ALUMINUM HYDRIDE

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THESIS

This is to certify that the

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THE REDUCTION OF SOME AROMATIC
HALIDES WITH LITHIUM ALUMINUM HYDRIDE

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Gerasimos J. Karabatsos
Major professor

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ABSTRACT

THE REDUCTION OF SOME AROMATIC HALIDES WITH LITHIUM ALUMINUM HYDRIDE

by Robert Larry Shone

Phenyl and related aromatic halides have previously been considered resistant to attack by lithium aluminum hydride (1, 2). Forty-eight different aromatic halides were reduced with lithium aluminum hydride in ether, tetrahydrofuran, and diglyme. The yields of reduced hydrocarbon were influenced by reaction temperature and nature of the aromatic halide. Higher reaction temperatures increased yields. Aromatic halide reactivity increased in the presence of electron withdrawing groups on the aromatic nucleus and varied with the nature of the carbon-halogen bond in the order I > Br > Cl > F.

The steric relationship of the halogen atom to other substituents present on the aromatic nucleus was found to be important. Increase in steric interaction between halogen and substituent led to increase of substrate reactivity. Addition of methanol to the reduction slurry of lithium aluminum hydride, aromatic halide, and solvent greatly increased the yield of reduced product.

REFERENCES

(1) N. G. Gaylord, "Reduction with Complex Metal Hydrides," New York: Interscience Publishers, Inc., 1956.

(2) J. F. Corbett and P. F. Holt, J. Chem. Soc., 2385 (1963).

THE REDUCTION OF SOME AROMATIC HALIDES WITH LITHIUM ALUMINUM HYDRIDE

By

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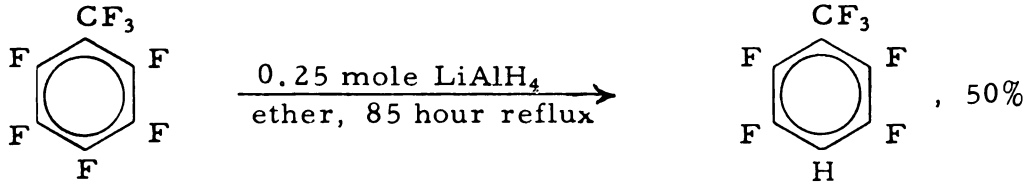
INTRODUCTION

The reduction of aliphatic halides with lithium aluminum hydride is a useful synthetic reaction and has been reviewed by Gaylord (2). Equation (1) illustrates this reaction when X = Cl,

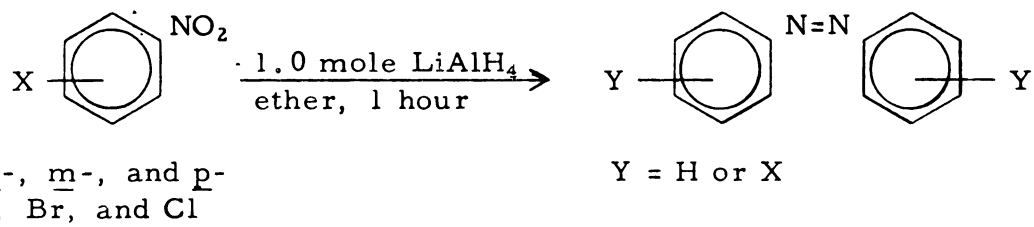
$$4\ R\text{-}X + LiAlH_4 \longrightarrow 4\ R\text{-}H + LiAlX_4 \qquad (1)$$

Br, or I and R is an alkyl group. Fluoro compounds are generally unreactive and aromatic halides have been considered resistant to attack by lithium aluminum hydride (1, 2). Gaylord (2) reported fifty haloaromatic compounds substituted with reactive functional groups that were reduced to the corresponding halogenated compounds in good yields. Several examples of aromatic carbon-halogen bond cleavage have been noted in the literature. Johnson and co-workers (3) treated p-bromotoluene with a mixture of lithium aluminum hydride and lithium hydride in refluxing tetrahydrofuran and obtained a 14% yield of toluene. Trevoy and Brown (4) found that o-chloroiodobenzene gave a 40% yield of chlorobenzene after treatment with lithium aluminum hydride in refluxing tetrahydrofuran for one-half hour.

Extensive halogen reduction has been observed when activating groups are present on the aromatic nucleus. Alsop and co-workers (5)



obtained a 50% yield of 2, 3, 5, 6-tetrafluorotrifluoromethylbenzene from 2, 3, 4, 5, 6-pentafluorotrifluoromethylbenzene after refluxing in ether with lithium aluminum hydride for eighty-five hours. Braithwaite and co-workers (6) found that 4, 4'-diiodo-5, 5'-dimethyl-2, 2'-dinitrobiphenyl was deiodinated when treated with excess lithium aluminum hydride in refluxing ether to give a 43% yield of 2, 9-dimethylbenzo(c)cinnoline. Corbett and Holt (7) subsequently reduced thirty-three halogenated nitrobenzenes and nitronaphthalenes to the



corresponding dehalogenated azo compounds in greater than 75% yield whenever ortho-, meta-, and para-iodo or ortho-bromosubstrates were employed. The ortho-, meta-, and para-chloro and meta- and para-bromonitrocompounds were not dehalogenated and gave the corresponding chloro and bromoazobenzenes as products.

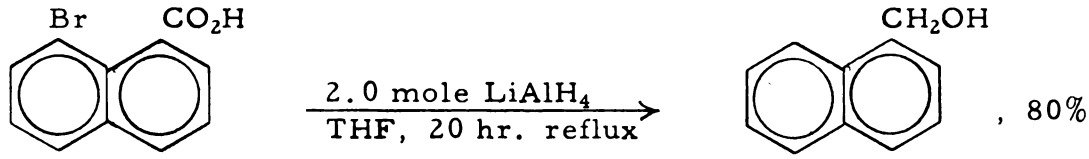
The lithium aluminum hydride reduction of aromatic halides is an unexplored area of investigation. Since little information existed in the literature, experiments were undertaken to elucidate structural features and reaction conditions that favored such reductions.

RESULTS AND DISCUSSION

A. Isolation and Identification of the Carbinol Obtained from Lithium Aluminum Hydride Reduction of 8-Bromo-1-Naphthoic Acid

Reduction of carboxylic acids to alcohols with lithium aluminum hydride is a standard preparative method (2, 9, 10). Both 1-naphthoic acid and 8-methyl-1-naphthoic acid are easily reduced by this method to the corresponding carbinols in ether solution (11). The alcohols obtained from the aforementioned acids are colorless needles that are easily recrystallized from cyclohexane and melt at 60-61° (32) and 94-95° respectively.

Reduction of 8-bromo-1-naphthoic acid with 0.8 mole of lithium aluminum hydride per mole of acid in refluxing ether for twenty-four hours gave an oil and 19% recovered carboxylic acid. Reduction of the bromoacid with 2.0 moles of lithium aluminum

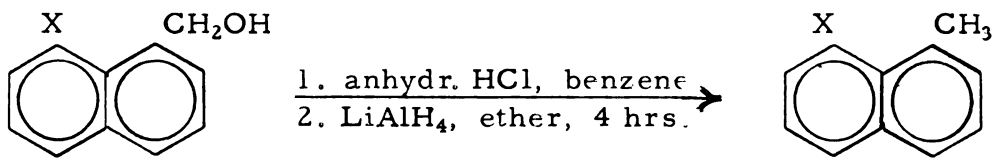


hydride in refluxing tetrahydrofuran gave colorless needles of a carbinol with m.p. 60-61°. The carbinol was identified as 1-naphthylcarbinol on the basis of the following evidence:

1. The melting point of the unknown carbinol is the same as that of 1-naphthylcarbinol (m.p. 60-61° (32)).
2. Mixtures of the unknown carbinol and 1-naphthylcarbinol in

approximately 1 : 3, 1 : 1, and 3 : 1 proportions all melted at 60-61°.

3. The infra-red spectra of the two carbinols in methylene dibromide are identical in all respects (see Figures 9 and 10).
4. The n.m.r. spectra of the two carbinols in carbon disulfide show identical aromatic multiplets at τ 1.92-2.66, a methylene singlet at τ 5.15, and a concentration dependent hydroxyl singlet. The integrated area ratios of both carbinols are 7 : 2 : 1.
5. If silver nitrate solution is added to the aqueous dilute sulfuric acid layer obtained from workup of the bromoacid reduction, a heavy yellow precipitate of silver bromide is instantly formed together with a white precipitate of silver sulfate. Qualitative bromide ion tests using potassium permanganate in carbon tetrachloride (12) on the same solution were positive. Similar qualitative tests on a solution obtained by adding lithium aluminum hydride to distilled water were negative.
6. The unknown carbinol was converted to a carbinyl chloride with anhydrous hydrogen chloride, reduced with lithium



aluminum hydride, and the crude oil distilled to give a 30% yield (based on X = H) of a colorless oil with refractive index 1.6172. The refractive index of 1-methylnaphthalene is 1.6174 (13).

7. The 8-bromo-1-naphthoic acid reduced was checked to show that it did contain a bromine atom and was not contaminated with any 1-naphthoic acid.

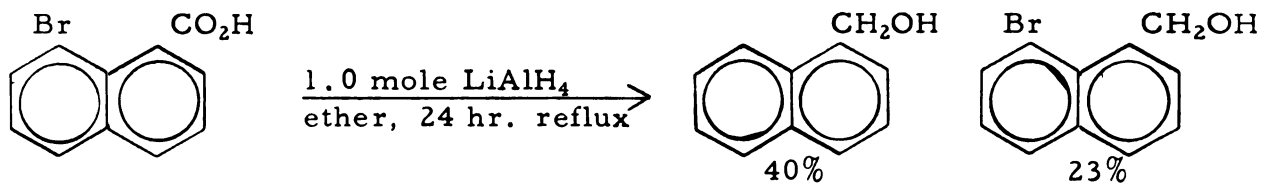
A. The melting point of the bromoacid, 180-181°, was close to that recorded in the literature, 177-78° (15).

B. Mixtures of 8-bromo-1-naphthoic acid and 1-naphthoic acid in approximately 1 : 3, 1 : 1, and 3 : 1 proportions showed large melting point depressions.

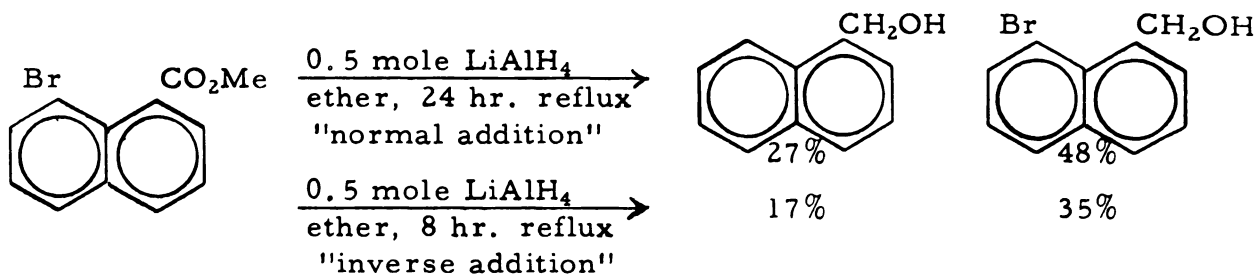
C. The neutralization equivalent (12) of the bromoacid gave a molecular weight of 253. The molecular weights of 8-bromo-1-naphthoic acid and 1-naphthoic acid are 251 and 172, respectively.

D. The infra-red spectrum of the bromoacid was different from that of 1-naphthoic acid.

N.m.r. analysis of the oil obtained from reduction of the bromoacid showed it to be a mixture of 1-naphthylcarbinol and 8-bromo-1-

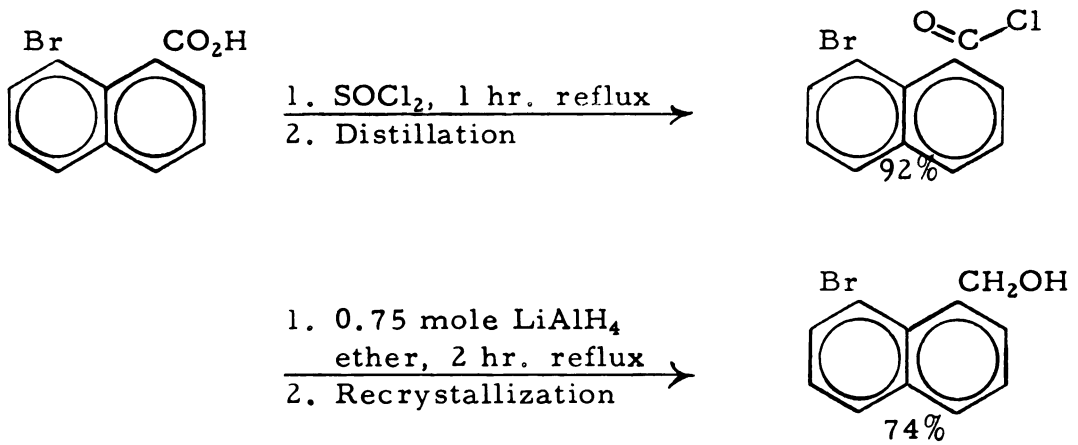


naphthylcarbinol. Subsequent reduction of methyl 8-bromo-1-naphthoate



by both normal and inverse addition of the reducing agent gave product mixtures that again contained substantial amounts of 1-naphthylcarbinol.

In order to prepare 8-bromo-1-naphthylcarbinol by lithium aluminum hydride reduction it was necessary to reduce 8-bromo-1-naphthoyl



chloride using mild conditions and a short reaction time. Good yields of the bromoalcohol were obtained (for experimental details see p. 51).

B. Factors Influencing the Ease of Carbon-Bromine Bond Cleavage in 8-Bromo-1-Substituted Naphthalenes

Concurrent reduction of an aromatic carbon-bromine bond and a carboxyl or carboalkoxy group with lithium aluminum hydride is unprecedented and novel (8). Several authors (5, 6, 7) have observed iodine, bromine, and fluorine bond cleavage in the lithium aluminum hydride reduction of activated aromatic halides (when nitro, trifluoromethyl, and polyfluoro substituents are present). However, a well-known monograph on lithium aluminum hydride reductions states that aromatic halides are resistant to attack by lithium aluminum hydride and cites supporting evidence (2). The extent of bromine cleavage in the 1, 8-naphthalene series is illustrated by the examples in Table I.

The peri-bromine of 8-bromo-1-naphthylcarbinol is reduced by a displacement process and is not eliminated via an aryne intermediate. The bromoalcohol was reduced with lithium aluminum deuteride in refluxing tetrahydrofuran and the reaction was quenched with deuterium oxide. The carbinol obtained was 8-deutero-1-naphthylcarbinol and not

Table I. Reduction of 8-Bromo-1-Substituted Naphthalenes

Compound	Diglyme, 100°	THF, 65°	Ether, 35°
1. 8-bromo-1-naphthoic acid	-[e]	58, 26	40, 23
2. 8-bromo-1-naphthoic acid	-	100, 0[a]	100, 0[b]
3. methyl 8-bromo-1-naphthoate	-	96, 4	60, 40
4. 8-bromo-1-naphthylcarbinol	-	99(97, 36)[c]	19
5. 8-bromo-1-methylnaphthalene	100	46	11
6. 1-bromonaphthalene	61	-	6
7. 8-bromo-1-naphthylcarbinyl chloride	-	-	5, 73[d]

Note: Reductions were performed with 1.0 mole of lithium aluminum hydride per mole of aromatic halide during a 24 hour reaction. Numbers are percent yield of hydrocarbon product. When two reduction products are possible the percent yield of bromine cleaved product is given first.

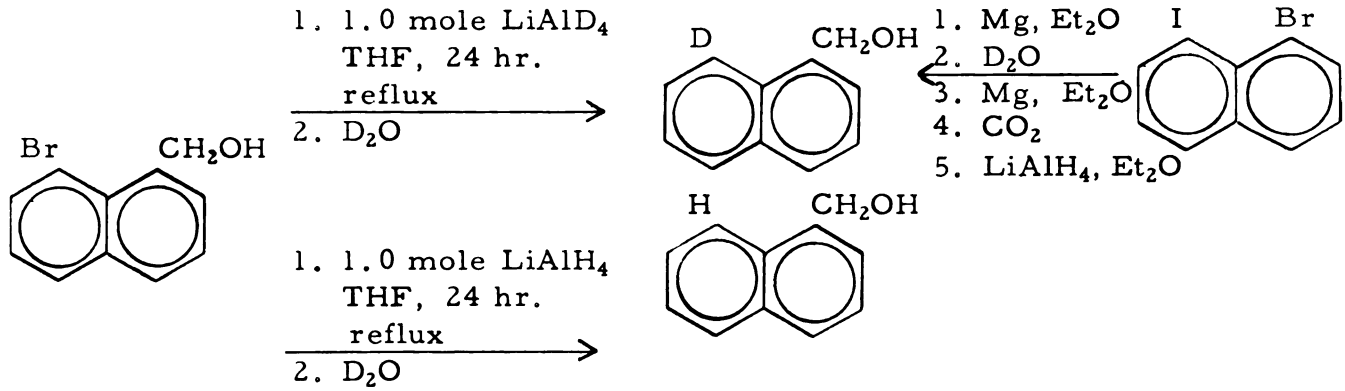
[a] 2.0 moles of lithium aluminum hydride per mole of acid were employed.

[b] 2.0 moles of lithium aluminum hydride per mole of acid and a 76 hour reflux period were employed.

[c] Percent yields for reductions with 8 and 1 hour reflux periods respectively.

[d] A four hour reflux period was used.

[e] - indicates that the substrate was not reduced under these conditions.



7,8-dideutero-1-naphthylcarbinol, the alcohol expected from an aryne intermediate. This conclusion is supported by comparing the n.m.r. spectrum of the deuteroalcohol obtained by reduction with that of 8-deutero-1-naphthylcarbinol prepared from 1-bromo-8-iodonaphthalene. If 15% by weight solutions of the deuteroalcohols in carbon disulfide are prepared and the aromatic multiplets observed, the two multiplets are identical and distinctly different from the aromatic multiplet of 1-naphthylcarbinol (see Figures 11 and 12). A 6 : 2 : 1 integrated area ratio of aromatic multiplet, methylene singlet, and hydroxyl singlet of the carbinol obtained from reduction suggests a 1,8-disubstituted naphthalene and supports the assigned structure. Other experimental evidence corroborates these results and conclusions: reduction of 8-bromo-1-naphthylcarbinol with lithium aluminum hydride followed by addition of deuterium oxide gave 1-naphthylcarbinol (see Figure 12).

The facile carbon-bromine cleavage in the 1,8-naphthalenes of Table I is promoted by the close spatial proximity of the peri substituents. The spatial arrangement of the bromine atom and the functional group apparently causes the enthalpy of activation for bromine cleavage to be significantly lower than that for a simple aromatic bromide. The reduction of 8-bromo-1-naphthoic acid will be considered in detail.

Two paths can be envisioned for the reduction of 8-bromo-1-naphthoic acid. If path 2 in Figure 1 is followed, 1-naphthoic acid might be found in the carboxylic acid recovered on work up of

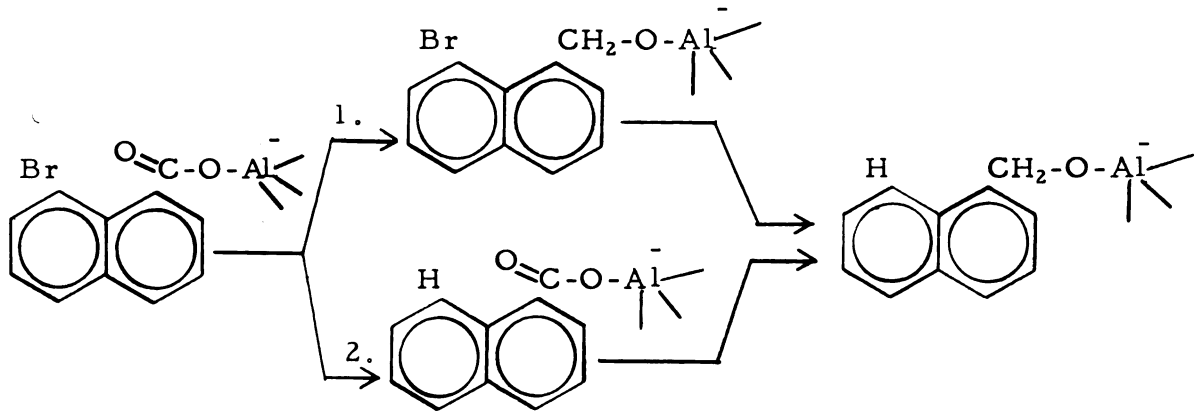


Figure 1

reduction mixtures. The carboxylic acids recovered from reductions of 8-bromo-1-naphthoic acid in ether (Table II) were esterified with diazomethane and the resulting methyl esters analyzed with vapor phase chromatography. No methyl 1-naphthoate was detected and all recovered acid melted sharply at 180-181° (lit. m.p. of 8-bromo-1-naphthoic acid is 177-178° (15)). The concentration of 8-bromo-1-naphthylcarbinol is greatest during the early stages of the reduction as the product composition and yields in Table II indicate. As the reduction proceeds further the bromoalcohol is reduced and its concentration decreases. The results in Table II are thus consistent with path 1, not path 2.

The ground state strain energies of 1,8-dimethylnaphthalene and 1-methylnaphthalene have been estimated to be 7.6 k. cal. per mole and 1.6 k. cal. per mole respectively (16). A similar ground state energy difference should exist in the two analogous compounds, 8-bromo-1-naphthylcarbinol and 1-bromonaphthalene. If the reaction coordinates for lithium aluminum hydride reduction of the two bromonaphthalenes are compared (Figure 2), the transition state energy difference for the two

Table II. Reduction of 8-Bromo-1-Naphthoic Acid

	Reaction Time	Product Composition			Product Yields		
		% Bromo alcohol	% 1-Naphthyl carbinol	Ratio[a]	% Bromo alcohol	% 1-Naphthyl carbinol	% Recovered acid
1.	1 hr.	82	18	4.56	18	4	78
2.	3 hrs.	73	27	2.70	30	11	59
3.	8 hrs.	36	64	0.56	23	41	36

Note: All reductions were carried out with 1.0 mole of lithium aluminum hydride per mole of acid in refluxing ether.

[a] Ratio of 8-bromo-1-naphthylcarbinol to 1-naphthylcarbinol.

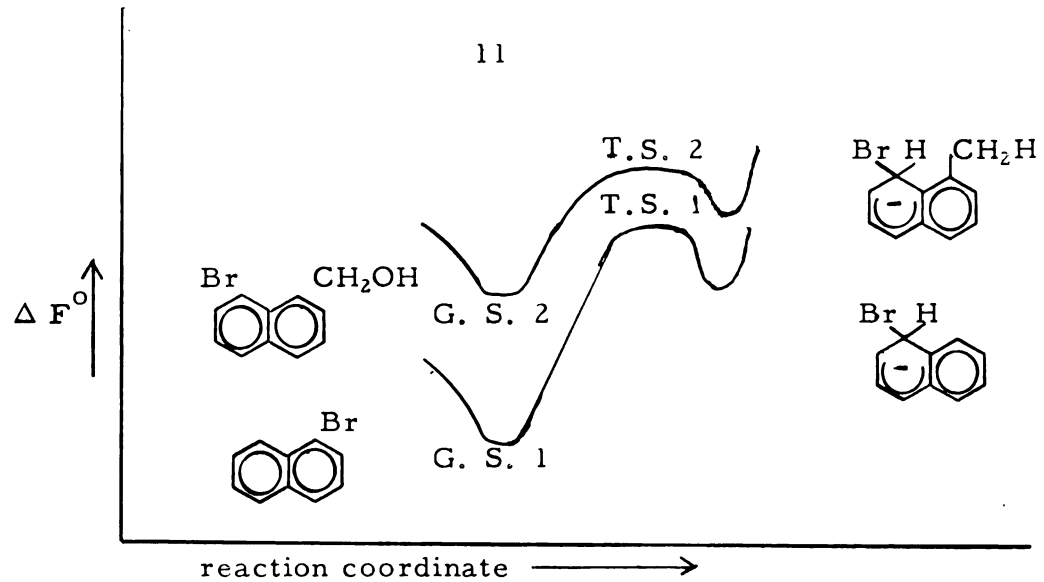


Figure 2

reductions will be less than the ground state energy difference (T. S. 2-T. S. 1 < G. S. 2-G. S. 1). It is assumed that the transition state for reduction resembles the tetrahedral intermediate (17) and that aromatic halide reduction proceeds by a process similar to that observed for other well studied aromatic nucleophilic displacement reactions (19, 31, 33). The 8-bromo-1-naphthylcarbinol should therefore be more reactive.

Other results from reduction of bromonaphthalenes (Table I, entries 5 and 6) support these ideas. Alpha-bromonaphthalene is reduced to naphthalene in 61% yield at 100° in diglyme but 8-bromo-1-methylnaphthalene, a system containing more ground state strain energy, is quantitatively reduced under the same reaction conditions. A similar argument has been used to explain the formolysis rate ratio of 85 observed for 8-methyl-1-naphthylcarbinyl chloride and 1-naphthylcarbinyl chloride (11).

Bromine cleavage in 8-bromo-1-naphthylcarbinol may also be facilitated by an intramolecular displacement process (Figure 3). Such a displacement would result in a net lowering of the free energy of

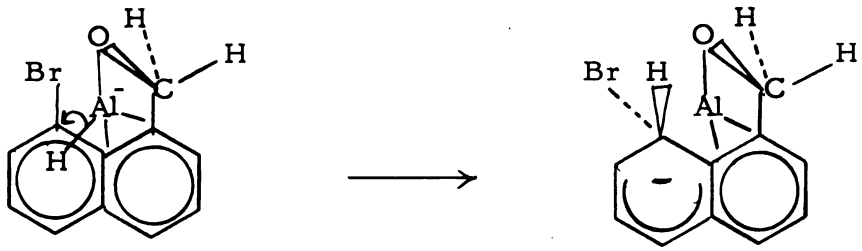


Figure 3

activation since the entropy of activation would be more positive than that of an intermolecular displacement. Intramolecular reduction requires the presence of a functional group that can bond with the reducing agent and is located so that a cyclic reduction path is favorable. These ideas are supported by comparing the results of lithium aluminum hydride reduction in refluxing tetrahydrofuran for the sterically similar systems 8-bromo-1-naphthylcarbinol and 8-bromo-1-methylnaphthalene. The former gives a 99% yield of 1-naphthylcarbinol after eight hours of reaction while the latter gives a 46% yield of naphthalene after a twenty-four hour reaction period.

Intramolecular halide displacements by lithium aluminum hydride are not unprecedented. Eliel and Traxler (18) found that lithium aluminum hydride reduction of chloroaliphatic acids gave the greatest yields of dehalogenated alcohols when alpha-, beta-, or gamma-chloroacids were reduced (see Table III). To account for these results a cyclic transition state (Figure 5) was postulated. An alternate explanation might be provided by an intramolecular bromine-aluminum

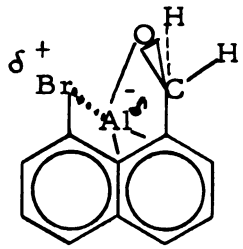


Figure 4

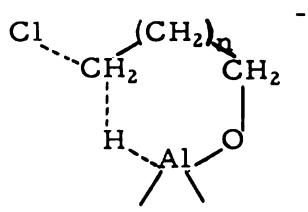


Figure 5

Table III. Reduction of I^{o} Chloroaliphatic Acids and Alcohols (18)

	Acid or Alcohol	n[a]	% Dechlorinated Alcohol
1.	alpha-chloroacetic	0	38
2.	3-chloropropionic	1	62
3.	4-chlorobutyric	2	45
4.	5-chlorovaleric	3	5
5.	3-chloropropanol	1	47

Note: All reductions were carried out with 1.0-1.5 moles of lithium aluminum hydride per mole of acid or alcohol during a 1-2 hour reflux period in ether.

[a]Refers to the number of carbon atoms in the cyclic transition state as illustrated in Figure 5.

coordination which would weaken the carbon-bromine bond and facilitate hydride attack at the aromatic carbon atom (Figure 4). Reduction of the isomeric bromobenzoic acids also suggests that steric effects contribute to the ease of bromine cleavage. Reduction of ortho-bromobenzoic acid with lithium aluminum hydride in ether gave a 19% yield of benzyl alcohol while the meta and para substituted acids gave no benzyl alcohol (see Table VII).

Comparison of the yields of debrominated products obtained from reduction of the ortho- and para-bromotoluenes and benzyl alcohols (see Table IV) supports increased carbon-bromine cleavage by an intramolecular displacement process. A prediction of the yield of benzyl alcohol that will be obtained from ortho-bromobenzyl alcohol may be made as follows. A 13% difference in yield between the ortho- and para-compound is observed (compare entries 1 and 2, Table IV). Another 13% difference in yield is observed from the difference in electronic effects in the substrate and reducing agent (compare entries 2 and 4, Table IV). The yield of benzyl alcohol should be 26% more than that obtained from the para-bromo isomer or 67%. Since the actual yield obtained is greater than 67%, the increase reflects the assistance of reduction by an intramolecular displacement process.

C. Differences in Yields of Reduction Product Obtained from Haloacids and Haloalcohols

The reduction of 8-bromo-1-naphthoic acid to 1-naphthylcarbinol has been postulated to occur in two steps: reduction of the carboxyl group to give 8-bromo-1-naphthylcarbinol followed by cleavage of the bromoalcohol to 1-naphthylcarbinol (see Figure 1). Since 8-bromo-1-naphthylcarbinol is an intermediate in the reduction of the bromo-acid, the yield of 1-naphthylcarbinol obtained from reduction of 8-bromo-1-naphthylcarbinol should be comparable to that obtained by reduction

Table IV. Reduction of Bromotoluenes and Bromobenzyl Alcohols

	Compound	% Debrominated Product
1.	o-bromotoluene	41
2.	p-bromotoluene	28
3.	o-bromobenzyl alcohol	80
4.	p-bromobenzyl alcohol	41

Note: Reductions were carried out with 1.0 mole of lithium aluminum hydride per mole of aromatic bromide in diglyme at 100° for twenty-four hours.

of the bromoacid. This is not observed experimentally. Whereas 8-bromo-1-naphthoic acid gives a 40% yield of 1-naphthylcarbinol after a twenty-four hour reaction in ether with one mole of lithium aluminum hydride per mole of acid, 8-bromo-1-naphthylcarbinol gives only a 19% yield of 1-naphthylcarbinol. Comparison of the yields of benzyl alcohol obtained from reduction of o-bromobenzoic acid and o-bromobenzyl alcohol (entries 5 and 11, Table VII) show the same qualitative result: a 19% yield of benzyl alcohol is obtained from reduction of the acid while reduction of the alcohol gives only a 4% yield of benzyl alcohol. A similar discrepancy was also observed by Eliel (18) in the reduction of chloroaliphatic acids and their corresponding chloroalcohols (see Table III). The yield of dechlorinated alcohol obtained by reduction of the chloroalcohol was always less than that obtained from reduction of the chloroacid.

Eliel (18) postulated that the difference in yield of dechlorinated alcohol could be attributed to a difference in the nature and strength of the reducing agent that cleaves the carbon-chlorine bond. It was assumed that reduction of the chloroacid occurred stepwise, e.g., the carboxyl group is reduced first followed by hydride displacement of chloride ion. Since X and Y (Figure 6) will be alkoxy groups when the chloroacid is reduced, displacement of chloride ion by hydride should be facilitated by participation of the unshared electron pairs of the oxygen atoms. When the chloroalcohol is reduced X and Y will be

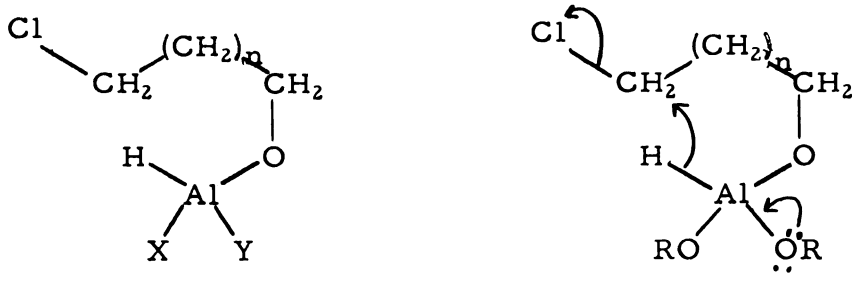


Figure 6

hydrogen atoms and the strength of the reducing agent will be weaker than when X and Y are alkoxy groups. Consequently less carbon-chlorine bond cleavage is observed when the chloroalcohol is reduced. To test this hypothesis Eliel reduced 2-chloro-1-propanol in ether containing methanol and found that the yield of n-propyl alcohol increased from 15% (no added methanol) to 24%. Similar results were found when water was added. When 8-bromo-1-naphthylcarbinol was reduced with added methanol an even greater increase (see Table V) in the yield of debrominated product was observed. Addition of two equivalents of methanol resulted in a 58% increase in the yield of 1-naphthylcarbinol.

Although Eliel's hypothesis explains the observed results, it may be criticized on several accounts. First, Brown (10, 37, 38) has found that lithium alkoxyaluminohydrides are less powerful reducing agents than is lithium aluminum hydride. The observed reactivity order for several lithium aluminohydrides is $LiAlH_4 > LiHAl(OMe)_3 > LiHAl(OEt)_3 > LiHAl(OtBu)_3$. The proceeding order was based on observations of reactivity differences of the various lithium aluminohydrides. For example, lithium tri t-butoxyaluminohydride reduces aldehydes, ketones, and acid chlorides at 0° in tetrahydrofuran but fails to react with esters and nitriles (39, 40). Under the same conditions both lithium trimethoxyaluminohydride and lithium aluminum hydride reduce esters and nitriles. Lithium trimethoxyaluminohydride fails to react in two hours with ethyl benzoate at -80° in tetrahydrofuran or diglyme while lithium aluminum hydride reduces the ester (37).

On the other hand lithium alkoxyborohydrides are stronger reducing agents than lithium borohydride (37). The reactivity difference of lithium alkoxyaluminohydrides and lithium alkoxyborohydrides in comparison with their parent hydrides, lithium aluminum hydride and lithium borohydride, has been interpreted (38) in terms of the difference

Table V. Reduction of Selected Aromatic Bromides with Added Methanol

	Compound	Solvent	Aromatic[a] bromide	$LiAlH_4$[a]	MeOH[a]	% Debrominated product
1.	8-bromo-1-naphthylcarbinol	ether	2.11	2.64	0	19
2.	8-bromo-1-naphthylcarbinol	ether	10.0	10.0	5.0	36
3.	8-bromo-1-naphthylcarbinol	ether	5.0	5.0	10.0	77
4.	p-bromotoluene	THF	10.0	10.0	0	7
5.	p-bromotoluene	THF	10.0	10.0	20.0	59

Note: Reductions were carried out at solvent reflux temperature for twenty-four hours.

[a]Figures are millimoles of reactants.

in Lewis acid strength of trialkoxy aluminates and borates. The electron withdrawing inductive effect of the alkoxy group increases the

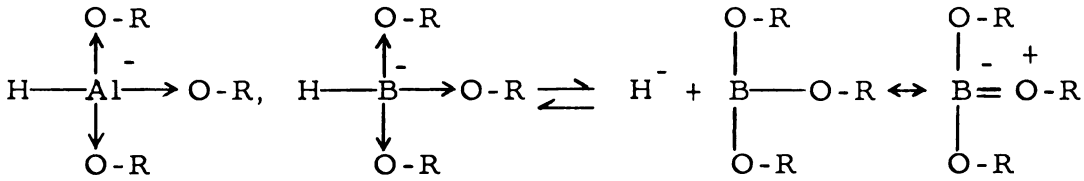


Figure 7

Lewis acid strength of both the aluminates and borates and conversely weakens the reducing strength of their alkoxyhydrides. However, alkoxyborates are weak Lewis acids since double bond structures (Figure 7) make significant contributions to the resonance hybrid. The additional resonance stabilization energy resulting from such structures is apparently large enough to overcome the adverse inductive effect of the alkoxy groups and make lithium alkoxyborohydrides stronger reducing agents than lithium borohydride. The lithium alkoxyaluminohydrides are not stronger reducing agents than lithium aluminum hydride since aluminum, a second row element, forms bonds with oxygen that have little double bond character. Consequently alkoxyaluminates are strong Lewis acids and lithium alkoxyaluminohydrides are weaker reducing agents than lithium aluminum hydride.

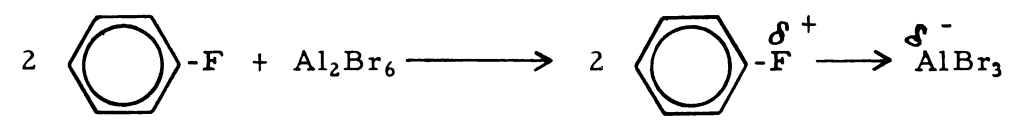
The observed reactivity order for lithium alkoxyaluminohydrides is opposite to that assumed by Eliel. If the difference in yield of dehalogenated alcohol obtained from reduction of haloacids and haloalcohols is to be explained by a difference in the reactivity of the reducing agent, more halogen cleavage should be found when the alcohol is reduced. This is contrary to what is observed. Also, addition of methanol to the reducing agent should decrease the yield of dehalogenated product when the alcohol is reduced--a prediction that is not supported by experiment.

A second criticism of Eliel's interpretation is that the identity of the active reducing agent or agents is not known with any degree of certainty. Brown (37) has found that the reaction of integral equivalents of alcohols with solutions of lithium aluminum hydride in ether, tetrahydrofuran, and diglyme is not simple and does not always result in the formation of the simplest possible lithium alkoxyaluminohydride. For example, addition of one equivalent of isopropyl alcohol to a solution of lithium aluminum hydride in ether did not result in the formation of lithium monoisopropoxyaluminohydride but 22% of the available aluminum was precipitated as lithium tetraisopropoxyaluminohydride. Addition of one equivalent of methanol to a solution of lithium aluminum hydride in ether resulted in 42% of the available aluminum being precipitated as lithium dimethoxyaluminohydride.

Since the reduction of chloroaliphatic acids and alcohols by Eliel and the reduction of 8-bromo-1-naphthoic acid and 8-bromo-1-naphthylcarbinol were carried out in a slurry of lithium aluminum hydride, ether, and precipitated alkoxide salts, the nature and composition of the reducing agent that participates in the cleavage of the carbon-halogen bond can only be surmised. It is likely that this reducing agent would be a soluble species such as lithium aluminum hydride, a lithium monoalkoxyaluminohydride, or possibly a lithium dialkoxyaluminohydride. Brown (37) has found that all lithium tetraalkoxyaluminohydrides and most lithium trialkoxyaluminohydrides are insoluble in ether at room temperature. The dialkoxyaluminohydrides are generally soluble in ether but lithium dimethoxyaluminohydride is not. All monoalkoxyaluminohydrides prepared were soluble in ether.

An explanation of Eliel's results and the results obtained from reductions in the 8-bromo-1-substituted naphthalene series may be given is it is assumed that differences in reducing strength of the various ether soluble reducing agents that are present during the

reduction, e.g., lithium aluminum hydride and lithium alkoxyaluminohydrides, are not the most important reaction variables. Instead, observed differences in yields of dehalogenated alcohols may primarily reflect the Lewis acid strengths of trivalent alkoxyaluminum hydrides formed during reduction. Coordination of trivalent aluminum species with the halogen atom should weaken the aromatic carbon-halogen bond and facilitate cleavage by increasing the amount of positive charge on the carbon atom that is attacked by hydride. Olah (34) has suggested that similar n-complexing takes place in the fluorobenzene-aluminum bromide system. Evidence for the complexation rests on carbon-fluorine infra-red frequency shifts and nuclear magnetic proton



and fluorine resonance shifts. If the postulated Lewis acid catalysis of carbon-halogen bond cleavage is effective in systems that undergo reduction by intramolecular catalysis, it should also increase yields of reduced product in systems that are catalyzed intermolecularly. To test this idea p-bromotoluene was reduced with lithium aluminum hydride and two equivalents of added methanol in refluxing tetrahydrofuran for twenty-four hours. The yield of toluene increased from 7% (no added methanol) to 59% (see Table V).

D. Scope and Generality of the Lithium Aluminum Hydride Reduction of Aromatic Halides

The scope and generality of the reduction of aromatic halides with lithium aluminum hydride is indicated by the data obtained from the reduction of 46 different iodides, bromides, chlorides, and fluorides (see Tables VI, VII, and VIII). All compounds were reduced with one

mole of lithium aluminum hydride per mole of aromatic halide for twenty-four hours under the following reaction conditions: in diglyme at 100°, in refluxing tetrahydrofuran, and in refluxing ether. The observed halogen reactivity order for the aromatic halides reduced was iodides > bromides > chlorides > fluorides.

All iodine compounds were quantitatively reduced in diglyme at 100° and showed significant reaction under milder conditions--in refluxing tetrahydrofuran and ether. Twenty different entries in Tables VI, VII, and VIII show greater yields of aromatic hydrocarbon from reduction of the iodo compound than from the bromo analog (for example, compare entries 20 and 21 in Table VI).

Aromatic bromides are reduced in diglyme at 100° in 15-60% yields depending upon the reactivity of the substrate. Bromophenols are the least reactive (entires 22 and 23, Table VI) while the bromobenzotrifluorides are the most reactive (entries 9 and 10, Table VI). Reduction of aromatic bromides under milder conditions (in refluxing tetrahydrofuran and ether) occurs only in activated substrates such as the bromobenzotrifluorides.

Only reactive aromatic chlorides are reduced in diglyme at 100°. Under these conditions ortho- and para-chlorobenzotrifluoride gave 27% benzotrifluoride and 1-chloronaphthalene gave 28% naphthalene. Unactivated chloroaromatics such as para-chlorotoluene and chlorobenzene are not reduced (entries 13 and 19, Table VI).

The usefulness of lithium aluminum hydride reduction of aromatic halides as a preparative method is largely unexplored. The reduction of p-iodotoluene was carried out on a large scale (0.2 mole of p-iodotoluene) but was not successful. A 36% yield of toluene was realized. The low yield is most likely due to loss of toluene during the removal of diglyme by washing with water. Toluene may show appreciable solubility in water saturated with diglyme. This problem is not

present in small scale reductions (10 millimoles of aromatic halide and lithium aluminum hydride, 25 ml. of solvent) since large water-diglyme ratios may be used to remove the solvent. It is unlikely that the low yield was due to incomplete reduction since n.m.r. analysis of the reduction residue showed no p-iodotoluene. Reduction of other halides on a small scale (10 millimoles) gave nearly quantitative yields of isolated products. Naphthalene and phenol were obtained in 94 and 97% yields from reduction of 1-iodonaphthalene and o-iodophenol (see experimental, p. 52.

The reduction of aromatic halides with lithium aluminum hydride should be useful as a means of introducing deuterium into an aromatic nucleus. Although the same results may be accomplished by a Grignard synthesis, labeling by reduction could be carried out with substrates that contained substituents that would prevent Grignard formation. Treatment of p-iodotoluene with lithium aluminum deuteride at 100° in diglyme gave p-deuterotoluene. The n.m.r. spectrum of the labeled toluene (see Figure 13) showed aromatic and methyl singlets at τ 2.95 and τ 7.70 in an integrated area ratio of 1.37 : 1.00 or 4 : 3.

E. Carbon-Oxygen Bond Cleavage in the Reduction of Haloanisoles

The reduction of ortho- and para-iodo and bromoanisole in diglyme at 100° gives, besides anisole, significant amounts of phenolic products (see Table VIII). Cleavage of ethers, other than epoxides, by lithium aluminum hydride is generally not observed (2). Indeed, ethers are used as solvents for lithium aluminum hydride reductions. Acetal, ketal, and tetrahydropyranyl ethers are not attacked by lithium aluminum hydride and have been used to protect carbonyl and hydroxyl groups during reductions (2). Activated ethers, e.g., allylaryl (21, 23), cyclohexyloxyacetic acid (22), and beta-alkoxy and aryloxyproprionitriles (24)

are partially cleaved by lithium aluminum hydride.

Bailey and Marktscheffel (25) noted that considerable amounts of n-butyl alcohol resulted when benzylphosphonium halides or benzyl chloride were reduced with excess lithium aluminum hydride in refluxing tetrahydrofuran. Cleavage of tetrahydrofuran to n-butyl alcohol during reduction of several aromatic halides (o-iodotoluene, p-iodotoluene, o-iodobenzotrifluoride, p-iodobenzotrifluoride, o-bromobenzotrifluoride, p-bromobenzotrifluoride, and 2-iodo-m-xylene) was detected by v.p.c. and is not unexpected when the results of Bailey are considered. Initial attack on the aromatic halide would result in aluminum hydride which in turn could catalyze ring opening by coordination with the oxygen atom of tetrahydrofuran (equations (1) and (3)).

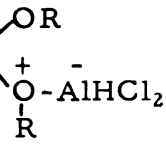
(1) $Ar\text{-}X + LiAlH_4 \longrightarrow Ar\text{-}H + LiX + AlH_3$

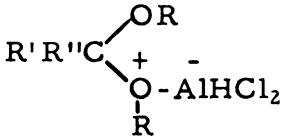
(2) $AlH_3 +$  $\longrightarrow$

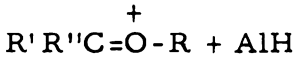
(3)  $+ AlH_4 \longrightarrow CH_3CH_2CH_2CH_2\text{-}O\text{-}AlH_3 + AlH_3$

Eliel and Rerick (26) found that addition of four moles of aluminum chloride to one mole of lithium aluminum hydride gave a reagent that reduced acetals, ketals, and tetrahydropyranyl ethers to hydroxy

(1) $LiAlH_4 + 3\ AlCl_3 \longrightarrow LiCl + 4\ AlHCl_2$

(2) $R'R''C(OR)_2 + AlHCl_2 \longrightarrow$ 

(3)  $\longrightarrow R'R''C{=}OR + RO\text{-}AlHCl_2$

(4)  $\longrightarrow R'R''CHOR$

ethers in good yields (60-90%). An ionization mechanism involving a carbonium ion intermediate was postulated as probable but not necessary. This mechanism has been further substantiated (27, 28, 29). Addition of aluminum chloride to lithium aluminum hydride (1.0 mole of aluminum chloride per 3.0 moles of lithium aluminum hydride) in refluxing ethers resulted in partial cleavage of di-n-butyl ether, dioxane, 1, 2-diethoxyethane, and tetrahydrofuran (25). Ether cleavage was also found to increase with increasing reaction temperature and time. These authors attributed the cleavage in the presence of aluminum chloride to carbon-oxygen bond weakening through formation of an aluminum hydride-ether complex salt. The following mechanism was proposed:

(1) $R\text{-}X + LiAlH_4 \longrightarrow R\text{-}H + LiCl + AlH_3$

or

(2) $AlCl_3 + 3\ LiAlH_4 \longrightarrow 3\ LiCl + 4\ AlH_3$

(3) $R\text{-}O\text{-}R + AlH_3 \longrightarrow R_2\overset{+}{O}\text{-}\overset{-}{A}lH_3$

(4) $R_2\overset{+}{O}\text{-}\overset{-}{A}lH_3 + H\text{-}Al\!\!\begin{array}{l}/\\\backslash\end{array} \longrightarrow R\text{-}H + R\text{-}OAl\!\!\begin{array}{l}/\\\backslash\end{array} + AlH_3$

No carbon-oxygen bond cleavage is observed during the reduction of ortho-iodoanisole in ethyl ether (entry 28, Table VI) but a 57% yield of phenol resulted when the reaction was carried out at 100° in diglyme (entry 1, Table VIII). This large difference may be attributed to a temperature effect. Comparison of the reduction results of para-iodoanisole in refluxing ether and in diglyme at 100° (entry 29, Table VI and entry 3, Table VIII) shows that no ether cleavage occurs at 35° or 100° with this anisole. The difference in yields of phenol obtained from ortho- and para-iodoanisole cannot be due to a difference in reaction temperature. The results in Table VIII also show that ortho-bromoanisoles undergo reduction to give considerable amounts of phenolic products while the para-bromoanisoles do not. These results

may be accounted for if ortho-haloanisoles are reduced by an intramolecular path. If the ortho halogen atom forms a coordinate bond with aluminum, the carbon-oxygen bond may cleave in an intramolecular

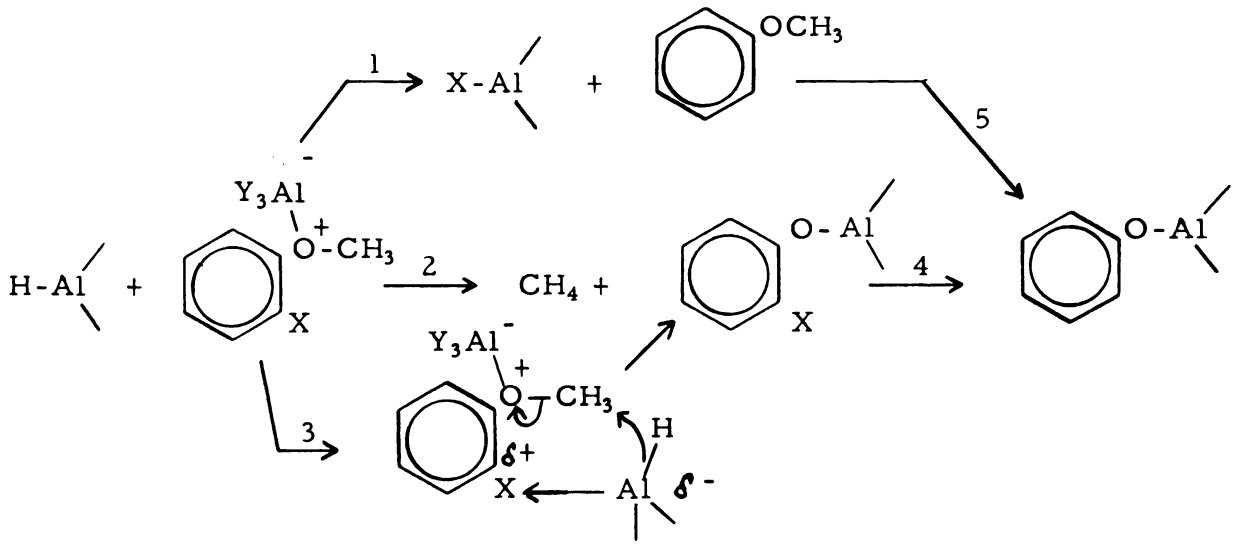
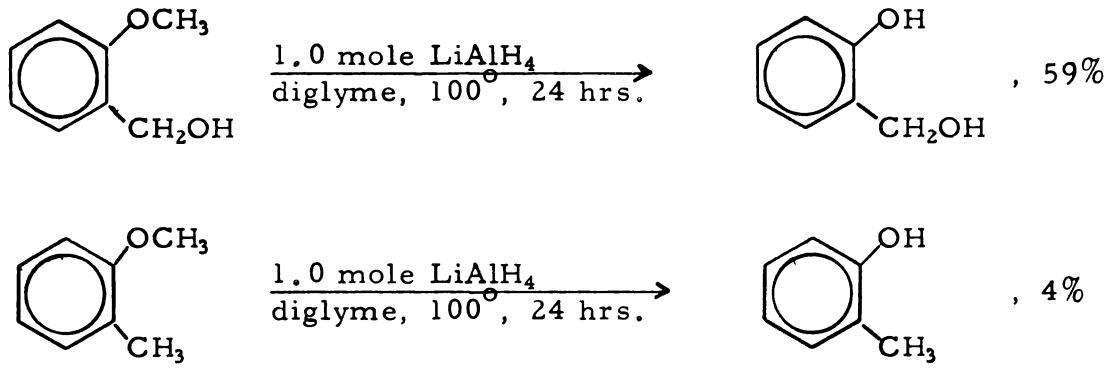


Figure 8

displacement reaction (path 3). The aluminum halophenoxide may then undergo further intermolecular reduction to phenol (path 4). Under the reaction conditions employed ortho-iodophenol is quantitatively reduced to phenol (entry 24, Table VI) and some reduction of ortho-bromophenol to phenol would be expected. The observed ratios of phenol to ortho-halophenols are thus not unreasonable. Since para-haloanisoles give little or no phenol, path 2 is probably unimportant in reduction of all isomeric halophenols. An alternant pathway, cleavage of the carbon-halogen bond followed by reduction of anisole to phenol (path 1 followed by 5), is improbable since anisole is reduced to phenol in only 4% yield under similar conditions. Such a mechanism also fails to account for the formation of halophenols.

Further support for the proposed intramolecular reduction is provided by a comparison of the observed products from reduction of ortho-methoxybenzyl alcohol and ortho-methylanisole. The former,



after forming the aluminum alkoxide, should reduce to ortho-hydroxybenzyl alcohol by an intramolecular assisted cleavage of the carbon-oxygen bond. This is indeed observed while ortho-methylanisole, possessing no group ortho to the methoxy group that can bond or coordinate with aluminum, is reduced to ortho-cresol to the same extent that anisole is reduced to phenol.

Table VI. Reduction of Selected Aromatic Halides

	Diglyme, 100°	THF, 65°	Ether, 35°
Naphthalenes			
1. 1-chloro	28	-	-
2. 1-bromo	61	49	6
3. 2-bromo	-	21	-[d]
4. 1-iodo	100	72	14
5. 2-iodo	100	75	19
6. 8-bromo-1-methyl	100	46	11
Benzotrifluorides			
7. ortho-chloro	27	-	-
8. para-chloro	27	-	-
9. ortho-bromo	98	59	-
10. para-bromo	91	40	-
11. ortho-iodo	100	78	62
12. para-iodo	99	71	30
Toluenes			
13. para-chloro	0	-	-
14. ortho-bromo	41	7	-
15. para-bromo	28	7	-
16. ortho-iodo	92	67	6
17. para-iodo	82	75	9
Xylenes			
18. 2-iodo-meta-	92	61	7
Benzenes			
19. chloro	4[a]	-	-
20. bromo	23	-	-
21. iodo	88	-	-
Phenols[b]			
22. ortho-bromo	14	-	-
23. para-bromo	18	-	-
24. ortho-iodo	100	51	-
25. para-iodo	92	46	-
Anisoles			
26. ortho-bromo	58[c]	-	-
27. para-bromo	35[c]	-	-
28. ortho-iodo	41[c]	-	26
29. para-iodo	91	-	5

Note: Reductions were performed with 1.0 mole of lithium aluminum hydride per mole of aromatic halide during a twenty-four hour reaction. Numbers are percent yield of reduced aromatic hydrocarbon product.

[a] A forty-eight hour reaction time was used.

[b] 1.25 moles of lithium aluminum hydride were used per mole of phenol.

[c] Phenolic products were also observed, see Table VIII.

[d] - indicates that the substrate was not reduced under these conditions.

Table VII. Reduction of Halobenzoic Acids

Acid	Diglyme, 100°	THF, 65°	Ether, 35°
1. para-fluoro	-[a]	0	-
2. ortho-chloro	13	3	-
3. meta-chloro	-	0	-
4. para-chloro	-	0	-
5. ortho-bromo	-	100(36)	21(19)
6. meta-bromo	-	63(28)	5(0)
7. para-bromo	-	68(27)	2(0)
8. ortho-iodo	-	100	100(26)
9. meta-iodo	-	100	65(23)
10. para-iodo	-	100	63(17)
11. ortho-bromobenzyl alcohol	(80)	(20)	(4)

Note: Figures are percent yields of benzyl alcohol. The benzoic acids were reduced with 2.0 moles of lithium aluminum hydride per mole of acid and 1.0 mole of lithium aluminum hydride per mole of acid. Per cent yields of benzyl alcohol are given in parenthesis when 1.0 mole of lithium aluminum hydride was used per mole of acid. All reactions were run for twenty-four hours and carboxyl group reduction was complete in all cases.

[a] - indicates that the substrate was not reduced under these conditions.

Table VIII. Reduction of Haloanisoles

Haloanisole	% Yield of Product		
	Anisole	Phenol	Halophenol
1. ortho-iodoanisole	41	57	3
2. ortho-bromoanisole	58	14	9
3. para-iodoanisole	91	0	0
4. para-bromoanisole	35	1	2
5. anisole	96	4	-[a]

Note: All reductions were carried out with 1.0 mole of lithium aluminum hydride per mole of aromatic halide for twenty-four hours in diglyme at 100°.

[a] - indicates that the substrate was not reduced under these conditions.

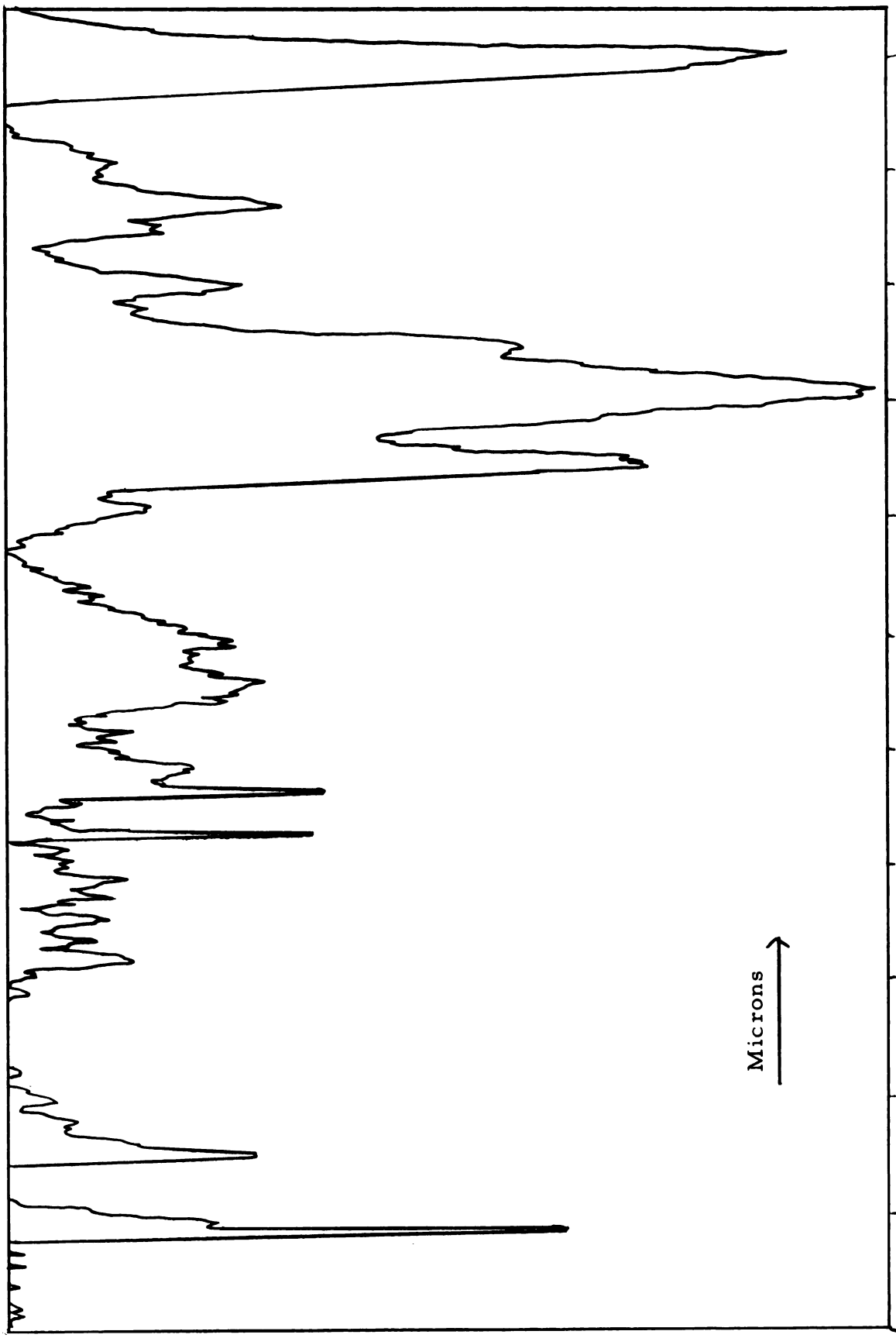


Figure 9. Infra-red spectrum of 1-naphthylcarbinol (in methylene dibromide) obtained by lithium aluminum hydride reduction of 1-naphthoic acid.

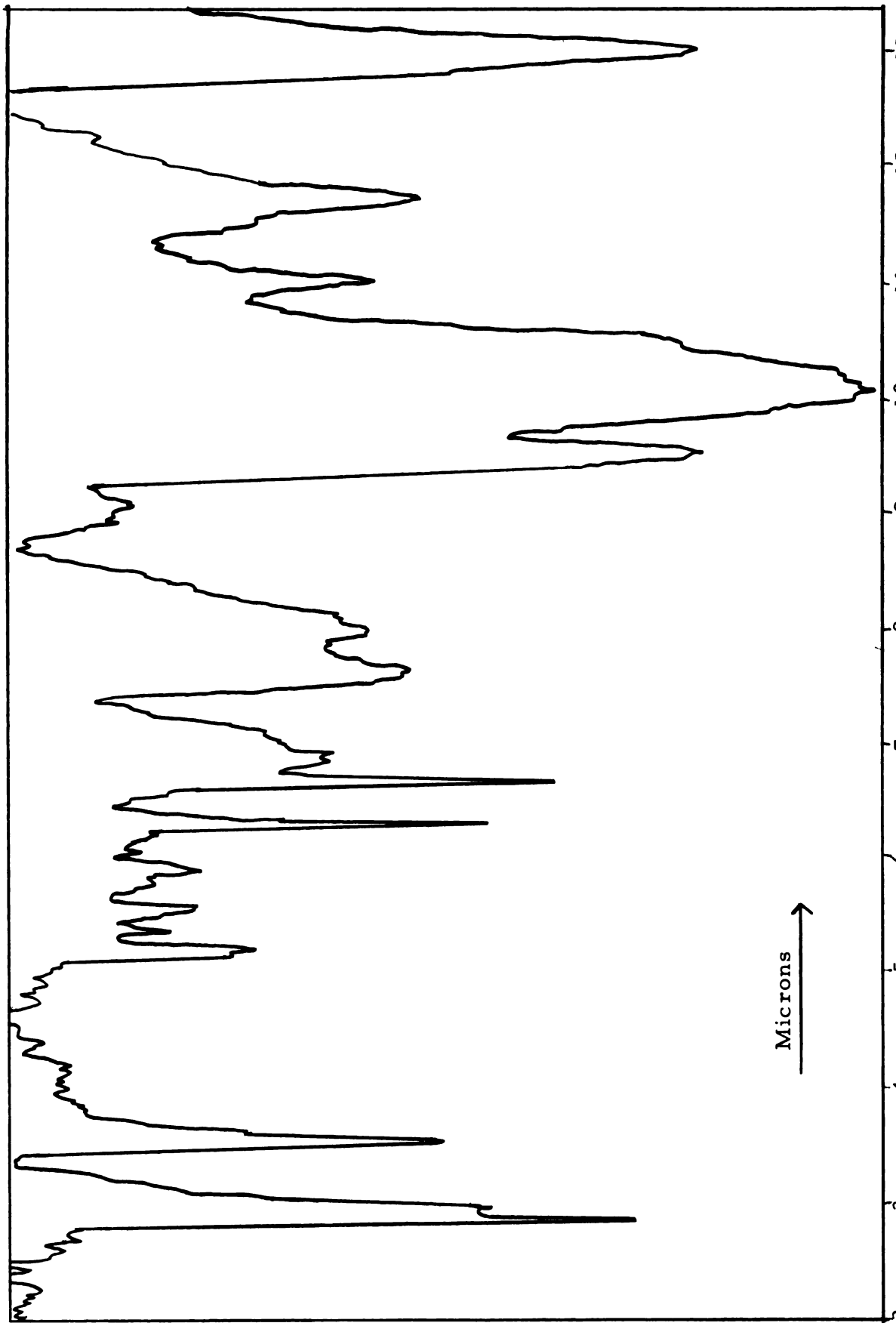


Figure 10. Infra-red spectrum of 1-naphthylcarbinol (in methylene dibromide) obtained by lithium aluminum hydride reduction of 8-bromo-1-naphthoic acid.

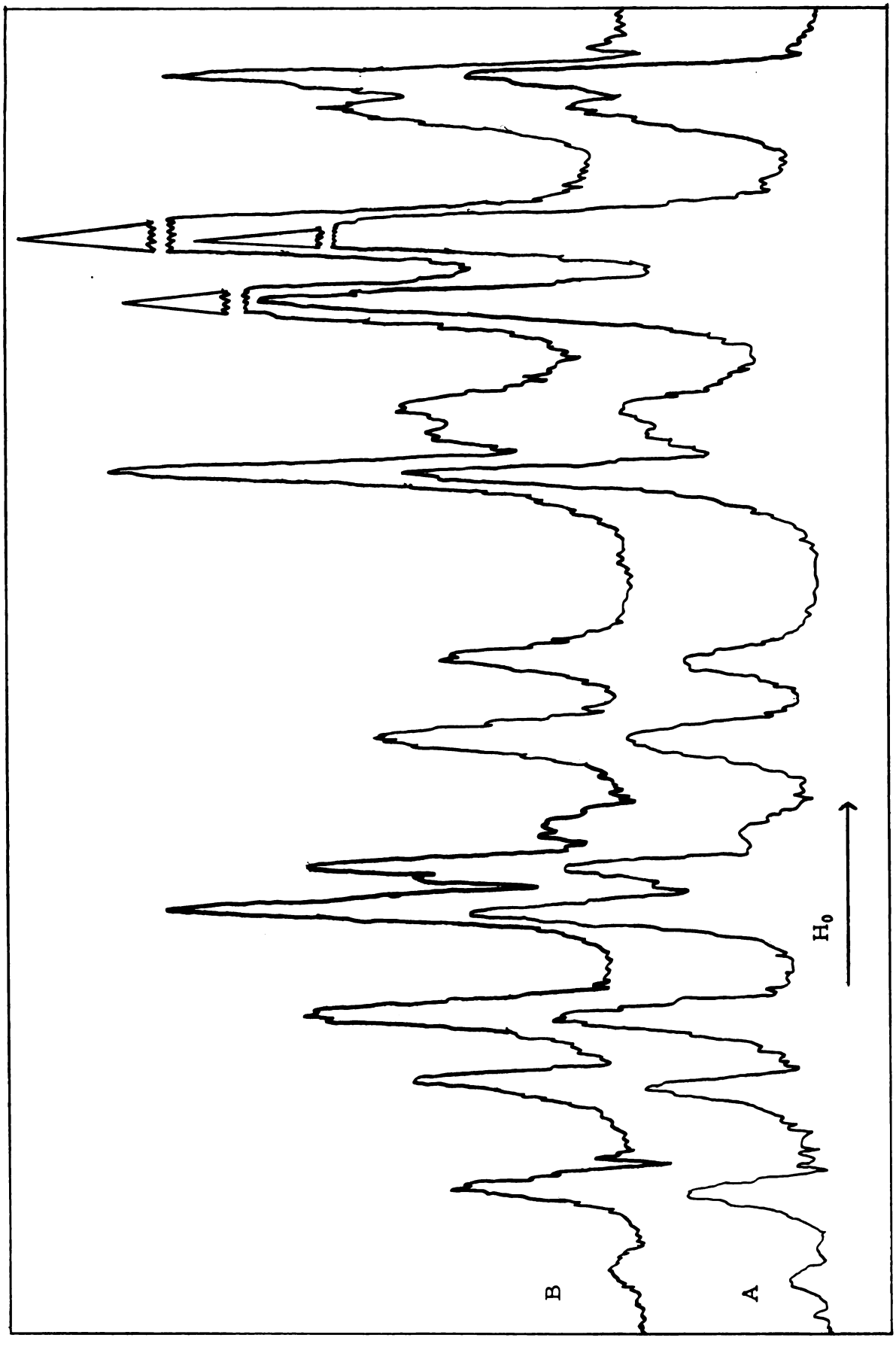


Figure 11. N.m.r. spectra of 8-deutero-1-naphthylcarbinol (15% in carbon disulfide) obtained by snythesis from 1-bromo-8-iodonaphthalene (A), and lithium aluminum deuteride reduction of 8-bromo-1-naphthylcarbinol (B).

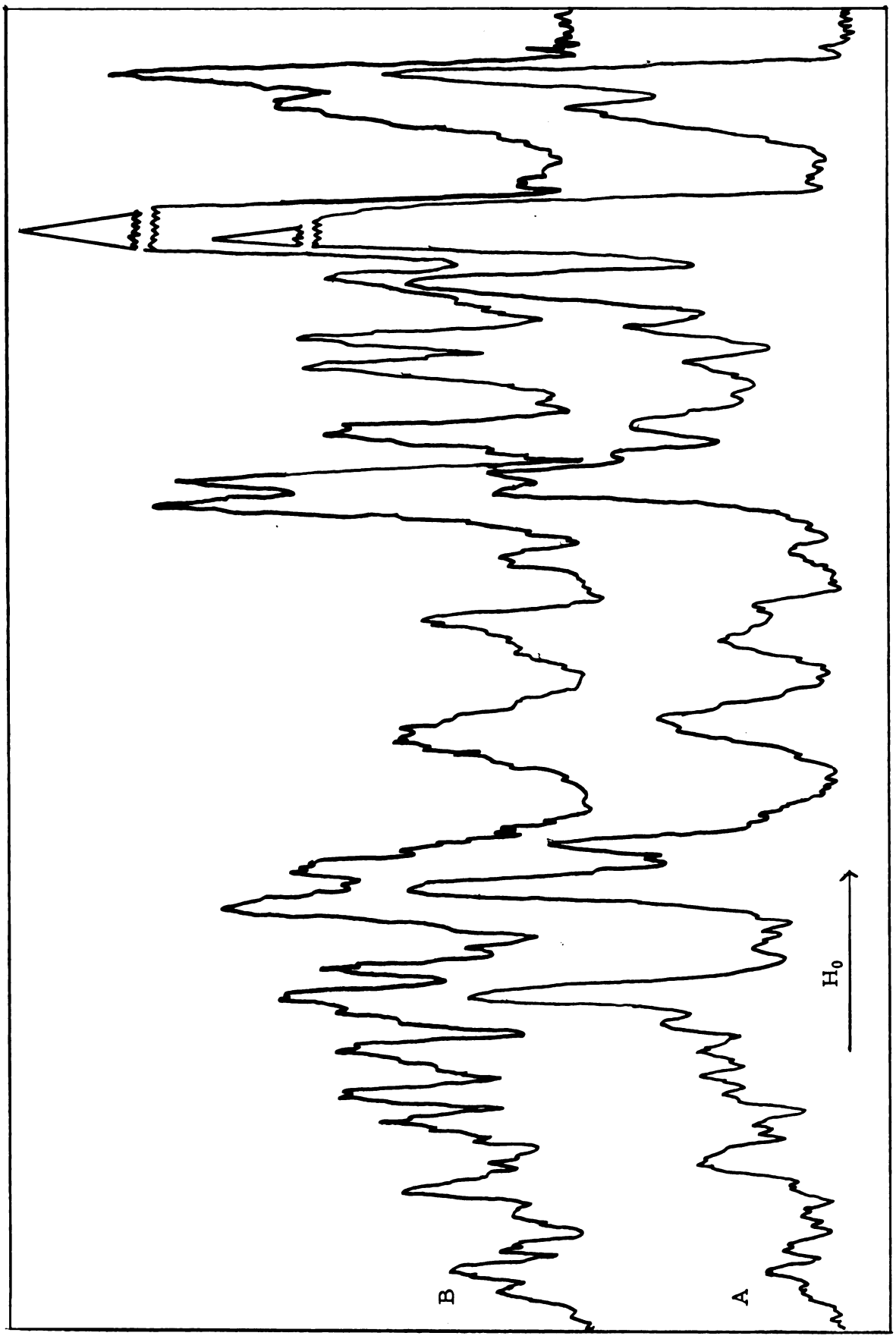


Figure 12. N.m.r. spectra of 1-naphthylcarbinol (15% in carbon disulfide) obtained by lithium aluminum hydride reduction of 8-bromo-1-naphthylcarbinol (A), and lithium aluminum hydride reduction of 1-naphthoic acid (B).

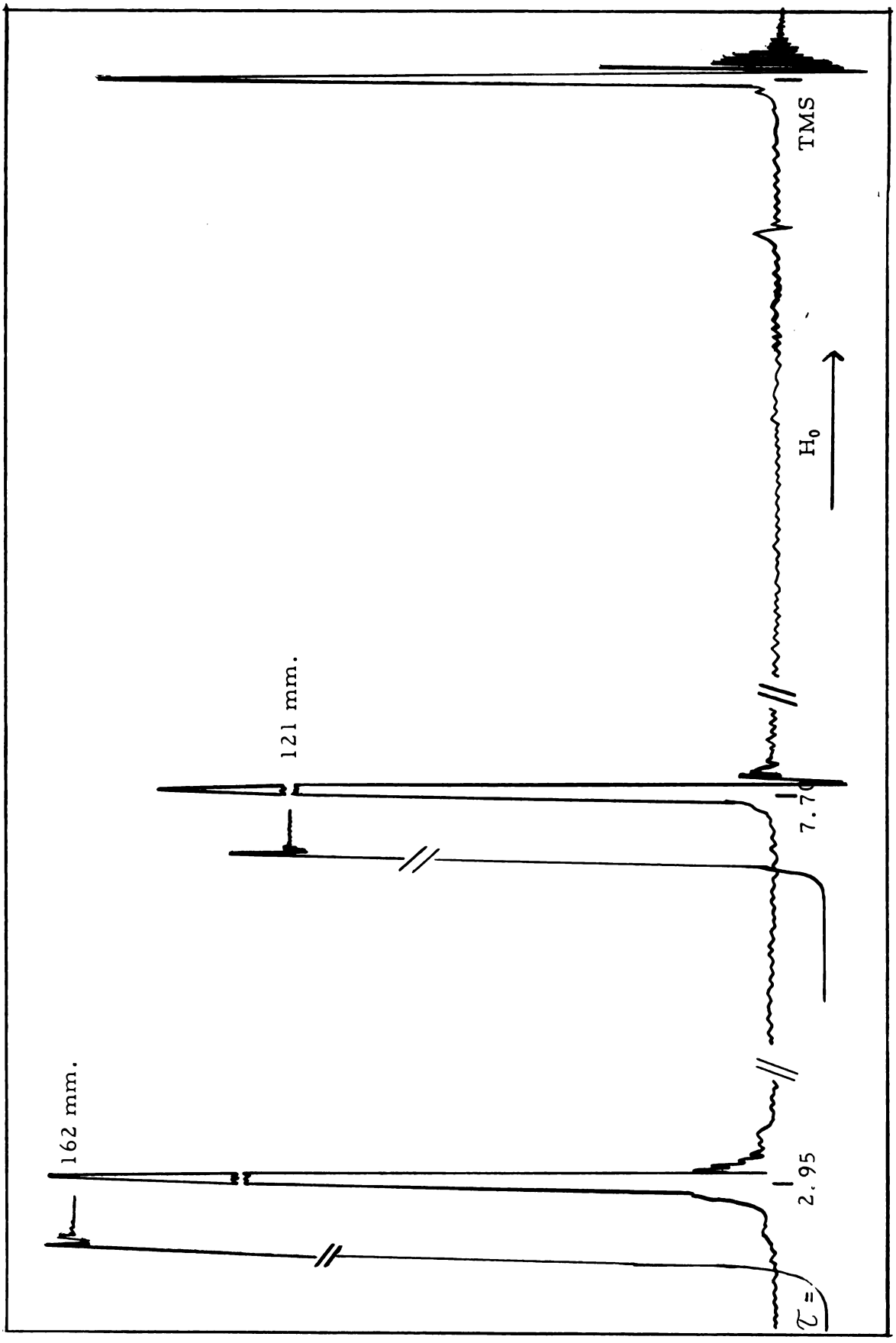


Figure 13. N.m.r. spectrum of para-deuterotoluene (in carbon tetrachloride).

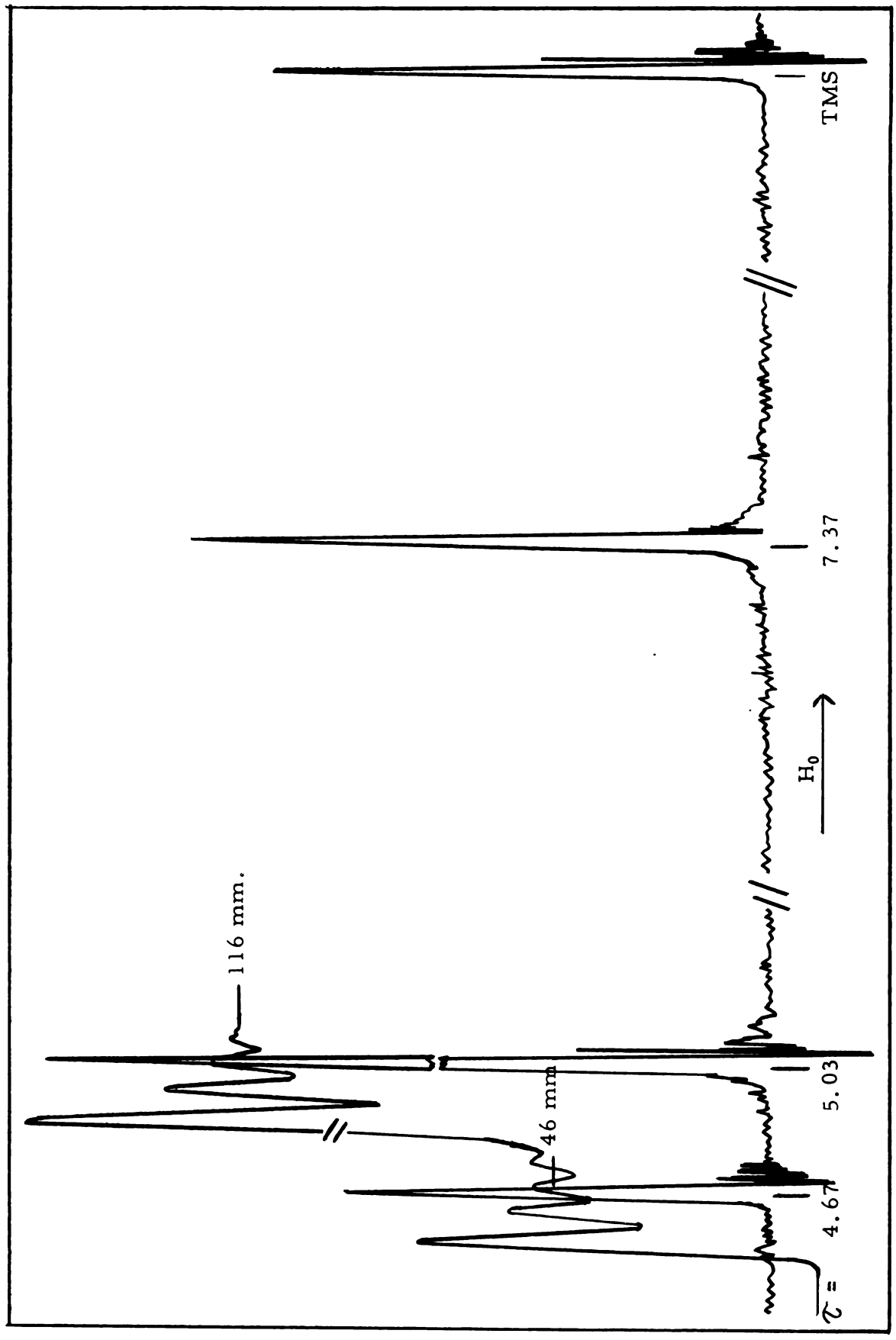


Figure 14. N.m.r. spectrum of mixture of 1-naphthylcarbinol and 8-bromo-1-naphthylcarbinol (in chloroform) obtained by lithium aluminum hydride reduction of 8-bromo-1-naphthoic acid in refluxing tetrahydrofuran for twenty-four hours.

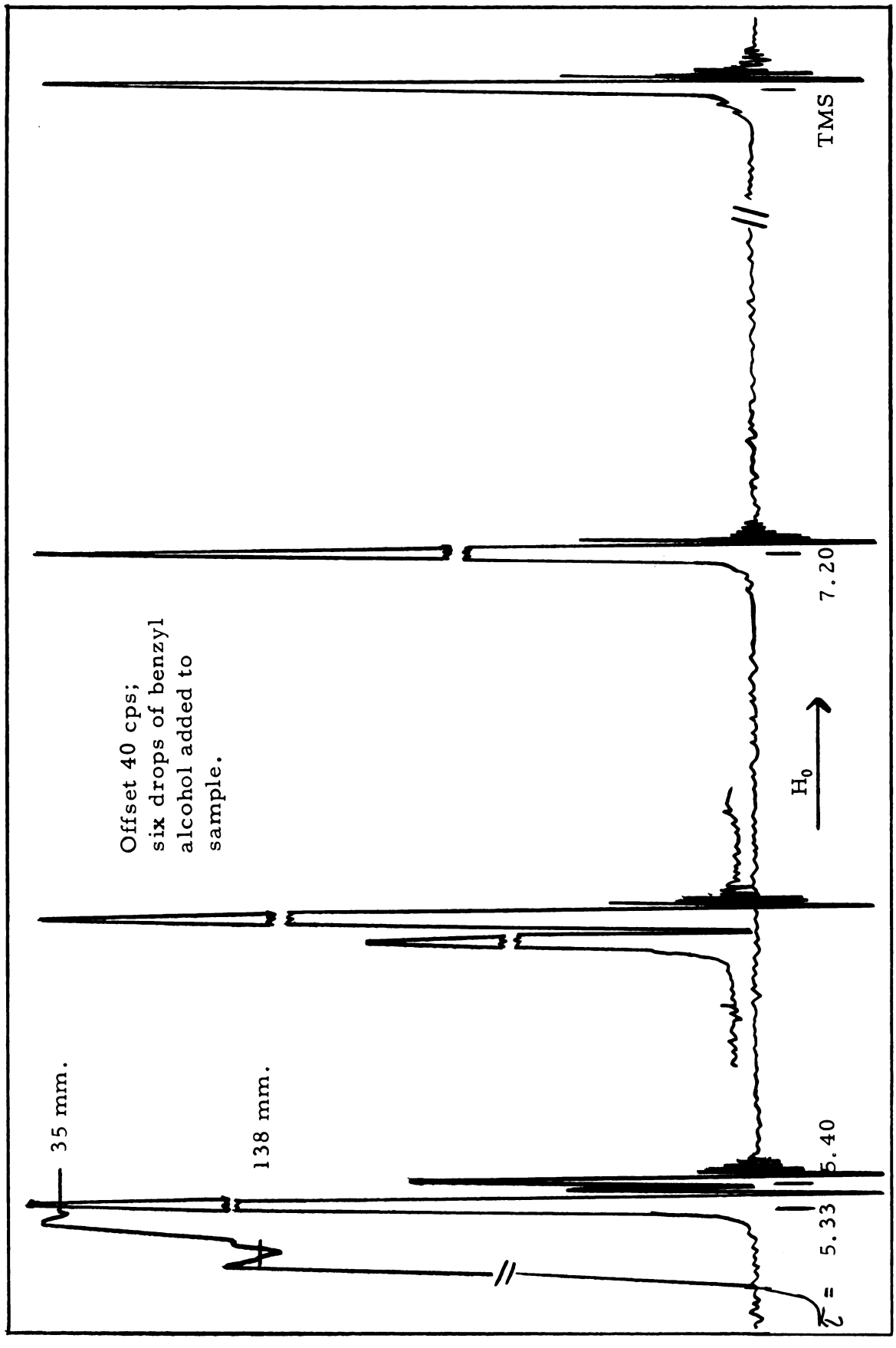


Figure 15. N.m.r. spectrum of mixture of benzyl alcohol and o-bromobenzyl alcohol (in chloroform) obtained by lithium aluminum hydride reduction of o-bromobenzyl alcohol in refluxing tetrahydrofuran for twenty-four hours.

EXPERIMENTAL

I. General Procedure for Reduction of Aromatic Halides with Lithium Aluminum Hydride

A. Apparatus

Lithium aluminum hydride, 0.36 g. (10 millimoles), was added to 25 ml. of dry solvent (ether, tetrahydrofuran, or diglyme) in a 50 ml. single-necked round-bottomed flask fitted with a six-inch water jacketed condenser to which was attached a calcium chloride drying tube. Ten millimoles of aromatic halide was added to the hydride slurry and the resulting mixture was then refluxed or heated at constant temperature in a thermostat controlled oil bath for twenty-four hours.

After reaction the flask and its contents were cooled in an ice bath and water was carefully added dropwise to quench unreacted lithium aluminum hydride. Next, 30 ml. of 10% sulfuric acid was added to dissolve the precipitated alkoxide salts. The contents of the flask were transferred to a 250 ml. separatory funnel and extracted three times with 75 ml. portions of ether. The combined ether extracts were washed once with 25 ml. of saturated sodium bicarbonate solution and 50 ml. of distilled water. After drying over anhydrous magnesium sulfate the ether was evaporated and the resulting residue analyzed for reduced product.

B. Aromatic Halide-Lithium Aluminum Hydride Ratio

All reductions were carried out using a 1 : 1 molar ratio of aromatic halide to lithium aluminum hydride, except the reduction of phenols, for which a 4 : 5 ratio was used, and the halobenzoic acids, for which both a 1 : 1 and 1 : 2 ratio was used.

C. Solvent Preparation

Ether, tetrahydrofuran, and diglyme were dried by distillation from lithium aluminum hydride slurries just prior to use. Diglyme was distilled at reduced pressure (b.p. 60° at 40 mm. Hg) and ether and tetrahydrofuran at atmospheric pressure. Precautionary measures in the distillation of diglyme from lithium aluminum hydride should be taken (20).

D. Solvent Removal

Tetrahydrofuran and diglyme were removed from the quenched reaction mixture by washing the combined ether extracts four times with 50 ml. portions of water.

E. Isolation of Acidic, Water Soluble Products

When phenols or anisoles were reduced the workup procedure was modified in the following manner. The initial ether extracts were washed twice with 25 and 10 ml. of 10% sodium hydroxide solution. The hydroxide extracts were then acidified with 20% hydrochloric acid and the acidified solution was saturated with sodium chloride and extracted three times with 50 ml. portions of ether. The ether extracts were then combined with the initial ether washings, washed once with 25 ml. of saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and evaporated to obtain the residue.

F. Recovery of Unreduced Carboxylic Acids

When carboxylic acids were reduced, recovery of unreduced acid was effected by acidification of the saturated sodium bicarbonate extract. The precipitated acid was filtered, dried, weighed, and the percent recovered acid was calculated.

G. Preparation of Aromatic Halides

Halogenated toluenes, benzenes, xylenes, anisoles, benzotrifluorides, benzoic acids, and naphthalenes were commercially available and were used as such without purification. The preparation of 8-bromo-1-substituted naphthalenes is described in the experimental section of this thesis. Commercial grade bromo and iodophenols and o-cresol were dried in ether over anhydrous magnesium sulfate prior to reduction. Ortho-methoxybenzyl alcohol and ortho- and para-bromobenzyl alcohol were prepared by lithium aluminum hydride reduction of the corresponding aldehydes. The iodobenzyl alcohols were prepared by lithium aluminum hydride reduction of ortho- and para-iodobenzoic acids.

H. Product Analysis

Reduction product mixtures were analyzed for reduced aromatic hydrocarbon and aromatic halide by nuclear magnetic resonance or vapor phase chromatography techniques. Aromatic halides which possessed proton containing functional groups (toluenes, benzyl alcohols, xylenes, and 8-bromo-1-substituted naphthalenes) gave mixtures that were analyzed by n.m.r. The chemical shift of the functional group of the aromatic halide differed by 0.5-35 cps from that of the same functional group in the reduced aromatic hydrocarbon. Five to fifteen percent by weight solutions of the reduction mixtures were prepared in a suitable solvent and the spectrum was obtained on a Varian Associates A-60 spectrometer. Integration of the appropriate signals gave the per cent reduced product. Representative spectra are given in Figures 14 and 15. Aromatic halides with no functional groups or functional groups that did not contain protons gave reduction product mixtures that were analyzed by v.p.c. on an aerograph A-90-P gas chromatograph.

II. Synthesis

A. Preparation of 1-Naphthylcarbinol by Lithium Aluminum Hydride Reduction of 8-Bromo-1-Naphthoic Acid

A slurry of 6.05 (0.16 mole) of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran was prepared in a three-necked 500 ml. round-bottomed flask that was fitted with a condenser, stirring motor, and a 250 ml. dropping funnel. A solution of 20 g. (0.08 mole) of 8-bromo-1-naphthoic acid in 100 ml. of tetrahydrofuran was added dropwise to the stirred slurry.

After a twenty hour reflux period the solution was cooled in an ice bath and water was added dropwise until hydrogen evolution had ceased. Next a 10% solution of sodium hydroxide was added until the precipitated alkoxide salts had dissolved. The resulting solution was extracted three times with 150 ml. portions of ether and the combined ether extracts were washed four times with 150 ml. portions of water. The ether extracts were then shaken twice with 50 ml. portions of saturated sodium bicarbonate solution and were dried over anhydrous magnesium sulfate.

Evaporation of the ether and recrystallization of the crude product from cyclohexane gave 9.37 g. (80%) of colorless needles of 1-naphthylcarbinol, m.p. 60-61° (lit. 59.5-60° (32)). The infra-red spectrum of 1-naphthylcarbinol in methylene dibromide showed absorptions at 2.86, 2.96, 3.55, 6.30, and 6.67 microns. The n.m.r. spectrum of the alcohol in carbon disulfide showed a multiplet at τ 1.92-2.66, a methylene singlet at τ 5.15, and a hydroxyl singlet at τ 6.47 in integrated area ratios of 7.3 : 2.0 : 1.0, respectively.

B. Preparation of 1-Methylnaphthalene from 8-Bromo-1-Naphthoic Acid

Five grams (31.6 millimoles) of 1-naphthylcarbinol (obtained from reduction of 8-bromo-1-naphthoic acid) was dissolved in 30 ml. of dry benzene in a 50 ml. single-necked round-bottomed flask that was fitted with a gas delivery tube. The flask was cooled in an ice bath and anhydrous hydrogen chloride was passed through the solution for one-half hour. The water formed was removed with anhydrous calcium chloride, the solution was decanted, and the benzene was removed by distillation at reduced pressure.

The residual oil was dissolved in 25 ml. of dry ether and added to a slurry of 0.81 g. (21.1 millimoles) of lithium aluminum hydride in 15 ml. of ether in a 150 ml. three-neck round-bottomed flask. The flask was fitted with a condenser, stirring motor, and 250 ml. dropping funnel. After four hours of reflux the ether solution was cooled and water was added dropwise until hydrogen evolution had ceased. Next 10% sodium hydroxide solution was added until the precipitated alkoxide salts had dissolved and the aqueous solution was then extracted three times with 50 ml. portions of ether. The ether was dried over anhydrous magnesium sulfate, evaporated, and the residual oil was distilled at reduced pressure (b.p. 77-81° at 1.30 mm. of Hg) to give 1.53 g. (29.8%) of 1-methylnaphthalene, a colorless oil with n_D^{20} = 1.6172 (lit. n_D^{20} = 1.6174 (13)).

C. Lithium Aluminum Hydride Reduction of Methyl 8-Bromo-1-Naphthoate

A 300 ml. three-necked round-bottomed flask was fitted with a reflux condenser, stirrer, and a 250 ml. dropping funnel. Dry ether, 100 ml., was introduced and 1.00 g. (28.0 millimoles) of lithium aluminum hydride was added. A solution of 12.93 g. (49.0 millimoles)

of methyl 8-bromo-1-naphthoate in 100 ml. of ether was added dropwise to the hydride slurry and the resulting solution was refluxed for twenty-three hours.

A workup procedure similar to that used for the reduction of 8-bromo-1-naphthoic acid was used. A 10% solution of sulfuric acid was used to dissolve the alkoxide salts. A light brown oil, 11.20 g., which solidified at room temperature was obtained. The infra-red spectrum of the oil in carbon tetrachloride showed absorbances at 2.80 and 5.79 microns. The n.m.r. spectrum of the oil in carbon disulfide showed a multiplet at τ 2.17-3.08, methylene singlets at τ 4.75 and τ 5.15, a methoxy singlet at τ 6.22, and a hydroxyl singlet at τ 6.70. Integration of the methylene and methoxy signals showed that the oil contained 48% 8-bromo-1-naphthylcarbinol, 27% 1-naphthylcarbinol, and 25% methyl 8-bromo-1-naphthoate.

Two recrystallizations of the crude solid from cyclohexane gave 1.86 g. (16%) of colorless needles of 8-bromo-1-naphthylcarbinol, m.p. 87-88°. The infra-red spectrum of the bromoalcohol in carbon tetrachloride showed absorptions at 2.83, 2.93, 3.32, 3.44, 3.47, 6.70, 7.27, 8.43, and 8.61 microns. The n.m.r. spectrum of the alcohol in carbon disulfide showed a multiplet at τ 2.25-3.25, a methylene singlet at τ 4.70, and a hydroxyl singlet at τ 7.28. The integrated area ratio was 6.0 : 2.0 : 1.0, respectively.

D. Lithium Aluminum Hydride Reduction of Methyl 8-Bromo-1-Naphthoate by Inverse Addition

The procedure and apparatus used were similar to those previously described for the reduction of methyl 8-bromo-1-naphthoate. A slurry of 0.53 g. (14.0 millimoles) of lithium aluminum hydride in 100 ml. of ether was added dropwise over two and one-half hours to a stirred solution of 7.42 g. (28 millimoles) of the ester in 50 ml. of ether.

The solution was stirred for an additional five and one-half hours after addition and then worked up. Integration of the n.m.r. spectrum of the resulting oil showed that it contained 35% 8-bromo-1-naphthylcarbinol, 17% 1-naphthylcarbinol, and 48% unreduced methyl 8-bromo-1-naphthoate.

E. Reduction of 8-Bromo-1-Naphthylcarbinol with Lithium Aluminum Deuteride

One gram (4.22 millimoles) of 8-bromo-1-naphthylcarbinol was added to a slurry of 0.18 g. (4.22 millimoles) of lithium aluminum deuteride in 25 ml. of tetrahydrofuran and the solution was refluxed for twenty-four hours. The apparatus and workup procedure used was similar to the general procedure described for aromatic halide reduction. Deuterium oxide instead of water was used to quench the reaction. Recrystallization of the crude product from 10 ml. cyclohexane - 1 ml. benzene gave 0.27 g. (40.3%) of colorless needles of 8-deutero-1-naphthylcarbinol, m.p. 58-60°. The n.m.r. spectrum of a 15% by weight solution of the carbinol in carbon disulfide showed a multiplet at τ 2.17-3.00, a methylene singlet at τ 5.37, and a hydroxyl singlet at τ 6.28. The integrated area ratio of the three signals was 6.1 : 2.0 : 0.9, respectively. The multiplet observed at 100 cps width was identical in all respects to the multiplet of 8-deutero-1-naphthylcarbinol obtained from 1-bromo-8-iodonaphthalene and distinctly different from the aromatic multiplet of 1-naphthylcarbinol. For comparison of the three spectra see Figures 11 and 12.

F. Preparation of Para-deuterotoluene

The apparatus and procedure used were similar to the general procedure described for the reduction of aromatic halides. Para-iodotoluene, 1.09 g. (5.0 millimoles), was added to a slurry of 0.21

g. (5.0 millimoles) of lithium aluminum deuteride in 25 ml. of diglyme and was placed in a thermostat controlled oil bath at 100° for twenty-four hours. The crude oil was distilled in a microcolumn and gave approximately 0.3 ml. of p-deuterotoluene, a colorless liquid. The infra-red spectrum of the p-deuterotoluene in carbon tetrachloride showed absorptions at 3.28, 3.43, 3.50, and 4.42 microns. The n.m.r. spectrum of the p-deuterotoluene in carbon tetrachloride (see Figure 13) showed singlets at τ 2.95 and τ 7.70 in an integrated area ratio of 1.37 : 1.0, or approximately 4 : 3.

G. Preparation of Toluene by Lithium Aluminum Hydride Reduction of Para-iodotoluene

A slurry of 7.60 g. (0.20 mole) of lithium aluminum hydride in 300 ml. of dry diglyme was prepared in a 500 ml. single-necked round-bottomed flask fitted with a condenser to which was attached a calcium chloride drying tube. Next, 21.80 g. (0.20 mole) of p-iodotoluene was added and the resulting solution was kept at 100° for seventy-two hours in a thermostat controlled oil bath.

After cooling in an ice bath the unreacted lithium aluminum hydride was destroyed by careful dropwise addition of water. The precipitated alkoxide salts were dissolved by adding 400 ml. of 20% sulfuric acid and the resulting solution was extracted four times with 150 ml. portions of ether. The combined ether extracts were bleached with 100 ml. of saturated sodium sulfite solution, washed three times with 300 ml. portions of water, once with 100 ml. of saturated sodium bicarbonate solution, and washed again with 300 ml. of water. After drying over anhydrous magnesium sulfate the ether was concentrated by distillation to approximately 200 ml. volume, was washed four times with 50 ml. portions of water, and was again dried over anhydrous magnesium sulfate. After distillation of the remaining ether the residue was distilled at 108-110° to give 6.68 g. (36%) of toluene.

H. Reduction of 8-Bromo-1-Naphthylcarbinol with Lithium Aluminum Hydride and with Methanol Added

The procedure and apparatus used was similar to the general procedure for aromatic halide reduction already described. A slurry of 0.19 g. (5.0 millimoles) of lithium aluminum hydride in 25 ml. of ether containing 0.32 g. (10.0 millimoles) of methanol was prepared and 1.19 g. (5.0 millimoles) of 8-bromo-1-naphthylcarbinol was added. The resulting solution was refluxed with stirring for twenty-four hours. After workup 0.88 g. (100% recovery) of a light yellow oil was obtained. Analysis of the oil by n.m.r. showed it contained 77% 1-naphthylcarbinol and 23% 8-bromo-1-naphthylcarbinol.

I. Preparation of 1,8-Aziminonaphthalene

Commerciably available 1,8-diaminonaphthalene was purified according to the following procedure. The crude diamine, 90 g. (0.57 mole), was dissolved in 1.3 l. of hot 95% ethanol and the resulting solution was treated with Norite decolorizing charcoal. The solution was filtered, cooled in an ice bath, and 330 ml. of concentrated hydrochloric acid was added followed by 300 ml. of ether. The precipitated dihydrochloride was filtered, dried, and weighed to give 131 g. (86%) of 1,8-diaminonaphthalene dihydrochloride. The dihydrochloride was converted to 1,8-aziminonaphthalene according to the method of Klemm and co-workers (30).

J. Preparation of 8-Bromo-1-Naphthylamine

The method of Fieser and Seligman (14) was used to prepare 8-bromo-1-naphthylamine from 1,8-aziminonaphthalene. Light copper turnings were used in place of copper bronze and the addition of 1,8-aziminonaphthalene was performed according to Klemm's modification (30).

K. Preparation of 1-Bromo-8-Iodonaphthalene

Conversion of 8-bromo-1-naphthylamine to 1-bromo-8-iodonaphthalene was carried out according to the procedure of Fieser and Seligman (14).

L. Preparation of 1-Methyl-8-Bromonaphthalene

The preparation of 1-methyl-8-bromonaphthalene was carried out according to the method of Fieser and Seligman (14).

M. Preparation of 8-Methyl-1-Naphthoic Acid

A 300 ml. three-necked round-bottomed flask was fitted with a stirrer, 250 ml. dropping funnel, and a reflux condenser. The apparatus was swept free of air with dry argon gas and was heated with a flame until dry. Next, 5.67 g. (0.237 g. atom) of Domal high purity magnesium and 50 ml. of dry ether were added. A mixture of 15.00 g. (0.068 mole) of 1-methyl-8-bromonaphthalene and 14.78 g. (0.136 mole) of ethyl bromide in 100 ml. of ether was added dropwise at a brisk rate to the stirred ether-magnesium slurry. The resulting solution was refluxed for four hours. A thick milky precipitate formed during the reflux period.

The Grignard solution was poured slowly onto 60 g. of dry ice and 100 ml. of ether was added. After all carbon dioxide evolution had ceased, 60 ml. of 20% hydrochloric acid was slowly added to the carbonated Grignard reagent along with enough ice to keep the ether solution cool during acidification. The aqueous and ether layers were separated and the ether layer was washed three times with 75 ml. portions of water. The ether solution was then extracted with 45 ml. of 10% sodium hydroxide solution and the carboxylic acid was precipitated by neutralization of the base solution with 20 ml. of 20% hydrochloric acid. After filtration and drying the crude acid was

recrystallized from 30% ethanol to give 10.16 g. (81.2%) of colorless platelets of 8-methyl-1-naphthoic acid, m.p. 155-56° (lit. m.p. 152-53° (41)). The infra-red spectrum of the acid in carbon disulfide showed absorptions at 3.38, 3.76, 4.47, 5.94, 7.81, 8.02, 8.79, and 12.14 microns.

N. Preparation of Methyl 8-Methyl-1-Naphthoate

A solution of 20.0 g. (0.107 mole) of 8-methyl-1-naphthoic acid in 400 ml. of ether was prepared in a 1.0 l. single-necked round-bottomed flask and was cooled in an ice bath. Approximately 7.0 g. (0.17 mole) of diazomethane in 300 ml. of ether was prepared (42) and added slowly to the ethereal carboxylic acid solution. After standing for one-half hour the excess diazomethane was destroyed by addition of acetic acid until the characteristic yellow color of diazomethane had disappeared.

The ether solution was then washed once with 50 ml. of saturated sodium bicarbonate solution, three times with 100 ml. portions of water, and was dried over anhydrous magnesium sulfate. After evaporation of the ether the crude ester was distilled at reduced pressure twice to give 14.84 g. (69.0%) of methyl 8-methyl-1-naphthoate, a colorless oil with $n_D^{25} = 1.5986$ and b.p. 127-28° at 0.7 mm. Hg. The infra-red spectrum of the ester in carbon tetrachloride showed absorptions at 3.31, 3.42, 5.21, 5.82, 6.64, 6.85, 6.92, 6.98, 7.26, 7.49, 7.84, 8.06, 8.39, 8.76, 9.18, 9.86, and 10.29 microns. The n.m.r. spectrum of the ester in carbon tetrachloride showed a multiplet at τ 2.00-2.83, a methoxy singlet at τ 6.10, and a methyl singlet at τ 7.45 in integrated area ratios of 1.98 : 1.03 : 1.00, respectively.

O. Preparation of 8-Methyl-1-Naphthylcarbinol

A 1.0 l. three-necked round-bottomed flask was fitted with a stirrer, 250 ml. dropping funnel, and a reflux condenser. The apparatus was swept free of air with dry argon gas and heated with a flame until dry. Dry ether, 150 ml., was introduced into the flask and 16.30 g. (0.43 mole) of lithium aluminum hydride was added. A solution of 40.0 g. (0.215 mole) of 8-methyl-1-naphthoic acid in 500 ml. of dry ether was added dropwise to the stirred hydride slurry and the resulting solution was refluxed for forty-two hours.

After cooling in an ice bath, water was added dropwise to the stirred hydride solution until evolution of hydrogen had ceased. Dilute (10%) sulfuric acid was then added dropwise until the precipitated alkoxide salts had dissolved. The aqueous and ether layers were separated and the aqueous layer was extracted twice with 100 ml. portions of ether. The combined ether solution was washed once with 100 ml. of saturated sodium bicarbonate solution, twice with 100 ml. portions of water, and was dried over anhydrous magnesium sulfate. After evaporation of the ether the crude alcohol was recrystallized from cyclohexane to give 26.5 g. (72%) of colorless needles of 8-methyl-1-naphthylcarbinol, m.p. 95.5-96.5°. The infra-red spectrum of the carbinol in carbon tetrachloride showed absorptions at 2.82, 2.95, 3.32, 3.42, 3.49, 5.22, 6.33, 6.88, 7.28, 8.57, 9.05, 9.45, 9.74, 10.15, and 10.18 microns. The n.m.r. spectrum of the alcohol in carbon disulfide showed a multiplet at τ 2.25-2.95, a methylene singlet at τ 5.10, a methyl singlet at τ 7.15, and a hydroxyl singlet at τ 8.27.

P. Preparation of 8-Bromo-1-Naphthoic Acid

The procedure of Rule and Purcell (15) was used to prepare 8-bromo-1-naphthoic acid with the following modifications:

1) Commercially available 1,8-naphthalic anhydride was purified by

recrystallization from nitric acid and was used as the starting material instead of naphthalic acid. 2) Commercial grade mercuric acetate was used instead of generating it in situ with mercuric oxide and acetic acid.

Q. Preparation of Methyl 8-Bromo-1-Naphthoate

The methyl ester was prepared by the procedure already described for the preparation of methyl 8-methyl-1-naphthoate. Treatment of 12.55 g. (0.05 mole) of 8-bromo-1-naphthoic acid with excess diazomethane afforded 12.93 g. (97.5%) of crude methyl 8-bromo-1-naphthoate. The ester was used as such for reductions with lithium aluminum hydride. The infra-red spectrum of the ester in carbon tetrachloride showed absorptions at 3.31, 3.42, 5.78, 6.67, 6.87, 6.98, 7.33, 7.50, 7.85, 8.38, 8.75, 9.23, 9.40, 9.85, and 10.46 microns. The n.m.r. spectrum of the ester in carbon tetrachloride showed a multiplet at τ 2.08-3.00 and a methyl singlet at τ 6.10 in an integrated area ratio of 2.09 : 1.00, respectively.

R. Preparation of 8-Bromo-1-Naphthoyl Chloride

A 50 ml. single-necked round-bottomed flask containing 15 g. (59.7 millimoles) of 8-bromo-1-naphthoic acid was fitted with a six inch water-jacketed condenser. One end of a gas delivery hose was attached to the top of the condenser and the other end was submerged in a 10% sodium hydroxide solution contained in a beaker. Thionyl chloride, 14.30 g. (120 millimoles), was added dropwise from a glass capillary to the flask (vigorous evolution of sulfur dioxide and hydrogen chloride gases). The resulting solution was refluxed for one hour.

Excess thionyl chloride was removed by distillation at reduced pressure and the crude product was distilled to give 14.90 g. (92.2%) of 8-bromo-1-naphthoyl chloride, a colorless solid with m.p. 67-68^{o}

and b.p. 138-40° at 0.35 mm. Hg. The infra-red spectrum of 8-bromo-1-naphthoyl chloride in carbon tetrachloride showed absorptions at 3.30, 3.41, 5.61, 5.66, 5.90, 6.72, 6.91, 7.04, 7.35, 7.54, 7.80, 8.14, 8.38, 8.59, 9.26, 9.34, 9.74, 10.92, and 11.64 microns. The n.m.r. spectrum of the acid chloride in carbon tetrachloride showed only an aromatic multiplet at τ 2.00-2.83.

S. Preparation of 8-Bromo-1-Naphthamide

A solution of 25 ml. of liquid ammonia was prepared in a 100 ml. beaker and 1.01 g. (3.75 millimoles) of 8-bromo-1-naphthoyl chloride was added as a solid. The solution was stirred until all of the ammonia had evaporated and 25 ml. of water was then added. The crude solid was filtered, washed well with water, and dried to give 0.69 g. (73.4%) of a colorless solid, m.p. 214-15°. The crude solid was recrystallized from 3 : 1 ethyl acetate-benzene to give 0.47 g. (50%) of colorless needles of 8-bromo-1-naphthamide, m.p. 215-16°. The infra-red spectrum (potassium bromide pellet) of the amide showed absorptions at 3.02, 3.21, 6.11, 6.69, 6.87, 7.13, 7.37, 7.47, 8.18, 8.37, 8.77, and 10.0 microns.

T. Preparation of 8-Bromo-1-Naphthylcarbinol

A 300 ml. three-necked round-bottomed flask was fitted with a stirrer, 250 ml. dropping funnel, and a reflux condenser. The apparatus was swept free of air with dry argon gas and was heated with a flame until dry. Next, 50 ml. of dry ether was introduced into the flask and 1.46 g. (38.4 millimoles) of lithium aluminum hydride was added. A solution of 13.80 g. (51.2 millimoles) of 8-bromo-1-naphthoyl chloride in 125 ml. of dry ether was added dropwise to the stirred hydride slurry. After a two hour reflux period the flask was cooled in an ice bath and water was added dropwise until evolution of hydrogen had ceased.

A workup procedure similar to that described for the lithium aluminum hydride reduction of 8-methyl-1-naphthoic acid was used. Recrystallization of the crude alcohol from cyclohexane gave 8.94 g. (73.6%) of colorless platelets of 8-bromo-1-naphthylcarbinol, m.p. 86-88°. The infra-red spectrum of the alcohol in carbon tetrachloride showed absorptions at 2.80, 2.88, 3.28, 3.41, 3.45, 6.26, 6.41, 6.66, 6.78, 7.00, 7.23, 7.36, 8.38, 8.53, 8.75, 9.11, 9.24, 9.30, 9.48, 9.72, 10.12, 10.20, 10.51, and 11.25 microns. The n.m.r. spectrum of the alcohol in carbon disulfide showed a multiplet at τ 2.09-3.03, a methylene singlet at 4.67, and a hydroxyl singlet at τ 7.45 in an integrated area ratio of 3.18 : 1.0 : 0.48 or approximately 6 : 2 : 1.

U. Preparation of Naphthalene by Lithium Aluminum Hydride Reduction of 1-Iodonaphthalene

Ten millimoles, 2.54 g., of 1-iodonaphthalene was reduced according to the general procedure described for aromatic halide reduction. Workup resulted in 1.20 g. (94%) of colorless platelets of naphthalene, m.p. 79-81° (lit. m.p. 80.3° (32)). The infra-red spectrum of the naphthalene in carbon tetrachloride matched well with the literature spectrum (35). The n.m.r. spectrum of the naphthalene in carbon tetrachloride showed a characteristic A_2B_2 (36) line pattern centered at τ 2.55.

SUMMARY

Forty-eight aromatic halides were reduced to the corresponding hydrocarbon with lithium aluminum hydride. The halogen reactivity order for a given substrate was found to be I > Br > Cl > F. The yield of reduced hydrocarbon increased with an increase in reaction temperature. Electron withdrawing groups on the aromatic nucleus also increased product yields. All aromatic iodides studied were reduced quantitatively by lithium aluminum hydride. Aromatic chlorides and fluorides were generally unreactive and gave poor yields of reduced product. Aromatic bromides exhibited a reactivity intermediate between that of the iodides and chlorides.

The facile carbon-bromine cleavage observed in 8-bromo-1-substituted naphthalenes occurred by a displacement process and was promoted by the steric interaction of the peri-substituents. The steric relationship of the halogen atom to ortho-substituents also favored halogen cleavage in certain halobenzenes. Addition of methanol to reduction mixtures greatly increased the yield of reduced product.

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