(29°, 745 mm.). Calc. for $C_{14}H_{13}O_2N_3$ (mol. wt., 255): C, 65.88; H, 5.09; N, 16.47. Found: C, 65.82; H, 5.21; N, 16.44.

Camphor-4-*p*-tolylsemicarbazone, $C_{10}H_{16}NNHCONHC_6H_4CH_3$.—Difficulty was experienced in bringing about the condensation with camphor and the method used above could not be employed. It was modified as follows. To a saturated solution of 0.2 g. of tolylsemicarbazide hydrochloride and 0.18 g. of sodium acetate in water was added 0.18 g. of camphor dissolved in 20 cc. of glacial acetic acid. The mixture was boiled under a reflux condenser for 25 minutes to effect solution and then set aside for slow crystallization. A small amount of water aided the separation. The product consisted of colorless needles that melted at 225–229° to a brownish liquid.

Anal. Subs., 0.1058: CO_2, 0.2810; H_2O, 0.0773. Subs., 0.0724: 9.5 cc. of N_2 (23°, 746 mm.). Calc. for $C_{18}H_{25}ON_3$ (mol. wt., 299): C, 72.24; H, 8.36; N, 14.04. Found: C, 72.43; H, 7.73; N, 14.57.

Summary

1. 4-*p*-Tolylsemicarbazide was prepared by the action of hydrazine hydrate on tolylurea and obtained as lustrous plates, contracting at 157–159° and decomposing at 274°, doubtless forming tolylurazole by loss of ammonia.
2. This tolylsemicarbazide was condensed with acetone, acetophenone, benzophenone, *p*-quinone and camphor.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

A STUDY OF THE OPTIMUM CONDITION FOR THE PREPARATION OF NORMAL VALERIC ACID FROM BUTYLMAGNESIUM BROMIDE AND CARBON DIOXIDE

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Introduction

In connection with studies on some relationship between physiological action and chemical constitution it was necessary to synthesize relatively large quantities of certain aliphatic carboxylic acids from the Grignard reagent and carbon dioxide. This reaction has found rather general application in the synthesis of a wide variety of carboxylic acids. Scattered through the very comprehensive literature on the subject are detached accounts of methods of manipulation which are helpful in the preparation of certain acids with improved yields. Unfortunately, the results of some of the few apparently complete studies have been questioned.

The experiments described here concern the effect of the variation of some factors on the yield of *n*-valeric acid from butylmagnesium bromide and carbon dioxide. The yields of two other acids, benzoic and cyclo-

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[1] This paper is an abstract of a part of a thesis presented by Harold H. Parker in fulfilment of the requirements for the degree of Master of Science in Chemistry at Iowa State College.

hexylcarboxylic, have been determined under the optimum condition found for valeric acid. Quite probably most of the results obtained here can be extended to the preparation of other acids. Furthermore, related reactions involving the action of gases other than carbon dioxide on RMgX compounds can be effected very likely with advantage by the observance of some of the conditions found to be of help in this study.

Grignard[2] published the first account of the synthesis of acids by the action of carbon dioxide on RMgX compounds. In a comparatively short time, many extended this synthesis to an almost complete variety of acids. These include carboxylic acids formed by the action of carbon dioxide on an —MgX group attached not only to carbon, but also to nitrogen and oxygen. Some of the simple types of acids have been prepared from reagents other than carbon dioxide: namely, ethyl carbonate, ethyl chloro-carbonate and ethyl orthoformate, as well as many more special reagents such as acid chlorides. However, excluding a large number of reactions leading to the formation of derivatives of acids, it is doubtful whether any of these reagents compares at all favorably with carbon dioxide in the replacement of the —MgX group by a carboxyl group. Other different acids have been synthesized from the Grignard reagent by such compounds as sulfur dioxide, carbon disulfide and carbonyl sulfide.

Undoubtedly, temperature is the most important factor affecting the yields of acids prepared from carbon dioxide. Bodroux[3] showed in a striking manner that the yield of *p*-bromo- and *p*-chlorobenzoic acids is increased markedly with a lowering of temperature. Concurrently, the yields of ketones formed by a side reaction suffer a corresponding decrease. Some of the conclusions which Meyer and Tögel[4] drew from a large number of quantitative experiments concerned with the preparation of benzoic acid have been questioned and misinterpreted by Schroeter.[5] Grignard[6] has shown that prolonged heating and the use of an *excess* of RMgX compound leads to the formation of tertiary alcohols. The authors find that extensive refluxing subsequent to the passage of sufficient carbon dioxide to use up all the RMgX compound has no appreciable effect on the yield. The results of all these authors under the specific conditions of heating which they mention are probably correct.

Schmidlin[7] reports an excellent yield (83%) of triphenylacetic acid when carbon dioxide is bubbled through a refluxed ether solution of triphenylmethylmagnesium chloride. This is an outstanding exception to the now generally accepted harmful effect of elevated temperature. It is rather interesting that the same author with Hodgson[8] obtained a poor yield of *p*-tritolylacetic acid. This is due largely to the difficulty of preparing *p*-tritolylmethylmagnesium chloride.

The time of addition of carbon dioxide has extended over wide limits. Zelinsky[9] prepared a number of acids and considered the reaction completed when carbon dioxide had been passed in for five to ten minutes. Under these conditions he reported a 60% yield of benzoic acid from phenylmagnesium iodide. Houben[10] continued the bubbling of car-

[2] Grignard, *Ann. chim. phys.*, [7] **24,** 433 (1901).

[3] Bodroux, *Bull. soc. chim.*, [3] **31,** 24–30 (1904).

[4] Meyer and Tögel, *Ann.*, **347,** 55 (1906).

[5] Schroeter, *Ber.*, **40,** 1584 (1907).

[6] Grignard, *Compt. rend.*, **138,** 152 (1904).

[7] Schmidlin, *Ber.*, **39,** 628 (1906).

[8] Schmidlin and Hodgson, *Ber.*, **41,** 438 (1908).

[9] Zelinsky, *Ber.*, **35,** 2692 (1902).

[10] Houben, *Ber.*, **35,** 2519 (1902).

bon dioxide up to 12 hours in a preparation of *p*-bromobenzoic acid from *p*-bromophenyl magnesium bromide.

The use of solid carbon dioxide has been reported by Bodroux,[3] and by Spencer and Stokes[11] who also used solid phenylmagnesium iodide.

In some cases carbon dioxide has been added simultaneously with the formation of the Grignard reagent. Two typical cases will suffice to illustrate the desirability, at times, of such a procedure. First, Houben[12] used it in the preparation of vinyl acetic acid from allyl bromide. This is a generally necessary procedure in the preparation of allyl types, because the allylmagnesium halide first formed reacts rapidly with more allyl halide to give diallyl and magnesium halide. Second, Malmgren[13] added carbon dioxide during the reaction of bromocamphor and magnesium to get camphor carboxylic acid. Although the reaction was delayed, he reports an 11% improvement in yield over that obtained when carbon dioxide is added subsequently to the formation of the RMgX compound. This procedure is desirable sometimes when the formation of an RMgX compound is so retarded that considerable external heat must be applied. Under such conditions the Grignard reagent may react with unaltered RX compound to give an R-R compound and magnesium halide.

The yields reported for a number of acids vary quite widely at times. Some of the higher yields appear to be unreasonable, even though the reaction with carbon dioxide is an excellent one and may give yields approaching those calculated when based on the quantity of RMgX actually available. By way of illustration, two have reported yields of 90–98% of α-naphthoic acid based on α-bromonaphthalene. In some studies on the yields of RMgX compounds, Gilman and McCracken[14] estimated that the yield of α-naphthylmagnesium bromide is about 70%. Because of the high yields reported for α-naphthoic acid, this value was subsequently checked and re-checked. A probable reason for such discrepancies, where solid acids are involved, lies in the impurity of the acid. Such acids may not be wholly dry and may be contaminated with by-products. In the present work on benzoic acid it was found that more reliable data are to be found when the supposedly dry acid is titrated with standard alkali. This procedure of estimation has generally shown a smaller yield of acid than the weight of product warrants.

By-products invariably accompany the formation of acid by this method. Even with the favorable conditions determined for the preparation of *n*-valeric acid, small amounts of *n*-octane, *n*-butyl alcohol, *n*-butyl-*n*-valerate and tri-*n*-butyl carbinol[15] were obtained. It is probable that a very small quantity of di-*n*-butyl ketone was also present although none was found. All of these compounds are typical of generally observed

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[11] Spencer and Stokes, *J. Chem. Soc.*, **93**, 68 (1908).

[12] Houben, *Ber.*, **36**, 2897 (1903).

[13] Malmgren, *Ber.*, **36**, 2608 (1903).

[14] Gilman and McCracken, THIS JOURNAL, **45**, 2462 (1923).

[15] This compound was first prepared in the Eastman Kodak Laboratories from butylmagnesium bromide and ethyl *n*-valerate. The constants of our product agree with the constants of theirs: b. p., 113° (15 mm.), and n^{20}, 1.4245.

side reactions. In addition, smaller amounts of other by-products are sometimes noted. For example, Meyer and Tögel[4] have identified triphenylmethane in the preparation of benzoic acid. They account for this by the reducing action of unchanged magnesium and the acid used in hydrolysis.

A consideration of some of these by-products is of interest in connection with a change of manipulation used in this Laboratory for the preparation of some acids otherwise obtained in poor yields. First, the formation of ketone and tertiary alcohol is dependent obviously on an excess of RMgX compound. Second, Grignard[6] has shown that even at low temperatures some reaction occurs between the RCOOMgX compound and the excess of RMgX to give a tertiary alcohol. It should be possible, therefore, to decrease the extent of such side reactions by spraying the RMgX compound into an atmosphere of carbon dioxide.

This was done in connection with another study involving the preparation of α-pyrrole carboxylic acid from pyrrolemagnesium bromide and carbon dioxide. The yield so obtained exceeded by 7.5–12.5% that reported by Oddo.[16] The only other difference in the two methods is in the preparation of the pyrrolemagnesium halide. For this purpose ethylmagnesium bromide was used instead of methylmagnesium iodide.[17] The same spraying procedure was used in the valeric acid studies. Here, only a slight improvement in yield was noted. Probably the side reactions mentioned take place to a less extent with cooling in the preparation of valeric acid than is the case in the preparation of α-pyrrole carboxylic acid. Although the method involves but little extra effort it is recommended for special cases only.

Chemicals and Apparatus

The organic halides, with the exception of iodobenzene which was redistilled, were stock chemicals of standard purity. Anhydrous ether was prepared from the ordinary, commercial variety by first washing with saturated calcium chloride solution, then drying over calcium chloride and finally over sodium. It was then distilled and collected over sodium. The benzene was distilled over sodium. The carbon dioxide, obtained directly from a cylinder, was passed successively through concd. sulfuric acid, calcium chloride and phosphorus pentoxide.

The reactions were carried out in a 500cc. three-necked flask provided with a dropping funnel, mercury-seal stirrer and condenser. Two runs were usually made at the same time using two small motors, as it was found that the viscous nature of the product made a pulley arrangement impracticable. A flowmeter was used to measure the rate of addition of carbon dioxide.

In the experiments in which the Grignard reagent was sprayed into an atmosphere of carbon dioxide, an ordinary, thick-walled, wide-mouthed bottle of about 1 liter capacity was fitted with a 4-holed rubber stopper. The ether solution of butylmagnesium bromide was allowed to drop slowly onto vanes about two-thirds removed from the bottom of the bottle. Vanes were also attached to the bottom of the stirrer.

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[16] Oddo, *Gazz. chim. ital.*, **39**, 649 (1909).

[17] Work of Mr. R. M. Pickens.

Experimental

Procedure.—The butylmagnesium bromide was prepared in each run under like conditions and with the same quantities of reagents except in those experiments in which the volume of ether alone was varied; 4.8 g. or 0.2 mole of magnesium turnings was placed in the flask, and 65 cc. of ether added; 27.4 g. or 0.2 mole of butyl bromide, weighed to 0.001 g., was transferred to the dropping funnel. Complete transfer was insured by washing the weighing flask with two 15cc. portions of ether. These washings together with an additional 55 cc. of ether were added to the butyl bromide.

The ether solution of halide was added at room temperature, over a period of an hour, to the well-stirred mixture.

Cyclo-hexylmagnesium chloride, phenylmagnesium bromide and phenylmagnesium iodide were prepared in the same manner in 0.2 *M* quantities.

Analysis.—When the addition of carbon dioxide was completed, the reaction product was hydrolyzed with iced 5% sulfuric acid. The ether and water layers were poured together into a 3-liter round-bottom flask and steam-distilled; 1500 cc. of distillate was collected and titrated with 1.7352 *N* sodium hydroxide, using phenolphthalein as an indicator.

Practically all of the acid was obtained in this manner. Three successive 200cc. aliquot portions of distillate were generally found to contain 0.64%, 0.36% and 0.20%, respectively, of the approximately 75% of valeric acid.

The distillate was tested a number of times for sulfate and bromide to insure the absence of sulfuric and hydrobromic acids.

Another possible error might have been due to the hydrolysis during steam distillation of any butyl valerate formed by side reactions. Check experiments using a weight of ester in considerable excess of that formed in a run, showed the error due to valeric acid from this source to be well under 1%.

A number of experiments were checked and several were re-checked. These showed that duplicate runs agreed within 2%.

The *cyclo*-hexyl carboxylic acid was analyzed in the same manner as the valeric acid. However, the benzoic acid was estimated by a different method. Here steam distillation was not used. The solid obtained after working up the ether layer in the customary manner was dried and then analyzed by titration. This was done by dissolving an aliquot portion of the somewhat crude acid in 50% alcohol and titrating with standard sodium hydroxide. Experiments with pure benzoic acid, analyzed under corresponding conditions, indicated that the error involved was less than 0.5%.

All yields are based on the quantity of organic halide used.

Discussion and Conclusions

The effects of several factors were studied. Because the temperature influence appeared to be of primary importance it was studied first. Succeeding variations in conditions incorporated where possible the earlier found optimum factors.

Temperature.—The 0.2 mole of butylmagnesium bromide in 300 cc. of ether was treated with 45 liters of carbon dioxide, which is about 9 times the calculated quantity. The exit tube of the gas was just over the surface of the solution. Using a so-called average rate of stirring, about 845 revolutions per minute, the carbon dioxide was admitted at the rate of $^1/_2$ liter per minute.

With no exterior cooling, and the ether allowed to boil gently because of the heat of reaction, the yield was 47.3%. Cooling by means of circulating tap water at a temperature of 16° increased the yield to 75.2%. At 0° the yield was 78.9% and at —15° it was 78.7%.

Apparently, nothing is to be gained by cooling below 0° in the preparation of aliphatic acids. It appears, however, from some of the results of others[3,4] that an ice-salt mixture can be used with advantage in the preparation of aromatic acids.

Concentration of Butylmagnesium Bromide in Ether.—Using a temperature of 0° and retaining the other conditions mentioned above, it was found that the volume of ether could be progressively decreased from 300 cc. to 150 cc. without producing any appreciable effect on the yield. With the 0.2 mole of butylmagnesium bromide in 100 cc. of ether, the yield dropped to 70.8%. The limiting factor under the designated conditions is determined largely by the consistency of the reaction mixture. Obviously, when the volume of solvent becomes too small, stirring is impeded considerably and as a consequence the rate of reaction is retarded.

Pressure.—At 0° and with 150 cc. of ether, several experiments with various small pressures of carbon dioxide gave yields corresponding with those obtained when no pressure was used. Pressures up to 3 cm. of mercury were used.

Rate of Addition of Carbon Dioxide.—It was shown that the rate of admission for the 45 liters of carbon dioxide previously used (namely, $^1/_2$ liter per minute) was, by a purely fortuitous circumstance, the best under the conditions. The yield dropped to 72.1% and 64.4% when the rates were one liter and 1.5 liters per minute, respectively. Nothing is gained by a rate slower than $^1/_2$ liter per minute.

Quantity of Carbon Dioxide.—With 30 liters of carbon dioxide instead of 45 liters, the yield dropped 4%. An additional drop of 10% was noted when 15 liters was used. There appears to be practically no advantage in the use of more than 45 liters of carbon dioxide. Actually, a slight drop was noted in two runs when 75 liters was used.

It is quite probable that a quantity less than 45 liters can be used without impairing seriously the yield if a slower rate is adopted. However, it is equally certain that a liberal excess of carbon dioxide over that required theoretically must be used when the gas is not kept confined, as is the customary procedure in the preparation of acids by this method.

Rate of Stirring.—As was to be expected, the yield is affected considerably by the rate of stirring. The yield of acid suffered a very decided drop (about 40%) when the rate of stirring was lowered from 845 to 200 revolutions per minute. Conversely, by increasing the rate of stirring, about the same yield could be obtained in much less time from 45 liters of carbon dioxide. At 2000 revolutions per minute and a rate of 1.5 liters per minute, the yield was only slightly less than that at 845 revolutions per minute and a rate of $^1/_2$ liter per minute.

Refluxing After the Addition of Carbon Dioxide.—After the carbon dioxide has been added, it appears that refluxing for as long as 6.5 hours has no effect on the yield. However, as the previously enumerated yields under "**Temperature**" indicate, the yield drops decidedly when the solution is allowed to reflux during the addition of carbon dioxide.

Mode of Addition of Carbon Dioxide.—In all of the experiments already mentioned, the carbon dioxide was admitted in such a manner that the entry tube was about 12 mm. above the surface of the ether solution. Practically no variations in yields were noted when this distance was either slightly increased or decreased, and when the entry tube was extended either to the middle or to the bottom of the solution. Furthermore, there appeared to be but a slight improvement in yield when the butylmagnesium bromide was thoroughly sprayed into an atmosphere of carbon dioxide.

It is recommended that the entry tube be slightly above the surface of the ether solution. In this way, the frequently observed difficulty of clogging is overcome without any impairment of yield.[18]

The Yields of Some Other Acids

Benzoic acid, prepared under the optimum condition described for valeric acid, was obtained in yields of 71.5% and 72.5% from phenylmagnesium bromide. Refluxing for eight hours subsequent to the addition of carbon dioxide gave a yield of 69.5%. The same acid prepared from phenylmagnesium iodide gave yields of 32.5% and 35.4%. Freshly distilled iodobenzene raised the yield to 46%. All of these runs were made in 0.2 M quantities. The yields were determined by titrating aliquot portions of the solid reaction product with standard alkali.

Under corresponding conditions, cyclo-hexane carboxylic acid was obtained in a 68% yield.

The yield of cyclo-hexanesulfinic acid prepared from cyclo-hexylmagnesium chloride and sulfur dioxide was 28%. This yield is undoubtedly low because of oxidation by the air to the corresponding sulfonic acid. Generally, the sulfinic acids prepared by this method are used in the form of their more stable salts.

The authors wish to express their appreciation to Mr. L. C. Heckert for some preliminary experiments on this work and for valuable suggestions.

Summary

A study has been made of some of the factors that influence the yield in the preparation of *n*-valeric acid from *n*-butylmagnesium bromide and carbon dioxide.

AMES, IOWA

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[18] Dr. H. T. Clarke of the Eastman Kodak Co., has used this method for some time.