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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Comparison of the Reactions of Grignard Reagents and Dialkylmagnesium Compounds in Addition, Reduction, and Enolization Reactions[1]

DWAINE O. COWAN AND HARRY S. MOSHER

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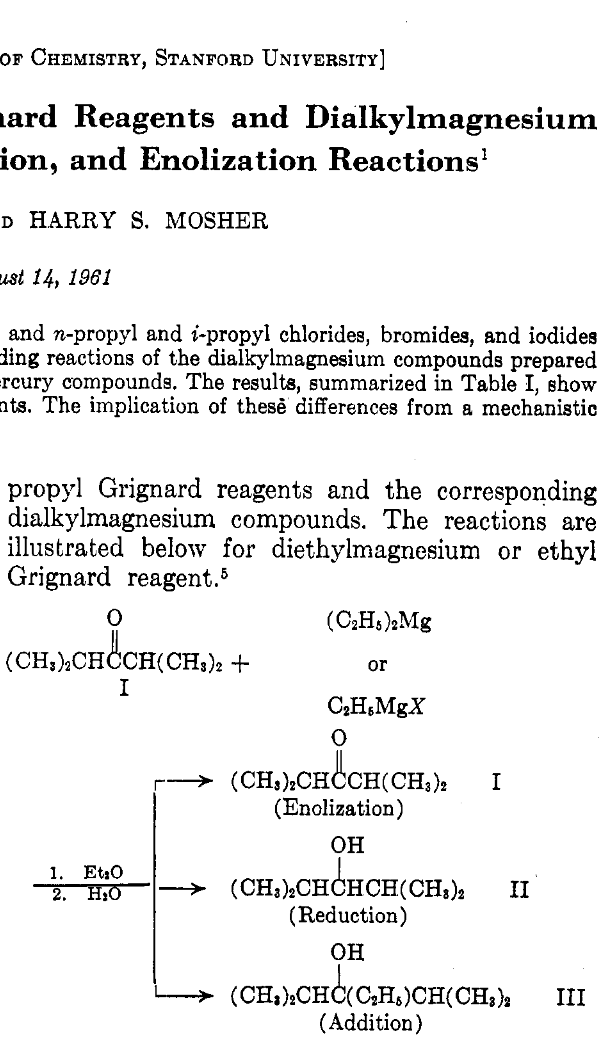
The reactions of the Grignard reagents from ethyl bromide and *n*-propyl and *i*-propyl chlorides, bromides, and iodides with diisopropyl ketone have been compared to the corresponding reactions of the dialkylmagnesium compounds prepared both *via* the dioxane precipitation method and the dialkylmercury compounds. The results, summarized in Table I, show very interesting differences between these two types of reagents. The implication of these differences from a mechanistic point of view are discussed.

It has been postulated repeatedly that the Grignard reagent is $R_2Mg \cdot MgX_2$ and the recent definitive work of Dessy and coworkers[2] adds strong support to this postulate. In spite of the many times Grignard reagents and dialkylmagnesium compounds have been used, we are unaware of any previous study dealing specifically with a comparison of these two reagents with simple carbonyl compounds. The differences in the enolization reaction of these two types of reagents with benzoin and related compounds have been studied carefully by Wright and co-workers[3] and the reactions of of these two reagents with epoxides have been thoroughly studied and reviewed.[4]

We have now made a study of the yields of addition, reduction, and enolization products from diisopropyl ketone with ethyl, *n*-propyl, and *i*-propyl Grignard reagents and the corresponding dialkylmagnesium compounds. The reactions are illustrated below for diethylmagnesium or ethyl Grignard reagent.[5]



$$(CH_3)_2CH\overset{O}{\overset{\|}{C}}CH(CH_3)_2 + \begin{matrix}(C_2H_5)_2Mg\\ \text{or}\\ C_2H_5MgX\end{matrix}$$

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$$\xrightarrow[2.\ H_2O]{1.\ Et_2O} \begin{cases} (CH_3)_2CH\overset{O}{\overset{\|}{C}}CH(CH_3)_2 & \text{I} \quad \text{(Enolization)}\\ (CH_3)_2CH\overset{OH}{\overset{|}{C}}HCH(CH_3)_2 & \text{II} \quad \text{(Reduction)}\\ (CH_3)_2CH\overset{OH}{\overset{|}{C}}(C_2H_5)CH(CH_3)_2 & \text{III} \quad \text{(Addition)}\end{cases}$$

METHOD

Dialkylmagnesium compounds were prepared by two methods. The addition of dioxane to a Grignard reagent and the subsequent removal of the suspended magnesium halide-dioxane complex by centrifugation,[6] while simple, in our experience did not

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[1] We acknowledge with gratitude the support of this investigation by a grant from the National Science Foundation.

[2] (a) R. E. Dessy, G. S. Handler, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **79**, 3476 (1957); (b) R. E. Dessy and G. S. Handler, *J. Am. Chem. Soc.*, **80**, 5824 (1958); (c) R. E. Dessy and R. M. Jones, *J. Org. Chem.*, **24**, 1685 (1955).

[3] (a) G. F. Wright, *J. Am. Chem. Soc.*, **61**, 1152 (1939); (b) C. A. Guthrie, E. Y. Spencer, and G. F. Wright, *Can. J. Chem.*, **35**, 873 (1957).

[4] (a) S. Winstein and R. B. Henderson in Elderfield's *Heterocyclic Compounds*, Wiley, New York, 1950, Vol. I, p. 55; (b) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Non-metallic Substances*, Prentice-Hall, New York, 1954, p. 967.

[5] The conventional formula C_2H_5MgX is used to symbolize the Grignard reagent without implying that this is its precise structure.

[6] C. R. Noller and W. White, *J. Am. Chem. Soc.*, **59**, 1354 (1937).

TABLE I

REACTION OF DIISOPROPYL KETONE WITH ORGANOMAGNESIUM COMPOUNDS

Organomagnesium Compound[e]	Organomagnesium Ketone Ratio[c]	% Yields[f] of			Material Balance[h]
		Enolization	Reduction	Addition	
EtMgBr	1.3[a]	1	21	78	98
	1.5	1	19	80	96
	2.5	1	15	84	—
	1.2[g]	2[g]	21[g]	77[g]	100[g]
Et_2Mg [R_2Hg]	1.4	9	41	50	—
Et_2Mg [R_2Mg]	1.4	8	40	52	100
by gas analysis	1.4	11[i]	38[i]	52[i]	—
Et_2Mg [Dioxane]	1.4	11	36	52	95
	2.5	1	18	81	95
n-Pr. MgCl	1.2	2	51	46	96
	1.2	1	51	48	—
	2.5	1	37	62	—
n-Pr MgBr	1.2	1	64	35	99
	1.4[g]	2[g]	60[g]	36[g]	98[g]
n-Pr MgI	1.2	2	69	30	99
$(n\text{-}Pr)_2Mg$ [Dioxane]	1.2	14	54	32	100
	1.3[d]	12	58	31	101
$(n\text{-}Pr)_2Mg$[R_2Mg]	1.2[a]	9	57	34	103
	1.3	11	55	34	102
i-Pr MgCl	1.2	28	72	0	100
i-Pr MgBr	1.2	31	69	0	98
	1.4[g]	29[g]	65[g]	0	94[g]
i-Pr MgI	1.4	30	70	0	100
$(i\text{-}Pr)_2Mg$ [Dioxane]	1.2	48	52	0	97
	1.5	41	59	0	99
$(i\text{-}Pr)_2Mg$ [R_2Mg]	1.3[b]	62	38	0	—

[a] Triple sublimed magnesium was used in these reactions in place of Baker's Grignard Magnesium. We are indebted to the Dow Chemical Co., Midland, Mich., for this sample of highly purified magnesium. [b] The solution of diisopropylmagnesium contained a large amount of basic magnesium, probably in the form of $(Et_2O)_2Mg$ as described in the experimental section. [c] This ratio is No. equiv. organomagnesium compound/No. equiv. ketone where equivalents refer to available alkyl group. [d] The ether and dioxane in these reageuts was removed by heating at 80–100° at 0.2 mm. pressure for one hour and the reagent then redissolved in ether. [e] The formula RMgX refers to the standard Grignard reagent whatever its actual structure in ether solution may be. The designation $R_2Mg[R_2Hg]$ refers to reagent synthesized *via* the dialkyl mercury compound; R_2Mg [Dioxane] refers to reagent prepared by the dioxane precipitation procedure. [f] These per cent yields are the relative yields of these three products obtained by gas chromatographic analysis. The analytical procedure was standardized by use of known standard mixtures. [g] Values from experiments by F. C. Whitmore and S. George [*J. Am. Chem. Soc.*, **64**, 1239 (1942)]. [h] This represents the total amounts of all the products based on the weight of crude concentrated reaction mixture and its analysis by gas chromatography. [i] These percent yields are based on gas analysis by mass spectrometry; the ethane representing enolization, ethylene reduction, and addition deduced by difference.

remove all of the halogen. Furthermore, we found that dioxane was still retained even when the ether solution of di-*n*-propylmagnesium was evaporated to dryness and the residue heated for several hours at 0.2 mm. and at a temperature above 100°. Thus it became necessary to show that the halogen and dioxane present in the dialkylmagnesium solution did or did not affect the distribution of products upon reaction with the ketone, 2,4-dimethyl-3-pentanone. The second but less convenient method of preparing dialkylmagnesium compounds *via* the dialkylmercury derivatives[7] eliminates any question about the effect of small amounts of dioxane or halogen. The reactions were carried out in diethyl ether by the normal addition procedure. The products, after isolated by the usual method, were fractionated and analyzed by gas chromatographic procedures.

RESULTS

It was observed that the results from the use of the dialkylmagnesium compounds were the same, within experimental variation, whether the reagent was made by the dioxane precipitation procedure or *via* the dialkylmercury intermediate (Table I). Secondly, it was found that substitution of an equivalent quantity of a dialkylmagnesium compound for the Grignard reagent in the reaction with diisopropyl ketone resulted in an *increase in enolization and reduction at the expense of addition* (Table I). In the experiments where isopropyl Grignard reagent or diisopropylmagnesium was used, no addition was observed. Replacement of the Grignard reagent by the dialkylmagnesium reagent

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(7) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **49**, 2328 (1927).

TABLE II

Preparation of Dialkylmercury Compounds

Grignard Reagent	Grignard, Moles	$HgCl_2$, Moles	Yield G.	Yield %	B.P. °C.	B.P. Mm.	n_D^{20}
i-Propyl	1.7	0.68	170	87	39–41	2	1.5329
n-Propyl	0.8	0.33	84	89	65–67	8	1.5164
Ethyl	1.0	0.40	69	67	53–56	15	1.5450

in this example resulted in an increase in the enolization and a decrease in the reduction product.

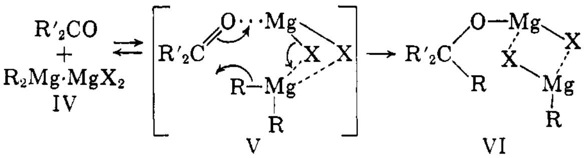
The third important result was the significantly different ratios of addition to enolization and reduction products observed when the Grignard reagents prepared from the chloride *versus* bromide or iodide were compared. A striking exception was found, however, for the *reactions of isopropylmagnesium halides where no addition products were formed;* in this case the ratio of enolization to reduction product was invariant with the halogen of the isopropyl Grignard reagent employed.

DISCUSSION

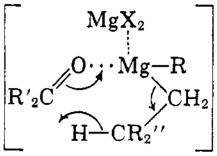
Several conclusions can be drawn from these results. Because of the differences found in the reactions with the Grignard reagents and dialkylmagnesium compounds, it can be concluded that the active species in the Grignard reagent is *not* R_2Mg unassociated with magnesium halide. The only alternate way in which the observed differences might be explained and still have the same reactive species in both reagents (namely R_2Mg complexed with ether but not magnesium halide) is to assume that the magnesium halide complexed with the carbonyl compound instead of the dialkylmagnesium and that the differences arose by virtue of this. The profoundly greater electrophilic nature of the magnesium atom in a dialkylmagnesium compound than of the oxygen atom in a ketone makes this alternative extremely unlikely.

It is well known that the nature of the halogen in the Grignard reagent influences the distribution of products in Grignard reactions. Shine[8] has concluded that the extent of "anomalous reaction"—*i.e.*, reduction and enolization—depends upon the nature of the halogen of the Grignard reagent. In all of Shine's experiments some addition and/or condensation occurred but we have found that in the reaction of isopropyl Grignard reagents with diisopropyl ketone where no addition and no condensation occurred, the same amounts of reduction and enolization products were formed regardless of the halogen of the Grignard reagent. Thus it appears that, in this example, reduction and enolization are unaffected by the nature of the halogen and it is in fact the normal addition reaction which varies with the change in the halogen atom of the reagent. From this it may be concluded that in those cases where addition occurs, reduction and enolization are affected by a change in the halogen of the Grignard reagent in the sense that, with three competing reactions, a change in one—*i.e.*, addition—would result in a change in the other two as well. There are three fundamental ways in which the nature of the halogen might influence the course of the Grignard reaction: first, through the making or breaking of a halogen bond; second, by virtue of the greater inductive effect in going from iodide to bromide to chloride; and third, the increased steric effect in going from chloride to bromide to iodide. These results seem to indicate that, whatever the mechanism which is operating here, the effect of the halogen is more important in the addition reaction than the reduction and enolization reactions.

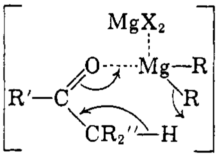
The mechanism for the Grignard addition reaction previously postulated on kinetic evidence[9] in which the halogen is directly involved as a halogen bridge as represented in V would be in accord with this finding, as both the steric nature of the halogen as well as its inductive effect would be crucial in determining the rate of the reaction. It would certainly have an effect, but very likely a lesser one, on the course of the reduction and enolization processes by the postulated mechanisms, VII and VIII, respectively, for these competing reactions. Mechanistically, enolization and reduction with the dialkylmagnesium compounds would differ from that with the Grignard reagent only in the complexing of solvent instead of magnesium halide for the first stage of the reaction. This leaves unanswered the details concerning the mechanism of the *addition reaction with the dialkyl-*



IV V VI



VII



VIII

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[8] H. J. Shine, *J. Chem. Soc.*, 8 (1951).

[9] J. Miller, G. Gregoriou, and H. S. Mosher, *J. Am. Chem. Soc.*, **83**, 3966 (1961).

magnesium compound which cannot go by a process strictly analogous to V (unless solvent molecules or alkyl groups act as bridges between the magnesium atoms).

When the amount of ethyl Grignard reagent in excess was increased in the reaction with diisopropyl ketone, only a minor effect was observed on the ratio of products. However, increasing the amount of dialkylmagnesium reagent so that only one of the two alkyl groups present in each molecule was necessary for reaction shifted the ratio of products to values not far from those observed for the reaction with the Grignard reagent. It is not surprising that there should be a substantial difference in the reactivity of, and the distribution of products from, the first and second R groups of R_2Mg. It is established in the related trialkylaluminum compounds (R_3Al) that Grignard-like addition takes place with the first alkyl group, but that dialkylalkoxyaluminums (R_2AlOR) are inert to further addition.[10]

We are continuing these investigations with a kinetic study on the reaction of dialkylmagnesium compounds parallel to that conducted with Grignard reagents[9] and by experiments designed to isolate the first and second stages of the Grignard and dialkylmagnesium reactions with carbonyl compounds.

EXPERIMENTAL

Reagents. Alkyl halides, used in preparation of Grignard reagents, were fractionated through a 500 × 15 mm. column packed with 3/32″ Pyrex helices and fitted with a total-reflux, variable take-off still head. The halides after fractionation were shown to contain only trace impurities by gas liquid partition chromatography.

Diisopropyl ketone, 2,4-dimethyl-3-pentanone, was made by the oxidation of 2,4-dimethyl-3-pentanol with potassium dichromate using the method of Whitmore and Laughlin[11] and fractionated through the column described above. Gas liquid partition chromatography on a Carbowax column indicated that the center cuts contained less than 1% of second component which was not removed by refractionation and proved to be 3-hexanone, presumably formed from 3-hexanol which was not removed by fractionation from the starting material.

Preparation of Grignard Solutions. Grignard solutions were prepared in the conventional manner in about 1.5 molar concentration using Mallinckrodt anhydrous ether and either Baker's Grignard Magnesium or triple sublimed magnesium, both of which gave the same results in these experiments. The Grignard solutions were filtered by forcing them out of the reaction flask under nitrogen pressure through a glass wool plug into a graduated flask. All subsequent transfers were made with a nitrogen siphon. The concentration of the Grignard reagent was established by titration of an acid hydrolyzed aliquot with standard base using phenolphthalein as the indicator.[12]

Dialkylmagnesium compounds via dialkylmercury intermediates. Dialkylmercury compounds were prepared by a modification of the method of Reynolds, Dessy, and Jaffe.[13] A typical example of this method is the preparation of diisopropylmercury.

To an *ether* solution (1 l.) containing 1.7 moles of Grignard reagent from isopropyl chloride was added dropwise 185 g. (0.68 mole) of mercuric chloride dissolved in 400 ml. of anhydrous tetrahydrofuran. The addition required six hours during which time the solution was rapidly stirred. After addition of the mercuric chloride was complete, the thick white slurry was refluxed by heat from an infrared lamp for four hours and then allowed to stand overnight. The excess isopropyl Grignard was decomposed with 100 ml. of water and the reaction mixture was poured into a liter of water and ice to dissolve the magnesium chloride formed in the reaction. The organic layer and the ether extracts of the aqueous layer were combined and dried over magnesium sulfate. After the ether and tetrahydrofuran had been removed under a column, the residue was vacuum distilled to give 170.1 g. (87%) of diisopropylmercury. Other dialkylmercury compounds prepared in this manner are listed in Table II.

Pyrex Carius bomb tubes containing 0.15 mole of the dialkylmercury compound and 0.3 mole of sublimed magnesium turnings were sealed and heated in a tube furnace for 24 hours at 115–120°. The tubes were cooled in liquid nitrogen and opened under a nitrogen atmosphere. The contents of the tubes were extracted with anhydrous ether, the extract centrifuged, and siphoned under nitrogen pressure into a calibrated flask. Titration, as in the determination of Grignard solutions, indicated at 81% conversion of diethylmercury, and 89% conversion of di-*n*-propylmercury into the corresponding dialkylmagnesium compounds. The reaction with diisopropylmercury was erratic. There was an apparent reaction on heating it with magnesium, a gray powder replaced the magnesium turnings and liquid diisopropylmercury, yet the ether extract of the gray powder did not give a positive Gilman test for organomagnesium compounds and titration indicated the absence of basic magnesium in any form. The gray powder reacted with H_2O to give large quantities of a gas which was shown to be 99+% hydrogen by Orsat analysis. It was suspected that diisopropylmagnesium, when formed, decomposed at this temperature into propylene and magnesium hydride. The reaction in the presence of ether was partially successful. Two Carius bomb tubes, each containing 10 g. (0.035 mole) diisopropylmercury, 1.6 g. (0.066 mole) magnesium (sublimed), and 25 ml. of anhydrous ether, were heated for 24 hours at 130° C. Titration for basic magnesium indicated a 42% yield of diisopropylmagnesium. The amount of dialkylmagnesium compound determined by gas-analysis established that the actual yield was 19%. This means that 23% of the basic magnesium calculated as diisopropylmagnesium was in some other form. Hydrolysis of an aliquot of this solution and subsequent analysis of the ether solution by GLPC showed that a large amount of ethyl alcohol was present. The reaction of diisopropylmagnesium with oxygen would have given isopropyl alcohol. We are forced to ascribe the formation of the ethyl alcohol to cleavage of the ether solvent. The one reaction carried out using diisopropylmagnesium was from this preparation (Table I).

Magnesium hydride formation could also be a minor side reaction in the preparation of diethylmagnesium and di-*n*-propylmagnesium, but as it is insoluble in ether[14] it would not interfere with later reactions.

Dialkylmagnesium compounds by the dioxane precipitation method.[2] To a rapidly stirred Grignard solution prepared in the usual manner, from the chlorides, bromide, or iodide slowly was added 1.3 moles of anhydrous purified dioxane per mole of Grignard. After stirring for 24 hours the

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(10) K. Ziegler, *Experientia*, Suppl. #2, 14, 279 (1955).

(11) F. C. Whitmore and K. C. Laughlin, *J. Am. Chem. Soc.*, **54**, 4392 (1932).

(12) H. Gilman, E. Zoellner, and J. Dickey, *J. Am. Chem. Soc.*, **51**, 1576 (1929).

(13) G. F. Reynolds, R. E. Dessy, and H. H. Jaffe, *J. Org. Chem.*, **23**, 1217 (1958).

(14) D. T. Hurd, *Chemistry of the Hydrides*, Wiley, New York, 1952, p. 51.

precipitate was removed from the resulting slurry by centrifugation. The supernatant solution was transferred to a graduated storage vessel by means of a nitrogen pressure siphon which excluded air at all times. The concentration of the organomagnesium compound was determined by titration of an acid hydrolyzed aliquot with standard base using phenolphthalein as the indicator. The yields of the dialkylmagnesium compound by this method varied from 62–76%.

Reaction of Grignard reagent and dialkylmagnesium compounds with diisopropyl ketone. In each reaction 11.4 g. (0.1 mole) of diisopropyl ketone, diluted to 50 ml. with anhydrous ether, was added over a period of 2 hours to a rapidly stirred solution of the organomagnesium compound. The concentration of the organomagnesium compound was adjusted before the reaction so that it would be approximately 1 *N*. The number of equivalents[15] of organomagnesium compound per 0.1 mole of ketone can be obtained by multiplying a particular value in column 2, Table I, by 0.1. In reactions involving both Grignard and dialkylmagnesium compounds it was noted that as each drop of ketone hit the solution a faint yellow color developed and immediately disappeared. The temperature of the reaction mixture during addition was maintained between 30 and 35°. After addition was completed, the solution was stirred for two additional hours at room temperature and then allowed to stand overnight. The reaction mixture was hydrolyzed with just enough water so that the magnesium hydroxide formed was crystalline.[16] The ether solution was decanted from the crystals of magnesium hydroxide and the precipitate was washed several times with anhydrous ether. Combined ether solutions were dried over a small amount of anhydrous magnesium sulfate and most of the ether removed by fractionation through a 2 ft. column packed with 1/8-in. Pyrex helices. The product ratios were determined by gas-liquid partition chromatography of the residue. Values were calculated from area per cent in comparison with known standard mixtures. The material balance was obtained in the same way based on the total weight of concentrated reaction mixture. The accuracy of the values for the ratio of the products was slightly better than the values determined for the material balance, as the latter included the determination of the amount of solvent ether in the concentrate which was the major component.

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[15] By definition: 1 equivalent of Grignard equals 1 formula weight of $RMgX$ or $^1/_2$ formula weight of $R_2Mg \cdot MgX_2$; 1 equivalent of dialkylmagnesium equals $^1/_2$ formula weight of R_2Mg.

[16] B. F. Landrum and C. T. Lester, *J. Am. Chem. Soc.*, **74**, 4954 (1952).

[CONTRIBUTION FROM THE DEWEY & ALMY A.-G.]

Reaction of Metallic Sodium with Naphthalene.[1] Dihydronaphthalenedicarboxylic Acids-1,4 and -1,2 and Related Compounds

THEODOR M. LYSSY[2]

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The reaction product of the carbonation of sodiumnaphthalene was investigated. It consists of an isomeric mixture of dihydronaphthalenedicarboxylic acids, the carboxyl groups being in position 1,4 and 1,2, in agreement with the mechanism proposed by D. E. Paul, D. Lipkin, and S. I. Weissmann.[3] The isomers of dihydronaphthalene-and tetralindicarboxylic acid-1,4 and -1,2 and the anhydrides of the 1,2-acids were isolated and/or prepared, and the configuration thereof demonstrated. The ΔpK^*_{MCS} values of the dicarboxylic acids are discussed.

J. F. Walker and N. D. Scott[4] were the first to describe the preparation of dihydronaphthalenedicarboxylic acids from sodiumnaphthalene and carbon dioxide in ethereal solvents. In the course of their investigation they found two product fractions. One contained a dicarboxylic acid, m.p. 230°, which is practically insoluble in hot or cold water. The authors claimed to have isolated 1,4-dihydronaphthalenedicarboxylic acid-1,4 (IIa/IIIa); however, it was later shown by Stanley Hsi-Kwei Jiang[5] that the acid in question was 1,2-dihydronaphthalenedicarboxylic acid-1,4 (IVa). None of the authors reported any stereo isomers. The other acid fraction (m.p. range 140–180°) which is readily soluble in hot water and organic solvents was said to consist of 1,2-dihydronaphthalenedicarboxylic acid-1,2.[4]

1,2-Dihydronaphthalenedicarboxylic acid-1,2 and related compounds are described extensively by K. Alder and K. Triebeneck[6] who treated maleic anhydride with α-bromostyrene in boiling toluene to receive, after subsequent elimination of hydrogen bromide, followed by saponification, 1,2-dihydronaphthalenedicarboxylic acid-1,2 (XIIIa/XVIIa).

Methods. Ultraviolet spectroscopy was used to establish the position of double bonds. *Infrared spectroscopy* was helpful in isolated cases. The *micro titrations* of the dicarboxylic acids were carried out by the method of W. Simon and E.

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[1] Part of this work was presented at the spring meeting of the Swiss Chemical Society, February 1960, in Geneva, Switzerland.

[2] Present address: Department of Chemistry, Swiss Federal Institute of Technology, Zurich, Switzerland (ETH).

[3] D. E. Paul, D. Lipkin, and S. I. Weissmann, *J. Am. Chem. Soc.*, **78**, 116 (1956).

[4] J. F. Walker and N. D. Scott, *J. Am. Chem. Soc.*, **60**, 951 (1938).

[5] Stanley Hsi-Kwei Jiang, *Hua Hsüeh Pao*, **23**, 351 (1957); *Chem. Abstr.*, 15481 (1958).

[6] K. Alder and K. Triebeneck, *Ber.*, **87**, 237 (1954).