

TABLE I

Cpd.	Formula	Yield, %	M. p., °C. ^a	Analysis, %			
				Calcd.		Found ^b	
			C	H	C	H	
I ^c	C ₁₇ H ₂₄ O ₄	94	145-146	72.85	4.32	72.81	4.58
II ^{d,e}	C ₁₂ H ₁₆ O ₄	94	173-174	66.05	4.62	65.91	4.67
III ^e	C ₁₁ H ₇ O ₂ N	35	224-226	65.67	3.50	65.46	3.47
IV ^f	C ₁₁ H ₁₂ O ₅	62	81-83 ^g	62.90	4.87	63.00	4.78
V ^e	C ₁₁ H ₁₄ O ₄	33	155-156.5	62.06	4.86	62.12	4.83

^a Corrected. ^b Analyses by Miss Sarah H. Miles. ^c Recrystallized from ethyl acetate-petroleum ether. ^d Condensation effected in ethyl acetate. ^e Recrystallized from methyl ethyl ketone. ^f Reported m. p. 96° (Perkin and Robinson, *J. Chem. Soc.*, 105, 2382 (1914)). ^g Obtained by slow crystallization from benzene-petroleum ether; rapid crystallization gave the higher melting modification.

HARRISON LABORATORY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA 4, PENNA. RECEIVED DECEMBER 7, 1947

Relative Stabilities of D-Glucose-Amine Derivatives

BY ALI MOHAMMAD AND HAROLD S. OLCOTT

It has recently been shown that the development of a brown color in dried whole eggs containing more than 2% moisture is due in part to a reaction between the free glucose and the free amino groups of the egg proteins.^{1,2} In attempts to determine the mechanism of this reaction, the behavior of the addition compounds of glucose with aliphatic amines has been studied.

Mitts and Hixon³ prepared a number of such substances. For their preparation of glucosyl-N-butylamine they report C₁₀H₂₃O₆N, although the glucoside formulation requires C₁₀H₂₁O₅N. Since it was of importance to determine whether the instability of this compound¹ could be ascribed to the presence of water of crystallization, the anhydrous product was prepared. It was found to decompose at a readily measurable rate at 56.5° *in vacuo*. In contrast, D-glucosyl-N-ethanolamine appeared to be entirely stable under the same conditions. Glucamines, obtained by hydrogenation either of the glucosylamines or of mixtures of D-glucose with the amines, were found, as expected, to be stable products. D-Glucosyl-N-ethanolamine and the corresponding glucamine have not previously been described.

Cavalieri and Wolfrom⁴ recently have demonstrated by ultraviolet absorption spectra measurements that the brown coloration which develops in aqueous solutions of D-glucosyl-N-butylamine on standing is caused by hydrolysis of the compound, followed by the action of the liberated hydroxyl ion upon the D-glucose. Such a simple explanation does not appear to be applicable to the decomposition of this compound in the pure, dry, and, presumably, neutral state.

(1) H. S. Olcott and H. J. Dutton, *Ind. Eng. Chem.*, **37**, 1119 (1945).

(2) E. C. Bate-Smith and J. R. Hawthorne, *J. Soc. Chem. Ind.*, 297T (1945).

(3) E. Mitts and R. M. Hixon, *THIS JOURNAL*, **66**, 483 (1944).

(4) Cavalieri and Wolfrom, *ibid.*, **68**, 2023 (1946).

Experimental

D-Glucosyl-N-butylamine.—The compound, prepared according to Mitts and Hixon³ from D-glucose and *n*-butylamine, was recrystallized repeatedly from absolute alcohol. The final crystallizate was washed with petroleum ether and dried to constant weight over phosphorus pentoxide at 35° *in vacuo*, m. p., 96-97°.

Anal. Calcd. for C₁₀H₂₁O₅N: C, 51.06; H, 8.93; N, 5.95. Found: C, 51.1; H, 8.93; N, 5.87.

At 56.5° (Abderhalden drying tube heated with boiling acetone vapors) and at approximately 0.3 mm. pressure the compound lost weight, gradually turned brown, and finally (in three days) melted to a deep brown sirup. The loss of weight from a 100-mg. sample was, in one day, approximately 6%, in two days, approximately 12%.

N-Butylglucamine.—The product obtained by reduction with hydrogen and Raney nickel catalyst from D-glucosyl-N-butylamine melted, as reported by Mitts and Hixon,³ at 127-128°.

Anal. Calcd. for C₁₀H₂₃O₂N: N, 5.9. Found: N, 5.9.

The same compound was prepared as follows: A mixture of 5 g. of D-glucose, 4.5 g. of butylamine, 1 ml. of 0.5 *N* hydrochloric acid, 130 mg. of platinum oxide and 50 ml. of absolute alcohol was hydrogenated for thirty hours at 40 lb./sq. in. hydrogen pressure (23°). The solution was filtered, evaporated to dryness at reduced pressure, and taken up in hot methanol, from which the D-glucamine crystallized.

After a second crystallization the dried product melted at 127-128°, yield, 5 g. An approximately 1% solution was at pH 10.2. There was no apparent decomposition in a sample held at 105° for eighteen hours.

D-Glucosyl-N-ethanolamine.—A mixture of 18 g. of D-glucose (0.1 mole), 6.1 g. of ethanolamine (0.1 mole), and 50 ml. of absolute alcohol was heated for one hour on a steam-bath. The brown solution was partially decolorized with carbon. Addition of ether caused an oil to separate. No crystals appeared in three weeks at 0°. The solvent was decanted, and the oil dissolved in absolute ethanol. Crystallization occurred at room temperature. After several crystallizations from methanol, the product contained 6.24% N (calcd., 6.26), m. p., 115-116°. A sample was heated *in vacuo* at 56.5° for forty-eight hours without change in weight or color.

N-Ethanol-D-glucamine.—A mixture of 18 g. of D-glucose, 6.1 g. of ethanolamine, 2 g. (approx.) of Raney nickel, and 50 ml. of absolute ethanol was shaken in a steel bomb for twenty-four hours under 1000 lb./sq. in. hydrogen pressure and at 77°. The contents were filtered and partially concentrated. Crystallization occurred at room temperature. After several recrystallizations from methanol, the compound decomposed at 96-103°.

Anal. Calcd. for C₈H₁₉O₂N: N, 6.22. Found: N, 6.18.

All the compounds described were difficult to obtain in analytically pure form. Whether the numerous crystallizations effected gradual removal of impurities or of water of crystallization is not known.

Elementary analyses were performed by L. M. White.

WESTERN REGIONAL RESEARCH LABORATORY
BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY
AGRICULTURAL RESEARCH ADMINISTRATION
U. S. DEPARTMENT OF AGRICULTURE
ALBANY 6, CALIFORNIA RECEIVED NOVEMBER 26, 1946

Metalation of Compounds That Have Meta-directing Groups and the Electrophilic Character of Organoalkali Metal Reagents

BY AVERY A. MORTON

A recent paper by Roberts and Curtin¹ reports that the metalation of trifluoromethylbenzene by

(1) Roberts and Curtin, *THIS JOURNAL*, **68**, 1658 (1946).

butyllithium results in five parts ortho-metalation to one part meta-substitution, whereas the trifluoromethyl group should be largely meta-directing if the reagent were truly electrophilic.² Moreover, the degree of activation toward metalation of the benzene ring by various substituting groups accords with that predicted if the inductive effect were most important and hence the removal of a proton by a nucleophilic process would be the determining factor. The implication of this work is that the position taken by the entering metal and the rate of substitution offer critical tests of whether organoalkali metal reagents should be classed as electrophilic or nucleophilic. In order to avoid future misunderstanding, a statement of the real basis for the electrophilic interpretation of these reactions is appropriate.

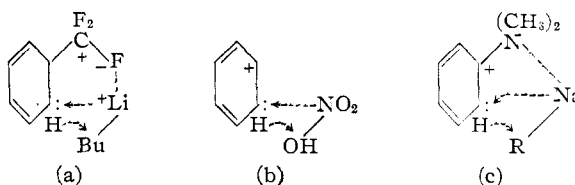
The primary reason for the electrophilic concept rests in a comparison of the organoalkali metal salts with inorganic salts. The relation and the deduction therefrom can be summarized under three points. In the first place the organoalkali metal compounds are regarded as salts, certainly no unusual viewpoint. Conant and Wheland³ and McEwen,⁴ for example, have so referred to methylsodium and have estimated the acidity of methane as 10^{-40} . Factors that affect the acidity of strong acids similarly affect the acidity of weak acids.^{2b}

In the second place, the cation is regarded as exerting an influence on the anion. This view also is common. Fajans⁵ used it to explain the color of mercuric iodide and other phenomena; Sidgwick⁶ discussed the distortion of the anion by attractive force of the cation; and Palmer⁷ referred to the effect of cations on their anionic neighbors and exemplified the effect by reference to the thermal stability of the sodium and other alkali metal carbonates as contrasted with the instability of the alkali earth carbonates. Palmer referred also to the cation as anchoring the electrons in the oxygen of superoxides. Now if the cation can influence the electrons in anionic neighbors derived from comparatively strong acids, how much more will it exert an influence on the electrons of a carbanion, particularly since carbon has very little affinity of its own for electrons and acquires a complete octet only on a basis of sharing them with other atoms.

In the third place, a logical deduction can be made as to the manner such a salt, dissolved or suspended in a medium that permits no dissociation of the ions, can react. According to the nucleophilic view, the carbon component,

which has little attraction for its electrons, can, nevertheless, tear itself loose as an anion from the field of cation influence and react independently. That suggestion is unreasonable. According to the electrophilic view, other compounds with electrons must be brought to the vicinity of the cation which will permit transformations leading to the formation of more stable salts. The anion participates in and aids the reaction materially but only after, or as, the attractive influence of the positive pole, that is the cation, is given another outlet. This view is reasonable. The application to the reactions of organoalkali metal compounds leads to the conclusion that disproportionation^{2a} in the Wurtz reaction begins with the action of the metal ion on the halogen of the alkyl halide rather than with the action of the anion, as a hydrocarbon base, on a proton; that the process of metalation of an aromatic ring is initiated by the seeking out by the cation of the position of maximum electron availability rather than by removal of a proton; and that acid-salt interchange is markedly influenced by the nature of the cation. The reactions as a whole, of course, are the work of the ion pair.² Both components are obviously important, and the classification of the reagent as electrophilic is not intended to convey that the cation is responsible for all of the work done.

A picture can be drawn that illustrates how the cooperative effect of the two ions, spearheaded by the influence of the cation, might take place in the process of metalation. In the sketch (a) below the intermediate complex, initially formed by attraction of the metal for the electrons about the fluorine atom, contains an ionized fluorine atom, an adjacent carbonium ion and a negatively charged carbon atom, each more or less in an incipient state. Within this complex the metal can enter the ring and a proton leave (see dotted arrows) by a push-pull type of reaction. Such an intermediate explains all the known facts in the present instance and has the added advantage of a low energy requirement. This idea of an active complex is not unlike some that have been postulated⁸ for other aromatic substitutions, one form of which in nitrations might be pictured as in (b). A similar formula can be used to picture a reactive intermediate (c) in the metalation of dimethylaniline, regarded as typical of systems in which a pseudo five-membered ring is present in the metalation process.



(2) (a) Morton, Little and Strong, *THIS JOURNAL*, **65**, 1339 (1943); (b) Morton, *Chem. Rev.*, **35**, 1 (1944).

(3) Conant and Wheland, *THIS JOURNAL*, **54**, 1212 (1932).

(4) McEwen, *ibid.*, **58**, 1124 (1936).

(5) Fajans, "Chemical Forces," McGraw-Hill Book Company, New York, N. Y., 1931; "Chemistry at the Centenary (1931)," British Association Advancement of Science, 1932, p. 49.

(6) Sidgwick, "The Covalent Link in Chemistry," Cornell University Press, Ithaca, N. Y., 1933.

(7) Palmer, "Valency," The University Press, Cambridge, 1945.

(8) Ingold, *Ann. Repts.*, **23**, 134 (1927); Wheland, "The Theory of Resonance," J. Wiley and Sons, Inc., New York, N. Y., 1944, p. 259.

With respect to the metalation of benzotrifluoride,¹ the electrophilic interpretation would be that the start of the process is the attraction of the metal component for electrons. If these electrons are found on one of the three fluorine atoms, coordination occurs and the succeeding migrations of proton and metal lead to ortho substitution; if the electrons are found on the aromatic nucleus, direct substitution occurs at the meta position because of the influence of the trifluoromethyl group. These places of high electron density are attacked in the ratio of about five to one. The initial force that operates is the same for either position. The subsequent steps are conditioned to the spatial and other influences present.

With respect to the velocity of the substitution a complete statement is possible only after each reaction has been given much more study than has so far been made. The electrophilic viewpoint would cause the prediction, however, that the position of any phenoxide ion would not be the same when substitution is carried out in aqueous solution as it would be in a non-dissociating solvent because in the former medium, the phenoxide ion would act independently while in the latter it would be under the influence of the strong electron-attracting influence of the adjacent cation and the system would act as an ion-pair. Metalation should be and is retarded. This problem has already been considered in a previous publication⁹ from this laboratory. Many of the other systems are also liable to have unusual rates because of coordination which may influence the reaction intermolecularly as well as by the intramolecular process pictured above. Considerable work on the influence of coordination has already been carried out in this Laboratory and will be published in the future. In general, however, the order of reactivity of groups, as far as substitution in the ortho position is concerned, has long been known to be subject to special influences, such as steric effects and the many variations of chelation, under which might be included the pseudo ring systems under discussion.

Finally, attention is called to the fact that the electrophilic viewpoint explains correctly the metalation in the para position of cumene and biphenyl, where coordination has no influence, and the reaction with cumene is admitted by Roberts and Curtin¹ to be incapable of explanation by the nucleophilic viewpoint. In general, the electrophilic interpretation can be readily used to explain the phenomena so far known without contradicting the nucleophilic viewpoint for reactions of alkali metal salts in aqueous media where the cation influence is removed by solvation.

CHEMICAL LABORATORY,
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASS. RECEIVED AUGUST 27, 1946

(9) Morton and Letsinger, *THIS JOURNAL*, **67**, 1537 (1945).

Preparation of Ethyl β -Benzylaminopropionate and Benzyl-di-(β -carbethoxyethyl)-amine

BY GILBERT STORK AND S. M. McELVAIN

In a recent note describing the hydrogenolysis of ethyl β -benzylaminopropionate (I), Mattocks and Hartung¹ used the reaction of benzylamine with ethyl β -bromopropionate to prepare this secondary aminoester; the same reactants had been used earlier in this Laboratory for the preparation of I, which had served as an intermediate in the preparation of benzyl-di-(β -carbethoxyethyl)-amine² (II). We now are able to report much simpler methods of preparation of I and II. In connection with a study of certain 4-piperidones,³ we investigated the preparation of II, the precursor of 1-benzyl-4-piperidone, by the addition of benzylamine to ethyl acrylate and found that this addition could readily be controlled to produce either the secondary aminoester (I), or the tertiary aminoester (II). The former was obtained in 87% yield by the interaction of benzylamine and one equivalent of ethyl acrylate in alcohol solution for twenty-four hours at room temperature. The aminoester II was obtained in 84% yield by allowing benzylamine to react with a 20% excess of two equivalents of ethyl acrylate for four to five days at room temperature. The practically exclusive formation of I from these reactants is in decided contrast to the addition of ammonia^{3a} and methylamine to acrylic esters; the latter amine, for example, with an equivalent of methyl acrylate gives a 31% yield of the secondary amine together with a 37% yield of tertiary amine.⁴ This peculiar property of benzylamine to give more of the product that results from the reaction of only one of its amino hydrogens also has been used to advantage in the Mannich reaction.⁵

Experimental

Ethyl β -Benzylaminopropionate (I).—Benzylamine was prepared by the method of Winans⁶: the catalytic reduction of benzaldehyde in the presence of alcoholic ammonia with Raney nickel as a catalyst. In the handling of benzylamine it is essential to exclude carbon dioxide as it rapidly forms an addition compound with benzylamine.

To a solution of 58 g. of benzylamine in 400 ml. of absolute alcohol was added 50 g. of commercial ethyl acrylate. There was very little evolution of heat. The resulting alcoholic solution showed a slight pink coloration at first, but after standing for twenty-four hours at room temperature it became orange-red. After this time, the alcohol was removed under reduced pressure and the residue distilled; 90 g. (87%) of ethyl β -benzylaminopropionate² (I) was collected as a colorless liquid, b. p. 133–135° (2 mm.); n_D^{20} 1.5060. This ester turns brown on long standing.

Benzyl-di-(β -carbethoxyethyl)-amine (II).—In the preparation of this compound, it is necessary to use at least 20% excess of two equivalents of ethyl acrylate

- (1) Mattocks and Hartung, *THIS JOURNAL*, **68**, 2108 (1946).
- (2) Thayer and McElvain, *ibid.*, **49**, 2862 (1927).
- (3) (a) McElvain and Stork, *ibid.*, **68**, 1049 (1946); (b) *ibid.*, **68**, 1053 (1946).
- (4) Morsch, *Monatsh.*, **63**, 220 (1933).
- (5) Mannich and Hieronimus, *Ber.*, **75**, 49 (1942).
- (6) Winans, *THIS JOURNAL*, **61**, 3506 (1939).