No trace was found of a pure compound having melting point 132° as reported by Martin, although one of the preceding mixtures obtained from acetone–ether solution melted in this vicinity.

Fraction 3 (8.7 g.) was a mixture very similar to fraction 2, but containing a larger proportion of trimethylolphenol.

Fraction 4 (2.7 g.) (complete evaporation of solvent) formed a clear resin on standing and was not studied further.

It should perhaps also be pointed out that one compound cited by Martin as a derivative of trimethylolphenol obtained by reaction with *p*-chlorophenol and concd. hydrochloric acid at 80° is more probably the hexanuclear product of reaction of the tetramethyloldihydroxydiphenylmethane XI with *p*-chlorophenol. The calculated chlorine content for the trimethylolphenol derivative, $C_{27}H_{18}O_4Cl_3$ is 20.63% Cl. The calculated value for the hexanuclear product $C_{41}H_{32}O_6Cl_4$ is 18.62% Cl. The experimentally determined value given by Martin[8] is 18.76% Cl.

NOTE ADDED IN PROOF.—Two additional articles on the subject of this paper have appeared recently: R. W. Martin, THIS JOURNAL, **74**, 3024 (1952); J. Reese, *Angew. Chem.*, **64**, 399 (1952).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF FORDHAM UNIVERSITY]

The Preparation of Thiazole Grignard Reagents and Thiazolyllithium Compounds[1,2]

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By application of the entrainment method Grignard reagents have been prepared from some 2-, 4- and 5-halothiazoles. These Grignard reagents have been reacted with aldehydes and ketones to give the corresponding carbinols. In addition the halogen–metal interconversion reaction with *n*-butyllithium has been successfully applied to 2-bromothiazole, 2,4-dimethyl-5-bromothiazole and 2-methyl-4-bromo-5-ethoxythiazole to prepare the corresponding thiazolyllithium compounds. The phenylcarbinols obtained, when the Grignard reagents or thiazolyllithium compounds were treated with benzaldehyde, were oxidized to the corresponding **ketone** derivatives with sodium dichromate and acetic acid.

Various attempts to prepare Grignard reagents from halothiazoles have met with failure. Ganapathi and Venkataraman[3] reported that they were unable to prepare a Grignard reagent from 2,4-dimethyl-5-bromothiazole by the standard method. Travagli[4] reported several unsuccessful attempts to prepare Grignard reagents from several 2-iodo- and 5-iodothiazoles. In view of these reported failures to prepare Grignard reagents from 2- and 5-halothiazoles attempts were made in this Laboratory to prepare the organomagnesium compounds of 2,4-dimethyl-5-bromothiazole, 2,4-dimethyl-5-iodothiazole and 2-bromothiazole by the classical method. Since these attempts were unsuccessful, an investigation of the entrainment method[5] with 2-, 4- and 5-halothiazoles was undertaken. By this method 2-bromothiazole, 2-bromo-5-methylthiazole, 2-bromo-4,5-dimethylthiazole, 2-methyl-4-bromo-5-ethoxythiazole, 4-methyl-5-bromothiazole, 2,4-dimethyl-5-bromothiazole, 2,4-dimethyl-5-iodothiazole and 2-chloro-4-methylthiazole have reacted successfully to give Grignard reagents. These Grignard reagents have been treated with one or more of the following compounds to give the corresponding carbinols: formaldehyde, benzaldehyde, acetophenone and benzophenone (Table I).

In his original work with the entrainment method, Grignard[5] used equimolar amounts of ethyl bromide and his bromo compound with an excess of magnesium. Overhoff and Proost[6] found that 0.04 mole of ethyl bromide was sufficient for the preparation of 2-pyridylmagnesium bromide from 0.1 mole of 2-bromopyridine. Wibaut, Van der Voort and Markus[7] used equimolar amounts of ethyl bromide and 3-bromopyridine and later used 0.3 mole of ethyl bromide to 0.1 mole of 3-bromopyridine. They found that the yield of 3-pyridylcarbinols increased with increasing ratio of ethyl bromide to 3-bromopyridine.

At the start of this investigation of the entrainment method in the thiazole series, 0.3 mole of ethyl bromide and 0.1 mole of halothiazole were used. An investigation of 2-bromothiazole and 2,4-dimethyl-5-bromothiazole using a ratio of 2 to 1 and 1 to 1 of ethyl bromide to halothiazole indicated that the yield of phenylcarbinol (obtained by reaction of the Grignard reagent formed with benzaldehyde) was the same or better when the lowest ratio of reactants, *i.e.*, 1 to 1, was used.

Some of the phenylcarbinols obtained by reaction of the Grignard reagents with benzaldehyde were oxidized to the corresponding ketone derivatives (Table II) by reaction with sodium dichromate in acetic acid according to the method of Erne and Erlenmeyer.[8]

The only reported organolithium compound in the thiazole series is 4,5-dimethyl-2-thiazolyllithium prepared by the hydrogen–metal interconversion reaction between phenyllithium and 4,5-dimethylthiazole.[8] This has been treated with gaseous formaldehyde and benzaldehyde to give the 2-hydroxymethyl-4,5-dimethylthiazole and 4,5-dimethyl-2-thiazolylphenylcarbinol, respectively. Many organic halides do not react satisfactorily with metallic lithium to form RLi compounds or with metallic magnesium to form Grignard reagents. However, the desired organolithium compound often can be obtained by a halogen–metal interconversion reaction.

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(1) Portions of this paper were presented before the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., September 10–13, 1951.

(2) Taken from a dissertation submitted by Raymond P. Kurkjy to Fordham University in partial fulfillment of the requirements for the Ph.D. degree, May, 1952.

(3) K. Ganapathi and A. Venkataraman, *Proc. Ind. Acad. Sci.*, **22A**, 343, 362 (1945).

(4) G. Travagli, *Gazz. chim. ital.*, **78**, 592 (1948).

(5) V. Grignard, *Compt. rend.*, **198**, 625 (1934); V. Grignard, *ibid.*, **198**, 2217 (1934).

(6) J. Overhoff and W. Proost, *Rec. trav. chim.*, **57**, 179 (1938).

(7) J. P. Wibaut, H. Van der Voort and R. Markus, *ibid.*, **69**, 1048 (1950).

(8) M. Erne and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 652 (1948).

TABLE I

CARBINOLS FROM THIAZOLE GRIGNARD REAGENTS

Compounds 1, 8, 11, 12 and 13 were recrystallized from petroleum ether (90–100°); 2 from benzene–ligroin (1:10); 3, 7, 9, 10 and 14 from petroleum ether (60–75°); 4 from ethanol; 5, 6 and 15 from benzene; 16 from ether–petroleum ether

	Substance, carbinol	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	2-Thiazolylphenyl-	108.5–109	50	$C_{10}H_9NOS$	62.80	63.50	4.74	4.62
2	4-Methyl-2-thiazolylphenyl-	96[a]	20	....	...	...	..	..
3	5-Methyl-2-thiazolylphenyl-	89[b]	90	....	...	...	..	..
4	4,5-Dimethyl-2-thiazolylphenyl-	124–125[c]	85	....	...	...	..	..
5	4-Methyl-5-thiazolylphenyl-	108.5	65	$C_{11}H_{11}NOS$	64.45	64.60	5.41	5.31
6	2,4-Dimethyl-5-thiazolylphenyl-	125–125.5	73	$C_{12}H_{13}NOS$	65.85	65.57	5.98	5.68
7	2-Methyl-5-ethoxy-4-thiazolylphenyl-	67	31	$C_{13}H_{15}NO_2S$	60.25	60.33	5.83	5.56
8	2-Thiazolyl-phenylmethyl-	108–108.5	42	$C_{11}H_{11}NOS$	64.50	64.72	5.41	5.31
9	5-Methyl-2-thiazolylphenylmethyl-	89–89.5	48	$C_{12}H_{13}NOS$	65.85	66.33	5.98	5.66
10	4,5-Dimethyl-2-thiazolylphenylmethyl-	93.5–94	70	$C_{13}H_{15}NOS$	66.90	67.48	6.48	6.36
11	2,4-Dimethyl-5-thiazolylphenylmethyl-	134–134.5	39	$C_{13}H_{15}NOS$	66.90	67.48	6.48	6.37
12	2-Thiazolyldiphenyl-	116–117	93	$C_{16}H_{13}NOS$	71.90	71.76	4.90	4.67
13	5-Methyl-2-thiazolyldiphenyl-	128.5	10	$C_{17}H_{15}NOS$	72.60	72.92	5.38	4.85
14	4,5-Dimethyl-2-thiazolyldiphenyl-	105–105.5	32	$C_{18}H_{17}NOS$	73.25	72.78	5.82	5.42
15	2-Hydroxymethylthiazole	66	35	C_4H_5NOS	41.70	42.13	4.38	4.08
16	4,5-Dimethyl-2-hydroxymethylthiazole	44–45[c]	35	....	...	...	..	..

[a] H. Erlenmeyer, H. Baumann and E. Sorkin, *Helv. Chim. Acta*, **31**, 1978 (1948). [b] M. Erne, *ibid.*, **32**, 2205 (1949). [c] Reference 8.

TABLE II

OXIDATION PRODUCTS FROM SOME OF THE PHENYLCARBINOLS IN TABLE I

Compound 1 was recrystallized from petroleum ether (90–100°), 2 from petroleum ether (30–60°).

	Substance	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	2-Benzoylthiazole	44–44.5	95	$C_{10}H_7NOS$	63.49	63.27	3.73	3.52
2	5-Methyl-2-benzoylthiazole	43–43.5	95	$C_{11}H_9NOS$	65.10	65.49	4.47	4.09
3	2,4-Dimethyl-5-benzoylthiazole[a]		95	....	...	...	..	..

[a] B.p. 137° (0.6 mm.), m.p. of 2,4-dinitrophenylhydrazone, 187–188°. *Anal.* Calcd. for $C_{18}H_{15}N_5O_4S$: C, 54.40; H, 3.81. Found: C, 54.52; H, 3.47.

The halogen–metal interconversion has been investigated in this Laboratory with 2-bromothiazole, 2,4-dimethyl-5-bromothiazole and 2-methyl-4-bromo-5-ethoxythiazole by treating these compounds with *n*-butyllithium. The corresponding thiazolyllithium derivatives have reacted in turn with benzaldehyde (Table III) to give the corresponding phenylcarbinols. 2-Bromothiazole and 2,4-dimethyl-5-bromothiazole gave better yields of the respective phenylcarbinols than those obtained by the Grignard reaction using the entrainment method. The 2-methyl-4-bromo-5-ethoxythiazole gave about the same yield of the corresponding carbinol as that obtained by the Grignard reaction.

TABLE III

COMPARISON OF THE YIELDS OF THIAZOLYLPHENYLCARBINOLS OBTAINED FROM THE GRIGNARD REAGENTS AND FROM THE LITHIUM COMPOUNDS

Substance, carbinol	Starting compound, mole	Grignard reaction Ethyl bromide, mole	Grignard reaction Gram-atoms, mg.	Yield, %	Halogen–lithium interconversion yield, %
2-Thiazolylphenyl-	0.1	0.1	0.2	71	91
	.1	.2	0.3	68	
	.1	.3	.4	50	
2,4-Dimethyl-5-thiazolylphenyl-	.1	.1	.2	65	95
	.1	.3	.4	73	
2-Methyl-5-ethoxy-4-thiazolyphenyl-	.05	.15	.20	31	30

The reactions of these halothiazoles with magnesium and butyllithium indicate that the Grignard reaction and the halogen–methyl interconversion reaction can be accomplished regardless of the position of the halogen on the thiazole ring.

Experimental[9,10]

The preparations of 2,4-dimethyl-5-bromothiazole, 2,4-dimethyl-5-iodothiazole and 4-methyl-5-bromothiazole have been described previously.[11]

2-Bromothiazole.—This substance was prepared from commercially available 2-aminothiazole according to the procedure of Ganapathi and Venkataraman.[3] 2-Bromothiazole was obtained in 51% yield, b.p. 69° (15 mm.), lit. b.p. 171–174°. Attempts to distil this substance at atmospheric pressure resulted in much decomposition.

2-Bromo-5-methylthiazole.—This substance was prepared from 2-amino-5-methylthiazole according to the procedure of Ganapathi and Venkataraman.[3] 2-Bromo-5-methylthiazole was obtained in 55% yield, b.p. 82–84° (12 mm.), lit. b.p. 192–200°. The 2-amino-5-methylthiazole utilized was prepared by condensation of thiourea with α-bromopropionaldehyde.[12]

2-Bromo-4,5-dimethylthiazole.—The preparation of 2-amino-4,5-dimethylthiazole has been reported[13] but, since the experimental details were unavailable, they are reported here. Thiourea (76 g., 1.0 mole) was suspended in 200 ml. of 95% ethanol and 151 g. (1.0 mole) of methyl α-bromo-

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[9] All melting points are uncorrected and were taken by use of the Fisher–Johns melting point block.

[10] All analyses are by A. A. Sirotenko of this Laboratory.

[11] R. P. Kurkjy and E. V. Brown, THIS JOURNAL, **74**, 5778 (1952).

[12] B. Prijs, J. Ostertag and H. Erlenmeyer, *Helv. Chim. Acta*, **30**, 1200 (1947).

[13] K. A. Jensen and Th. Thorsteinsson, *Dansk. tids. farm.*, **15**, 41 (1941); *C. A.*, **35**, 5109 (1941).

ethyl ketone[14] was added during 30 minutes. As the reaction proceeded, the thiourea dissolved and the temperature rose. The 2-amino-4,5-dimethylthiazole hydrobromide precipitated as a white crystalline material as the reaction continued. After completion of the addition, the mixture was heated on the water-bath for one hour more, cooled and filtered. The hydrobromide was dissolved in water and the solution was neutralized with sodium hydroxide solution. 2-Amino-4,5-dimethylthiazole separated as an oil. The mixture was extracted with ether, the ether extract dried over sodium sulfate and the ether removed by distillation at reduced pressure. The crystalline residue of 2-amino-4,5-dimethylthiazole, m.p. 82-83°, weighed 108 g. (85% yield).

2-Amino-4,5-dimethylthiazole (38.4 g., 0.3 mole) was dissolved in dilute sulfuric acid (75 ml. of concd. acid in 200 ml. of water), and treated as above. The yield of 2-bromo-4,5-dimethylthiazole was 35 g. (60%), b.p. 95-96° (12 mm.), m.p. 31.5-32°.

Anal. Calcd. for C_5H_6BrNS: C, 31.25; H, 3.15. Found: C, 30.95; H, 2.90.

2-Methyl-4-bromo-5-ethoxythiazole.—This compound was prepared by the reaction of 2-methyl-5-ethoxythiazole with N-bromosuccinimide.[15]

The 2-methyl-5-ethoxythiazole used in this investigation was prepared by a procedure which proved to be much simpler than that reported in the literature.[15] N-Acetylglycine ethyl ester (100 g., 0.69 mole)[16] and 100 ml. of toluene (dried over sodium wire) were heated to the reflux temperature. To the mixture 200 g. of phosphorus pentasulfide was added in small portions. As the reaction proceeded and evolution of hydrogen sulfide commenced, the size of the portions added was increased until the addition was completed. Heating was continued for several hours afte all the phosphorus pentasulfide had been added. The mixture was then treated with 20% potassium hydroxide solution while being cooled in an ice-water-bath and when basic the mixture was separated. The aqueous layer was extracted several times with toluene and the combined toluene extracts were dried over sodium sulfate. After removal of the toluene by distillation at reduced pressure, the residue was fractionated to yield 55 g. (65%) of 2-methyl-5-ethoxythiazole, b.p. 85-87° (15 mm.), lit. b.p. 102-103° (38 mm.).[15]

Preparation of the Grignard Reagent.—A mixture of 33 g. (0.3 mole) of ethyl bromide and 0.1 mole of halothiazole was added dropwise to 10 g. (0.4 g.-atoms) of magnesium turnings in 50 ml. of anhydrous ether after the reaction had been initiated by adding a few drops of ethyl bromide. The rate of addition was so regulated that the liquid just boiled. A yellow-brown or red-brown solution resulted. In some cases a precipitate also formed. The mixture was boiled on the water-bath for an hour and subsequently cooled with an ice-bath.

Reaction of the Grignard Reagent with Benzaldehyde or Acetophenone.—Benzaldehyde (0.4 mole) or acetophenone in 50 ml. of anhydrous ether was added dropwise with ice-cooling. A definite evolution of heat took place and the mixture solidified by the end of the addition.

Reaction of the Grignard Reagent with Benzophenone.—The Grignard reagent was prepared from 0.1 mole of halothiazole and 0.1 mole of ethyl bromide. Benzophenone (0.2 mole) in 100 ml. of anhydrous ether was added as above in the case of benzaldehyde or acetophenone.

Reaction of the Grignard Reagent with Formaldehyde.—The dropping funnel was replaced by a wide bore glass tube (about 12 mm. inside diameter) which reached to, but not below the surface of the liquid. This tube was connected directly to the side arm of a 250-ml. distilling flask containing 20 g. of excess paraformaldehyde (32 g., 0.35 mole) which had been previously dried for two days in a vacuum desiccator over phosphorus pentoxide. The Grignard reagent was stirred vigorously with ice-cooling and the flask containing the paraformaldehyde was heated in an oil-bath at 180-200°. The formaldehyde formed by depolymerization was carried over into the Grignard reagent and, at the end of an hour and a half, the reaction was over as indicated by the reaction mixture turning completely solid.

Hydrolysis of the Grignard Complexes.—The solid reaction mixtures obtained above were heated on the water-bath for one hour, cooled in an ice-bath and hydrolyzed by the slow addition of 40 g. of ammonium sulfate in 150 ml. of water with stirring. The aqueous layer was separated from the ether layer, and the aqueous layer was extracted with ether. The combined ether extracts were extracted repeatedly with 40-ml. portions of dilute sulfuric acid (1 ml. concd. acid to 40 ml. of water) until the acid extracts no longer yielded the thiazolylcarbinols on neutralization with ammonium hydroxide. The neutralized acid extracts were extracted with ether, dried over sodium sulfate and the ether removed by distillation. The residue was recrystallized to give the pure thiazolylcarbinol.

Oxidation of the Thiazolylphenylcarbinols to the Corresponding Ketone Derivatives.—The carbinol (1.0 g.) in 10 ml. of glacial acetic acid was treated with 0.8 g. of sodium dichromate in 2 ml. of water and then refluxed for one hour. The green solution was then poured on ice and, after a short time, the oxidation product crystallized. The mixture was neutralized with sodium carbonate and extracted with ether. The ether extract was dried over sodium sulfate, the ether removed by distillation at reduced pressure and the residue distilled or recrystallized.

4-Methyl-2-thiazolylphenylcarbinol.—This compound was prepared from 0.1 mole of ethyl bromide, 0.1 mole of 2-chloro-4-methylthiazole and 0.2 gram-atom of magnesium followed by reaction with 0.2 mole of benzaldehyde. The resulting mixture was treated as above and the product isolated. The 2-chloro-4-methylthiazole was prepared from 2-hydroxy-4-methylthiazole[17] by the action of phosphorus oxychloride.

2-Methyl-5-ethoxy-4-thiazolylphenylcarbinol.—This compound was prepared from 0.05 mole of 2-methyl-5-ethoxy-4-bromothiazole, 0.15 mole of ethyl bromide and 0.2 gram-atom of magnesium. During the reaction the magnesium lost its usual metallic gleam and reaction ceased. When an additional 1.0-g. quantity of magnesium turnings was added, the reaction started again and a brownish reaction mixture containing much precipitate resulted. This was treated with 0.2 mole of benzaldehyde and the product isolated as described above.

The Halogen-Lithium Metal Interconversion Reaction.—Butyllithium was prepared by the method of Gilman and co-workers.[18] A solution of *n*-butyllithium prepared from 18 g. of *n*-butyl bromide and 0.3 gram-atom of lithium wire was cooled to −40° and a solution of 0.1 mole of halothiazole in 20 ml. of ether was added. The dark reaction mixture was stirred for 15 minutes, and 0.1 mole of benzaldehyde was added at a temperature of −30°. The temperature was then allowed to rise to −15° and the mixture, after being stirred for 45 minutes, was poured on dilute hydrochloric acid and ice. The acid layer was separated, made alkaline with gaseous ammonia and the mixture extracted with ether. The ether extracts were dried over sodium sulfate, filtered and, after removal of the ether, the residue was recrystallized.

2-Bromothiazole and 2,4-dimethyl-5-bromothiazole were treated as described above. 2-Methyl-4-bromo-5-ethoxythiazole reacted in the same manner using half quantities.

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