

### Summary

1. *p,p'*-Bis(dimethylamino)-benzohydrol, better known as Michler's hydrol, condenses with the imides of succinic and phthalic acids to succinyl- and phthalyl-leucauramines, which can be hydrolyzed by alkali to the corresponding amidic acids. The results of the condensation were the same whether carried out in conc. sulfuric acid or in alcoholic solution.

2. Phthalyl-leucauramine exists in a labile, colorless (m. p. 90°), and a stable, greenish-yellow, modification (m. p. 186.7°), which are interconvertible.

3. These acyl leucauramines yield the corresponding carbinols when oxidized by lead dioxide, or give dinitro derivatives when treated with nitrous acid.

4. Phthalimidine and the hydrol do not condense in alcoholic solution.

5. Phthalide reacts with two moles of the hydrol.

6. 3-Amino-phthalimide also condenses with 2 moles of hydrol, one entering the amino and the other the imide group. 4-Nitro-phthalimide, on the other hand, does not react.

7. The hydrol is a delicate reagent for detecting saccharin in alcoholic solution, giving a deep blue coloration even in dilute solutions.

8. Dehydrothio-*p*-toluidine condenses readily with the hydrol in alcoholic solution.

9. Anthraquinone, its  $\alpha$ - or  $\beta$ -amino derivative, alizarin, thio-urea or benzoylene-urea, fails to react with the hydrol, under the conditions of our experiments.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]  
**A NEW METHOD FOR THE INTRODUCTION OF AN ETHYL GROUP. THE REACTION BETWEEN ORGANOMAGNESIUM HALIDES AND DIETHYL SULFATE**

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### Introduction

A large number of commonly employed methods of synthesis in organic chemistry owe their extensive application and comparative importance to reactions which make it possible to introduce an alkyl or an aryl group in a great variety of compounds. Needless to say, these methods differ widely in procedure, in the kinds of R groups which can be introduced, and in the yield. The utility of a given method is generally circumscribed. In the present work there is described a method which,

<sup>1</sup> This paper is an abstract of a thesis presented by R. E. Hoyle in partial fulfillment of the requirements for the degree of Master of Science in chemistry at Iowa State College.

it is believed, will extend the present means at the disposal of the organic chemist for the synthesis of compounds otherwise prepared with difficulty and for the solution of some problems concerned with the determination of structure and the mechanism of reaction.

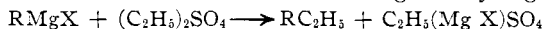
In connection with some work on the mechanism of the reaction between the Grignard reagent and compounds having more than one group capable of reacting with it, a need was felt for a reagent which would react with the product to give a compound indicating the position taken up by the Mg X group. The requirements for such a reagent are essentially rigid: it should react smoothly, at a low temperature (for our work, the boiling point of ether), and give a stable compound which would lend itself to comparatively ready identification. Among other compounds which suggested themselves were the dialkyl sulfates. Two of these are now available in large quantities at reasonable prices, dimethyl sulfate and diethyl sulfate. The former has been long known and has found extensive application in both the industries and research laboratories. Diethyl sulfate has only recently<sup>2</sup> been prepared on a technical scale, and its several desirable properties assure a wide adoption in synthetic work. Other dialkyl sulfates are known, but these are largely laboratory curiosities because of the difficulties at present attendant on their preparation. It is quite probable that in time satisfactory methods will be devised for the large scale production of some of them, inasmuch as they give promise of great use, and the alcohols from which they are prepared (particularly *isopropyl* and *n-butyl* alcohols) are now to be had at low cost.

Before using the dialkyl sulfates for work on the mechanism of reactions involving the Grignard reagent, it was desirable to try the effect of these reagents on organomagnesium halides of known structure. The Grignard reagent reacts with a great variety of compounds, and one characteristic reaction is addition. In such reactions the R group attaches itself to one element, and the magnesium halide very often to another element. Not a few compounds are known where these groups are on the same element but where the reactive grouping has any kind of a double or triple bond the RMgX adds generally after the manner of hydrogen or bromine to a double bond. Whatever the mode of addition the magnesium halide group is attached to an element such as carbon, oxygen and nitrogen, as well as other less commonly occurring polyvalent elements which go to make up organic compounds. The problem was, therefore, to determine the reaction of dialkyl sulfates with organomagnesium halides having the "MgX" group on a carbon, oxygen or nitrogen atom.

In this work diethyl sulfate was selected because the technical quality is pure enough for immediate use with the very sensitive RMgX com-

<sup>2</sup> G. O. Curme, Jr., and H. R. Curme, *Chem. Met. Eng.*, **25**, 957 (1921).

pounds, and because it is safer to handle than dimethyl sulfate. It soon became apparent that the reaction went smoothly with a great variety of compounds to give ethyl derivatives in varying yields. The reaction may be written in this manner, R standing for any organo grouping.



Fortunately, the better yields were obtained in the synthesis of those compounds otherwise prepared, directly or indirectly, with difficulty. By replacing the MgX group on carbon, oxygen, and nitrogen by an ethyl group there were obtained hydrocarbons, ethers and esters, and amines, respectively. There is no reason for believing that the reaction is restricted to these elements. Furthermore, the reaction should widen the fields of synthesis where other metals and metalloids, such as mercury, zinc, arsenic, etc., are present in both organic and inorganic compounds.

Such a reaction can also be extended by the use of other dialkyl sulfates and diaryl sulfates, on which work is now being done in this laboratory. Some time ago, a study<sup>3</sup> was made of the reaction between the Grignard reagent and dimethyl sulfate, and a few hydrocarbons were made by this method. The corresponding homologs made by the use of diethyl sulfate gave comparable yields.

It should be emphasized that some of the compounds described here, particularly the ethers and esters, can be made more conveniently by the direct use of diethyl sulfate. This applies also to the preparation of ethyl amines. Already some ethyl amines are made technically by simply heating the amine with diethyl sulfate. In this latter case, however, the introduction of an ethyl group by the intermediate formation of an organomagnesium halide may enjoy, at times, the advantage of avoiding side-reactions. For example, if a primary amine is treated directly with diethyl sulfate to form a secondary amine, it is often very difficult to avoid the simultaneous formation of a tertiary amine. However, if the primary amine should be treated first with a compound of the general formula, RMgX, at low temperatures only one hydrogen atom is replaced; and, if this organomagnesium compound should then be treated with one equivalent of diethyl sulfate, the chances of having more than one ethyl group enter the molecule would be decreased. In this connection, it should be mentioned that no work has as yet been done to prove whether the second ethyl group in diethyl sulfate can be made to replace an MgX group. Undoubtedly, if the reaction should take place it would require a higher temperature.

### Procedure

In all the experiments there were several uniform procedures. The reactions involved in a given preparation were successively carried out

<sup>3</sup> Werner and Zilkens, *Ber.*, **36**, 2116 (1903). Houben, *ibid.*, **36**, 3083-6 (1903); **37**, 488-9 (1904). Werner, *ibid.*, **36**, 3618 (1903).

in the same flask. For this purpose a 3-neck flask was used provided with a stirrer and mercury seal, a condenser and a dropping funnel. First, the organomagnesium halide was prepared in the customary manner by adding an ethereal solution of the appropriate RX compound to magnesium turnings. Second, a solution in ether of the compound selected to react with the Grignard reagent was slowly added to the previously prepared compound. During the first stages of addition the reaction mixture was kept cold by an ice-bath. When all the compound had been added, the solution or sometimes the suspension was gently warmed to complete the reaction. Third, an ethereal solution of diethyl sulfate was then slowly added. Invariably this reaction was accompanied by the liberation of sufficient heat to cause the ether to boil gently, which was indicated by the slow and orderly refluxing of the solution. Fourth, an excess of dil. hydrochloric acid was slowly added to the cold reaction mixture to decompose any unaltered organomagnesium halide, and concurrently, of course, to dissolve any basic magnesium halide. In the preparation of most amino compounds it is desirable to replace the dil. hydrochloric acid by an aqueous solution of ammonium chloride, or by ammonium chloride and ammonium hydroxide.

These four successive procedures gave the desired reaction product, generally completely dissolved in the ether used in the reactions, or partly dissolved in the ether and the remainder suspended very often at the interface of the ether and water layers. In the former case the ether layer was separated from the water layer, washed with water, dried with an appropriate drying agent, and then fractionally distilled when the product was a liquid. In the latter case the solid was first removed by filtration and worked up independently of the ether layer. Mechanical stirring was used throughout.

The reagents employed underwent no special preliminary treatment for purification. The ether was dried in the customary way. In all reactions but one, equal molecular quantities of reagent were taken. The yields, therefore, can be based on any of the reagents used: the alkyl or aryl halides, the magnesium, the organic compound brought into reaction with the Grignard reagent, or the diethyl sulfate.

As a matter of general information it should be stated that all experiments were carried out without using a hood. When ordinary precautions were observed and work was performed at low temperatures, no harmful physiological effects were apparent. This bears out, in part, the claims of the comparative harmlessness of diethyl sulfate.

For reasons as yet unknown it appears that ethyl magnesium bromide is much better suited than such compounds as methyl or ethyl magnesium iodide for replacing the acidic hydrogen in acetylenic compounds by the MgX group. An excess of ethyl magnesium bromide and therefore of

diethyl sulfate is probably not required. It was used here because the failure of methyl and ethyl magnesium iodides to react with the acidic

TABLE I  
RESULTS

Reagent	Taken for the reaction		Substance formed	Yield		Boiling point <sup>a</sup> ° C.
	G.	Moles		G.	%	
Bromobenzene	471	3	Ethyl benzene	105.00	33.00	134-136
<i>p</i> -Bromotoluene	85.5	0.5	<i>p</i> -Ethyl toluene	27.0	45.00	160-161
Benzyl chloride	63.0	0.5	<i>n</i> -Propyl benzene	59	quant.	155-156
$\alpha$ -Bromonaphthalene	103.5	0.5	$\alpha$ -Ethyl naphthalene	55	70.5	256-259
Butyl bromide	102.6	0.75	<i>n</i> -Hexane <sup>a</sup>	45	69.4	68.00
Bromocyclohexane	56	0.5	Ethyl cyclohexane <sup>b</sup>	45	80.3	128-130
<i>p</i> -Bromo-anisole	70	0.37	<i>p</i> -Ethyl anisole <sup>c</sup>	45.5	89.4	199-200
Phenyl acetylene	20.4	0.2	Ethylphenyl acetylene <sup>d</sup>	18.3	70.3	198-201
			Ethyl ether of benzhydrol <sup>e</sup>			
Benzaldehyde and Bromobenzene	53	0.5	Ethyl ether of triphenylcarbinol	35.00	35.7	282-284
Benzophenone and Bromobenzene	91	0.5		120	92.3	(triphenylcarbinol; only a small quantity of the ethyl ether 83-84 (m. p.) was formed)
C <sub>6</sub> H <sub>5</sub> COOMgI	...	0.5	Ethyl benzoate <sup>f</sup>	13	17.3	210-211
Benzalaniline	45.25	0.25	N-ethyl-N-phenylbenzohdrylamine	65	90.5	191 (5 mm.)

<sup>a</sup> In this experiment because of the low boiling point of *n*-hexane, extra precautions were observed to keep the solutions cold, particularly during the addition of dil. hydrochloric acid and the subsequent operations.

<sup>b</sup> During the addition of the diethyl sulfate the unusual thickening of the reaction mixture necessitated extensive dilution with anhydrous ether.

<sup>c</sup> A small fraction which was not identified distilled over at 170°.

<sup>d</sup> Two-fifths mole of ethyl magnesium bromide was used. The reaction was slow in starting. To the reaction mixture was added  $\frac{2}{5}$  mole of diethyl sulfate, and because of the considerable thickening the mixture was further diluted with ether. There was also obtained 5.6 g. of unchanged phenyl acetylene, so that the yield based on this compound was practically quantitative.

<sup>e</sup> The product was first distilled at 150-160 mm. and the fraction boiling between 190° and 195° collected. This was redistilled at atmospheric pressure and 35 g. or 35.7% was collected at 282-284°.

<sup>f</sup> Dry carbon dioxide was bubbled through an ethereal solution containing  $\frac{1}{2}$  mole of phenyl magnesium iodide to give C<sub>6</sub>H<sub>5</sub>COOMgI. From the oil remaining in the flask after steam distillation there was obtained a very small amount of triphenyl carbinol. The bulk of the apparently intractable oil was not further investigated.

hydrogen was ascribed in part to an insufficiency of these RMgX compounds.

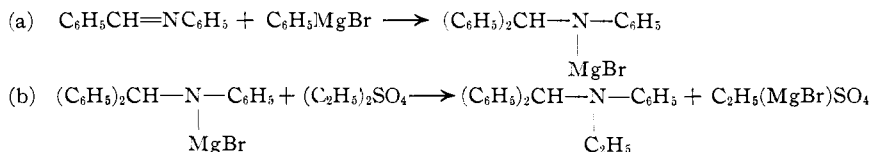
**N-ethyl-N-phenylbenzohdrylamine** [(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CHN(C<sub>2</sub>H<sub>5</sub>)C<sub>6</sub>H<sub>5</sub>].—The reaction mixture was decomposed with ammonium hydroxide and ammonium chloride. After

<sup>1</sup> The temperatures recorded in this paper are uncorrected.

separating the ether layer and drying with sodium sulfate, the ether was removed by distillation from a water-bath; the final product was a thick, clear oil which darkened on standing;  $d_4^{20}$  1.06;  $n_D^{25}$ , 1.597.

*Analyses.* Calc. for  $C_{21}H_{21}N$ : N, 4.88. Found: 4.91, 5.06.

The probable mechanism of these reactions follows.



The analysis and the calculated refractive index are in agreement with the formula  $(C_6H_5)_2CHN(C_2H_5)C_6H_5$ . To further establish its identity the compound was prepared by known reactions and was found to boil at the same temperature, 191° at 5 mm. pressure. This was done according to the method of Busch and Rinck<sup>5</sup> by adding  $1/4$  mole of benzalaniline to  $1/4$  mole of phenyl magnesium bromide and working up in the customary manner to give *o*-phenylbenzylaniline,  $C_6H_5NHCH(C_6H_5)C_6H_5$ . This amine was found to boil at 165° at 5 mm. pressure. Its hydrochloride was prepared by passing dry hydrogen chloride into a cold mixture of ether and ethyl alcohol from which the salt was precipitated directly in a pure condition melting at 199°. The hydrochloride was then heated directly with one molecular equivalent of diethyl sulfate for 6 hours at 110–120°. The amine was set free by sodium hydroxide, taken up in ether, washed with water, dried over sodium sulfate and then distilled. As previously mentioned, the boiling point agreed with that of the compound made by treating the organomagnesium halide directly with diethyl sulfate.

### Summary

1. A study has been made of the reaction between diethyl sulfate and organomagnesium halides having the MgX group on carbon, oxygen and nitrogen.
2. In all cases the MgX group has been replaced by an ethyl group.
3. The yields of reaction products in several experiments are decidedly good. In addition to its value for synthetic purposes the reaction is recommended as a reliable method for the determination of the mechanism of certain reactions.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

### CERTAIN TRIPHENYLMETHANE DYES<sup>1</sup>

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The preparation in a pure state of a number of dyes of the malachite green series was undertaken as a part of a study of the bactericidal action of dyes in general. In the course of these studies we have had occasion

<sup>5</sup> Busch and Rinck, *Ber.*, **37**, 2691 (1904); **38**, 1761 (1905).

<sup>1</sup> Presented at the Annual Meeting of the American Chemical Society, September, 1921.