

of cryolite in the different salt solutions in all cases, excepting ferric chloride, follows in the order of the solubility of the corresponding sodium salts. Ferric chloride solutions act normally in concentrations up to 10.0 molar, at which point the solubility reaches a maximum then falls below that of the sulfate and continues to decrease with any further increase in concentration. This difference in behavior is in accord with the facts of the case and may be readily interpreted by a consideration of the ferric chloride-sodium chloride system.

It will be seen also that cryolite dissolves to a greater extent in aluminum salt solutions and that the amount dissolved is practically the same for the different iron and aluminum salts at the lower concentrations. Undoubtedly, in these dilute solutions a considerable portion of the cryolite is

dissolved at the expense of the free acid resulting from the hydrolysis of the salts.

### Summary

The solubility of cryolite has been determined at 25° over a wide range of concentrations in aqueous solutions of iron and aluminum chloride, nitrate and sulfate. It has been found that the solubility was greatest in the aluminum salt solutions, and that the amount dissolved by the different salts was in all cases, excepting ferric chloride, in the order of the solubility of the corresponding sodium salt.

An explanation of the mechanism of the reaction has been offered based on the formation of a double salt.

PHILADELPHIA, PENNA.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 143]

## Condensations by Sodium. VII. A General Method for Stopping the Wurtz Reaction at the Intermediate Organo-Metallic Stages

BY AVERY A. MORTON AND INGENUIN HECHENBLEIKNER

Previous work<sup>1</sup> has revealed that alkyl sodium compounds, if formed as intermediates in the Wurtz synthesis, are stable only at low or moderate temperatures. Their great reactivity enables the final stage of reaction with more alkyl chloride to be completed easily. Such considerations suggested that a Wurtz synthesis might be stopped at this intermediate point if the reaction were carried out at low temperatures in the presence of excess sodium. Experiments have amply confirmed this conclusion. When *n*-amyl chloride was added gradually with stirring to a suspension of sodium sand in pentane or ligroin, the mixture stirred until after no more evolution of heat occurred, and the product carbonated, there was obtained both caproic and butylmalonic acids. The yield of combined acids, around 50% in many experiments, was sufficiently high to remove any suspicion that they were formed because of a concurrent reaction during carbonation. The general application of this method for obtaining organo-metallic compounds was demonstrated by runs with butyl halides (chloride, bromide and iodide), and a secondary, a tertiary and an aromatic chloride.

(1) Morton and Hechenbleikner, *THIS JOURNAL*, **58**, 1024 (1936).

So far the best yield, 57% of total carboxylic acids, has been obtained with *n*-amyl chloride. Other chlorides in order of decreasing yield are *n*-hexyl chloride, chlorobenzene, *n*-butyl chloride, *t*-amyl chloride, 2-chloro-3-methylbutane and *n*-propyl chloride. Factors such as the temperature at which the reagents could be induced to react, the thermal stability of the resulting organo-metallic compound, and the readiness with which the product reacts with more organic chloride to complete a Wurtz synthesis, must be considered in each case. The first attempts were unsuccessful because the importance of these factors was not recognized. Subsequent experiments with amyl chloride demonstrated the possibilities under controlled conditions and the preliminary test with other halides confirmed the conclusion that the proper factors for preparation of organo-metallic compounds by direct action of sodium on the chloride had indeed been recognized.

An earlier discovery of an organo-metallic compound in a Wurtz synthesis has been recorded in some interesting work by Gilman and Wright,<sup>2</sup> who studied the action of sodium-potassium alloy on 3-iodofuran. A very small yield, 0.5%, of 3-

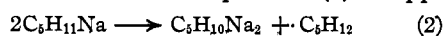
(2) Gilman and Wright, *ibid.*, **55**, 2893 (1933).

furoic acid was obtained. The obtention of the organo-metallic compound in that instance was ascribed to the extraordinary inertness of iodine in 3-iodofuran.

Continued evidence of the formation of a dicarboxylic acid from a monohalogen compound has been found in this work. The over-all equation for amyldiene disodium used in calculating the yields of butylmalonic acid is

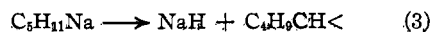


A possible mechanism by which amyldiene disodium could be formed is by dismutation of amyldiene sodium as illustrated in equation (2). Oppor-



tunity was found to test this idea and adverse conclusions were drawn. In two series of experiments the intermediate sodium compounds were subjected to the action of heat, first at 60° and then at 80°. The products were carbonated and caproic and butylmalonic acids isolated. It was found that the yield of caproic acid progressively decreased with extended time at these temperatures, that a quantity of tarry acids appeared and continually increased with added severity of conditions, and that the amount of butylmalonic acid was unchanged. Amyldiene sodium was thus seen to be unstable thermally but amyldiene disodium was not one of the primary decomposition products.

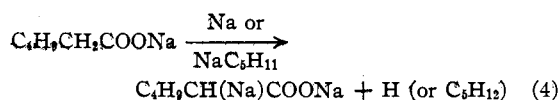
These facts permit a similar dismissal of any manner of thermal decomposition of the monosodium compound as a source of malonic acid. One such mechanism is shown in equation (3) which represents amyldiene sodium decomposing to sodium hydride and amyldiene.



The bivalent carbon atom would then add two atoms of sodium giving amyldiene disodium. Carothers and Coffman<sup>3</sup> found good reasons for suggesting such a breakdown to explain their results with ethyl sodium. Our attempts to apply a parallel decomposition with amyldiene sodium have been without success as judged by the unchanged yield of the malonic acid. Negative tests for sodium hydride, reported in the previous paper on the action of sodium on diamyl mercury, while not conclusive by themselves, are nevertheless in full agreement with the view that equation (3) does not represent the decomposition of this compound.

(3) Carothers and Coffman, *THIS JOURNAL*, **51**, 588 (1929).

The same authors have also pointed out that the hydrogen atoms in "sodium ethide" may be considered as being slightly acidic and capable of further replacement by sodium. An acidic nature of the hydrogen adjacent to sodium in amyldiene sodium was not revealed in our study of the feasibility of applying equation (2) to our results. It is possible, however, to derive a type of acidity from the presence of a carboxyl group and to consider that such a reactive hydrogen would be displaced by either sodium metal or the sodium in amyldiene sodium<sup>4</sup> after the manner set down in equation (4). Against this idea can be cited the fact



that no increased yield of butylmalonic acid was observed (a) when a large (over 100%) excess of sodium sand was used in the reaction; (b) when amyldiene sodium was formed in the presence of freshly prepared sodium caproate. The observation of Bachmann and Clarke<sup>5</sup> that sodium acting on isoamyldiene bromide gave some pentadecane as well as the expected decane adds weight to the view that the disodium intermediate was formed prior to carbonation.

A reasonably safe conclusion can be drawn at this time that the malonic acids formed in the sodium condensations being reported in this series do not arise from any reaction of an intermediate alkyl sodium. Our data do not permit a differentiation between the plausible free radical-disproportionation path and the direct formation of an idene intermediate by splitting out of hydrogen chloride (Michael's mechanism).<sup>6</sup>

In addition to the discovery of a general method of interrupting the Wurtz synthesis, and the elimination of amyldiene sodium as a source of the malonic acid, a brief comment might be made on the surprising stability of amyldiene disodium. A period of fourteen hours of heating at 80° left the amyldiene disodium practically unaffected as contrasted with the 63% decomposition of amyldiene sodium under the same conditions.

### Experiments

The reactions were carried out in a 3-necked 250-ml. flask provided with a mercury-sealed stirrer, dropping funnel, condenser, nitrogen inlet tube and thermometer.

(4) We are grateful to a reviewer on a previous article for the suggestion of a reaction with amyldiene sodium.

(5) Bachmann and Clarke, *THIS JOURNAL*, **49**, 2097 (1927).

(6) Michael, *Am. Chem. J.*, **25**, 419 (1901).

TABLE I  
 REACTIONS IN PENTANE

Constant factors: sodium sand, 12 g. in 50 ml. of *n*-pentane unless otherwise noted; *n*-amyl chloride, 25 ml. dissolved in 50 ml. of *n*-pentane unless otherwise noted.

No.	Addition of RX Time, min.	Temp., °C.	Stirred after Time, hrs.	addition Temp., °C.	Caproic acid		Butylmalonic acid		Total car- boxylic acid, %
					G.	%	G.	%	
1	75	0-2	0.5	O-R <sup>a</sup>	4.9	22	2.2	13	35
2	75	0-4	13 <sup>b</sup>	R	5.0	22.7	3.9	24	47
3	90	0	3	37-39	7.1	32	2.5	15.3	47
4	90	18-22	0.5	18-22	5.1	22.8	3.5	21.8	45
5	75 <sup>c</sup>	36-38	.25	36-38	7.5	33.8	2.6	16.2	50
6	90 <sup>d</sup>	36-38	.25	36-38	7.9	35.6	2.5	15.3	51

<sup>a</sup> Room temperature. <sup>b</sup> No stirring during this period. <sup>c</sup> Amyl chloride added undiluted with any pentane.

<sup>d</sup> Amyl chloride added undiluted to 12 g. of sodium sand in 200 ml. of pentane.

TABLE II

EFFECT OF TEMPERATURE ON STABILITY OF INTERMEDIATE COMPOUNDS

Constant factors: sodium sand, 10 g. in 50 ml. of E. K. Co. ligroin, b. p. 90-120°; *n*-amyl chloride (E. K. Co. technical grade), 20 ml. in 50 ml. of ligroin; time required for addition of the alkyl chloride to sodium was 75 min. unless otherwise indicated; temperature 18-22°

No.	Stirred after addition Time, hrs.	Temp., °C.	Caproic acid		Butylmalonic acid		Total car- boxylic acids, %
			G.	%	G.	%	
7	1	20	3.2	16	2.4	17	33
8	14	R	3.2	16	2.2	16	32
9	0.8	60	2.5	13	2.4	18	31
10	2	60-65	1.9	10	2.3	17	27
11	0.5	77	2.5	13	2.0	15	28
12	1	78	1.7	9	1.8	13	22
13	1	80	1.7	9	1.9	14	23
14	1	80	0.8	4	3.1	23	27
15	14	80	1.2	6	2.0	15	21
16 <sup>e</sup>	0.3	60-62	1.3	7	9.5	7	14

<sup>e</sup> Ninety minutes required for addition of alkyl chloride, temperature 60-62°.

The sodium sand (from a stock quantity made by stirring 500 g. in hot kerosene) was placed in the flask with the desired solvent and the organic chloride added through the dropping funnel. Usually a little over an hour was required for addition. Stirring was continued for some period afterward, at least until no more heat was given off by the reaction. The temperature at any stage of the process was regulated by a bath or by the boiling point of the solvent. The color of the reaction mixtures usually changed from purplish-blue to green and red (on heating) during the reaction. Carbon dioxide was finally admitted (all colors disappeared) and the products separated in the same manner as described in the earlier paper.<sup>7</sup> Yields were calculated on the basis of the halide added. In Tables I and II (the numbering of the runs is for convenience in reference only) experiments in *n*-pentane (E. K. Co. practical grade) and in ligroin, respectively, are described. Attempts were made to isolate the products from pyrolysis of amyl sodium in experiments 9 to 15. Tarry acids insoluble in water and ligroin were found. The amount qualitatively increased with greater severity of the pyrolysis conditions. Only a poorly crystalline product

(7) Morton, LeFevre and Hechenbleikner, THIS JOURNAL, 58, 754 (1936).

TABLE III

COMPARISON OF BUTYL IODIDE, BROMIDE AND CHLORIDE

Constant factors: alkyl chloride dissolved in 25 ml. of *n*-pentane; sodium sand in 75 ml. of same solvent; temperature 0-5° during addition of the alkyl halide; one hour required for addition of alkyl chloride except in number 18 in which the time was two hours; one hour of stirring at room temperature after addition of alkyl chloride was completed

No.	Halide	Sodium,		Valeric acid		Propyl-malonic acid		Total carboxylic acids, %
		G.	g.	G.	%	G.	%	
17	Butyl iodide	13	50	Trace		Trace		
18	Butyl bromide	20	55	0.49	3.3	0.80	7.5	10.8
19	Butyl chloride	20	36	1.32	5.9	1.27	7.9	13.8

TABLE IV

EFFECT WITH OTHER ORGANIC CHLORIDES

Constant factors: *n*-pentane used as a solvent in all runs except in No. 21 where ligroin was employed; organic halide dissolved in 25 ml. of solvent; sodium sand (12 g. in all runs except in No. 24 where 10 g. was used) in 75 ml. of the solvent; one and one-half hours required for addition of the chloride

No.	Chloride,	ml.	Temp. during addition, °C.	Mono-acid		Di-acid	
				G.	%	G.	%
20	2-Chloro-3-methylbutane	25	Room	Traces		Traces	
21	Chlorobenzene	25	<sup>a</sup>	5	16.8		
22	<i>t</i> -Amyl chloride	25	37-38 <sup>b</sup>	0.15	0.7		
23	<i>n</i> -Hexyl chloride	30	37-38 <sup>c</sup>	5.1	17.6	1.74	9.2
24	<i>n</i> -Propyl chloride	20	45-20 <sup>d</sup>	Traces		Traces	

<sup>a</sup> Reaction started by addition of 1 ml. of *n*-hexyl chloride. Before carbonation the mixture was allowed to stand fourteen hours after addition was completed. <sup>b</sup> After addition and before carbonation the stirring was continued for one hour. <sup>c</sup> Stirring continued for one-half hour after addition and before carbonation. <sup>d</sup> Reaction started by addition of 5 ml. of *n*-hexyl chloride. The traces of acid products may be due to this starting agent. The mixture was stirred for one-half hour after addition and before carbonation.

could be isolated from the crude mass. A titration of the acidity on the dried sample indicated that one carboxyl group per amyl residue was present. The amount was too small for further identification.

TABLE V

## RESULTS WITH OTHER ALKALI METALS

Constant factors: *n*-amyl chloride (E. K. Co. tech. grade) 20 ml.; metal sand in 100 ml. of ligroin

No.	Metal	G.	Total time, hrs.	Caproic acid G.	%	Butylmalonic acid G.	%
25	Potassium	19	2.5 <sup>a</sup>	0.27	1.4	0.07	0.5
26	Lithium	4	0.7 <sup>b</sup>	.36	1.9	.36	2.7

<sup>a</sup> Two hours required for addition of amyl chloride. Mixture stirred for one-half hour longer before carbonation. <sup>b</sup> Upon addition of the first 5 ml. of amyl chloride the temperature rose to 80°. The mixture was cooled to 35° and the remainder of the amyl chloride added at once. Stirring was continued one-half hour more before carbonation.

that the pyrolysis of sodium amyl did not lead to amyldiene disodium; (g) the decidedly lower yield for both mono- and dicarboxylic acids when the temperature during addition of alkyl chloride to sodium was raised (reaction no. 16) to 62°.

In Tables III and IV the results with a number of other halides are given. The general method of separation of the mono- and the dicarboxylic acids was the same as described before.

Comparison of butyl iodide, bromide and chloride, Table III, showed that there was an increasing amount of interruption in the order named. This difference was not surprising in view of the common opinion of decreased activity of the halogen atoms in progressing from iodide to chloride. The butyl sodium formed in the initial phase can be assumed to react less readily with the least reactive halide and therefore can be isolated in larger amounts from the chloride reaction. The list in Table IV shows the results with a secondary, an aromatic and a tertiary chloride. In addition, experiments on two more primary chlorides

TABLE VI

## MISCELLANEOUS EXPERIMENTS

Constant factors: sodium sand in 50 ml. of ligroin unless otherwise indicated; amyl chloride in 50 ml. of ligroin unless otherwise indicated

No.	Sodium, g.	Amyl chloride, ml.	Addition Time, min.	Temp., °C.	Stirred after addition Time, min.	Temp., °C.	Carbonation temp., °C.	G.	Caproic %	Butylmalonic G.	%	Total carboxylic acids, %
27	20	20	75	22	60	30	25	8.5	44.2	1.6	12.5	57
28	10 <sup>a</sup>	15	40	25	180	20	30	4.4	30	1.7	14.8	45
29 <sup>b</sup>	10	20	45	28	..	..	..	8.1	42	1.5	11.1	53
30 <sup>c</sup>	12	25		0	30		0 <sup>e</sup>	7.5	31	1.3	8	39
31	20 <sup>d</sup>	40 <sup>e</sup>		-25	10	-25	0	10.7	27.7	0.78	2.9	31
32 <sup>f</sup>	10 <sup>g</sup>	20	30		60	80	30	1.5	7.5	1.2	8.8	17
33	10	20	180	22	60	22	30	6.7	34.6	1.5	10.7	45
34	10	20	23	20	30	25	30	4.6	24	1.3	9.9	34
35	10	20	<sup>h</sup>	20		20	20	5.1	26.6	1.8	13.8	41

<sup>a</sup> The sodium was first fused with 1.5 g. of mercury and then made into sand in the usual way. <sup>b</sup> Carbon dioxide was passed through the mixture during the addition. No oxalic acid was found among the products. <sup>c</sup> Pentane used as a solvent. Temperature rose to 20° during carbonation. <sup>d</sup> 10 ml. of solvent used. <sup>e</sup> 40 ml. of solvent used. Toward the end of the reaction the mass became so viscous that 50 ml. more ligroin was added. <sup>f</sup> *n*-Octane used as a solvent. <sup>g</sup> Only 30 ml. of solvent used with the sodium. <sup>h</sup> Half of the alkyl chloride added, and product carbonated after which the remainder was added, followed by a final carbonation.

Special attention is called to (a) the nearly complete agreement in respect to yields of reaction 7 and 8, although in the latter case the mixture stood thirteen hours before carbonation; (b) the constancy of the yields of butylmalonic acid which in 12 out of 16 runs varied between 13 and 17% in spite of wide fluctuations in time and temperature conditions to which the amyldiene disodium intermediate was subjected; (c) the surprising stability of the amyldiene disodium compound which in fourteen hours' heating at 80° (run No. 15) was not appreciably decomposed; (d) the lack of thermal stability of the monosodium compound as exemplified by decreasing yield of caproic acid (to 10%) as the period of heating at 60° before carbonation was extended in reactions 9 and 10; (e) the greater thermal instability of the mono-sodium compound at the 80° level in reactions 11 to 15 where the yield of caproic acid fell to around 6%; (f) the general failure to observe any gain in butylmalonic acid in spite of a great loss of caproic acid (see reactions 9 to 15) thereby showing

are given. No attempt was made to discover the conditions which were best for each compound. A major difficulty was in getting the reaction started. The yield of benzoic acid was not in agreement with what might have been expected from the inactivity of the halogen atom in chlorobenzene (compare with *n*-hexyl chloride) which might suggest that an inactive halogen atom was not the only factor involved in isolation of intermediate products.

For the experiments with other alkali metals, Table V, potassium sand was prepared by shaking the metal in ligroin solution; lithium sand by stirring in hot kerosene. Potassium, the most active metal, reacted with such vigor that amyl chloride had to be added very slowly. Less than 2% of carboxylic acid was obtained. Since lithium is the least active of the alkali metals, a high yield could be expected. Lithium alkyl compounds have been shown already<sup>8</sup> to be isolable in benzene solution and capable of

(8) Ziegler and Colonius, *Ann.*, **479**, 135 (1930).

being used in the same manner as the Grignard reagent. The unfortunately low yields of carboxylic acids which we obtained upon carbonation are not due therefore to any absence of the intermediate lithium alkyl but to the formation of secondary products as already shown by Gilman and Van Ess.<sup>9</sup> The position of the alkyl sodium appears to be unique in that it lacks the reactivity necessary to complete the Wurtz reaction under these conditions, yet does not participate in the formation of secondary products with sodium caproate.

Data for a number of miscellaneous experiments are set down in Table VI. Many of these runs were made in an effort to locate some factor which would lead to increased yields of butylmalonic acid. Special mention can be made of (a) the effect of using over 100% excess of sodium sand—reaction No. 27—which resulted in a maximum yield of 57% of combined carboxylic acids; (b) the failure to obtain an improved yield of butylmalonic acid in No. 28 from the simultaneous presence of mercury, a test inspired by the higher yields of this acid in some of the experiments reported in the previous paper on the action of sodium on di-*n*-amyl mercury; (c) the failure of the simultaneous presence of carbon dioxide to increase materially the yield of combined organic acids over what was obtained when the *n*-amyl chloride was first allowed to react until long after all evidence of reaction—judged by a temperature rise—had ceased; (d) the failure to note any marked increase in the

yield of malonic acid in reaction No. 35 when *n*-amyl chloride was added to sodium in the presence of freshly prepared sodium caproate in order to test the validity of equation 4; (e) the continued constancy in the yields of butylmalonic acid in runs 27, 28, 29 and 35.

### Conclusions

The Wurtz reaction can be interrupted at the intermediate organo-metallic stage if the alkyl halide is added to excess sodium at low or moderate temperatures. The reaction has been studied in some detail with *n*-amyl chloride and has been tested in a preliminary way with a number of other organic halides.

In the case of *n*-amyl chloride, caproic and butylmalonic acids were obtained upon carbonation. The yield of combined acids in one instance was as high as 56%.

The formation of the malonic acid by way of the monosodium compound has been shown to be unlikely.

Amylidene disodium is thermally more stable than *n*-amyl sodium.

(9) Gilman and Van Ess, *THIS JOURNAL*, **55**, 1258 (1933).

CAMBRIDGE, MASS.

RECEIVED JUNE 12, 1936

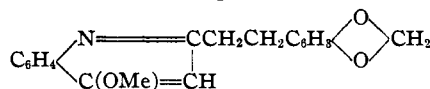
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

## Researches on Quinazolines. XLIII. The Synthesis of a Quinazoline Derivative Structurally Analogous to Cusparine

BY DOMENICK PAPA<sup>1</sup> AND MARSTON TAYLOR BOGERT

In a recent communication<sup>2</sup> from these Laboratories, there was described the synthesis of quinazoline derivatives akin structurally to the angostura alkaloids galipine and galipoline.<sup>3</sup>

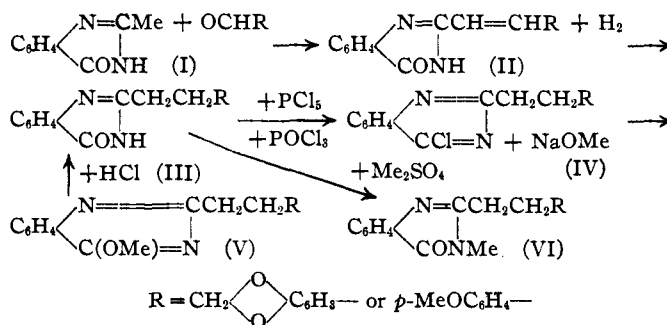
The most important angostura alkaloid, however, is cusparine



The synthesis of its quinazoline analog is described in the following pages. The *p*-methoxyphenylethyl derivatives were also prepared, because they correspond, respectively to the galipoline and galipine analogs referred to above, but possess one less methoxyl group, and it seemed desirable

therefore to include them in the series for pharmacological examination.

The steps involved in these syntheses were the following



### Experimental

**2-*p*-Methoxystyryl-4-quinazolone (II).**—A mixture of 5 g. of 2-methyl-4-quinazolone (I) and 4.5 g. of *p*-anisaldehyde was heated for two hours at 170–175°. It liquefied after half an hour of heating and at the end of two hours

(1) Fritzsche Fellow in Organic Chemistry, Columbia University, 1935–1936.

(2) Marr and Bogert, *THIS JOURNAL*, **57**, 729 (1935).

(3) Through an unfortunate error in proofreading, this alkaloid appears in that article as "galipine."—M. T. B.