[CONTRIBUTION FROM THE WESTINGHOUSE RESEARCH LABORATORIES]

Synthesis of the Polymethylols of Phenol

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The compounds, 2,6-dimethylolphenol, 2,4-dimethylolphenol and 2,4,6-trimethylolphenol have been synthesized by means of reduction of corresponding acetoxyphenyl esters with lithium aluminum hydride. The polymethylols of phenol are crystalline compounds of sharp melting point and are easily soluble in water. 2,6-Dimethylolphenol is dimorphic. Preparation of 2,4,6-trimethylolphenol by direct reaction of phenol and formaldehyde is also described.

Ever since Manasse[1] and Lederer[2] first succeeded in isolating *o*- and *p*-monomethylolphenol from a reaction mixture of phenol and formaldehyde, chemists have speculated over the probable existence of the other possible methylol derivatives of this compound, 2,4-dimethylol-, 2,6-dimethylol- and 2,4,6-trimethylolphenol. These compounds are of considerable importance to the theory of phenolic resin formation since they may serve readily as cross-linking agents, and inability to obtain pure samples of them has been a considerable handicap in past studies of this reaction.

Granger,[3] Seebach[4,5] and Imoto,[6] among others, have reported unsuccessful attempts to prepare these compounds or to isolate them from a mixture. Certain derivatives of some of these substances had been prepared[7,8] and Sprengling and Freeman[9] demonstrated the presence of the 2,4-dimethylol- and 2,4,6-trimethylolphenol in a reaction mixture by means of separation and isolation of the corresponding 4-methoxyisophthalic and methoxytrimesic acids after methylation and oxidation of the mixture. The existence of 2,6-dimethylolphenol remained speculative and all three polymethylol compounds themselves remained unknown.

In the course of a recently reported study of the first stage of the phenol–formaldehyde reaction by means of paper chromatography,[10] the synthesis of these unknown compounds became imperative. Efforts to synthesize them were successful and are described here.

During the progress of this work, the successful synthesis of 2,4,6-trimethylolphenol by Carpenter and Hunter[11] in England, using a technique similar to one of the two methods employed here, was announced. It is felt however that the improved yields obtained, the greater feasibility of the method, and the successful synthesis of this compound by the alternative method involving direct condensation of phenol and formaldehyde justify its inclusion in this paper.

The method employed in the synthesis of each of these polymethylol compounds is reduction of the corresponding esters by means of lithium aluminum hydride. This reagent has been employed for the preparation of similar compounds by several investigators.[11,12]

In a reduction using lithium aluminum hydride it is preferable to carry out the reaction in ether solution because of the extremely low solubility of the reagent in dioxane and other solvents. In work with methylolphenols the lower reflux temperature of ether is also an advantage since it reduces the tendency toward resinification. Efforts to carry out the reduction of hydroxytrimesic acid trimethyl ester and the hydroxyisophthalic acid dimethyl esters to prepare the polymethylolphenols met with only indifferent success and provided only trace amounts of product, due apparently to the ether insolubility of the lithium aluminum salts formed at the first contact of the reagent with substances having reactive hydroxyl groups.[13] By means of esterification of hydroxytrimesic and 2- and 4-hydroxyisophthalic acids followed by acetylation of the phenolic group, the ether solubility was maintained enabling the reduction by lithium aluminum hydride to proceed smoothly to the corresponding methylolphenols. The acetoxy group is removed and the phenolic group regenerated during the reaction and the additional step involved (acetylation) is more than compensated by the increased yield obtained.

The polymethylol compounds are crystalline substances of sharp melting point and exhibit a considerable degree of stability when pure. They are quite soluble in aqueous systems as might be expected due to the large number of hydroxyl groups. 2,4,6-Trimethylolphenol appears slightly hygroscopic and eventually forms a tough clear resin on standing in open air. It may however be kept indefinitely in a desiccator. The 2,6-dimethylolphenol exhibits dimorphism.

The formation of the polymethylolphenols by means of direct condensation of phenol and formaldehyde is of obvious interest and has now been clearly demonstrated by paper chromatographic studies.[10] We have also found that sodium trimethylolphenate prepared by a slight modification of Martin's directions gives pure trimethylolphenol in good yield upon neutralization with acid. In fact trimethylolphenol samples for chromatographic study were first obtained by this means.

The 3,3′,5,5′-tetra-(hydroxymethyl)-4,4′-dihydroxydiphenylmethane first prepared by Seebach[4,5] and reported by Martin[8] to be the only recognizable product of neutralization of the sodium salt of trimethylolphenol was also prepared according to di-

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(1) O. Manasse, *Ber.*, **27**, 2409 (1894).

(2) L. Lederer, *J. prakt. Chem.*, **50**, 223 (1894).

(3) F. S. Granger, *Ind. Eng. Chem.*, **24**, 442 (1932).

(4) F. Seebach, *Ber.*, **72**, 1635 (1939).

(5) F. Seebach, *ibid.*, **73**, 1338 (1940).

(6) M. Imoto, H. Kakiuchi and S. Kondo, *J. Inst. Polytechnics, Osaka Univ., Japan*, **2** [2] Series D, 1–4 (1951).

(7) H. A. Bruson and C. W. MacMullen, THIS JOURNAL, **63**, 270 (1941).

(8) R. W. Martin, *ibid.*, **73**, 3952 (1951).

(9) G. R. Sprengling and J. H. Freeman, *ibid.*, **72**, 1982 (1950).

(10) J. H. Freeman, *Anal. Chem.*, **24**, 955 (1952).

(11) A. T. Carpenter and R. F. Hunter, *J. Appl. Chem.*, **1**, 217 1951).

(12) S. R. Finn and J. W. G. Musty, *ibid.*, **1**, 182 (1951).

(13) W. G. Brown, "Organic Reactions," Vol. VI, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, Chapt. 10, p. 474.

rections of the latter. The study of the relative rates of formation of these two compounds, 2,4,6-trimethylolphenol and the tetramethylol dihydroxydiphenylmethane is still incomplete. However, it appears that the latter compound is not formed during the neutralization of sodium trimethylolphenate by acid as Martin believed, but that it was formed under alkaline conditions when the reaction is carried out according to his directions. In an experiment run under his conditions the two compounds were found to be present together as the alkaline salts. The same tetramethylol compound has been obtained by Imoto and Oshima[14] using sodium, barium, strontium, lithium or magnesium hydroxides and also metallic magnesium as catalysts and was, of course, originally prepared by Seebach[5] and also by Zinke and Hanus[15] using magnesium hydroxide. The tetramethylol compound is the more stable of the two and the one more easily obtained in the crystalline form when both are present in a mixture.

Tests of 2,4,6-trimethylolphenol have revealed its efficiency as a gelling agent for novolaks and demonstrated its role as a cross-linking agent in phenolic resins.

Experimental

All melting points are corrected. Compounds for which analyses are given are new. Hydroxytrimesic acid and 2- and 4-hydroxyisophthalic acids were prepared as described in a previous paper.[9]

2-Hydroxyisophthalic Acid Dimethyl Ester (I).—Prepared by saturating a hot solution of 2-hydroxyisophthalic acid in excess methanol with dry hydrogen chloride, filtering hot and evaporating filtrate to one-half its volume. A little water was added and on standing masses of white prisms were obtained; dried in vacuum desiccator, yield 80%, m.p. 71–72°, m.p. reported 72°.[16]

2-Acetoxyisophthalic Acid Dimethyl Ester (II).—Dry pyridine (20 ml.), excess acetic anhydride (7.5 ml.) and 10.5 g. (0.05 mole) of I were mixed and refluxed 20 minutes. The mixture was cooled, poured into 200 ml. of cold water and acidified with dilute hydrochloric acid. The white crystalline product was separated by filtration, washed with 100 ml. of saturated sodium carbonate solution to remove unacetylated material, then with water, and dried in a vacuum desiccator; yield 10.7 g. (85%). After recrystallization from methanol containing a few drops of water the compound melted at 81.5–82°.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.45, 57.23; H, 4.68, 4.48.

4-Hydroxyisophthalic Acid Dimethyl Ester (III).—Prepared by esterification of 4-hydroxyisophthalic acid in a manner similar to I; yield 90%, m.p. 94–96°, reported m.p. 96°.[17]

4-Acetoxyisophthalic Acid Dimethyl Ester (IV).—Obtained by acetylation of III in a manner similar to II; yield 65%. White platelets after two recrystallizations from methanol, m.p. 93–94°. Substance is neutral to *p*H paper and gives no reaction with ferric chloride solution; insoluble in water; soluble in chloroform, benzene, hexane, carbon tetrachloride, alcohol and ether. Mixture of III and IV melted at 62°.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.05, 57.29; H, 4.67, 4.89.

Hydroxytrimesic Acid Triethyl Ester (V).—Obtained by Fisher esterification of hydroxytrimesic acid in ethanol as in prepn. of I; yield 83%, white needles, m.p. 80.5–81.5°, reported m.p. 81°.[11] The compound gives a strong red color with alcoholic ferric chloride solution.

Acetoxytrimesic Acid Triethyl Ester (VI).—Prepared by acetylation of V by same procedure used for II; recrystallized from aqueous ethanol, yield 97%, short white prisms, m.p. 90–90.5°, no reaction with ferric chloride solution; mixture of V and VI melted at 70°.

Anal. Calcd. for $C_{17}H_{20}O_8$: C, 57.95; H, 5.72. Found: C, 58.22, 58.24; H, 5.59, 5.66.

Reduction Experiments with Lithium Aluminum Hydride.—All the polymethylolphenols were prepared by means of reduction with this reagent of the corresponding acetoxy esters according to the following procedure. Ortho, meta and para monomethylolphenols may be prepared by an analogous method.

An excess of lithium aluminum hydride (5.7 g., 0.15 mole) (Metal Hydrides Inc., Beverly, Mass.) was dissolved in 200 ml. of dry ether by refluxing eight hours in a three-necked flask fitted with addition funnel, mercury sealed stirrer and condenser with drying tube attached. The appropriate polyester (II, IV or VI) (0.02 mole) in 150 ml. of dry ether was then added dropwise through the addition tube over a period of 3/4 hour with constant stirring. A bright yellow, pink or orange precipitate, depending on the compound being reduced, appeared on contact of the two solutions. Stirring was continued one hour after addition of the ester was complete. The mixture regained its grey color. It was then refluxed gently for three hours and allowed to stand overnight protected from the atmosphere.

To decompose excess lithium aluminum hydride, 25 ml. of ether containing 5 ml. of ethyl acetate was added and the mixture refluxed 15 minutes. Then 50 ml. of ether containing 2 ml. of water was added through the condenser and the mixture allowed to stand 1–2 hours. The methylolphenol compounds were then freed from their alkali salts by acidification. Sulfuric acid (28 g., 0.57 equiv.) in 100 ml. of water was added carefully while stirring continuously. This is slightly less than the calculated amount of acid necessary to neutralize all the alkali present but the reaction mixture became acidic (red to Alkacid paper). The water volume should be kept small due to solubility of the polymethylols. After decanting the solution through a filter, solid sodium bicarbonate was added until the first trace of cloudiness indicated formation of aluminum hydroxide. The ether layer was separated and the aqueous portion extracted twice with fresh ether. Ethereal portions were combined and dried over Drierite. Extraction of the aqueous portion with ethyl acetate following the ether extractions was not found to add significantly to the yield obtained.

After drying, the ether solution was filtered and carefully evaporated. The temperature was not allowed to rise above 40° at any time but the solution was kept warm to minimize the condensation of moisture from the atmosphere caused by cooling action of the evaporating ether. (Do not evaporate ether with a current of air at room temperature.) When the volume of ether was reduced to about 20 ml. the solution was transferred to a desiccator and allowed to stand for several days. Residual ether was decanted from the crystals formed and drying completed in a vacuum. All three polymethylols of phenol give a deep blue color with ferric chloride solution.

2,6-Di-(hydroxymethyl)-phenol, (2,6-Dimethylolphenol) (VII).[18]—Prepared by reduction of II with lithium aluminum hydride in ether; yield 70%. Soluble in water, alcohol, hot chloroform and ethyl acetate. After recrystallization from hot chloroform (charcoal) the compound was obtained as pearly platelets; m.p. 94.7–95.2°. Chromatographic R_f value in 4:1, butanol:ammonium hydroxide, 0.67.[10]

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.43, 62.40; H, 6.76, 6.49.

This compound exhibits enantiotropic polymorphism.[19,20]

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[14] Private communication from M. Imoto, Univ. of Osaka, Japan.

[15] A. Zinke and F. Hanus, *Ber.*, **74**, 212 (1941).

[16] C. Graebe and H. Kraft, *ibid.*, **39**, 800 (1906).

[17] R. Loewenherz, *ibid.*, **25**, 2796 (1892).

[18] Since this paper was submitted there has come to the author's attention the paper by S. R. Finn and J. W. G. Musty, *J. Appl. Chem.*, **2**, 88 (1952), reporting the preparation of this compound in about 8% yield by dehalogenation of *p*-chlorophenol dimethylol with Raney nickel in alkali. They reported a melting point of 101° and prepared a phenylurethan derivative, m.p. 232°. The benzene insoluble phenylurethan of compound VII melted sharply at 239–240° and this was not further increased by recrystallization from alcohol.

[19] E. E. Jelley, "Technique of Organic Chemistry," Vol. 1, 2nd Ed., A. Weissberger, Ed., 1949, Interscience Publ., New York, N. Y., Part I, Chapt. XV, p. 886–889.

[20] G. R. Sprengling, S. Beatty and K. B. Adams, THIS JOURNAL, **72**, 4314 (1950).

A sample melted at 94.7–95.2° and at 96° minute seed crystals of the second form were observed. If the sample was removed from the bath at this point, it crystallized almost instantaneously (one second) and subsequently melted at 98.2–98.4°.

If allowed to remain in the slowly rising temperature bath the seed crystals disappear at 98°. When removed from the bath at 99° the sample crystallized very slowly (15–30 minutes) and thereafter melted again at 94.7–95.2°. This phenomenon could be demonstrated several times on the same sample and either form obtained at will. A mixture of the high and low melting forms melted at 94–96°.

2,4-Di-(hydroxymethyl)-phenol, (2,4-Dimethylolphenol) (VIII).—Obtained by reduction of IV with lithium aluminum hydride in ether; yield 79%; soluble in water, alcohol, acetone and ethyl acetate; insoluble in hexane, benzene, chloroform, ethylene chloride and nitroethane. Recrystallization from ethylene chloride containing 3% of absolute ethanol gave white micro needles; washed with chloroform and dried in vacuum; m.p. 91.7–92.5°. Chromatographic R_f in 4:1, butanol:ammonium hydroxide, 0.61.[10] A 1:3 mixture of compounds VIII and IV melted at 84°.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.64, 62.43; H, 6.67, 6.91.

2,4-Di-(hydroxymethyl)-anisole.—Prepared by methylation of 1.5 g. (0.01 mole) of VIII with excess diazomethane in ether. Evaporated ether (below 50°) and recrystallized residue from benzene containing a little absolute ethanol; yield 0.3 g. (18%); white granular crystals; m.p. 98°, reported m.p. 100°.[21] An equal parts mixture with compound VIII melted at 82°. The substance fails to give a color with ferric chloride solution.

2,4,6-Tris-(hydroxymethyl)-phenol, (2,4,6-Trimethylolphenol) (IX).—Obtained by reduction of VI with lithium aluminum hydride in ether; yield 27%; white platelets; m.p. 74–75° (resinifies), m.p. reported 76°[11]; chromatographic R_f in 4:1 butanol:ammonium hydroxide, 0.34.[10] Methylation with diazomethane gives water-miscible yellow oil which fails to give a color with ferric chloride solution.[8]

2,4,6-Tris-(2′-hydroxy-5′-methylbenzyl)-phenol (X).—Prepared as a derivative of IX. Five grams of *p*-cresol, 0.1 g. of IX and a trace of *p*-toluenesulfonic acid were heated five hours on the steam-bath. Excess *p*-cresol was removed by steam distillation and the product recrystallized from benzene; yield 0.12 g. (47%) of X; m.p. 182°, reported m.p. 184–185°.[11] A sample of X obtained from 2,4,6-tri-(acetoxymethyl)-phenyl acetate[7] and *p*-cresol according to Carpenter and Hunter[11] had m.p. 185°. A mixture of samples of X obtained from the two sources melted at 182–184°.

2,4,6-Trimethylolphenol (IX) by Direct Reaction of Phenol and Formaldehyde.—Martin[8] had described the preparation of the sodium salt of this compound and reported his inability to convert the salt into the free phenol. He obtained instead the tetramethyloldihydroxydiphenylmethane. This step has now been successfully carried out with only minor but apparently important modifications of his method.

Preparation of Sodium 2,4,6-Trimethylolphenate.—Sodium hydroxide (4.0 g., 0.1 mole) was dissolved in 10 ml. of water and added to 9.4 g (0.1 mole) of phenol (Mallinckrodt anal. reagent). After cooling to room temperature, 24.4 g. (0.3 mole) of formalin (37%) was added to the solution of sodium phenate. No further cooling was necessary except for larger batches. (Martin employed more concentrated alkali with the result that sodium phenate crystallized out of solution. He also used a 20% excess of formaldehyde and 10% excess sodium hydroxide.) The solution gradually turned yellow and was allowed to stand for 6–7 days, then poured into 300 ml. of isopropyl alcohol. An immediate thick white precipitate formed and was removed by filtration after 10–15 minutes, washed with isopropyl alcohol, and dried in a vacuum desiccator several days; yield 90–99%. Chromatograms run on the mother liquor and on the product (sodium salt) showed only the trimethylolphenol as the product, no by-products or intermediates by this method. Repeat experiments using double and treble the amounts indicated were equally successful.

The sodium salt deteriorates on standing. After several months the white solid had become reddish-brown and the odor of formaldehyde was noticeable on opening the container. *Attempts to neutralize the salt at this stage gave only resinous products.*

Neutralization of Sodium 2,4,6-Trimethylolphenate. Preparation of 2,4,6-Trimethylolphenol (IX).—The sodium salt of IX (20.6 g., 0.1 mole) was suspended in 500 ml. of C.P. acetone and 150 ml. of acetone containing 6.0 g. (0.1 mole) of glacial acetic acid was added slowly with stirring. The salt dissolved and sodium acetate precipitated. After ten minutes the faintly acidic solution was filtered. The filtrate was concentrated to 90–100 ml. by warming at 50°, cooled, and 50–60 ml. of ether added in portions. On standing in a desiccator a yellow oil precipitated. On three occasions this oil gradually crystallized forming white waxy crystals. The residual solvent was decanted and the product dried in vacuum; yield 71%, m.p. 74–75°. A 1:2 mixture with a sample of IX prepared by reduction of acetoxytrimesic acid triethyl ester melted at 73–75°. Chromatographic R_f in 4:1, butanol:ammonium hydroxide was 0.34.[10] Paper chromatograms also showed the oil to be essentially pure trimethylolphenol even when it failed to crystallize, probably due to presence of excess moisture. Attempted further purification by recrystallization was not satisfactory due to considerable resinification. Addition of a few drops of 10% sodium hydroxide to a sample of trimethylolphenol in isopropyl alcohol reverses the reaction as evidenced by an immediate white precipitate.

3,3′,5,5′-Tetra-(hydroxymethyl)-4,4′-dihydroxydiphenylmethane (XI).—This compound was prepared from 1 mole of phenol, 1.1 moles of 50% sodium hydroxide and 3.6 moles of formalin allowed to stand five days at room temperature and poured into 3 l. of ethanol, all proportions being exactly as described by Martin.[8] After standing two hours *the ethanol solution* was filtered and the precipitate rinsed with acetone and ether and dried in a vacuum. The yield of sodium salt was about 50% of the theoretical amount.

Quantitative paper chromatograms of the alkaline salt prepared in this way showed that as early as the third day, the tetramethylol dihydroxydiphenylmethane was present in the ratio of about one part to ten of trimethylolphenol and by the fifth day the mole ratio of these compounds was about 1:1. Martin's yield of tetramethylol compound on neutralization is in the vicinity of 20%. It is unfortunate that none of the analytical criteria employed by him would have been capable of distinguishing between a pure trimethylolphenol sodium salt and a mixture containing up to about 25% of tetramethyloldihydroxydiphenylmethane salt.

After suspending 84.5 g. (0.41 mole) of the sodium salt in 670 ml. of acetone and adding slightly less than an equivalent of acetic acid (23.4 g., 0.39 mole) dissolved in 170 ml. of acetone, unreacted substance and the sodium acetate formed were removed by filtration and the volume of filtrate reduced by evaporation at room temperature. Four consecutive fractions were obtained by adding an equal volume of ether to the acetone solution as evaporation progressed beginning when the volume reached 200 ml., filtering and then re-evaporating to a smaller volume and again adding ether.

Fraction 1 (10.2 g.) crystallized readily. It was purified by dissolving 3 g. in 40 ml. of water (preheated to 75–80°—the compound resinifies in boiling water). Charcoal was added and the mixture filtered hot, cooled to room temperature and decanted from some resinous droplets which formed. On chilling a white crystalline powder was obtained, m.p. 143–144°. The substance froths in the tube at 145°. The compound appears identical in all respects to the substance XI described by four other authors.[5,8,14,15] On a chromatogram this substance gave a single spot at R_f = 0.48[10] quite separate and distinct from any of the polymethylolphenol spots.

Fraction 2 (19.8 g.) was a tough white amorphous solid resinifying at 125°. A chromatogram showed it to be composed of approximately equal parts of 2,4,6-trimethylolphenol (IX, R_f = 0.34) and the tetramethylol dihydroxydiphenylmethane (XI, R_f = 0.48). Recrystallization from water (75°) gave crystals of XI, m.p. 144°, the trimethylol remaining in the water solution. Recrystallization from 4:1, methyl acetate:methanol gave soft white micro crystals of XI, m.p. 143° (preheated bath).

Recrystallization of a sample from acetone plus a little ether gave crystals melting at 133° which were shown by a chromatogram to consist of a large amount of XI and a small amount of trimethylolphenol IX. Addition of excess ether to the acetone solution precipitated a yellow oil, shown by a chromatogram to consist chiefly of trimethylolphenol IX with a small amount of XI.

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[21] R. Quelet and I. Anglade, *Compt. rend.*, **203**, 262 (1936).

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).

EAST PITTSBURGH, PA.

[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).