were obtained at a *p*H of about 1. A note of caution should be added here concerning attempts to couple in solutions of a *p*H between 7 and 10: such solutions have been observed to explode with great violence during the coupling process, even though kept at temperatures below 5°.

In a few cases it was possible to couple 1-N-morpholino-2-nitropropane in basic solution. The other nitroamine was insoluble even in hot sodium hydroxide solution. For coupling in alkaline solution the diazotized solution was neutralized in the cold with an excess of 2 *N* sodium hydroxide, the nitroamine dissolved in dilute, hot sodium hydroxide solution, cooled and coupled in the cold. The product was precipitated by acidification with hydrochloric acid.

The melting points of all the compounds prepared were sharp, decomposition taking place in some cases. The azo-compounds were insoluble in water and in dilute mineral acids, as well as in most organic solvents. They were slightly soluble in dilute bases and quite soluble in hot ethanol. They ranged from bright yellow to deep red in color. A few of them, particularly those derived from *p*-chloroaniline, decomposed on prolonged standing. A list of the physical constants is given in Table I.

Summary

Twelve new azo-compounds were prepared by the coupling, usually in acid solution, of amino-substituted secondary nitroparaffins with aryldiazonium salts or hydroxides, and certain of their physical properties determined.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Quantitative Analysis of Alkyllithium Compounds[1]

BY HENRY GILMAN AND A. H. HAUBEIN

The simple acid titration procedure[2] for the quantitative analysis of organometallic compounds which give bases on decomposition by water yields values that may be high, particularly with RM compounds that cleave ether. For example, the lithium hydroxide formed by hydrolysis of an aliquot of an organolithium compound is derived not only from the RLi compound but from ROLi compound, as well as from lithium hydroxide and lithium oxide due, respectively, to traces of water and oxygen.

Ziegler and co-workers[3] obtained true titration values by a differential based on titration of two aliquots. One titration was for the total lithium hydroxide present. The other titration was for the lithium hydroxide present after destroying the RLi compound, and the difference between the two titrations gave the quantity of RLi compound. Prior to the second titration, the RLi compound was destroyed by adding *n*-butyl bromide and then dibenzylmercury; the benzyllithium, formed by reaction of the RLi compound and dibenzylmercury, was promptly decomposed by the butyl bromide.

We have found that benzyl chloride is a more convenient reagent than the butyl bromide–dibenzylmercury combination for removing the RLi compound. The reaction which occurs appears to be like that observed earlier by Späth[4] and by Fuson[5] with Grignard reagents, three coupling products being formed

$$n\text{-}C_4H_9Li + C_6H_5CH_2Cl \longrightarrow n\text{-}C_8H_{18} + C_6H_5CH_2C_4H_9\text{-}n + C_6H_5CH_2CH_2C_6H_5$$

The above over-all reaction is not a complete picture of the transformations involved. Benzyllithium is an intermediate compound, formed as a consequence of a halogen-metal interconversion[6] reaction

$$C_2H_5Li + C_6H_5CH_2Cl \longrightarrow C_6H_5CH_2Li + C_2H_5Cl$$

The benzyllithium formed in this manner undoubtedly accounts for part of the bibenzyl by a coupling reaction with some of the benzyl chloride. The transitory yellow color observed when benzyl chloride is added to *n*-butyllithium is due to benzyllithium. More particularly, the benzyllithium was captured as phenylacetic acid when a mixture of ethyllithium and benzyl chloride (cooled to −50° to reduce the rate of coupling) was very rapidly carbonated by solid carbon dioxide.

The quantitative analysis procedure is applicable to alkyllithium, but not to aryllithium compounds. It cannot be used with methyllithium and with phenylethynyllithium, very probably because of their lesser reactivity.

Experimental

Analytical Procedure.—The solution of an alkyllithium compound[7] is filtered under nitrogen, preferably through a sintered glass funnel, to remove insoluble material. An

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(1) Paper LVI in the series: "The relative reactivities of organometallic compounds"; the preceding paper with Van Ess and Shirley is in THIS JOURNAL, **66**, 1214 (1944).

(2) Gilman, Wilkinson, Fishel and Meyers, THIS JOURNAL, **45**, 150 (1923).

(3) Ziegler, Crössmann, Kleiner and Schäfer, *Ann.*, **473**, 31 (1929).

(4) Späth, *Monatsh.*, **34**, 1965 (1913).

(5) Fuson, THIS JOURNAL, **48**, 2681 (1926); Ellingboe and Fuson, *ibid.*, **55**, 2960 (1933).

(6) Gilman and Jones, *ibid.*, **63**, 1441 (1941).

(7) Gilman, Langham and Moore, *ibid.*, **62**, 2327 (1940).

aliquot of 5 or 10 cc. is withdrawn, by means of a rubber suction bulb connected to a pipet, and hydrolyzed in 10 cc. of distilled water. Titration with standard acid, using phenolphthalein as an indicator, gives the total alkali. Another 5 or 10 cc. aliquot is added to 10 cc. of dry ether containing 1 cc. of benzyl chloride.[8] As the alkyllithium solution is dropped into the benzyl chloride, as rapidly as it drains from the pipet, a yellow color flashes through the liquid. If the RLi solution is concentrated, a white precipitate of lithium chloride forms with the disappearance of the yellow color. The ether solution may become warm enough to boil, but it is not cooled. The mixture is allowed to stand one minute after the addition, then hydrolyzed, and titrated with standard acid. Care must be taken not to overstep the end-point in this titration since the aqueous layer decolorizes before the ether layer. This may be overcome by vigorous shaking near the end point.

The benzyl chloride must be dissolved in ether because coupling with the RLi compound takes place much less readily in most other solvents. In analyses of RLi compounds prepared in petroleum ether, the benzyl chloride should be dissolved in a relatively large volume of ether.

Lithium *n*-butoxide did not cleave benzyl chloride under the conditions of the analysis. When these two reagents were refluxed for one minute and then hydrolyzed, no chloride ion was found in the aqueous layer.

Reaction of Benzyl Chloride with *n*-Butyllithium.—To a large excess of benzyl chloride (0.6 mole) in ether was added 250 cc. (0.158 mole) of *n*-butyllithium. Vigorous refluxing took place, even with a moderate rate of addition. The products isolated were: a small quantity of *n*-octane, 5 g. (21%) of *n*-amylbenzene, and 8.2 g. (31%) of bibenzyl. The bibenzyl was identified both by a mixed m. p. determination, and by the 1,3,5-trinitrobenzene–bibenzyl complex (m. p. 103–104°).[9] Incidentally, no bibenzyl was isolated from reactions of benzyl chloride with either α-naphthyllithium or *p*-dimethylaminophenyllithium.

Capture of Benzyllithium from Reaction of Benzyl Chloride with Ethyllithium.—Ethyllithium was prepared in a customary manner from 43.2 g. (0.4 mole) of ethyl bromide and 5.6 g. (0.8 g. atom) of lithium in 400 cc. of ether. The solution, free of lithium, was cooled to −50°, and 15 g. of benzyl chloride in 50 cc. of cold ether was added rapidly.[10] The usual characteristic yellow color formed, and the colored solution was carbonated with Dry Ice within one minute after the benzyl chloride was added. Subsequent to hydrolysis and removal of the ether, the solution was extracted with petroleum ether, before and after acidification. The petroleum ether and then the propionic acid were removed leaving a small quantity of oil (20 mg.) having a pronounced odor of phenylacetic acid. The oil solidified after standing a week, and the phenylacetic acid was characterized by the preparation of the *p*-bromophenacyl ester (mixed m. p.).

Summary

It has been shown that benzyl chloride is a convenient reagent for the quantitative estimation of organolithium compounds. In the reaction of benzyl chloride with an alkyllithium compound, three coupling products are formed: R.R, R-benzyl and bibenzyl. Benzyllithium is formed transitorily in this reaction as a consequence of a halogen–metal interconversion reaction: $C_2H_5Li + C_6H_5CH_2Cl \rightarrow C_6H_5CH_2Li + C_2H_5Cl$.

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(8) The benzyl chloride was purified by drying over phosphorus pentoxide and then distilling at reduced pressure.

(9) Sudborough, *J. Chem. Soc.*, **109**, 1339 (1916).

(10) Under ordinary conditions, the alkyllithium compounds couple so rapidly with benzyl chloride that a negative color test [Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925)] is obtained within one-half minute after mixing the two solutions.

AMES, IOWA RECEIVED JUNE 24, 1944

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

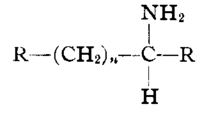
Aminoalkanes as Pressor Substances

BY EWALD ROHRMANN AND H. A. SHONLE

In 1910 Barger and Dale[1] reported a study of the pressor activity of a number of primary aliphatic amines in which the amino group was located on the terminal carbon. They concluded that the pressor activity increases as the length of the carbon chain increases until *n*-hexylamine is reached, this being the most active aliphatic amine which they investigated. *n*-Heptyl and *n*-octylamines were reported to be distinctly less active. They also presented evidence indicating that branching of the carbon chain brought about a decrease in activity.

During the past decade there has been an increased interest shown in some of the secondary aliphatic amines, some of which have been claimed to have high antispasmodic activity. A thorough review of the literature on the pharmacology of the aliphatic amines has been made recently by Dunker and Hartung.[2]

Until the results of the present investigation were known aliphatic amines were considered to be of no practical value as pressor substances. In undertaking this investigation careful consideration was given to the known information concerning the pressor activities of those primary amines containing an aromatic nucleus.[3] In this series of amines, which may be represented as



$$R\text{—}(CH_2)_n\text{—}\overset{\displaystyle NH_2}{\underset{\displaystyle H}{C}}\text{—}R_1$$

(where R = phenyl or substituted phenyl and R_1 = hydrogen or alkyl), the position of the amino group with respect to the aromatic nucleus has a very profound effect on the magnitude of the pressor action. For example, compounds such as β-phenethylamine, 1-phenyl-2-aminopropane, etc., show high pressor action, while compounds such as benzylamine and 1-phenyl-3-

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(1) Barger and Dale, *J. Physiol.*, **41**, 19 (1910).

(2) Dunker and Hartung, *J. Am. Pharm. Assoc.*, **30**, 619 (1941).

(3) Hartung, *Chem. Rev.*, **9**, 389 (1931).