2. This ester has been converted into several cyclopropane derivatives and their properties compared with certain closely related homologs.

3. In all reactions involving the ring, it was opened in the 1,2 position. This is in agreement with the results found with previous cyclopropanes of this type, but different from those having a phenyl group in the 2 position.

MONTREAL, CANADA RECEIVED FEBRUARY 23, 1933
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Coupling Action of the Grignard Reagent. V. The Influence of the Halogen Atom of the Reagent

BY ELLSWORTH ELLINGBOE AND REYNOLD C. FUSON

The coupling action of the Grignard reagent on halogen compounds involves the linking of the radicals of the reagent as well as those of the compound upon which the reagent reacts. It has been observed in a large number of cases and is especially pronounced in connection with compounds containing the aryl halomethyl grouping, $\mathrm{Ar}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{X}$. The surprising fact that aryl polyhalomethyl derivatives such as benzal chloride and benzotrichloride also undergo coupling has recently been reported.[1] To these peculiarities of the reaction is to be added a much more puzzling observation—*that the course of the reaction depends on the nature of the halogen atom of the alkyl halide used in preparing the reagent.* This is demonstrated by the sharp contrast in the action of methylmagnesium *iodide* with that of methylmagnesium *chloride* on the benzal halides.[2]

The action of methylmagnesium iodide on benzal chloride has been found to give α-stilbene dichloride according to the equation

$$2C_6H_5CHCl_2 + 2CH_3MgI \longrightarrow C_6H_5CHClCHClC_6H_5 + CH_3CH_3 + MgI_2 + MgCl_2$$

but when benzal chloride was treated with methylmagnesium chloride *no α-stilbene dichloride was produced.* Instead there was obtained a mixture which has been shown to consist of four different compounds: namely, cumene, 1,2-diphenyl-1-chloropropane (I), and two forms of 2,4-diphenylbutane (II).

$$\begin{array}{ccc} C_6H_5CH(CH_3)CH(CH_3)C_6H_5 & C_6H_5CH(CH_3)CHClC_6H_5 & C_6H_5C(CH_3){=}CHC_6H_5 \\ \text{II} & \text{I} & \text{III} \end{array}$$

This difference in the action of the two methylmagnesium halides has been corroborated by numerous repetitions of the experiments in ques-

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(1) Fuson and Ross, THIS JOURNAL, **55**, 720 (1933).

(2) That the halogen atom of a Grignard reagent has an influence on the course of the coupling reaction has been previously observed by Späth, *Monatsh.*, **34**, 1965 (1913).

tion.[3] While the results with methylmagnesium chloride are unlike that obtained by use of methylmagnesium iodide, they are similar to those reported by Reychler[4] in a study of the reaction between phenylmagnesium bromide and benzal chloride. He obtained triphenylmethane and *sym*-tetraphenylethane, products which are clearly analogous to cumene and to 2,4-diphenylbutane, respectively.

The Identification of the Products.—The two solid ethane derivatives (I and II) were difficult to separate because of the fact that mixtures of these two compounds formed solid solutions. They could not be separated by the usual methods and it was, of course, not possible to use their melting points as criteria of purity.

The **2,4-diphenylbutane** (II) was obtained in pure form by treating the mixture in such a way as to decompose the chloro compound. This could be accomplished by heat or by treatment with a boiling solution of alcoholic potassium hydroxide. The isolation of the α-methylstilbene (III) produced by the elimination of hydrogen chloride from the chlorine derivative (I) is described below.

The identity of the 2,4-diphenylbutane was established by analysis and by two independent syntheses. In the first of these α-bromoethylbenzene was treated with sodium. Later, it was found that treatment of α-bromoethylbenzene with magnesium gave 2,4-diphenylbutane as a reaction product.

The identification of **1,2-diphenyl-1-chloropropane** (I) in the original reaction mixture was accomplished by indirect methods. An authentic specimen of the compound was prepared by the method of Tiffeneau.[5] The pure compound melted at 139° and mixtures with the 2,4-diphenylbutane (melting point 126°) melted sharply at points between 126 and 139°. This showed that the two compounds formed solid solutions.

To prove conclusively that the chloro compound was actually present in the original mixture parallel experiments were carried out on both the pure chloro compound and the mixture obtained when benzal chloride was treated with methylmagnesium chloride. The pure chloro compound was treated with an alcoholic solution of potassium hydroxide and an unsaturated compound was obtained which melted at 48°. Ozonolysis of this compound gave benzoic acid and acetophenone. That the compound was α-**methylstilbene** (III) was further checked by analysis.

The mixture under the same treatment gave in addition to the diphenylbutane a colorless solid which when purified by recrystallization

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(3) It should perhaps be pointed out that the terms methylmagnesium chloride and methylmagnesium iodide are used here to describe the *solutions* obtained when the corresponding methyl halides react with magnesium in ether. That the difference in behavior of the two solutions may be due to other molecular species than the RMgX compounds in question is indeed a probability. For example, the difference might be due entirely to a difference in the amounts of magnesium dimethyl contained in the two solutions.

(4) Reychler, *Bull. soc. chim.*, **35**, 737 (1906).

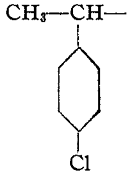
(5) Tiffeneau, *Ann. chim. phys.*, [8] **10**, 176 (1907).

from methyl alcohol melted at 48°. This compound was shown to be identical with the methylstilbene described above. When mixed with the latter it gave no depression of the melting point. Its analysis and its behavior toward ozone gave results which correspond to those described for methylstilbene.

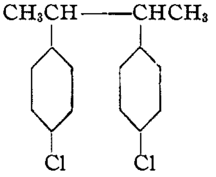
The identity of the α-methylstilbene is further supported by the fact that when heated in acetic acid containing a drop of hydrobromic acid it was isomerized into the known α-methylstilbene, melting at 82°.[6] The two hydrocarbons are evidently geometrical isomers.

The two liquid reaction products obtained when benzal chloride and methylmagnesium chloride reacted were cumene and a liquid form of 2,4-diphenylbutane. The identity of the cumene was established by a comparison of its physical properties with those of a very pure specimen of cumene prepared by the catalytic hydrogenation of 2-phenylpropene obtained by the dehydration of methylphenylcarbinol. The liquid form of 2,4-diphenylbutane has not been prepared synthetically. Consequently, its identity has not been proved. Its analysis and properties, however, support the structure assigned.

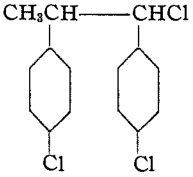
The Action of Methylmagnesium Chloride on *p*-Chlorobenzal Chloride.—The results obtained by treating *p*-chlorobenzal chloride with methylmagnesium chloride present a close parallel with those just described in the case of benzal chloride. The products obtained were *p*-chlorocumene (IV), 2,3-di-(*p*-chlorophenyl)-butane (V) and 1,2-di-(*p*-chlorophenyl)-1-chloropropane (VI).



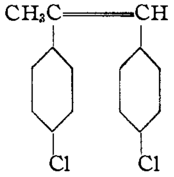
IV



V



VI



VII

From the mixture of V and VI it was possible to obtain VI in pure form by repeated recrystallization. Pure V was obtained from the mixture by treatment of the latter with alcoholic potassium hydroxide and then recrystallizing the crude product. *p*-Chlorocumene (IV) was obtained in very small amounts; it was identified by comparison with a synthetic sample of *p*-chlorocumene.

Discussion

It remains to mention certain experiments designed to throw light on the mechanism of the reaction under consideration. It seems obvious that the products obtained by the interaction of methylmagnesium chloride and benzal chloride arise from the processes of alkylation and

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[6] Klages, *Ber.*, **35**, 2648 (1902).

coupling operating concurrently or in sequence. For example, it might be supposed that stilbenedichloride and 1,2-diphenyl-1-chloropropane are intermediates in the formation of 2,3-diphenylbutane. Efforts to prepare the latter by treatment of the chloro compounds with methylmagnesium chloride have, however, been unavailing. In every case the chloro compounds were recovered unchanged.

Another mechanism was considered which postulated α-chloroethylbenzene as the intermediate in the formation of 2,3-diphenylbutane. However, when α-chloroethylbenzene was treated with methylmagnesium chloride cumene was the sole product obtained.

Experimental

Benzal Chloride and Methylmagnesium Chloride.—Twenty-five grams of benzal chloride was added to 200 cc. of an approximately 2 molal ether solution of methylmagnesium chloride over a period of two hours with continuous stirring. The mixture was then refluxed over a steam-bath for two hours, after which the excess Grignard reagent was decomposed with ice and dilute hydrochloric acid. The ether layer was washed with water and the ether was then evaporated. A semi-solid residue was obtained which yielded a colorless crystalline solid and a yellow lachrymatory liquid; the yield of crude solid was about 5 g.

The solid contained chlorine and after several recrystallizations from alcohol, glacial acetic acid, ethyl acetate or toluene was obtained as hard colorless prisms. The melting points of the mixtures obtained in a number of runs varied from 125 to 132°; one portion melted at 139°. Analyses showed about 8% chlorine for the substance melting at 132° and a maximum of 13.2% chlorine for the highest melting sample obtained. The yellow lachrymatory liquid was distilled under reduced pressure and three fractions were collected. A small amount of cumene distilled at 65° at 20 mm.; when it was boiled with alcoholic potassium hydroxide and refractionated it distilled at 148° at 747 mm.; n^{20}_{D} 1.4942; d^{20}_{20} 0.8799. The second fraction consisted of unchanged benzal chloride boiling at 85° at 20 mm. Finally a portion distilled at 150–152° at 20 mm., and partially solidified on standing. The colorless crystals from this fraction melted at 126–127° when pure; the liquid portion when further purified had the following constants: b. p. 150–151° at 20 mm., n^{20}_{20} 1.5594, d^{0}_{0} 0.9917. Both of these compounds were shown by analysis to have the composition corresponding to 2,3-diphenylbutane.

Anal. Calcd. for $C_{16}H_{18}$: C, 91.4; H, 8.6. Found for the solid: C, 91.3; H, 8.5. Found for the liquid: C, 91.1; H, 8.6.

2,3-Diphenylbutane (II). **First Method.**[7]—Nineteen grams of α-bromoethylbenzene dissolved in 75 cc. of ether was treated with 2.5 g. of finely cut metallic sodium and stirred rapidly at room temperature for twenty hours. The solution was then filtered and the ether was evaporated. In this way the diphenylbutane was obtained as a colorless solid which when recrystallized from alcohol melted at 124–125°.

Second Method.—Twenty grams of α-bromoethylbenzene was added with stirring to 2.5 g. of magnesium in 100 cc. of ether in an attempt to prepare the Grignard reagent. Benzaldehyde was added to this, but 3.2 g. of 2,3-diphenylbutane was the only new substance obtained.

Mixed melting points of the specimens of the hydrocarbon, as prepared above, with

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(7) Engler and Bethge [*Ber.*, **7**, 1127 (1874)] have prepared this compound by a similar method starting with α-chloroethylbenzene.

each other and with that obtained from the action of methylmagnesium chloride on benzal chloride showed them all to be identical.

α-Methylstilbene. (III).—Three grams of 1,2-diphenyl-1-chloropropane prepared by the method of Tiffeneau[5] was added to 100 cc. of a 5% solution of alcoholic potassium hydroxide and the mixture was refluxed on a steam-bath for eight hours. The solution was then filtered and the alcohol was evaporated by passing a stream of air over it. Water was added to the solid residue, the crystals were filtered and washed with water. After two recrystallizations from methyl alcohol, the α-methylstilbene melted at 48°.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.8; H, 7.2. Found: C, 92.4; H, 7.3.

Two grams of the α-methylstilbene was dissolved in about 100 cc. of carbon tetrachloride and ozone was bubbled into the solution for two hours. The solvent was then evaporated under diminished pressure and the ozonide was decomposed with boiling water and a small amount of dilute hydrochloric acid. A colorless precipitate was obtained which was recrystallized from alcohol and water; it melted at 122°. A mixed melting point identified it as benzoic acid. About 1 cc. of an oil remained from the hydrolysis, and this was extracted with ether, dried over sodium sulfate and distilled. A small amount of liquid boiling at 195–205° was obtained. This was converted into a phenylhydrazone melting at 105° and was thus shown to be acetophenone.

Separation of the Mixture of 1,2-Diphenyl-1-chloropropane and 2,3-Diphenylbutane.—Thirty grams of the product (m. p. 132°) obtained by the action of methylmagnesium chloride on benzal chloride was refluxed with 100 cc. of a 10% solution of alcoholic potassium hydroxide for eight hours. The solution was cooled and filtered; the alcohol was evaporated by a stream of air. The residue on the filter was washed with cold water and then about 50 cc. of water heated to 55° was filtered through in small portions. The oily layer in the filtrate was extracted, allowed to solidify and then was recrystallized from methyl alcohol. The crystals so obtained were next subjected to the warm water extraction process just described. The material obtained in the second extraction melted at 48° after two recrystallizations. Ozonization converted it into benzoic acid and acetophenone. When mixed with α-methylstilbene it did not depress the melting point. The crystals remaining in the funnel after the warm water extraction were purified from ethyl alcohol. They melted at 125–126° and proved to be 2,3-diphenylbutane.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.8; H, 7.2. Found: C, 92.3; H, 7.2. Calcd. for $C_{16}H_{18}$: C, 91.4; H, 8.6. Found: C, 91.1; H, 8.6.

Cumene.—Thirty grams of 2-phenylpropene was dissolved in alcohol and hydrogenated by the method of Adams, Voorhees and Shriner.[8] The product was fractionated to remove the alcohol, washed with a dilute water solution of potassium permanganate and dried over calcium chloride. It was finally distilled twice through a Widmer column; boiling point 147–148° (747 mm.); n^{20}_{D} 1.4940; d^{20}_{20} 0.8833.

Conversion of the Low-Melting α-Methylstilbene into its Geometrical Isomer.—About 0.5 g. of α-methylstilbene (m. p. 48°) was dissolved in 20 cc. of glacial acetic acid to which a drop of concentrated hydrobromic acid had been added. The solution was heated on the steam cone for one-half hour, and was then poured into about 100 cc. of cold water. The solid hydrocarbon precipitated and was filtered. After one recrystallization from methyl alcohol, the colorless crystals melted at 82–83°.

The Action of Methylmagnesium Chloride on *p*-Chlorobenzal Chloride.—Thirty-one and five-tenths grams of *p*-chlorobenzal chloride was treated with 200 cc. of a 2 molal methylmagnesium chloride solution following the procedure used for benzal chloride. There was obtained 7.3 g. of crude colorless solid and a considerable amount of lachrymatory liquid.

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(8) "Organic Syntheses," John Wiley and Sons, New York, 1932, Coll. Vol. I, p. 452.

The solid product after three or four recrystallizations from glacial acetic acid melted at 160–161°; but after many more crystallizations the melting point rose to a maximum of 167°. Analysis showed this compound to be *1,2-di-(p-chlorophenyl)-1-chloropropane (VI)*.

Anal. Calcd. for $C_{15}H_{13}Cl_3$: Cl, 35.5; C, 60.0; H, 4.3. Found: Cl, 35.4; C, 60.2, H, 4.5.

The material (m. p. 160°) obtained from the crude solid after three crystallizations from glacial acetic acid was treated with boiling 10% alcoholic potassium hydroxide for twelve hours. The alcohol was evaporated by a current of air, the residue washed well with water and then recrystallized from alcohol. After two recrystallizations, the colorless crystals melted at 147–148°. The analysis corresponds to that calculated for *2,3-di-(p-chlorophenyl)-butane (V)*.

Anal. Calcd. for $C_{16}H_{16}Cl_2$: Cl, 25.4; C, 68.9; H, 5.7. Found: Cl, 25.2, 25.4; C, 69.1; H, 6.1.

A mixture of compounds V and VI melted sharply at 159–160°—midway between the constants for the pure substances.

The mother liquor of compound VI obtained by the alcoholic potassium hydroxide treatment was allowed to evaporate to dryness; two different types of crystals were found in the residue. These were separated mechanically and each was recrystallized. The diamond-shaped crystals proved to be compound VI and the slender prisms gave a product melting at 80° after several recrystallizations from alcohol. This compound gave positive tests for unsaturation with permanganate and bromine and otherwise corresponded to the expected 1,2-di-(*p*-chlorophenyl)-propene (IV).

Anal. Calcd. for $C_{15}H_{12}Cl_2$: Cl, 27.0; C, 68.4; H, 4.6. Found: Cl, 27.0; C, 68.2; H, 4.6.

p-Chlorocumene (IV). Isolation.—The lachrymatory liquid obtained along with compounds V and VI was shown to consist of *p*-chlorobenzal chloride and *p*-chlorocumene. The former was partially removed by fractional distillation. Treatment of the impure *p*-chlorocumene with alkali followed by sodium bisulfite removed the last traces of the benzal chloride and gave *p*-chlorocumene boiling at 79–81° at 15 mm.; n^{20}_{D} 1.5158; d^{20}_{20} 1.0411.

Synthesis.—2-(*p*-Chlorophenyl)-propene was prepared by dehydration of the carbinol obtained by condensing *p*-chloroacetophenone with methylmagnesium iodide by the method used by Tiffeneau[9] for the synthesis of 2-phenylpropene. It boiled at 89° at 14 mm.; n^{20}_{D} 1.5527; d^{20}_{20} 1.0750.

Anal. Calcd. for C_9H_9Cl: Cl, 23.4. Found: Cl, 23.7.

Ten grams of the propene was hydrogenated by the method of Adams, Voorhees and Shriner. The *p*-chlorocumene obtained in this way had the following physical constants: b. p. 81° at 15 mm.; n^{20}_{D} 1.5120; d^{20}_{20} 1.0257.

Comparison.—The two samples of *p*-chlorocumene were shown to be identical by converting them into the corresponding *p*-chlorocumenesulfonamide. This was effected by sulfonation with chlorosulfonic acid in the usual way and treatment of the resulting sulfonyl chloride with ammonia. In both cases there resulted a sulfonamide melting at 91°; mixtures of the two amides showed no depression of the melting point. The derivative is probably 2-chloro-5-isopropylbenzenesulfonamide.

Anal. Calcd. for $C_9H_{12}O_3SNCl$: N, 6.0; Cl, 15.2. Found: N, 6.3; Cl 15.1.

Summary

It has been shown that methylmagnesium chloride reacts with benzal chloride to give cumene, 1,2-diphenyl-1-chloropropane and two forms of

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[9] Tiffeneau, *Ann. chim. phys.*, [8] **10**, 145 (1907).

2,3-diphenylbutane. Similar results were obtained with *p*-chlorobenzal chloride.

Previous work has shown that methylmagnesium iodide reacts with benzal chloride to give stilbene dichloride.

From these results it is clear that solutions of methylmagnesium iodide and methylmagnesium chloride differ widely in their action on benzal chloride.

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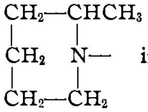
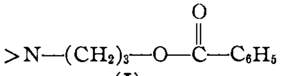
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

2-Methylpiperidinopropyl Thiol- and Thionbenzoates

BY S. A. KARJALA AND S. M. MCELVAIN

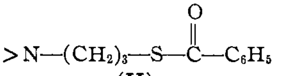
Since practically all of the local anesthetics containing an ester structure are derived from oxygen acids, it seemed desirable to undertake the preparation of compounds derived from certain thio acids in order that the pharmacological effect of this exchange of oxygen for sulfur might be ascertained. Of the simpler types of aminoalkyl benzoates which have been prepared in this Laboratory the methylpiperidinopropyl benzoates[1] have been found to be the most efficient. On account of the rather considerable pharmacological work which has been done[2] on 2-methylpiperidinopropyl benzoate (I) it was decided to prepare the sulfur analogs of this anesthetic. The present paper reports the preparation and properties of 2-methylpiperidinopropyl thiolbenzoate (II) and the corresponding thionbenzoate (III)

>N— represents  in subsequent formulas



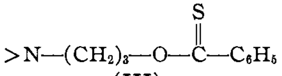
$>N-(CH_2)_3-O-\overset{O}{\overset{\|}{C}}-C_6H_5$

(I)



$>N-(CH_2)_3-S-\overset{O}{\overset{\|}{C}}-C_6H_5$

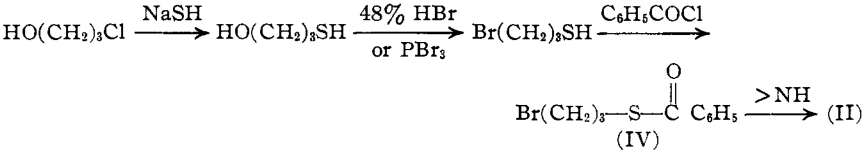
(II)



$>N-(CH_2)_3-O-\overset{S}{\overset{\|}{C}}-C_6H_5$

(III)

The thiolbenzoate (II) was prepared by the following series of reactions



$$HO(CH_2)_3Cl \xrightarrow{NaSH} HO(CH_2)_3SH \xrightarrow[\text{or } PBr_3]{48\%\ HBr} Br(CH_2)_3SH \xrightarrow{C_6H_5COCl} \underset{(IV)}{Br(CH_2)_3-S-\overset{O}{\overset{\|}{C}}\ C_6H_5} \xrightarrow{>NH} (II)$$

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(1) McElvain, THIS JOURNAL, **49**, 2835 (1927).

(2) (a) Coles and Rose, *J. Lab. Clin. Med.*, **15**, 239 (1929); (b) *ibid.*, **15**, 731 (1930); (c) Meeker, *Surg., Gynecol. Obstet.*, **50**, 997 (1930).