of Mosher and Cox[17] using concentrated chromic acid gave a 48% yield of product, b.p. 123.5–127°, freezing point −64°, n^{20}_D 1.4060, d^{20}_4 0.8165 (reported[18] b.p. 122–124°, n^{20}_D 1.4040), MR_D 34.35 (calcd. 34.54).

The 2,4-dinitrophenylhydrazone of VI had m.p. 97.1–98.2° (reported[19] m.p. 100°).

The semicarbazone of VI had m.p. 173–174° (reported m.p. 173.5–175.5°[20] and 176°[21]).

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The Direct Preparation of Benzyllithium

BY HENRY GILMAN AND RICHARD D. GORSICH

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No direct synthesis of benzyllithium has been reported but a number of indirect methods[1-4] which in every case require several intermediate steps, has been described. Consequently, it was desirable to find a method by which benzyllithium might be made directly from a benzyl halide and lithium. Also, because of its high order of reactivity as compared to the corresponding Grignard reagent and because of its value as a synthetic intermediate, benzyllithium could prove to be an extremely useful synthetic tool if it were possible to prepare by a simple, direct method.

Benzyllithium has been obtained in trace amounts in a metalation reaction and in a halogen–metal interconversion reaction. In the former case toluene was metalated laterally to give a very small yield of benzyllithium.[5] In the latter case benzyl chloride reacted with ethyllithium at −50° to give a trace amount of phenylacetic acid upon carbonating the reaction mixture.[6] In another similar reaction it was found that benzyl bromide and phenyllithium reacted to form an almost quantitative yield of bibenzyl.[7]

In this Laboratory we have been able to synthesize benzyllithium directly though in small yields by the reaction of benzyl chloride with lithium ribbon in purified dioxane. As in previous work, the

$$C_6H_5CH_2Cl + 2Li \longrightarrow C_6H_5CH_2Li + LiCl$$

main difficulty encountered in this investigation was that the benzyllithium reacted rapidly with excess benzyl chloride to yield bibenzyl. To minimize this side-reaction, conditions were varied and different

$$C_6H_5CH_2Li + C_6H_5CH_2Cl \longrightarrow C_6H_5CH_2CH_2C_6H_5 + LiCl$$

solvents were tried. Of the various solvents used, benzyllithium could be prepared only in purified dioxane. Also, of the two types of lithium tried, namely ribbon and wire, benzyllithium was formed only when the ribbon was employed. This may have been due to the fact that the cuttings of the lithium ribbon afforded a greater surface area than the cuttings of lithium wire.

Despite the high dilution, the large excess of lithium ribbon and a relatively low temperature, the coupling reaction could not be diminished to any great extent.

The low yield of benzyllithium, as determined by carbonation, may have been partly due to the ineffectiveness of the carbonation. This difficulty arises because of the high freezing point of dioxane. In most cases the reaction mixture solidified in contact with the Dry Ice–ether slurry. In an attempt to alleviate this difficulty, the reaction mixture was diluted with ether prior to carbonation. This modification appeared to improve the facility of the carbonation but not enough to increase the yield appreciably.

A greater lithium surface should increase the yield of benzyllithium and decrease the yield of coupling products. This finds experimental support in the improved yields of some other RLi compounds when lithium dispersion is used.[8] The excess of lithium ribbon that can be used is limited, since beyond a certain quantity the lithium ribbon interferes with the stirring efficiency which is also very important.

Experimental[9]

Reaction of Benzyl Chloride with Lithium Ribbon.—To a 500-ml., three-necked flask fitted with a thermometer, nitrogen inlet, mechanical stirrer and addition funnel were added 7.25 g. (1.04 gram atoms) of lithium ribbon ($^1/_4'' \times {}^1/_{32}''$), cut into approximately $^1/_4''$ squares and 40 ml. of anhydrous ether. After washing the lithium ribbon with two additional such portions of ether, the ether was replaced with 100 ml. of purified dioxane.[10] To the rapidly stirred lithium ribbon suspension was added dropwise 6.0 g. (0.047 mole) of benzyl chloride dissolved in 50 ml. of dioxane over a period of 1.5 hours. The addition was continued at room temperature until a lemon-yellow color was evident at which time the reaction mixture was cooled to 10° by means of an ice-bath and the remaining benzyl chloride was added at this temperature. After about 10 ml. of the benzyl chloride solution had been added, the reaction mixture turned brown. The reaction mixture was stirred at 10° for 15 minutes upon completing the addition of the benzyl chloride and then it was carbonated by pouring the mixture jetwise through a glass wool plug alternately in two 1000-ml. beakers containing Dry Ice–ether slurries which were constantly being stirred. Prior to the carbonation Color Test I[11] was strongly positive. During the carbonation it was necessary to add anhydrous ether intermittently in order to prevent freezing of the carbonated mixture. After the carbonated mixtures were allowed to warm to room temperature, they were hydrolyzed with water. Subsequently, the solutions were combined and to the resulting solution was added about 10 ml. of 5% sodium hydroxide. The aqueous layer was separated and subsequently extracted with ether for 20 hours in a 1-liter, liquid–liquid extractor. The aque-

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[9] All melting points reported herein are uncorrected and all reactions were carried out under an atmosphere of dry, oxygen-free nitrogen.

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TABLE I

STUDIES CONCERNED WITH THE DIRECT PREPARATION OF BENZYLLITHIUM

	Lithium, type	Lithium, g. atom	Benzyl chloride, mole	Solvent	Temp., °C.[a] during addition	Addition[b] time, hr.	Products[c]
1	Ribbon	1.18	0.0952	Dioxane	20	0.25[d]	Bibenzyl (57.2%) Phenylacetic acid, 0.048 g.
2	Ribbon	0.783	.047	Dioxane	10[e]	1[f]	Bibenzyl (69%) Phenylacetic acid, 0.089 g.
3	Ribbon	1.04	.047	Dioxane	10	1.5[g]	Bibenzyl (67.5%) Phenylacetic acid, 0.068 g.
4	Ribbon	0.663	.047	Dioxane	8	1[h]	Bibenzyl not isolated Phenylacetic acid, trace
5	Wire	.310	.063	Tetrahydrofuran	−25	0.75[i]	Bibenzyl (72.8%) No acidic material[j]
6	Ribbon	.797	.047	Tetrahydrofuran	− 5	1[k]	Bibenzyl (75.5%) No acidic material[j]
7	Wire	.563	.047	Ethylene glycol dimethyl ether	−25	1[m]	Bibenzyl (85%) No acidic material[j]

[a] Initially the reaction was started at room temperature and the remaining benzyl chloride solution was added at the temperature listed. [b] The time required to add the benzyl chloride. [c] No attempt was made to recover any unreacted benzyl chloride in any run. [d] Aliquots were carbonated every 15 minutes during the addition. [e] The first one-half of the benzyl chloride solution was added between 20 and 25° while the remaining one-half was added at 10°. [f] The reaction mixture was carbonated immediately when the addition of benzyl chloride was completed. [g] The reaction mixture was stirred for 15 minutes after completing the addition of benzyl chloride. [h] The mixture was stirred at 0° for 1.5 hours prior to carbonation. [i] The reaction mixture was stirred at −50° for 2 hours prior to carbonation. [j] Color Test I was negative throughout the course of the reaction. [k] The mixture was stirred at room temperature for 48 hours after adding the benzyl chloride solution. [m] The mixture was stirred at −50° for one hour prior to carbonation.

ous layer was made acidic with hydrochloric acid and then extracted again with ether for 16 hours. After drying the ethereal solution over anhydrous sodium sulfate and then filtering off the sodium sulfate, the ether was distilled under reduced pressure; the resulting residue was an oil which possessed the odor of phenylacetic acid. The oil was dissolved in a minimum amount of water and filtered while hot. Upon cooling to 5° colorless plates crystallized out. Further concentration of the mother liquor yielded more of the same type of crystals. The total yield of product was 0.068 g., m.p. 76.5–78°. A mixed melting point with an authentic sample of phenylacetic acid (m.p. 77–78°) showed no depression.

The organic layer obtained after carbonation was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the ether. Further distillation of the residue under reduced pressure yielded 2.9 g. (67.5%) of material melting at 51.5–53°. A mixed melting point of this material with an authentic sample of bibenzyl (m.p. 53°) showed no depression.

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The Effect of Borate and Sulfate Ions upon the Electrophoretic Mobility of Mucoproteins[1]

BY E. GOLDWASSER AND M. B. MATHEWS[2]

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During a study of the physical properties of the carbohydrate-containing protein from human plasma that is an inhibitor of hyaluronidase,[3] we noted an appreciable increase in electrophoretic mobility when the buffer contained borate or sulfate ions. It seemed plausible to assume that the mobility increase was due to a similar complex with the carbohydrate moiety of the mucoprotein because of the well known ability of borate to form charged complexes with a variety of carbohydrates. The action of sulfate remained unexplained. These studies were thus extended to include bovine serum albumin as well as another serum mucoprotein.[4]

Experimental.—Crystalline bovine serum albumin was obtained from Armour and Co. Dr. R. J. Winzler of the University of Illinois, generously supplied a sample of the purified serum mucoprotein, orosomucoid, while the serum inhibitor of hyaluronidase was isolated from human serum in earlier experiments.[3] Electrophoresis was carried out in buffers of ionic strength 0.1 and pH 8.6, with only the composition altered (Table I), in a Spinco model H electrophoresis apparatus, with standard 11-ml. cells at 1° and at field strengths of 4.5 to 5.2 volts/cm. for serum albumin and orosomucoid. The hyaluronidase inhibitor was run in a semi-micro cell (2 ml.) at a field strength of 0.75 volt/cm. The results are summarized in Table II.

TABLE I

COMPOSITION OF BUFFERS, 0.1 μ AND pH 8.6

Component	Veronal–borate, M	Veronal–sulfate, M	Borate–sulfate, M
Veronal	0.011	0.0037	...
Sod. veronal	.075	.025	...
Boric acid	.086	....	0.086
Sod. borate	.025	....	.025
Sod. sulfate	...	.025	.025

TABLE II

DESCENDING MOBILITIES ($\times 10^5$ CM.^{2} VOLT^{-1} SEC.$^{-1}$) IN VARIOUS BUFFERS AND RATIO TO MOBILITY IN VERONAL BUFFER

Buffer	Albumin[a] Mobility	Albumin[a] Ratio	Orosomucoid[a] Mobility	Orosomucoid[a] Ratio	Serum inhibitor[b] Mobility	Serum inhibitor[b] Ratio
Veronal	−6.7	1.0	−5.2	1.0	− 5.4	1.0
Borate–sulfate	−8.1	1.2	−7.1	1.4	−10.2	1.9
Veronal–borate	−6.6	1.0	−6.2	1.2	− 7.5	1.4
Veronal–sulfate	−8.0	1.2	−6.8	1.3	....	..

[a] Concentration was 5 mg./ml. [b] Concentration was 3 mg./ml.

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[1] This research was supported in part by a grant from the Chicago Heart Association.

[2] Work done during tenure of an established investigatorship of the American Heart Association.

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