

The latter compound was prepared for us by Mr. L. A. Burrows of this Laboratory. The results are shown in Table I.

TABLE I
RELATIVE ACIDITIES

Morpholine-()-hydrochloride	P_H	0.5% solution P_H at precipitation
Ethyl benzoate	4.0	8.0 no precipitation
Ethyl <i>p</i> -aminobenzoate	4.2	6.7
Propyl benzoate	4.3	8.0 no precipitation
Propyl <i>p</i> -aminobenzoate	4.4	6.9
Procaine	5.2	8.0 no precipitation
Diethylaminoethyl benzoate hydrochloride	4.8	7.9

Summary

1. A series of local anesthetics of the alkamine ester type in which the dialkylamino group has been replaced by a morpholine ring has been prepared and described.

2. Some preliminary pharmacological tests on these compounds have been made.

3. These compounds have been found to possess considerable local anesthetic activity and low toxicity.

This investigation is to be continued.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY,
MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 72]

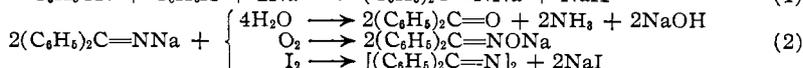
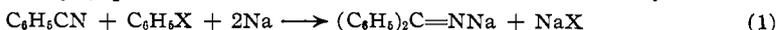
CONDENSATIONS BY SODIUM INSTEAD OF BY THE GRIGNARD REACTION. II.¹ REACTION WITH BENZONITRILE. PREPARATION OF DIPHENYLKETAZINE

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RECEIVED MAY 13, 1931

PUBLISHED JULY 8, 1931

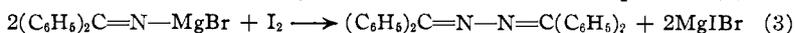
When benzonitrile is added to a mixture of chlorobenzene and sodium in ether the solution becomes intensely red. We ascribe the occurrence of this color to the presence of sodium diphenyl methylene imine, which is formed according to equation (1) below. This appears reasonable since the reactions of the solution with water, oxygen and iodine lead to the formation of benzophenone, benzophenone oxime and diphenylketazine, respectively (equation 2), in all of which the red color is destroyed.



The action of iodine on the corresponding magnesium compound, diphenyl methylene imino magnesium bromide, obtained by the addition

¹ First paper of this series, THIS JOURNAL, 53, 2244 (1931).

of benzonitrile to phenylmagnesium bromide has never been observed. It therefore followed naturally to try such a reaction, equation (3), with



the result that the diphenylketazine was prepared in good yield. This is a decided improvement over the older method of Curtius and Rauterberg.² The corresponding reaction of the magnesium compound with oxygen did not cause the formation of any oxime.

We are unable to say that sodium is better than magnesium with benzonitrile probably because of the strong tendency of the latter to polymerize under the influence of sodium.³ We overcame this in part by the use of a stirrer and the gradual addition of the benzonitrile to the reaction mixture. However, the work has led to a better method of preparing diphenylketazine and to the preparation of the oxime by the reaction of oxygen with a nitrogen-sodium linkage.

Further studies are being made on the decomposition of the sodium imine compound and the corresponding magnesium compound as well as other condensations by sodium instead of by the Grignard reaction.⁴

Experiments

Benzonitrile and Chlorobenzene.—The experiment was performed in an atmosphere of dry nitrogen: 4.6 g. of sodium sand was put into a three-necked flask with 200 cc. of anhydrous ether; 11.2 g. of chlorobenzene was added and the flask heated on a hot-plate while the mixture was stirred. As soon as the reaction began, 10.3 g. of benzonitrile in 30 cc. of ether was added slowly through a dropping funnel over a period of one and a half hours. The solution became of a very deep red color, probably owing to the formation of the sodium imine compound. At the first part of the reaction enough heat was evolved to maintain refluxing, but after all of the nitrile had been added the mixture was again heated on the hot-plate for two hours. The sodium imine compound was not isolated from this mixture but was treated directly with other substances.⁵

Reaction with Air.—When air was blown through the cold imine solution, with stirring, the red color disappeared. The mixture was then treated with water, the ether evaporated and the water solution filtered. When neutralized with dilute hydrochloric acid, 6 g. of benzophenone oxime, as shown by a mixed melting point, was precipitated; yield, 30.5%.

Reaction with Iodine.—Iodine added to the solution of the sodium imine prepared as described above decolorized the solution, the completion of the reaction being almost

² Curtius and Rauterberg, *J. prakt. Chem.*, [2] **44**, 198 (1891).

³ Hofmann, *Ber.*, **1**, 194 (1868); Lottermoser, *J. prakt. Chem.*, [2] **54**, 132 (1896).

⁴ In our study of the reaction of carbon dioxide with organic chlorides, chlorobenzene was heated under 30 pounds' pressure of carbon dioxide in the presence of sodium. The exothermic nature of the reaction once started was so great that it became uncontrollable and blew the container with explosive violence. This word of caution is given in advance of the article describing all of these experiments in order to emphasize again the care that must be exercised when working with sodium.

⁵ Preliminary experiments on the decomposition of the sodium imine compound with water showed a mixture of benzophenone and the corresponding oxime, the latter being due to the presence of air.

equivalent to an end-point in a titration. Much heat was evolved and a yellow solid was precipitated. The mixture was decomposed with water in the cold and filtered without evaporating the ether. The solid residue was extracted with carbon bisulfide and the latter was evaporated to dryness, yielding a yellow solid. Upon washing with hot acetone, 3 g. of a bright yellow crystalline solid (m. p. 160–162°) was obtained; yield, 16.7%. Diphenylketazine is recorded as melting at 162 and 164°. ^{2,8}

Anal. Calcd. for C₂₆H₂₀N₂: C, 86.67; H, 5.60. Found: C, 86.68, 86.47; H, 5.78, 5.81.

Preparation of the Sodium Imine Compound from Sodium and Diphenyl Methylene Imine.—Diphenyl methylene imine⁷ (approximately 0.05 g.) dissolved in anhydrous ether was sealed up in a small tube with a sliver of sodium. A deep red color, similar to that obtained in the reactions given above, developed. When iodine was added, a yellow precipitate formed but the material could not be purified sufficiently in the micro tube to determine whether it was the ketazine. However, when the sodium imine compound so prepared was kept in an open tube in a desiccator for two days so that air could come in contact with it (ether added to compensate for evaporation loss) benzophenone oxime was formed in quantities sufficiently large for easy identification, m. p. 141°.

Preparation of the Ketazine from the Magnesium Compound.—To a warm ether solution of phenylmagnesium bromide, made from 20 g. of bromobenzene and 3.1 g. of magnesium in 200 cc. of ether, was added 10 g. of benzonitrile. After five minutes the stirring was stopped and the ether solution was allowed to cool. The magnesium compound crystallized out in needles from a common center. The crystals were then broken up and 16 g. of iodine added to the mixture with heating and stirring. The stirring was continued for two hours and the mass allowed to stand for a day. It was again stirred for ten hours, the ether evaporated, the mass heated to 100° and stirred for two hours. It was then decomposed with dilute acid, the precipitate filtered, dried and extracted with hot benzene. The benzene was evaporated to 100 cc., an equal volume of petroleum ether added and the resulting precipitate washed with more petroleum ether. The solid had a melting point of 164° and showed no depression when mixed with the product obtained from the reaction of iodine with the sodium imine compound; yield, 10 g. (57.4%). Instead of using iodine the decomposition of the magnesium compound was carried out by the addition of bromine to the solution under a gentle refluxing. A large amount of heat was evolved but no hydrobromic acid was observed. When decomposed with cold dilute hydrochloric acid and purified as described above, 2 g. (7.6%) of ketazine, m. p. 162°, identical with that formed by the addition of iodine was obtained.

Attempted Reaction of the Magnesium Compound with Oxygen.—Oxygen was blown through a solution of the magnesium compound, prepared as above described, for ten hours, benzene being added to compensate for the loss of ether. No benzophenone oxime could be isolated. The experiment was repeated using dry lead dioxide instead of oxygen but again no oxime was found.

Conclusion

Benzonitrile reacts with phenyl halides in the presence of sodium forming, probably, sodium diphenyl methylene imine.

The mixture so obtained reacts with water, air and iodine forming benzophenone, benzophenone oxime and diphenyl ketazine.

⁶ Purgotti and Viganò, *Gazz. chim. ital.*, 31, II, 550 (1901).

⁷ Prepared according to the directions of Lachman, "Organic Syntheses," 10, 28 (1930).

The ketazine may also be prepared by means of the reaction of the corresponding magnesium compound with iodine.

The formation of the ketazine is a new and better method of preparing these compounds.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE COLLEGE OF LIBERAL ARTS,
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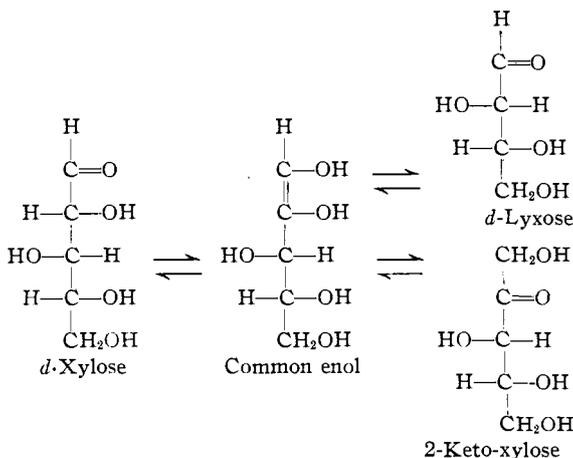
THE REACTIVITY OF THE METHYLATED SUGARS. IV. THE ACTION OF DILUTE ALKALI ON TRIMETHYLXYLOSE¹

BY CHARLES EZRA GROSS WITH W. LEE LEWIS

RECEIVED MAY 18, 1931

PUBLISHED JULY 8, 1931

The theory of intermediate enol formation² which has proved so valuable in elucidating sugar reactions has nevertheless rested more upon plausibility than proof. The methylated sugars lend themselves to testing more directly the mechanism of these reactions by limiting in a predictable manner enol formation.³ This follows from the lesser lability of the methyl group as compared with the replaced hydrogen of the sugar hydroxyl. Thus the theory of selective hydration and dehydration in enol formation



¹ Abstracted from a dissertation submitted to the Graduate School of Northwestern University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

² Lobry de Bruyn and van Ekenstein, *Rec. trav. chim.*, **14**, 156 (1895); Fischer, *Ber.*, **28**, 1149 (1895); Wohl and Neuberg, *ibid.*, **38**, 3099 (1900); Nef, *Ann.*, **357**, 214 (1907); **376**, 1 (1910); **403**, 204 (1914); Evans, *Chem. Reviews*, **6**, 281 (1929); Shaffer and Friedemann, *J. Biol. Chem.*, **86**, 345 (1930); Evans and Conaway, *THIS JOURNAL*, **52**, 3680 (1930).

³ (a) Gustus with Lewis, *ibid.*, **49**, 1512 (1927); (b) Wolfrom with Lewis, *ibid.*, **50**, 837 (1928); (c) Greene with Lewis, *ibid.*, **50**, 2813 (1928).