tion at 25° $10^5 K_{(\text{therm})} = 11.5$, compared to 1.76 for acetic acid and 4.88 for phenylacetic acid).[15] It may be mentioned here that the high dissociation constant for diphenylacetic acid might also be explained as a steric phenomenon along the lines of reasoning of Smith and McReynolds.[16]

Ethyl Cyclohexylacetate.—The kinetics of the saponification of ethyl cyclohexylacetate are strikingly similar to those for ethyl isovalerate and ethyl β-methylvalerate as indicated in Table V.

TABLE V

KINETICS OF SAPONIFICATION

Ethyl ester	10^3k_{25}	E, cal. mole^{-1}
Cyclohexylacetate	0.509	15,600
Isovalerate[12]	.427	15,700
β-Methylvalerate[6]	.411	15,700

In consideration of the structural similarities of the three esters, it seems probable that here the prime factor governing the influence of substituents is a spatial one. In this connection it is interesting to note that ethyl diisopropylacetate and ethyl dicyclopentylacetate, either of which may be compared structurally with ethyl diphenylacetate, were found by von Braun and Fischer[17] to be practically unsaponifiable. That ethyl diphenylacetate saponifies at all, then, may be attributed solely to the magnitude of the $-I$ due to two phenyls, which causes a lowering in E.

The general results given here seem to warrant the statement that although the phenyl group does have a negative inductive effect, this may be subservient to a much more powerful steric influence on both reaction rate and activation energy. By analogy it would seem likely that substitution of various alkyl groups in aliphatic esters affects saponification velocity chiefly through their steric effect, rather than by virtue of differences in the positive inductive effect $(-I)$ usually attributed to them.

Summary

1. The kinetics of saponification in 85% aqueous ethanol have been studied for ethyl phenylacetate, ethyl hydrocinnamate, ethyl γ-phenylbutyrate, ethyl δ-phenylvalerate, ethyl hydratropate, ethyl phenylethylacetate, ethyl diphenylacetate and ethyl cyclohexylacetate at four temperatures.

2. Evidence of the negative inductive effect attributed to phenyl is indicated.

3. The steric influence of phenyl in the α-position upon the rate and energy of activation for the saponification of these esters is of greater import to the kinetics of the reaction than is any polarization effect due to phenyl.

4. Analogy suggests that alkyl groups substituted in the acyl part of esters of aliphatic acids affect saponification kinetics chiefly through their steric influence.

BETHLEHEM, PA. RECEIVED JULY 5, 1940

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[15] Dippy and Williams, *J. Chem. Soc.*, 161, 1888 (1934).

[16] Smith and McReynolds, THIS JOURNAL, **61**, 1965 (1939).

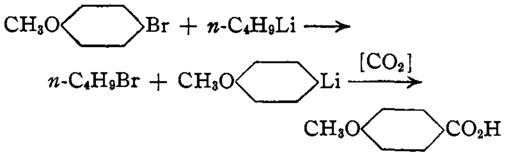
[17] Von Braun and Fischer, *Ber.*, **66**, 101 (1933).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE, AND PANHANDLE AGRICULTURAL AND MECHANICAL COLLEGE]

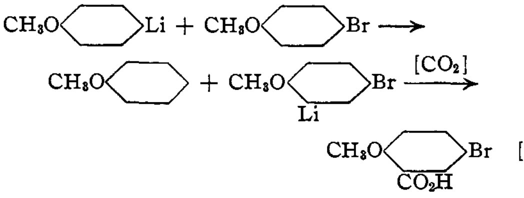
Some Interconversion Reactions of Organolithium Compounds

BY HENRY GILMAN, WRIGHT LANGHAM AND FRED W. MOORE

The Two-stage Metalation of Some Aryl Halides.—Evidence was presented in an earlier paper for the two-stage metalation of 2-bromodibenzofuran.[1a,b] A similar mechanism is also involved with *p*-bromoanisole and *p*-iodoanisole in their reactions with *n*-butyllithium.[1b]



[I]



[II]

That is, interconversion first takes place in ac-

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[1] (a) Gilman, Cheney and Willis, THIS JOURNAL, **61**, 951 (1939). (b) Gilman, Langham and Willis, *ibid.*, **62**, 346 (1940). (c) The only cases are those noted recently with 2,4,5-triphenyl-3-chlorofuran and phenylethynyl chloride in studies by Messrs. Melstrom and Haubein. (d) Wittig, Pockels and Dröge, *Ber.*, **71**, 1903 (1938); see, also, Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938). (e) Professor Wittig (private communication) has examined the reaction of the halogenoanisoles with phenyllithium. (f) Marvel, Hager and Coffman, THIS JOURNAL, **49**, 2323 (1927).

cordance with reaction [I] as is evidenced by the formation of *n*-butyl halide and *p*-methoxyphenyllithium, which on carbonation yields *p*-methoxybenzoic acid. Then the *p*-methoxyphenyllithium metalates the *p*-bromoanisole, in accordance with reaction [II] to give 2-methoxy-5-bromophenyllithium.

It is now clear that the nature of the reactants determines whether or not a halogen–metal interconversion reaction precedes a hydrogen–metal interconversion reaction or metalation, and the extent of such a two-stage process when it does occur. For example, *p*-chloroanisole and *n*-butyllithium react to give a 75% yield of 2-methoxy-5-chlorophenyllithium. Any yield in excess of 50% would rule out a complete two-stage process inasmuch as one-half the *p*-chloroanisole would be converted to anisole (reaction [II]) if the active metalating agent were *p*-methoxyphenyllithium and not *n*-butyllithium. Furthermore, a two-stage metalation of *p*-chloroanisole would involve a chlorine–lithium interconversion, and such a reaction has been observed exceedingly rarely.[1c] The nature of the RLi compound can be highly significant, for *p*-bromoanisole and *phenyl*-lithium give a 75% yield of 2-methoxy-5-bromophenyllithium.[1d]

p-Fluoroanisole reacts vigorously with *n*-butyllithium to give only a 12% yield of 2-methoxy-5-fluorobenzoic acid subsequent to carbonation.[1e] Despite the low yield of metalation product it is highly probable that no two-stage reaction is involved here because there is no known case of a fluorine–lithium interconversion reaction.

β-Bromostyrene and *n*-Butyllithium.—In the first study of the halogen–metal interconversion reaction using *n*-butyllithium, one of the RX compounds examined was β-bromostyrene.[1f] After allowing equivalent quantities of these reactants in petroleum ether (b. p. 35–50°) to stand for thirty-eight days in a sealed tube, the mixture was hydrolyzed and yielded 1-phenylhexene-1 and 1,4-diphenylbutadiene-1,3. There was no indication of the formation of octane, phenylethylene or phenylacetylene. We observed that when β-bromostyrene and *n*-butyllithium were *heated* in petroleum ether (b. p., 35–50°) for twenty hours and then carbonated a 23% yield of *trans*-cinnamic acid resulted. The yield, after heating for but one hour, was 19%. A mechanism would be a halogen–metal interconversion reaction, which is of two-fold interest because it involves a so-called aliphatic halogen and also leads to the relatively rare type of vinyl- or substituted vinylalkali compound.[2]

$$C_6H_5CH{=}CHBr + n\text{-}C_4H_9Li \longrightarrow C_6H_5CH{=}CHLi \xrightarrow{[CO_2]} C_6H_5CH{=}CHCO_2H$$

The two hydrocarbons isolated earlier[1f] probably owe their formation in part to the intermediately formed β-styryllithium.

However, the reaction between β-bromostyrene and *n*-butyllithium takes a somewhat different course when the medium is ethyl ether, for carbonation gave phenylpropiolic acid in yields up to 42.5%. The phenylpropiolic acid may owe its formation to several processes, two of which follow. First, the *n*-butyllithium may have removed hydrogen bromide.

$$C_6H_5CH{=}CHBr + n\text{-}C_4H_9Li \longrightarrow C_6H_5C{\equiv}CH \xrightarrow{[n\text{-}C_4H_9Li]} C_6H_5C{\equiv}CLi \longrightarrow C_6H_5C{\equiv}CCO_2H$$

Second, there may have been initial lateral metalation, followed by the loss of lithium bromide.

$$C_6H_5CH{=}CHBr \longrightarrow [C_6H_5CLi{=}CHBr] \longrightarrow C_6H_5C{\equiv}CH \longrightarrow C_6H_5C{\equiv}CLi$$

Preferential Reactions with Polyhalogen Compounds.—The wide variety of reactions reported at this time permits some broad generalizations. (1) Metalation of aryl ethers involves hydrogen or hydrogens on carbons *ortho* to the ether linkage. (2) All types of aryl bromides and iodides undergo the halogen–metal interconversion reaction. (3) Iodides react more readily than the bromides, and chlorides[1c] and fluorides are essentially not affected. (4) There are two chief competitive reactions: halogen–metal interconversions [III] and couplings [IV].

$$RX + R'Li \longrightarrow RLi + R'X \qquad [III]$$

$$RX + R'Li \longrightarrow RLi + R'X \longrightarrow RR' + LiX \qquad [IV]$$

The coupling reaction is not only the slower reaction (when the reactants are aryl halides and alkyllithium compounds), but also often follows the interconversion reaction [III]. As the reaction time is extended the coupling reaction predominates, and eventuates in the essential disappearance of RLi compound. For example, in a reaction between bromobenzene and *n*-butyllithium the newly formed *n*-butyl bromide reacts with the phenyllithium to give *n*-butylbenzene.

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[2] Wooster, *Chem. Reviews*, **11**, 21 (1932). See, also, Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1257 (1933), and Wright, *J. Org. Chem.*, **1**, 457 (1936).

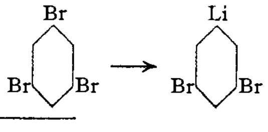
$$C_6H_5Br + n\text{-}C_4H_9Li \longrightarrow C_6H_5Li + n\text{-}C_4H_9Br \longrightarrow n\text{-}C_4H_9C_6H_5 + LiBr$$

That is, the coupling reaction of an alkyl halide and an aryllithium compound proceeds more rapidly than the coupling reaction of an aryl halide with an alkyllithium compound. Fortunately, it is possible to vary experimental conditions so that the coupling reaction is highly subordinated. A striking illustration is the 97% yield of α-naphthyllithium from α-bromonaphthalene and *n*-propyllithium.[3a]

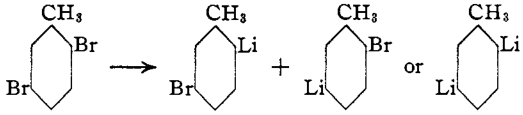
In the orienting studies we have not as yet examined extensively the coupling reactions. These coupling reactions can be numerous and varied depending on both reactants and conditions. Some of the types starting with compounds like *p*-bromoanisole and *n*-butyllithium are: (1) $p\text{-}BrC_6H_4OCH_3 + n\text{-}C_4H_9Li \longrightarrow p\text{-}C_4H_9C_6H_4OCH_3 + n\text{-}C_4H_9Br$. The *p*-butylanisole might be formed by direct coupling or by a coupling reaction which followed a halogen–metal interconversion of the kind described in reactions [III] and [IV]. (2) Coupling after the metalation of *p*-bromoanisole yields 2-methoxy-5-bromophenyllithium, either by direct metalation by *n*-butyllithium or indirectly in accordance with reactions [I] and [II]. The 2-methoxy-5-bromophenyllithium might then couple to various degrees with (a) another like molecule, (b) *p*-bromoanisole or (c) butyl bromide. These several possibilities undoubtedly are responsible for the mixtures of neutral products sometimes obtained subsequent to carbonation.

By selection of appropriate experimental conditions it should also be possible to effect preferential halogen–metal interconversion reactions with some polyhalogen compounds. This is the case, as is shown by some results now reported. Mono-interconversion has been effected with 1,3,5-tribromobenzene [A]; a mixture of the mono-isomers or the di-product with 2,5-dibromotoluene [B]; and mono- or di-interconversions with *p*-dibromobenzene, 4,4′-dibromobiphenyl, 2,4,6-tribromoanisole [C] and 4,4′-dibromodiphenyl ether.[3b]

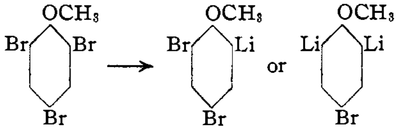
[A]



[B]



[C]



The reactions with 2,4,6-tribromoanisole supplement earlier observations on the preferential replacement of bromine or bromines which are *ortho* to an ether linkage.

Even though the yields in some of the reactions now reported are as high as 90%, no study was made of optimal conditions as was done with α-bromonaphthalene.[3a] It is quite probable that an examination of the factors varied in that study will give significant improvements, and without too much trouble by the convenient expedient of removing some aliquots from a few experiments. An additional useful experimental variation now reported involves the principle of the reaction of moderate or large quantities in consecutive small units by means of a simple apparatus like that pictured in Fig. 1 and used in several preparations described in the Experimental Part. This technique makes it possible not only to reduce local high concentrations but also to shorten the time of reaction and so decrease some secondary reactions like coupling.

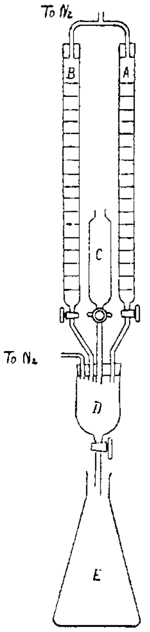


Fig. 1.

Isopropyllithium.—The Experimental Part contains an account of some modified directions for the manipulation of organolithium compounds. One of particular interest is the exclusive use of low boiling petroleum ether for the preparation of RLi compounds. Not only is petroleum ether of value in some preferential reactions, but it also makes it possible to obtain some organolithium compounds hitherto prepared with difficulty and in low yields. One of these is isopropyllithium, which could not be prepared directly at first[4a] and which was later obtained by direct reaction of isopropyl chloride and lithium in only a 20% yield.[4b] In low boiling petroleum ether, isopropyl

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(3) (a) Gilman and Moore, THIS JOURNAL, **62**, 1843 (1940). (b) See Geissman and Malatt, *ibid.*, **61**, 1788 (1939), for the reaction of hexabromobenzene with phenylmagnesium halides and phenyllithium.

(4) (a) Ziegler and Dersch, *Ber.*, **64**, 448 (1931); (b) Gilman, Zoellner, Selby and Boatner, *Rec. trav. chim.*, **54**, 584 (1935) [see Table IV on p. 592].

TABLE I

REACTION BETWEEN RX COMPOUNDS AND n-C_4H_9Li

	Halide	Mole	n-C_4H_9Li (mole)	Reaction medium	Reaction time, hours	RCOOH	%
1	C_6H_5Br	0.08	0.08	$(C_2H_5)_2O$	0.25^{a}	$C_6H_5CO_2H$	51^{b}
2	C_6H_5Br	.01	.02		.25		50.8
3	C_6H_5Br	$.05^{c}$	.05		$.5^{d}$		46
4	C_6H_5Br	...	...		1		36
5	C_6H_5Br	...	...		5		15
6	C_6H_5Br	...	...		20		Trace
7	C_6H_5Br	.05	.05		24		3.4^{e}
8	C_6H_5Br	.05	.05	Pet. ether (b. p., 35–50°)	0.25		None
9	C_6H_5Br	.05	.05	Pet. ether	24		44.8
10	C_6H_5I	.15	.15	$(C_2H_5)_2O$	0.25		49^{f}
11	C_6H_5I	.01	.02		.25		51
12	C_6H_5I	$.05^{g}$	.05		0.5, 1.0 5.0, 20		41, 27 13, trace
13	m-ClC_6H_4I	.04	.04		^{h}	m-$ClC_6H_4CO_2H$	41.5^{i}
14	p-ClC_6H_4Br	.02	.03		0.17	p-$ClC_6H_4CO_2H$	90^{j}
15	p-BrC_6H_4Br	.05	.05		.25	p-BrC_6H_4COOH	54^{k}
16	p-BrC_6H_4Br	.015	.033	Pet. ether	24	p-$HO_2CC_6H_4CO_2H$	88.7^{l}
17	1,3,5-$C_6H_3Br_3$	.016	.016	$(C_2H_5)_2O$	0.25	3,5-$Br_2C_6H_3CO_2H$	71^{m}
18	o-$BrC_6H_4CH_3$	.01	.02	$(C_2H_5)_2O$	.25	o-$CH_3C_6H_4CO_2H$	83.8^{n}
19	o-$BrC_6H_4CH_3$	.015	.033	Pet. ether	20	o-$CH_3C_6H_4CO_2H$	41.7^{o}
20	m-$BrC_6H_4CH_3$	.01	.02	$(C_2H_5)_2O$	0.25	m-$CH_3C_6H_4CO_2H$	65.4^{p}
21	m-$BrC_6H_4CH_3$	.015	.02	Pet. ether	20	m-$CH_3C_6H_4CO_2H$	46.1^{q}
22	p-$BrC_6H_4CH_3$	.05	.05	$(C_2H_5)_2O$	0.3	p-$CH_3C_6H_4CO_2H$	51^{r}
23	p-$BrC_6H_4CH_3$	.015	.033	Pet. ether	20	p-$CH_3C_6H_4CO_2H$	86.2^{s}
24	p-$IC_6H_4CH_3$	.01	.02	$(C_2H_5)_2O$	0.25	p-$CH_3C_6H_4CO_2H$	72^{t}
25	p-$BrC_6H_4C_6H_5$	.05	.05		.25	p-$C_6H_5C_6H_4COOH$	62^{u}
26	o-$BrC_6H_4OCH_3$	.01	.02		.25	o-$HO_2CC_6H_4OCH_3$	72.3^{v}
27	p-$BrC_6H_4OCH_3$	.02	.04		.17	p-$HO_2CC_6H_4OCH_3$	52^{w}
28	p-$IC_6H_4OCH_3$	.01	.02		.25	p-$HO_2CC_6H_4OCH_3$	78^{x}

[a] The mixture was allowed to stand at room temperature for fifteen minutes prior to carbonation. [b] There was recovered 20% of unreacted bromobenzene in addition to a small quantity of reddish oil. [c] Expts. 3, 4, 5 and 6 were carried out with 25-cc. aliquots of the 0.05-mole reaction mixture. [d] Room temperature; expts. 4, 5, 6 and 7 were refluxed. [e] In addition, there was isolated 31% of n-butylbenzene which was identified by physical constants and by permanganate oxidation to benzoic acid. In another experiment, a mixture of 0.11 mole of phenyllithium and 0.11 mole of n-butyl bromide was refluxed for twenty-four hours and then carbonated. The yield of benzoic acid was 0.75%, and the yield of n-butylbenzene was 75.5%. [f] Other products isolated were 8.3% of iodobenzene and 6.5% of n-butyl iodide. [g] From this 0.05-mole run, 25-cc. aliquots were withdrawn after the four different times listed to give the corresponding tabulated yields of benzoic acid. [h] Fifteen minutes were required for the addition of the m-chloroiodobenzene to the n-butyllithium. The solution turned amber in color, and carbonation was effected at once. [i] From a second experiment where carbonation was effected two minutes after the reactants were mixed, the yield of m-chlorobenzoic acid was 43%. [j] From another experiment in which the mixture was heated for twelve hours only a trace of acidic material was isolated. [k] With 0.02 mole of p-dibromobenzene and 0.04 mole of n-butyllithium and a fifteen-minute period of reaction, the yield of p-bromobenzoic acid was 78%. And with 0.01 mole of p-dibromobenzene and 0.03 mole of n-butyllithium (twenty-four-hour period of reaction), the acidic product was a mixture of p-bromobenzoic acid and terephthalic acid. It should be possible to prepare p-bromobenzoic acid in accordance with the following reaction: p-$LiC_6H_4Li + p$-$BrC_6H_4Br \rightleftarrows 2p$-$BrC_6H_4Li$. The following results are of interest in this connection. To an ether solution of 0.1 mole of p-dibromobenzene was added a very slight excess over 0.2 mole of n-butyllithium in ether. The solution was refluxed and aliquots were removed and carbonated at suitable intervals. The relative percentages of p-bromobenzoic acid and terephthalic acid (by acid titration) are included in the table which follows. After the 5.5 hour period, an excess of p-dibromobenzene was added, and the resulting mixture of acids (subsequent to carbonation) contained 99% of p-bromobenzoic acid and 1% of terephthalic acid.

Time, hours	p-$BrC_6H_4CO_2H$, %	p-$HO_2CC_6H_4CO_2H$, %
1	77	23
2.5	77	23
4	76	24
5.5	67	33

The actual yields of acids decrease with extended heating as a consequence of the coupling reaction described in the Introduction. These interconversion yields based on the mixtures of the two acids are: at the end of one hour, 93%; 2.5 hours, 82%; 4 hours, 52%; 5.5 hours, 35%;

and after adding the excess of *p*-dibromobenzene, 11%. [l] The terephthalic acid was identified as the dimethyl ester (mixed melting point). From a second preparation, 0.02 mole of *p*-dibromobenzene and 0.04 mole of *n*-butyllithium yielded 88.8% of terephthalic acid. In a third experiment a mixture of 0.015 mole of *p*-dibromobenzene and 0.033 mole of *n*-butyllithium in petroleum ether was allowed to stand for only fifteen minutes (no external heat), and the yield of *p*-bromobenzoic acid was 3.7%. [m] The 3,5-dibromobenzoic acid was identified by m. p., neutralization equivalent and melting point of its methyl ester. The ether solution of 1,3,5-tribromobenzene should be added slowly to the ether solution of *n*-butyllithium, for rapid addition results in a brown reaction mixture and a marked reduction in yield of 3,5-dibromobenzoic acid. The reaction can also be controlled by the readily accessible apparatus pictured in Fig. 1. A 0.01 mole quantity of *n*-butyllithium in 50 cc. of ether was placed in buret A, and 0.01 mole of 1,3,5-tribromobenzene dissolved in 50 cc. of ether was placed in buret B. Five cc. of ether was run into the reaction chamber D, from the dropping funnel C. The stopcocks of A and B were then regulated so that 5 cc. of solution per minute would drop from each buret into D. At one-minute intervals the stopcock to D was opened and its contents run into the flask E which contained powdered solid carbon dioxide. More ether was then run into D and the process repeated until the reaction was completed. From the carbonation mixture there was obtained 1.56 g. (56%) of 3,5-dibromobenzoic acid which melted at 214–215° without recrystallization. From the neutral fraction there was recovered 0.9 g. (28.5%) of 1,3,5-tribromobenzene. [n] With equivalent quantities of *o*-bromotoluene and *n*-butyllithium and a 15 min. reaction time at room temperature, the yield of *o*-toluic acid was 51.6%; the yield of recovered *o*-bromotoluene was 18.2%; and some *n*-butyl bromide was isolated. When aliquots were removed from a 0.05-mole run at the end of 0.5 hour, 1 hour, 5 hours and 20 hours, the respective yields of *o*-toluic acid were 44%, 31%, 17.6% and a trace. [o] In this reaction, the mixture was refluxed at 38° for 20 hours. From a corresponding experiment carried out for only fifteen minutes valeric acid was the only acidic material isolated. [p] Using equivalent quantities of *m*-bromotoluene and *n*-butyllithium, in a corresponding experiment, the products were *m*-toluic acid (50.9%), *m*-bromotoluene (26%) and 1.8 g. of *n*-butyl bromide. When aliquots were removed from a 0.05-mole run at 0.5, 1.0, 5 and 20 hours, the respective yields of *m*-toluic acid were 40, 35, 26 and 8%. [q] The reflux temperature in this experiment was between 35–40°. No *m*-toluic acid was isolated from a corresponding experiment carried out for fifteen minutes. [r] From the non-acidic fraction, there were isolated 24% of *p*-bromotoluene and 0.1 g. of di-*p*-tolyl ketone. From a corresponding experiment using 0.01 mole of *p*-bromotoluene and 0.02 mole of *n*-butyllithium the yield of *p*-toluic acid was 69.1%. When aliquots were removed from a 0.05 mole run at 0.5, 1.0, 5 and 20 hours, the respective yields of *p*-toluic acid were 50, 42, 25 and 4%. [s] A fifteen-minute experiment with *p*-bromotoluene and *n*-butyllithium gave only valeric acid. However, when the time was extended to 1.0, 5 and 22 hours, the respective yields (after refluxing in petroleum ether) were 7, 10.5 and 85% of *p*-toluic acid. [t] With equivalent quantities (0.12 mole) of reactants, there was obtained 46% of *p*-toluic acid, 20% of *p*-iodotoluene and 18% of *n*-butyl iodide. When aliquots were removed from a 0.05-mole run at 0.5, 1.0, 5 and 20 hours, the respective yields of *p*-toluic acid were 46%, 42%, 22% and a trace. The combined neutral fractions yielded 17.5% of *n*-butyl iodide. [u] In addition to the *p*-phenylbenzoic acid, there was isolated 16% of *p*-bromobiphenyl. The yield of *p*-phenylbenzoic acid in a 0.025-mole experiment was 64%. [v] From an experiment run under conditions described earlier [Gilman, Langham and Jacoby, THIS JOURNAL, **61**, 106 (1939)], there was obtained a 66% yield of *o*-methoxybenzoic acid and a 4% yield of *o,o'*-dimethoxybenzophenone. [w] Earlier references to the metalation aspect of this reaction are Gilman, Langham and Willis, THIS JOURNAL, **62**, 346 (1940), and the reference cited in footnote (*v*). [x] The crude *p*-methoxybenzoic acid gave no qualitative test for iodine. The higher yield from the iodide in contrast with the bromide is paralleled in a number of other types having various functional groups which normally react with RLi compounds.

chloride reacts smoothly with lithium to give isopropyllithium in 58% yield.

Experimental Part

The general procedure was essentially that described in preceding reports. The mixture of RX compound and *n*-butyllithium was occasionally allowed to stand at room temperature, but most often refluxed in either ether or petroleum ether (b. p. 35–50°). Carbonation was effected by pouring upon solid carbon dioxide.

The results with most of the RX compounds reported at this time are given in Table I and its accompanying footnotes. The results with others, involving a little more detail, follow the table. Then comes some general information on the preparation and manipulation of organolithium compounds, particularly in different media.

2,5-Dibromotoluene.—From a reaction mixture of 0.025 mole of 2,5-dibromotoluene and 0.025 mole of *n*-butyllithium which was carbonated after fifteen minutes, there was isolated 3.4 g. or a 63% yield of a mixture of bromotoluic acids; neut. equiv. (without purification), 214; calcd. for $(CH_3)(Br)C_6H_3CO_2H$, 215. The insoluble fraction obtained after crystallization from hot water (followed by recrystallization from dilute acetic acid) was shown to be 3-methyl-4-bromobenzoic acid (m. p. 210°) (29% yield) by catalytic debromination to *m*-toluic acid (mixed m. p.).

The other fraction was apparently 2-methyl-4-bromobenzoic acid (20.5% yield) on the basis of (1) neutralization equivalent and (2) catalytic debromination to *o*-toluic acid (mixed m. p.). However, the melting point of our 2-methyl-4-bromobenzoic acid was 158–158.5°.[5] We may be dealing here with mixed crystals. The non-acidic fraction yielded 19.2% of 2,5-dibromotoluene.

In a second experiment using 0.025 mole of 2,5-dibromotoluene and 0.03 mole of *n*-butyllithium and carbonating after two minutes, the yield of 3-methyl-4-bromobenzoic acid was 36.1% and the yield of 2-methyl-4-bromobenzoic acid was 22.3%. These yields were essentially duplicated

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(5) The melting point reported for 2-methyl-4-bromobenzoic acid is 187°, Nourrisson, *Ber.*, **20**, 1016 (1887).

in a third experiment in which the mixture was kept between 10–15° for the two minutes prior to carbonation.

There was no evidence of reaction when 0.033 mole of *n*-butyllithium in pet. ether (b. p. 35–50°) was added to 0.015 mole of 2,5-dibromotoluene in pet. ether. After refluxing for two hours a yellow flocculent precipitate started to form. Refluxing was continued for twenty hours, and then the mixture was carbonated. The resulting mixture of acids was separated by means of the barium salts to give 12.4% of 3-methyl-4-bromobenzoic acid and 51.8% of methylterephthalic acid. This latter acid melted between 320–324°, and its dimethyl ester melted at 72–73°; the corresponding values previously reported are 325–330° and 73–74°, respectively.[6]

From another petroleum ether reaction using 0.01 mole of 2,5-dibromotoluene and 0.04 mole of *n*-butyllithium and a twenty-hour period of refluxing there was obtained a 64.4% yield of pure methylterephthalic acid. *Neut. equiv.* Calcd., 90; found, 91.

3-Bromoacenaphthene.—An impure sample of 3-bromoacenaphthene (0.01 mole) and 0.015 mole of *n*-butyllithium were allowed to react for fifteen minutes prior to carbonation. The yield of 3-acenaphthoic acid, melting at 216–217° after crystallization from dilute alcohol, was 55%. *Neut. equiv.* Calcd., 198; found, 205. The acid amide melted at 198°. The corresponding reported[7] melting points are: acid, 217°; amide, 198°.

From another reaction, using 0.005 mole of 3-bromoacenaphthene and 0.01 mole of *n*-butyllithium, there was obtained 84.4% of crude acid (m. p. 206–208°) which after crystallization from dilute alcohol yielded 62% of acid melting at 216–217°.

4,4′-Dibromobiphenyl.—A solution of 0.02 mole of *n*-butyllithium in 50 cc. of ether was added to a suspension of 0.01 mole of 4,4′-dibromobiphenyl in 25 cc. of ether. At the end of fifteen minutes the dibromo compound had completely dissolved, and the mixture was then carbonated. The yield of 4-(4-bromophenyl)-benzoic acid was 65%. *Neut. equiv.* Calcd., 277; found, 280. The methyl ester melted at 130–131°. The yield of recovered 4,4′-dibromobiphenyl was 16%.

From a second experiment there was obtained 67% of 4-(4-bromophenyl)-benzoic acid and 0.7 g. or 30% of 4,4′-dicarboxybiphenyl.

In another experiment, 0.033 mole of *n*-butyllithium in 65 cc. of petroleum ether (b. p. 35–50°) was added to a suspension of 0.015 mole of 4,4′-dibromobiphenyl in 200 cc. of petroleum ether, and the resulting mixture was refluxed for twenty hours prior to carbonation. The yield of 4-(4-bromophenyl)-benzoic acid was 13%; and the yield of 4,4′-dicarboxybiphenyl was 60.6%. The dimethyl ester of the dibasic acid melted at 208–210°.[8]

Another reaction was carried out initially in petroleum ether using 0.01 mole of 4,4′-dibromobiphenyl and 0.04 mole of *n*-butyllithium. No water was circulated through the reflux condenser and the mixture was heated over a ten-hour period during which the petroleum ether was expelled, and at the end of this time the mixture in the flask was at a temperature of 78°. Subsequent to carbonation there was isolated a 91% yield of 4,4′-dicarboxybiphenyl.

β-Bromostyrene.—An ether solution of β-bromostyrene (0.05 mole) was added at once to an equimolecular quantity of *n*-butyllithium in ether. Carbonation was effected after fifteen minutes, and the yield of phenylpropiolic acid was 12.3%. This acid was identified by melting point, neutralization equivalent (calcd., 147; found, 147), and by reduction to cinnamic acid. From the neutral fraction there was recovered 47% of β-bromostyrene.

In a second experiment, the ratio of reactants was changed, and 0.05 mole of β-bromostyrene and 0.1 mole of *n*-butyllithium yielded 42.5% of phenylpropiolic acid. The recovery of β-bromostyrene was 15%.

In another experiment, a mixture of 0.025 mole of β-bromostyrene in 50 cc. of petroleum ether (b. p. 35–50°) and 0.025 mole of *n*-butyllithium in 60 cc. of petroleum ether was refluxed for twenty hours. The yield of *trans*-cinnamic acid (mixed melting point) was 23%. In addition, there was isolated 27% of β-bromostyrene and 0.1 g. of 1,4-diphenylbutadiene-1,3.

In another experiment in petroleum ether, 0.015 mole of β-bromostyrene and 0.03 mole of *n*-butyllithium were carbonated after one hour of heating to give 19% of *trans*-cinnamic acid. Carbonation at the end of ten minutes, with no heating, yielded only a trace of *trans*-cinnamic acid (m. p. 130–132°).

***p*-Chloroanisole.**—An ether solution of 0.05 mole of *p*-chloroanisole and 0.05 mole of *n*-butyllithium was refluxed for twenty hours and then carbonated. The neutral fraction yielded 11% of *p*-chloroanisole. The 5-chloro-2-methoxybenzoic acid isolated in 56% yield melted at 95°, and after recrystallization from ligroin (b. p., 70–80°) melted at 97.5°. *Neut. equiv.* Calcd., 186.5; found, 186.5. The melting point of our acid is at variance with that reported (80–82°).[9,10] However, the structure of our compound was established by three procedures. First, the acid obtained by means of *n*-butyllithium was shown to be identical with a sample prepared by the oxidation of 5-chloro-2-methoxytoluene.[10] Second, comparison (again, by the method of mixed melting points) was made with the chloromethoxy acid prepared by the action of methyl sulfate on 5-chloro-2-hydroxybenzoic acid. Third, the acid we obtained was demethylated by 80% sulfuric acid to 5-chloro-2-hydroxybenzoic acid (mixed m. p.).

From another reaction in which two equivalents of *p*-chloroanisole and one equivalent of *n*-butyllithium were used, the yield of 5-chloro-2-methoxybenzoic acid was 49%, and 42% of *p*-chloroanisole was recovered.

In a third experiment, 0.1 mole of *p*-chloroanisole was metalated by *n*-butyllithium at 51° in a 1:1 ether–benzene medium. Carbonation of aliquots after heating for 1, 5 and 15 hours gave yields in each case of 50% of crude 5-chloro-2-methoxybenzoic acid.

To examine the possibility of secondary coupling reactions that might be accelerated by heating, a mixture of 0.02 mole of *p*-chloroanisole and 0.03 mole of *n*-butyllithium was allowed to stand at 18–20° for twenty-four hours. The yield of pure 5-chloro-2-methoxybenzoic acid was 74%.

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(6) Bentley and Perkin, *J. Chem. Soc.*, **71**, 177 (1897).

(7) Gattermann and Hams, *Ann.*, **244**, 58 (1888).

(8) The reported m. p. of the dimethyl ester is 212–213°: Weiler, *Ber.*, **32**, 1081 (1899).

(9) Hirwe, Rana and Gavankar, *Proc. Indian Acad. Sci.*, **8A**, 208 (1938).

(10) Peratoner and Condorelli, *Gazz. chim. ital.*, **28**, I, 211 (1898).

p-Fluoroanisole.—To 0.1 mole of n-butyllithium in ether was added 0.1 mole of p-fluoroanisole. No external heat was applied, and within five minutes there was a violent exothermic reaction. The mixture immediately began to turn a dark, reddish-brown. Carbonation after twenty hours of heating at 34° gave a 13% yield of 5-fluoro-2-methoxybenzoic acid which melted, after recrystallization from ligroin (b. p. 70–80°), at 87°. *Neut. equiv.* Calcd., 170; found, 171.5.

From a second reaction in which the temperature was held at 24° for twenty hours, the yield of 5-fluoro-2-methoxybenzoic acid was 10%.

2,4,6-Tribromoanisole.—When 0.01 mole of 2,4,6-tribromoanisole in 25 cc. of ether was added to 0.015 mole of n-butyllithium in ether, a vigorous reaction took place and the mixture assumed a dark reddish-brown color. Immediate titration of a portion of the reaction mixture showed that most of the organometallic compounds were used up in some manner or other. Carbonation of the remainder of the reaction after ten hours of heating gave no acidic material, and the principal part of the neutral fraction was a large quantity of red-brown oil.

To better control the reaction, 0.02 mole of 2,4,6-tribromoanisole in 50 cc. of ether was treated with 0.01 mole of n-butyllithium in 50 cc. of ether, using the apparatus shown in Fig. 1. The bromo compound and the n-butyllithium were allowed to drop into the reaction chamber D from the burets A and B at the rate of 5 cc. per minute. Some reaction and discoloration were observed. The stopcock to D was opened and the contents carbonated at one-minute intervals. The total yield of acidic product was 1.4 g. and from this was obtained by means of the barium salt 1.0 g. or 16% of 3,5-dibromo-2-methoxybenzoic acid. *Neut. equiv.* Calcd., 310; found, 311. The methyl ester, prepared by means of methyl alcohol and hydrogen chloride, melted at 52–53°; the melting point reported[11] for the methyl ester is 53°. From the ether extract was obtained 52% of 2,4,6-tribromoanisole and a small quantity of reddish oil.

From a parallel reaction, using 0.1-mole quantities, there was obtained a 19.3% yield of 3,5-dibromo-2-methoxybenzoic acid. No 3,5-dibromo-4-methoxybenzoic acid was isolated from either of the reactions.

To a solution of 0.012 mole of n-butyllithium in 60 cc. of petroleum ether (b. p. 35–50°) was added at once 0.004 mole of 2,4,6-tribromoanisole in 25 cc. of petroleum ether. A heavy, flocculent, white precipitate formed at once and the mixture was carbonated after standing for ten minutes. A 75% yield of 2-methoxy-5-bromo-1,3-dicarboxybenzene, melting at 192–196° after recrystallization from water, was obtained. The structure of this acid was established by catalytic debromination to give 2-methoxy-1,3-dicarboxybenzene melting at 216°. The reported melting point is 216–218°.[12]

From another reaction using 0.01 mole of 2,4,6-tribromoanisole and 0.03 mole of n-butyllithium there was obtained 88% of 2-methoxy-5-bromo-1,3-dicarboxybenzene.

p-Bromophenyl Phenyl Ether.—A 0.01 mole quantity of p-bromophenyl phenyl ether in 25 cc. of ether was added at once to 0.02 mole of n-butyllithium in ether. Carbonation of the mixture fifteen minutes after addition gave 70% of p-phenoxybenzoic acid which was identified by a mixed m. p. determination with a specimen prepared by carbonating the Grignard reagent from p-bromophenyl phenyl ether. This reaction supports the idea that halogen–metal interconversion precedes the metalation[13] of p-bromophenyl phenyl ether.

4,4′-Dibromodiphenyl Ether.—A solution of 4,4′-dibromodiphenyl ether in 50 cc. of ether and 0.01 mole of n-butyllithium in 50 cc. of ether were added separately and dropwise to the reaction chamber (Fig. 1) at the rate of 5 cc. per minute. The reaction mixtures were carbonated at one-minute intervals, and the yield of 4-(4-bromophenoxy)-benzoic acid (mixed m. p.) was 56.3%. In addition to 30% of 4,4′-dibromodiphenyl ether there was also isolated a small quantity of unidentified silky, white leaflets melting between 188–192°.

In another experiment, 0.01 mole of 4,4′-dibromodiphenyl ether in 50 cc. of benzene was added to 0.04 mole of n-butyllithium in 100 cc. of ether. Then 150 cc. of benzene was added, and the mixture was refluxed for thirty minutes at 57–60°. From the mixture of acids was obtained 0.1 g. of 4-(4-bromophenoxy)-benzoic acid and 1.7 g. of an acid which did not melt below 300° and which is very probably 4,4′-dicarboxydiphenyl ether.[14]

Lithium.—Several procedures are now available for converting the small blocks of lithium currently available in this country to the generally more effective smaller particles.

A. By appropriate dies the lithium can be pressed out in the form of wires of suitable diameter. A rather sturdy press is necessary. Such wires are not only readily cut into pieces which are added directly to the reaction flask, but because of their uniformity their weight is readily determined by measuring the length after weighing a few of the wires to correlate weight with length. Such wires are conveniently stored in an inert solvent contained in stoppered Carius tubes.

B. In like manner, ribbons of various sizes can be pressed out and stored.

C. By the use of agitation in high-boiling inert solvents (like paraffin oil) it is possible to prepare lithium "powder" after the procedure used for the preparation of sodium powder or sand. Ordinarily, lithium of this state of aggregation is unnecessary. Furthermore, the rate of formation of lithium nitride (when nitrogen is used as the "inert" atmosphere) is markedly increased with very fine lithium.

D. Fine lithium can be prepared by means of a rasp, the particles being added directly from a weighed block of the lithium. This procedure is rather tedious and time consuming for moderately sized preparations.

E. An earlier method used a chisel, hammer and pliers. A more convenient, if not less noisy, procedure is to hammer the lithium, wet with benzene or toluene, into a thin sheet on an anvil. This is preferably done in a hood because lithium oxide dust is irritating to the nose and throat. The sheet so obtained (1 mm. or less in thickness) is cut into strips about 1 mm. wide, and these are then cut

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[11] Peratoner, *Gazz. chim. ital.*, **16**, 418 (1886).

[12] Schall, *Ber.*, **12**, 816 (1879).

[13] Gilman, Langham and Jacoby, THIS JOURNAL, **61**, 106 (1939).

[14] Tomita, *J. Pharm. Soc. Japan*, **57**, 391 (1937).

with scissors directly into the reaction flask, through a paper funnel contained in a neck of the flask and in an emerging stream of nitrogen. The lithium prepared in this manner has a large, oxide-free surface and is suitable for reaction with most organic halides.

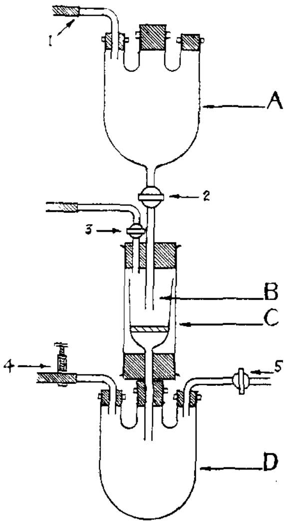

Fig. 2.

General Procedure.—As mentioned previously,[15a] Schlenk tubes are unnecessary and the preparations are conveniently effected in the conventional three-necked, round-bottomed flasks fitted with a mercury-sealed or other gas-tight stirrer, reflux condenser and a dropping funnel. An inert atmosphere of dry nitrogen, free of oxygen and carbon dioxide, is used in the preparation and subsequent reaction of the RLi compound. As is the case with Grignard preparations, the halide is added at a rate to maintain gentle refluxing. With those RX compounds which react slowly and which show no appreciable drop in yield with rapid addition, the RX compound is added at one time.[15a,b] In the preparation of some RLi compounds which require a relatively long time for completion there is the probability of using up some of the lithium and also the possibility of subsequent secondary reactions by the fairly rapid formation of lithium nitride. In these and other special cases it may be desirable at times to use another inert atmosphere with only occasional emergence of inert gas[15a,b] or by a trap for carrying out reactions in an inert atmosphere.[15c]

Filtration of Organolithium Solutions.—There are three general ways of handling organolithium solutions prior to mixing with a reactant. First, no filtration of the RLi solution from particles of unused lithium or lithium halide, oxide, carbonate and nitride may be needed for some reactions. Second, a rough separation may be adequate, and this can be effected either by allowing the suspended material to settle and then decanting or by filtration through loosely-packed glass wool, asbestos or related material. In this latter procedure the solution is poured through a glass tube connected with a Gooch adapter (containing the glass wool) held in one neck of another three-necked flask previously fitted with a condenser and stirrer. By means of a conventionally arranged T-tube a single stream of nitrogen provides an inert atmosphere for both flasks.

Third, a fine filtration can be realized by means of appropriate filter disks, sticks or funnels. This can be done in an apparatus provided with interchangeable ground joints or in a more accessible apparatus fitted with rubber stoppers. Figure 2 illustrates the essential features of an apparatus of the latter type.[16a] The solution to be filtered is transferred under nitrogen to flask A which is a standard three-necked flask to the bottom of which has been sealed a stopcock of fairly large bore (2–4 mm.). Flask A, provided with an inlet tube (1) for nitrogen, empties into the sintered glass funnel, B, enclosed in the glass jacket, C.

The original solution of RLi compound is allowed to settle, transferred to A, and then A is stoppered. The nitrogen inlet (4) on flask D is closed by a stopcock or screw clamp, and a *slightly* reduced pressure is effected by opening stopcock (5) to a water pump which has between it and stopcock (5) a drying tower and traps. Then stopcock (2) is opened to permit enough solution to run into funnel B to partially fill it. Stopcock (3) is useful for relieving excessive back pressure due to vaporization of low boiling solvents. The filtration rate is rapid, and by means of a sintered glass funnel of moderate porosity (average pore diameter, 20–30 microns)[16b] one-half liter of solution is filtered in fifteen minutes. Strong suction should not be applied at (5), particularly with low boiling solvents. A preliminary settling of the initial reaction mixture is recommended in order not to clog the filter unduly. The filtrate is uncommonly clear not only with organolithium compounds, but also with other RM compounds like some highly turbid organoaluminum halides. The filtered solution can be used directly, or can be stored in suitable graduated containers from which aliquots may be removed as desired.

Petroleum Ether as a Solvent.—Petroleum ether (b. p. 28–38°) is peculiarly suitable for the preparation of some RLi compounds, particularly when solutions are to be stored or when special solvents are later used to replace most of the petroleum ether. The rate of formation of *n*-butyllithium in petroleum ether approaches that in diethyl ether, and *n*-butyl chloride is really more effective in petroleum ether than in diethyl ether. Four particular advantages of petroleum ether might be mentioned. First, the difficulty of secondary reactions like cleavage, present in diethyl ether, is obviated. Second, indirect supplementary analyses[15d] are not necessary to determine the titer of solution, and the simple acid-titration analysis[15e] is adequate. Third, the by-products, like lithium halide, are insoluble in petroleum ether and so are removed on filtration. We have kept some of these solutions for extended periods with no significant change. Some higher boiling fractions of petroleum ether appear to be less satis-

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[15] (a) Gilman, Zoellner and Selby, THIS JOURNAL, **54**, 1957 (1932); **55**, 1252 (1933); Gilman, Zoellner, Selby and Boatner, *Rec. trav. chim.*, **54**, 584 (1935); (b) Gilman, Zoellner, Dickey and Selby, THIS JOURNAL, **57**, 1061 (1935); see, also, Gilman and Kirby, *ibid.*, **55**, 1265 (1933); (c) Gilman and Hewlett, *Rec. trav. chim.*, **48**, 1123 (1929); (d) Ziegler and Colonius, *Ann.*, **479**, 135 (1930); (e) Gilman, Wilkinson, Fishel and Meyers, THIS JOURNAL, **45**, 150 (1923).

[16] (a) A special tube [Edgar and Calingaert, *Ind. Eng. Chem., Anal. Ed.*, **2**, 104 (1930)] can replace both B and C if available. (b) Schott Jena-G3 has been found most satisfactory.

factory. Fourth, isopropyllithium is obtainable in 58% yield from isopropyl chloride. The yields of some other RLi compounds prepared in petroleum ether are: 50% ethyllithium from ethyl bromide; 60% *n*-propyllithium from *n*-propyl bromide; 70% *n*-butyllithium from the bromide and 75% from the chloride.

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Summary

On the basis of a series of new experiments some general principles have been formulated concerning metalation and halogen–metal interconversion reactions.

Preferential halogen–metal interconversions have been effected with some polyhalogen compounds.

Some new information has been provided on the preparation and manipulation of organolithium compounds.

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RECEIVED JUNE 15, 1940

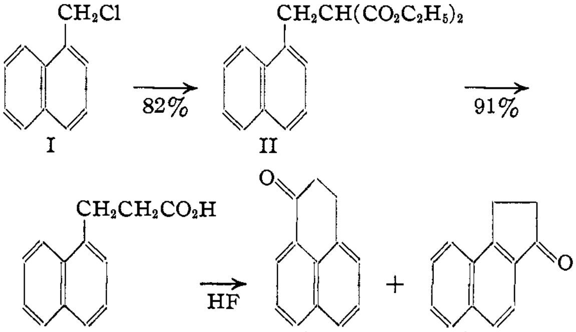
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthetic Experiments Utilizing Perinaphthanone-7

BY LOUIS F. FIESER AND MARSHALL D. GATES, JR.

This investigation was undertaken in the hope of obtaining 1′,9-dimethylene-1,2-benzanthracene by application of the general *o*-halide scheme of synthesis,[1] starting with the condensation of *o*-chlorophenylmagnesium bromide with perinaphthanone-7. Since the work was initiated a similar series of reactions proceeding from acenaphthenone has been applied successfully to the synthesis of 1′,9-methylene-1,2-benzanthracene.[2] As will be shown, a peculiarity specific to the perinaphthane series blocked the present approach to the goal indicated.

Although preparations regarded as consisting essentially of perinaphthanone-7[3] (IV) have been reported by other workers, the purity and identity of these preparations have not been established and some confusion exists concerning the characterization of the acid from which the ketonic material was produced by cyclization. Thus the following melting points are reported for the amide of β-(1-naphthyl)-propionic acid (III): 140°,[4] 85°,[5] 133°,[6] although investigators seem agreed as to the melting point of the acid obtained by the malonic ester synthesis from α-chloro- or bromomethylnaphthalene. We employed α-chloromethylnaphthalene prepared by chloromethylation in acetic acid solution according to Darzens and Lévy,[7] although like Cambron[8] we were unable to duplicate the yield. The reaction is not as easily controlled as in Cambron's procedure,[8,9] but after some experience it was possible to prepare the halide in 51.5% yield (not allowing for much recovered naphthalene). The condensation with malonic ester was improved considerably by using a large excess of the ester, and pure β-(1-naphthyl)-propionic acid was obtained on a large scale in excellent over-all yield. The amide, prepared both from the acid chloride and the crystalline methyl ester,[10] melted at 103–104° and had the expected composition. Mayer and Sieglitz[5] cyclized III by the action of aluminum chloride in ligroin on the acid chloride and obtained in poor yield a yellow ketonic substance melting at about 85–86°, but Cook and Hewett[11] found that material obtained in this way is a mixture and that the yellow color is due to the presence of a significant amount of the



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[1] Fieser and Seligman, THIS JOURNAL, **61**, 136 (1939).

[2] Fieser and Cason, *ibid.*, **62**, 432 (1940).

[3] "7,8-Dihydrophenalone-9" (Ref. 5); for comments on the present nomenclature, see Ref. 12.

[4] Willgerodt, *Ber.*, **21**, 534 (1888).

[5] Mayer and Sieglitz, *ibid.*, **55**, 1835 (1922).

[6] Darzens and Lévy, *Compt. rend.*, **201**, 902 (1935).

[7] Darzens and Lévy, *ibid.*, **202**, 73 (1936).

[8] Cambron, *Can. J. Research*, **17B**, 10 (1939).

[9] Fieser and Novello, THIS JOURNAL, **62**, 1855 (1940).

[10] Manske and Ledingham, *Can. J. Research*, **17B**, 14 (1939).

[11] Cook and Hewett, *J. Chem. Soc.*, 365 (1934).