[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Studies in the Dioxane Series. III. The Use of Zinc and Cadmium Chlorides in the Grignard Synthesis of Alkyl Substituted Dioxanes

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Small yields of alkyl substituted dioxanes have been obtained by the action of alkylmagnesium bromides with 2,3-dichloro-1,4-dioxane, the principal product being *p*-dioxene.[1] Blaise[2] has successfully modified the Grignard synthesis of ketones from acid chlorides first by a reaction of the Grignard reagent with anhydrous zinc chloride, forming as an intermediate an organozinc halide which need not be isolated. Yields of ketones as high as 80% have been obtained by this procedure.[3] By a similar use of anhydrous zinc chloride in the synthesis of 2,3-di-*n*-butyl-1,4-dioxane, the yield has been increased from about 2 to 37%.

In the Blaise ketone synthesis, the increased yield is probably partially due to the fact that organozinc halides are less reactive with the desired products, ketones, than are the corresponding magnesium compounds. The situation in our dioxane synthesis is different in that there are two competing reactions, the less active reagent favoring substitution and the more active reagent favoring dehalogenation. The above reasoning led to the substitution of cadmium chloride for zinc chloride in the dioxane synthesis, with the result that the yield was increased to 44%. The substitution of mercuric chloride would probably not result in an increased yield, as the alkylmercury halides are not sufficiently reactive for any reaction to take place.[4] Further increases in yield will depend on finding the optimum solvent and temperature.

The gases evolved in the reaction of methylmagnesium bromide with 2,3-dichloro-1,4-dioxane are ethane, 94%; methane, 5.4%; ethylene, 0.6%. The amounts of methane and ethylene are not in the proportion, two to one, that might be expected if both are derived from methyl radicals by some sort of disproportionation. The excess of methane may be accounted for by assuming that a small amount of hydrogen chloride was evolved by the 2,3-dichloro-1,4-dioxane, and reacted with the methylmagnesium bromide.

Dimethyldioxane is very soluble in water at room temperature. In this respect, it resembles *p*-dioxane, but differs from *p*-dioxene which is very insoluble. The introduction of a double bond in the latter compound seems to change the properties of the oxygen, so that hydrogen bonds[5] are no longer important.

Experimental

I. New Symmetrical 2,3-Dialkyl-1,4-dioxanes

The properties and analyses of new compounds described in this paper are presented in the tables. Details as to synthesis and purification are given in later sections.

TABLE I

NEW SYMMETRICAL 2,3-DIALKYL-1,4-DIOXANES

Substituent	Formula	B. p. °C.	B. p. Mm.	d^{20}_{20}	n^{20}_D
Methyl	$C_6H_{12}O_2$	127.7–129	750.8	0.960	1.4237
		132.2–132.7	750.8	.967	1.4259
Ethyl	$C_8H_{16}O_2$	166.5–168.5	739·	.940	1.4342
n-Propyl	$C_{10}H_{20}O_2$	87	12	.929	1.4414
		202–205	744[a]		
n-Butyl	$C_{12}H_{24}O_2$	129–130	22	.918	1.4462
		238–240	744[a]		
Allyl	$C_{10}H_{16}O_2$	90.2–90.7	16	.965	1.4650

[a] Asterisk designates *t*, uncorrected.

TABLE II

MOLECULAR WEIGHT DETERMINATIONS[a] AND CARBON AND HYDROGEN ANALYSES

Substituent	Molecular weight Calcd.	Molecular weight Found	Percentage composition Calcd. C	Calcd. H	Found C	Found H
Methyl[b]	116.10	113	62.02	10.42	62.09	10.47
Ethyl[c]	144.13	139	66.61	11.19	66.98	11.20
n-Propyl	172.16	171	69.70	11.71	69.81	11.70
n-Butyl	200.19	193	71.93	12.08	71.60	12.01
					71.64	11.93
Allyl	168.13	164	71.37	9.59	71.16	9.73

[a] Cryoscopic method using benzene.

[b] The fraction, b. p. 128–130.2° (737 mm.); n^{20}_D 1.4249; d^{20}_{20} 0.962. *Anal.* C, 62.18; H, 10.57.

[c] A fraction, b. p. 164–165° (748 mm.); n^{29}_D 1.4285. *Anal.* C, 66.20; H, 11.12.

II. Experiments Employing the Grignard Reagent

2,3-Dimethyl-1,4-dioxane.—Methylmagnesium bromide was obtained by reaction of 97 g. (1.02 moles) of Eastman practical grade of methyl bromide with the requisite quantity of magnesium, using 386 cc. of dry ether; 78.5 g.

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[1] Summerbell and Bauer, THIS JOURNAL, **57**, 2364 (1935).

[2] Blaise, *Bull. soc. chim.*, **9**, XIII (1911).

[3] Wohlgemuth, *Ann. chim. phys.*, **2**, 292 (1914).

[4] Since the submission of this paper, experiments have shown that neither methylmercuric bromide nor dimethyl mercury react with 2,3-dichloro-1,4-dioxane under conditions similar to those described for the other reagents.

[5] Hildebrand, *Science*, **83**, 21 (1936).

(0.50 mole) 2,3-dichloro-1,4-dioxane dissolved in 100 cc. of ether was then added. Following usual procedures, these fractions were obtained (°C., g.): 94–95, 29.3 (68% yield *p*-dioxene); 97–119, 0.7; 124–127, 4.7; 127–132, 1.1; 2.1 g. residue. The last two fractions yielded, after treatment with solid sodium hydroxide, then metallic sodium, 0.9 g., b. p. 128.5–129.7° (746 mm.), $n^{20}\mathrm{D}$ 1.4242 and 1.1 g., b. p. 130–132° (746 mm.), $n^{20}\mathrm{D}$ 1.4253; about a 3% yield of the 2,3-dimethyl-1,4-dioxane.

The gases evolved in the above reaction occupied 8.3 liters (S. T. P.). Analysis showed[6] ethane, 94%; methane, 5.4%; ethylene, 0.6%; hydrogen absent or present only in traces. No analysis was attempted for methyl chloride. The amount of ethane evolved corresponds remarkably well with the amount of *p*-dioxene isolated.

Other 2,3-Dialkyl-1,4-dioxanes.—The reaction of 5.64 moles of ethylmagnesium bromide with 398.8 g. (2.54 moles) 2,3-dichloro-1,4-dioxane yielded at 754 mm.: 117.5 g., b. p. 94–95° (54% yield pure *p*-dioxene); 26.1 g., b. p. 164–171° (crude 2,3-diethyl-1,4-dioxane).

This crude product, as well as other impure alkyl derivatives of dioxane described in this paper, was treated with 100 cc. of 15% potassium hydroxide at the temperature of a water-bath for five hours. Separation of the alkyl dioxane layer, addition of solid sodium hydroxide, and subsequently metallic sodium, gave upon fractionation at 739 mm. (g., °C.): 2.2, 165–166.5; 6.1, 166.5–168.5; 1.3, 168.5–169; 2.0 g. left in distilling flask. A 2% yield of pure 2,3-diethyl-1,4-dioxane was obtained.

When 1.581 moles of 0.9147 *N* allylmagnesium bromide[7,8] was treated with 141.3 g. or 0.900 mole of 2,3-dichloro-1,4-dioxane dissolved in 200 cc. of anhydrous ether, and the usual procedure of working up the products was followed, these fractions were obtained: 2 g., 1,5-hexadiene, b. p. 58–59° (758 mm.), $n^{20}\mathrm{D}$ 1.4038;[9] 3.3 g., b. p. 90–94° (753 mm.); and at 15 mm. (g., °C.): 1.4, 51–52; 1.5, 52–78; 2.1, 82–84; 5.0, 84–86.5; 32.8, 86.7–92; 2.4, 115; 41 g. residue. Upon redistillation of the 32.8 g. fraction, a colorless liquid, b. p. 89–91° (16 mm.); d^{18}_{20} 0.995; $n^{26}\mathrm{D}$ 1.4638, was obtained. When treated as an impure alkyl derivative (*e. g.*, potassium hydroxide, etc.), 24 g. (18% yield) 2,3-diallyl-1,4-dioxane, b. p. 90.2–90.7° (16 mm.); d^{20}_{20} 0.965; $n^{25}\mathrm{D}$ 1.4627, resulted. Determination of double bonds by bromine addition[10] gave the values, 2.15 and 2.00.

The 2,3-di(β,γ-dibromopropyl)-*p*-dioxane, which should form when 2,3-diallyl-1,4-dioxane is brominated, is a very viscous oil which has not crystallized.

A 2% yield of 2,3-di-*n*-butyl-1,4-dioxane[11] may be isolated when *n*-butylmagnesium bromide reacts with 2,3-dichloro-1,4-dioxane.

III. A Grignard-Zinc Chloride Experiment

2,3-Di-*n*-butyl-1,4-dioxane.—To prepare a Grignard reagent, 137 g. or 1.0 mole of *n*-butyl bromide, $n^{20}\mathrm{D}$ 1.4398, was treated with 24.3 g. or 1.0 mole of magnesium, using 460 cc. anhydrous ether. Pure dry zinc chloride (136.3 g. or 1.0 mole) was treated with anhydrous ether (148 g. or 2.0 moles). Over a period of one and three-fourths hours, the zinc chloride etherate was added to the Grignard reagent with stirring at 0°. Double decomposition was aided by refluxing for two hours by means of a water-bath heated to 40°. Dry toluene (350 cc.) was added to the reaction products and the ether removed at 25–35° under the vacuum of a water pump until the toluene began to distil appreciably.

Seventy-eight and five-tenths grams (0.50 mole) of 2,3-dichloro-1,4-dioxane was dissolved in 157 g. of dry toluene and added to the organometallic mixture over a period of two hours at a temperature of 25–40°. Stirring was continued for one and one-half hours at 40°. The reaction mixture was then treated with 300 cc. of water at 0°, the toluene layer separated, dried over anhydrous sodium sulfate, and the toluene distilled off at 744 mm. Upon three distillations, using a 20-cm. evacuated jacketed column of the Vigreux type, these fractions were obtained: (a) 5 g., b. p. 73–76° (21–22 mm.), 176–179° (744.2 mm.); $n^{21}\mathrm{D}$ 1.4348, d^{20}_{20} 0.950; (b) 37 g., b. p. 129–130° (22 mm.), 238–240° (744 mm.), $n^{22.5}\mathrm{D}$ 1.4452, d^{20}_{20} 0.918; (c) 6 g. of dark colored oil, b. p. 175–177° (4–5 mm.); (d) 7 g. of tarry residue. Fraction (b) is a 37% yield pure 2,3-di-*n*-butyl-1,4-dioxane, and possesses a castor oil-like odor.

IV. Grignard-Cadmium Chloride Experiments

The cadmium chloride used in these experiments was heated in a stream of dry hydrogen chloride for three hours at 400–500°. The excess hydrogen chloride was removed by placing the product in a desiccator attached to a vacuum pump.

An atmosphere of dry nitrogen was used in all experiments described in this paper when a Grignard reagent was involved. This is of particular importance in the following experiments, as the cadmium dialkyls of low molecular weight may ignite on exposure to air.

2,3-Di-*n*-butyl-1,4-dioxane.—The synthesis of this compound is given for comparison purposes. 2,3-Dimethyl-1,4-dioxane and 2,3-di-*n*-propyl-1,4-dioxane were prepared by the use of anhydrous cadmium chloride and the procedure was essentially that adopted in preparing this alkyl dioxane derivative.

To a Grignard reagent formed by the reaction of 113 g. (0.825 mole) *n*-butyl bromide with the required amount of magnesium using 385 cc. of dry ether, was added 151.2 g. (0.825 mole) of anhydrous cadmium chloride in 5–10 g. lots. The reaction products were then kept at 40° for two hours. After adding 260 cc. of dry toluene, the ether was removed as described previously, and 64.7 g. (0.412 moles) of 2,3-dichloro-1,4-dioxane dissolved in 130 g. of dry toluene was added over a period of two and one-half hours. Stirring was continued for two hours, the temperature being raised progressively to 70°. Then 350 cc. of water and enough 6 *N* sulfuric acid to dissolve the magnesium hydroxide was added. Following the usual procedure, the toluene layer yielded: 5.8 g., 78.5–81° (14.5 mm.); 36 g., 122–122.7° (16 mm.), 240–242° (747 mm.), $n^{22.5}\mathrm{D}$ 1.4452; 2 g. 130–175° (16 mm.); 6 g. 180° (15.5 mm.)—containing some 1,4,5,8-naphthodioxane,[12] m. p. 111°; 9.8 g. tarry

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(6) Courtesy of Mr. E. Field.

(7) Gilman and McGlumphy, *Bull. soc. chim.*, **43**, 1322 (1928).

(8) Young, Prater and Winstein, THIS JOURNAL, **55**, 4908 (1933).

(9) Value in literature, $n^{20}\mathrm{D}$ 1.4010, "International Critical Tables," McGraw-Hill Book Co., Inc., N. Y., Vol. 1, 1926, p. 276; identified by formation of 1,2,5,6-tetrabromohexane, m. p. 53–54°.

(10) Davis, Crandall and Higbee, *Ind. Eng. Chem., Anal. Ed.*, **3**, 108 (1931).

(11) Summerbell and Bauer, THIS JOURNAL, **57**, 2367 (1935).

(12) Böeseken, Tellegen and Henriquez, *Rec. trav. chim.*, **50**, 909 (1931).

residue. A 44% yield of the 2,3-di-*n*-butyl-1,4-dioxane has been obtained.

Difficulty was encountered in working up the reaction products in the 2,3-dimethyldioxane synthesis. The crude product yielded two fractions of practically equal quantity when fractionated by a small Vigreux column.

With a limited amount of material, the following experiment was attempted: 29 g. of the crude product, b. p. 127–133° (752 mm.), was heated with 100 cc. of 15% potassium hydroxide solution for seven hours. A quantity of anhydrous potassium carbonate was added, the dimethyldioxane layer separated, dried over solid sodium hydroxide for several hours, and metallic sodium added. After the liquid had stood over the metallic sodium one week, it was fractionally distilled, using a small (7-mm., 60-cm.) Podbielniak type column with a vacuum jacket. The bulb containing the material was heated by an oil-bath at 190–201°. These fractions were obtained at 752 mm. (g., °C., n^{20}_D): 1.3, 126.4–127.2, 1.4239; 9.9, 127–129, 1.4249; 11.3, 130.2–132.7, 1.4259; 3.2 g. left in bulb.

Redistillation resulted in two chief fractions: (a) b. p. 127.7–129° (750.8 mm.), n^{20}_D 1.4237, d^{20}_{20} 0.960; (b) b. p. 132.2–132.7° (750.8 mm.), n^{20}_D 1.4259, d^{20}_{20} 0.967. Each of these fractions give satisfactory analyses for $C_6H_{12}O_2$. Two 2,3-dimethyl-1,4-dioxanes are indicated by this work. This is interesting as it differs from the results on diaryldioxanes obtained from Grignard reagents, where only one form has been isolated.

Slightly lower yields of the dimethyl and di-*n*-propyl derivatives were obtained when cadmium chloride was used. Also, more difficulty was encountered in obtaining them pure.

Practically all the 2,3-dialkyl-1,4-dioxanes herein described tend to possess a boiling-point range.

Summary

1. A number of 2,3-dialkyl-1,4-dioxanes have been prepared for the first time.
2. The unisolated reaction product of cadmium chloride and a Grignard reagent has been used with excellent results as a reagent in synthesis.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

The Thermodynamics of Hydrochloric Acid in Methanol–Water Mixtures from Electromotive Force Measurements[1]

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Recently,[2] the electromotive force of the cell

$$H_2 \mid HCl\ (m)\ \text{in}\ X\ \%\ CH_3OH,\ Y\ \%\ H_2O \mid AgCl\text{-}Ag \qquad (1)$$

has been measured. Two solvents were employed which contained 10 and 20% methyl alcohol by weight. Results were obtained from 0 to 40° at 5° intervals and the acid concentration was varied between 0.004 and 0.1 *M*. From these the standard potential of the cell was determined from 0 to 40°. These measurements have now been extended to include results from 0.005 to 2 *M*. From these data, a study of the thermodynamics of hydrochloric acid in these solutions has been made, which when combined with the similar study of the properties of this acid in water made by Harned and Ehlers,[3] leads to a comprehensive knowledge of the behavior of an electrolyte in media of high dielectric constant.

Experimental Results

The electromotive forces of cell (1) as a function of the temperature may be computed with an accuracy of the order of ±0.05 mv. by the equation

$$E = a + b(t - 20) + c(t - 20)^2 \qquad (2)$$

Since the original observations were not made at round concentrations, each isothermal series of results was smoothed against a suitable function of *m*, and values of *E* at round concentrations were obtained. The constants of equation (2) were then evaluated by the method of least squares. These constants are given in Table I. Values of *E* computed by this equation are valid from 0 to 40°.

TABLE I

CONSTANTS OF EQUATION (2)

X = % Methanol by Weight

	$X = 10$			$X = 20$		
m	$a = E_{20}$	$(b \times 10^6)$	$(-c \times 10^6)$	$a = E_{20}$	$(b \times 10^6)$	$(-c \times 10^6)$
0.005	0.48989	382.53	4.034	0.48361	409.13	4.609
.01	.45629	271.17	4.016	.45012	297.73	4.571
.02	.42303	161.63	3.996	.41697	187.93	4.521
.05	.37960	15.03	3.865	.37374	47.13	4.494
.1	.34698	− 84.33	3.903	.34150	− 51.83	4.144
.2	.31400	−183.70	3.652	.30875	−153.07	4.229
.5	.26845	−323.17	3.158	.26370	−292.13	4.030
1	.23027	−427.83	2.896	.22594	−396.70	3.587
1.5	.20477	−493.63	2.596	.20084	−449.83	3.112
2	.18431	−537.47	2.240	.18049	−502.37	3.074

For purposes of theoretical calculations, it is necessary to know the concentrations of the acid

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[1] This communication contains material from a dissertation presented by Henry C. Thomas to the Graduate School of Yale University in partial fulfilment of the requirements for the Degree of Doctor of Philosophy, June, 1935.

[2] Harned and Thomas, THIS JOURNAL, **57**, 1666 (1935).

[3] Harned and Ehlers, *ibid.*, **55**, 2179 (1933).