly through the dropping funnel. From the condenser outlet, the evolved gases passed through a short calcium chloride tube and a trap surrounded by ice (except in the butyl chloride experiments where the trap was maintained at 10°). The gases were finally collected over water from which air had been removed by boiling. Usually the first 500 ml. of gas (which was mostly nitrogen) was discarded. The gases were all hydrocarbons and could be completely analyzed by determination of molecular weight and percentage unsaturation. These determinations were made in the vacuum-line apparatus of Fig. 1.

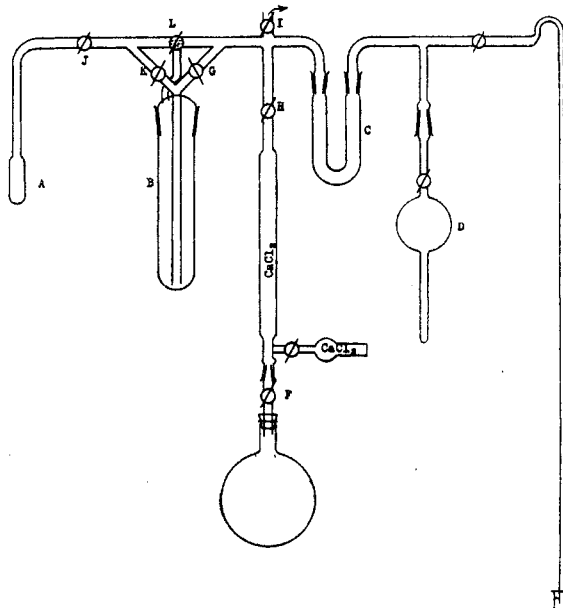


Fig. 1.—Vacuum line gas analysis apparatus.

Molecular weights were determined by the Dumas method in bulb (D). This bulb was first evacuated to 10<sup>-6</sup> mm. and accurately weighed. After it had been replaced on the line, the entire system was evacuated down to stopcock (F). After stopcocks (G) and (K) had been closed and (L) adjusted so that tube (A) was connected to the system but trap (B) eliminated, stopcock (I) was closed, and the gas sample was slowly admitted to the system through (F). Stopcock (H) was then closed, and a liquid nitrogen trap was placed at (A). The gas sample condensed and solidified in (A) while the manometer rose rapidly to within a millimeter of its high-vacuum reading.

(1) For previous references see Kharasch and Fields, THIS JOURNAL, 63, 2316 (1941).