was concentrated to 350 ml by distillation.[19] The mother liquor was decanted from the dark complex which had separated after standing for 1 day. This complex was recrystallized from 100 ml of benzene and the resulting complex was decomposed by treatment with sodium bicarbonate solution to yield 0.32 g of (−)-I, $[\alpha]^{20}_{\mathrm{D}}$ −91.3 ± 1° (*c* 1, benzene). In similar runs using (+)-TAPA, (+)-I having comparable positive rotation was obtained. Repetition of this process using 0.30 g of I having $[\alpha]^{20}_{\mathrm{D}}$ −91° and 1 equiv of (−)-TAPA in 60 ml of benzene yielded 0.20 g of (−)-I, $[\alpha]^{25}_{\mathrm{D}}$ −96 ± 1° (*c* 1, benzene). Since repetition of this process did not result in further change of rotation we assume that maximum rotation has been reached. Comparable results were obtained with (+)-TAPA and (+)-I had similar mp and rotation to (−)-I. The melting point of both (+)-I and (−)-I is 167–168° and there is no appreciable depression of the melting point on mixing with racemic I, mp 169–170°. Over 2 g each of pure (+)-I and (−)-I was obtained.

Resolution of 2-Methylcholanthrene (II).—The resolution of II was more difficult than that of I. A hot solution of 2.00 g of II and 3.32 g of (−)-TAPA in 600 ml of benzene was allowed to stand at room temperature[19] for 2 days. The solid complex (A) which had separated from the green solution was collected by filtration. The filtrate was concentrated to one-half volume and on standing a second crop of complex, B, was obtained. The above filtration and concentration procedure was repeated three times. Complex A was recrystallized and the filtrate was used to recrystallize B, etc. After a number of such treatments had been performed the hydrocarbon was isolated from the complex by alkaline extraction of the TAPA. In this way fractions amounting to 0.95 g of (−)-II, $[\alpha]^{20}_{\mathrm{D}}$ −45 to −50° (*c* 1, in benzene), were obtained, combined, and treated with 1.60 g of (+)-TAPA in 175 ml of hot benzene. The complex which separated was collected and the *filtrate* was worked up to yield 0.20 g of (−)-II, $[\alpha]^{20}_{\mathrm{D}}$ −58.5 ± 1° (*c* 1, benzene), mp 160–161°. This rotation was not increased by further treatments and we assume it to be the maximum. Melting points of (+)-II and (−)-II, mp 160–161°, with racemic II, mp 156–157°, were intermediate.

Quantities of maximally resolved I and II have been sent to research workers in the cancer field.[5]

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(19) All operations involving TAPA were carried out in apparatus shielded from light as much as convenient.

Nature of the Complex Formed When Phenyl Grignard Is Added to Fenchone

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Complex formation between a carbonyl group and a Grignard reagent has frequently been invoked in the mechanism of the Grignard addition reaction.[1] If a relatively stable Grignard–ketone complex could be isolated and shown to be an intermediate in the addition reaction then its structure would be of value in delineating the mechanism of this reaction.

With this in mind we have surveyed the various literature reports of stable complexes and reinvestigated the "phenyl Grignard–fenchone complex."

Pfeiffer and Blank noted a precipitate when the Grignard reagent prepared from ethyl bromide was added to benzophenone.[2] Upon hydrolysis of this reaction mixture benzophenone was isolated. As Bikales and Becker have pointed out, the complex was not isolated and then hydrolyzed.[3] When Nesmeyanov and Sazanova repeated Pfeiffer and Blank's work, but isolated and hydrolyzed the precipitate, they found that the corresponding carbinol was formed.[4] Thus it appears that the precipitate noted by Pfeiffer and Blank is not a Grignard–ketone complex, but is the magnesium salt of the carbinol formed from the addition and reduction reactions.

Meisenheimer obtained a precipitate from the reaction of benzaldehyde and ethylmagnesium bromide which he isolated by filtration and found that the solid released ethane upon hydrolysis.[5] However, the quantity of ethane was relatively small (2–5 mole %).

Klages[6] believed he had isolated a complex of acetomesitylene and ethylmagnesium bromide; however, Kohler[7] showed that this precipitate was the enolate salt of acetomesitylene.

Other carbonyl–Grignard complexes have been reported but with the exception of the fenchone–Grignard complex most of the carbonyl compounds contained other functional groups.[1a] Fenchone, however, was reported to combine with several aryl Grignard reagents to give products insoluble in ether. Prolonged heating of this precipitate in excess Grignard reagent was reported to give low yields of the addition product.[8] Nesmeyanov and Sazanova isolated this complex and carried out a partial analysis.[4] They noted that fenchone was regenerated when this precipitate was isolated and hydrolyzed. They also observed that the magnesium/bromide ratio was 1:14.

We have found that this precipitate is easily obtained in a granular form by the addition of the Grignard reagent from bromobenzene prepared in ether to fenchone dissolved in ether. The quantity of complex formed was variable, but in initial experiments about 8 g of precipitate could be isolated and dried under nitrogen from 15 g (0.1 mole) of fenchone. On heating the solid in a sealed capillary, a liquid is given off at 160°, just above the boiling point of fenchone. A KBr pellet of the precipitate shows a carbonyl absorption at 1630 while pure fenchone shows a carbonyl absorption band at 1740 cm^{-1}. No phenyl bands were observed. The precipitate was found to dissolve readily in tetrahydrofuran. Furthermore, when phenyl Grignard in tetrahydrofuran and fenchone are mixed, no precipitate is formed and the infrared spectrum of the solution shows the normal uncomplexed carbonyl absorption at 1740 cm^{-1}. There was no apparent reduction in the carbonyl intensity even on allowing the solution to stand for several days.

Weighed portions of the nitrogen-dried precipitate were hydrolyzed with a known amount of dilute sulfuric acid. The solution was extracted with carbon tetrachloride to remove ether, benzene, and fenchone. Aliquots of the aqueous phase were then used for (a) back titration with standard base to determine the

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(1) (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954; (b) J. Miller, G. Gregoriou, and H. S. Mosher, *J. Am. Chem. Soc.*, **83**, 3966 (1961); (c) M. Anteunis, *J. Org. Chem.*, **27**, 596 (1962); **26**, 4214 (1961); (d) H. O. House and D. D. Traficante, *ibid.*, **28**, 355 (1963); (e) S. G. Smith, *Tetrahedron Letters*, **No. 7**, 409 (1963).

(2) P. Pfeiffer and H. Blank, *J. Prakt. Chem.*, **153**, 242 (1939).

(3) N. M. Bikales and E. I. Becker, *Can. J. Chem.*, **41**, 1329 (1963).

(4) A. N. Nesmeyanov and V. A. Sazanova, *Bull. Acad. Sci. URSS Classe Sci. Chim.*, 499 (1941).

(5) J. Meisenheimer, *Ann.*, **446**, 76 (1926).

(6) A. Klages, *Chem. Ber.*, **35**, 2633 (1902).

(7) (a) E. P. Kohler, J. F. Stone, and R. C. Fuson, *J. Am. Chem. Soc.*, **49**, 3181 (1927); (b) E. P. Kohler and R. Baltzly, *ibid.*, **54**, 4015 (1932).

(8) S. Leroide, *Compt. Rend.*, **148**, 1611 (1909).

amount of basic magnesium in the complex, (b) determination of the bromide content by adding an excess of silver nitrate and collecting the silver bromide formed, and (c) determination of the total magnesium present in the precipitate as the 8-hydroxyquinolate.

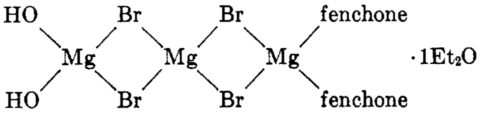
The quantity of benzene, fenchone, and ether in the organic phase was determined by gas chromatography using a flame-ionization detector and standard mixtures. The standard mixtures were subjected to the aforementioned work-up procedure to correct for losses in extraction. A summary of the results from six different preparations of the precipitate are given in Table I along with the calculated values for a proposed structure (1).

TABLE I

COMPOSITION OF THE FENCHONE-GRIGNARD PRECIPITATE

Component	Obsd for precipitate, %	Calcd structure I, %	Difference, %
Bromide	40.2	39.70	0.5
Basic magnesium	2.82	3.02	0.2
Total magnesium	8.76	9.05	0.29
Fenchone	37.2	37.81	0.61
Ether	8.8	9.20	0.4
Carbon[a]	35.54	35.80	0.26
Hydrogen[a]	5.2	5.51	0.3
Benzene	0.0	0.0	...

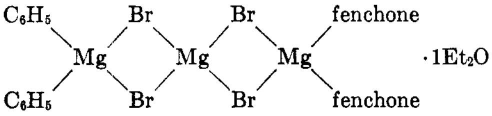
[a] Microanalyses for carbon and hydrogen were performed by Mr. J. Walter.



1

It is interesting to note that no benzene was observed. While the empirical formula for structure 1 is unique, structural formulas other than 1 can be written.

Since the hydroxyl groups could have resulted from the hydrolysis of phenylmagnesium bonds in a related structure 2 during the nitrogen-drying process, a sample of the precipitate was prepared in the usual fashion, rinsed free of Grignard reagent and excess ketone with Grignard dried ether, and then the precipitate was hydrolyzed without drying.



2

A gas chromatographic analysis indicated that the ether solution contained only traces of benzene from the approximately 10 g of precipitate. The magnesium hydroxide must therefore be formed before the drying process and the empirical formula as given by structure 1 does represent the precipitate formed in this process. It was found that when highly purified ketone and Grignard dried ether were used for the preparation of the complex the yield was drastically reduced.

Experimental Section

Reagents.—Tetrahydrofuran and ethyl ether, Baker anhydrous reagent grade, were used without purification except where noted. The Grignard reagent was prepared from Eastman Kodak's Grignard-grade magnesium turnings and bromobenzene. The fenchone from Eastman Kodak was distilled before use.

Preparation and Isolation of the Fenchone Precipitate.—To 23.0 g (0.15 mole) of fenchone dissolved in 50 ml of anhydrous ether was added with stirring 50 ml (2.9 N, 0.145 mole) of Grignard reagent prepared from bromobenzene. All preparations, transfers, and reactions were carried out under a nitrogen atmosphere. The precipitate was isolated by using nitrogen pressure to force the suspension through a sintered glass filter. The precipitate was rinsed with anhydrous ether (never exposing the precipitate to air) and dried to constant weight by passing a slow stream of dry nitrogen or argon through the precipitate contained on the sintered glass filter. Samples for hydrolysis, preparation of infrared pellets, and other tests were weighed out in a drybox which was constantly purged with nitrogen.

Determination of Basic Total Magnesium and Bromide.—A weighed sample of the precipitate was hydrolyzed with a known amount of dilute sulfuric acid. After extracting the aqueous phase with carbon tetrachloride an aliquot of the aqueous phase was back titrated with standard sodium hydroxide solution using phenolphthalein as the indicator to determine the amount of basic magnesium. The total amount of magnesium was determined on a second aliquot by precipitating the magnesium as the 8-hydroxyquinolate according to the method of Kolthoff and Sandall.[9]

A third aliquot of the aqueous phase was diluted with sufficient water to prevent precipitation of silver sulfate in the next step. A calculated excess of silver nitrate was used to precipitate the bromide ion as silver bromide. The results are summarized in Table I.

Determination of Fenchone, Benzene, and Ether.—The organic layer from the above extraction was gas chromatographed using an Aerograph Hi-Fi flame ionization detector and a 6 ft × $^1/_8$ in. DEGS column at 50 and 160°. Synthetic mixtures which had been subjected to the same extraction procedure were used to calibrate the chromatograph. The results of multiple runs are given in Table I.

Hydrolysis of the Precipitate without Drying.—The preparation of the precipitate was carried out as given above with the exception that the precipitate was washed by decantation using a nitrogen pressure siphon and Grignard dried ether. The precipitate was not dried but directly hydrolyzed with dilute sulfuric acid and the aqueous layer was extracted with ether. The ether layer was found to contain only traces of benzene.

Reaction of the Precipitate with Excess Phenyl Grignard.—A 5-g sample of the nitrogen-dried precipitate was suspended in 50 ml of 2.9 N phenyl Grignard reagent and the mixture was heated to reflux temperature for a period of 48 hr. From this reaction was isolated 75 mg of an impure carbinol with an infrared spectrum identical with one obtained from the addition product formed from phenyllithium and fenchone.

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(9) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," 3rd ed, The Macmillan Co., New York, N. Y., 1952.

Synthesis of Pyridazine Derivatives. XII. Friedel-Crafts Reaction with 3,6-Dichloropyridazine

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In connection with our studies in the pyridazine field[1] we were interested in investigating the behavior of 3,6-dichloropyridazine as an alkylating agent in the Friedel-Crafts reaction.

The inertness of halogenated heterocycles as alkylating agents in the Friedel-Crafts reaction is well known

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(1) Part XI: A. Pollak, B. Stanovnik, and M. Tišler, *Monatsh. Chem.*, in press.