Cyclohexylmetal Compounds. II. Nuclear Magnetic Resonance and Carbonation Results on (+)-Menthyllithium[1]

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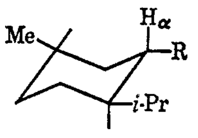
The organometallic product from the reaction of menthyl and neomenthyl chlorides and lithium metal has been investigated. Carbonation yields only 3-*p*-menthanecarboxylic acid (Ib), with only traces of the epimeric acid (IIb). Proton magnetic resonance data indicate that menthyllithium is conformationally rigid in hydrocarbon solvents to +50°, and in diethyl ether below 0°. The formation of considerable quantities of neomenthyllithium in dimethyl ether is indicated at −40°.

The purpose of the work which we shall describe in this series is twofold: (a) to seek evidence relating to the conformational integrity of carbon–metal centers, and (b) to study the stereochemistry of several characteristic reactions of organometallic reagents. In the initial papers, we shall report on alicyclic compounds of group IA metals, particularly lithium. In later reports we shall extend the investigation to other main-group metal alkyls.

Cyclohexyl derivatives are particularly suited for our purposes since, first, a great deal is known concerning the conformations of certain substituted six-membered rings,[3] and, second, the hybridization at the carbon–metal center is not much different from that of acyclic metal alkyls. Previous investigations with cyclopropyl-[4,5] and ethenyl-[6-8] metal systems were of limited usefulness since one could not confidently extrapolate the conclusions to saturated systems. The present paper is concerned with the preparation of menthyllithium Ic and evidence relating to its conformation in hydrocarbon and donor solvents.

Results and Discussion

Preparation and Carbonation.—Menthyl and neomenthyl chlorides (Ia and IIa, respectively) react with lithium metal in refluxing pentane with no difficulty. Carbonation of either reaction mixture yields only 3-*p*-menthanecarboxylic acid Ib with only small amounts of the neomenthyl epimer IIb (cases A–C in Table I).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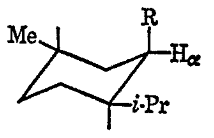
II

R	a	b	c
	Cl	COOH	Li

The epimeric content of the acid is determined by glpc after conversion to the methyl esters with diazomethane. The carbonation data suggest that only compound Ic, menthyllithium, is present in significant quantities in each reaction mixture, regardless of the halide used for the preparation.[9-11] This result is similar to that of Applequist and Chmurny[12] with *exo*- and *endo*-norbornyl chlorides. At room temperature the conversion of the halide is apparently accompanied by loss of stereochemical identity, perhaps through the formation of a radical intermediate at the metal surface.[5]

TABLE I

CARBONATION PRODUCTS FROM "MENTHYLLITHIUM" PREPARATIONS

Case	Chloride precursor[a]	Solvent[b]	Carbonation conditions, °C	Epimer ratio[c] Ib/IIb
A	Ia	Pentane	−70	>15
B	Ia	Pentane	+25	>15
C	IIa	Pentane	−70	>15
D[d]	Ia	Pentane	−70	>15
E[d]	Ia	Pentane	−70	>15
F[d]	IIa	Pentane	−70	>15
G[d]	Ia	Et_2O[e]	−70	>15
H[d]	Ia	Me_2O[e]	−70	5.7
I[d]	Ia	Me_2O[e]	−35	2.3

[a] Ia = menthyl chloride; IIa = neomenthyl chloride. [b] All preparations from the chlorides were carried out at the reflux temperature of the medium. [c] Determined by glpc as the methyl esters. [d] Crystallized organolithium used in these cases. [e] Et_2O = diethyl ether; Me_2O = dimethyl ether.

The formation of a single lithium with equatorial metal atom may seem surprising in view of the rather small size of the lithium atom. The large steric requirements of the lithium atom are probably a reflection of the well-known aggregation of lithium reagents.[13] Thus, the preponderance of the isomer with equatorial lithium may be a result of the very large steric requirements of the remainder of the oligomer, and not necessarily that of the lithium atom alone.

"Menthyllithium" is quite soluble in *n*-pentane but may be crystallized by removal of most of the solvent, our operations having been performed in a drybox. The white, needlelike crystals are pyrophoric and have been examined as discussed below. *Regardless of the*

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[1] Paper I in this series: W. H. Glaze and C. M. Selman, *J. Organometal. Chem.*, **11**, P1 (1968). Portions of this work were presented at the 3rd International Symposium on Organometallic Chemistry, Munich, Germany, Aug 1967.

[2] North Texas State University Fellow, 1965–1967.

[3] For an introduction to the subject, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

[4] D. E. Applequist and A. H. Peterson, *J. Amer. Chem. Soc.*, **83**, 862 (1961).

[5] H. M. Walborsky, F. J. Impastato, and A. E. Young, *ibid.*, **86**, 3283 (1964); H. M. Walborsky and A. E. Young, *ibid.*, **86**, 3288 (1964).

[6] E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2078 (1951).

[7] D. Y. Curtin and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **84**, 1967 (1962).

[8] A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, **1**, 158 (1957); A. N. Nesmeyanov, A. E. Borisov, and N. V. Novidova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1216 (1959).

[9] Many of the conclusions regarding the stereochemistry of organometallic reagents were based on the assumption that carbonation always proceeds with retention of configuration. This principle has subsequently been verified by nmr analyses of propenyllithium[10] and of norbornylmagnesium halides,[11] and in many cases carbonation remains the method of choice to determine the constituency of organometallic reagents.

[10] D. Seyferth and L. G. Vaughan, *J. Organometal. Chem.*, **1**, 201 (1963).

[11] F. R. Jensen and K. L. Nakamaye, *J. Amer. Chem. Soc.*, **88**, 3437 (1966).

[12] D. E. Applequist and G. W. Chmurny, *ibid.*, **89**, 875 (1967).

[13] The list of references is now rather lengthy; see, for example, P. West and R. Waack, *ibid.*, **89**, 4395 (1967).

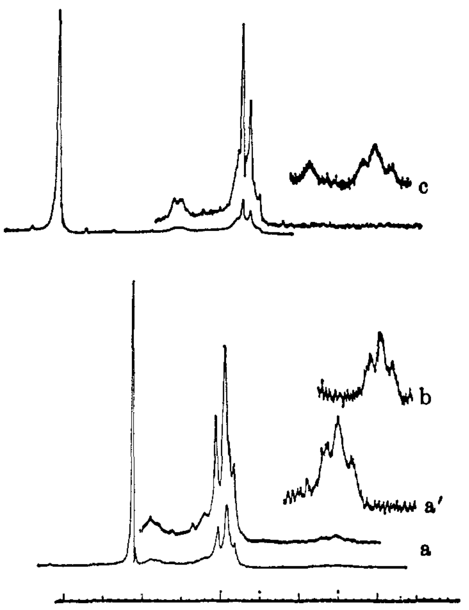

Figure 1.—Pmr spectra of "menthyllithium": (a) toluene solution, 35°; (a') ordinate expansion illustrating the character of the α-methinyl proton resonance at τ 10.50; (b) ordinate expansion of the α-methinyl resonance τ 11.00 in diethyl ether solutions, −40°; (c) dimethyl ether solutions, −40°, α-methinyl resonance at τ 10.95.

halide epimer used in the original preparation, the crystalline lithium alkyl obtained from the reaction mixture has identical properties. Carbonation of hydrocarbon solutions of the crystalline material yields essentially pure Ib with less than 5% of epimer IIb (cases D–F in Table I). Moreover, solutions of the crystalline material are optically active $[\alpha]_D$ +42° (*c* 3.61, cyclopentane).

The results described above indicate a preponderant amount of menthyllithium Ic in hydrocarbon solution but do not rule out a rapid equilibrium between Ic and the neomenthyl epimer IIc with a very low concentration of the latter. The nmr evidence in the following section bears on this subject.

Redissolving the crystalline organometallic in diethyl ether[14] at −45°, followed by carbonation at −70°, yields only acid Ib (case G in Table I). Carbonation of dimethyl ether solutions, however, yields acid IIb in significant quantities (cases H and I). Apparently, some mechanism for epimerization is possible in the latter solvent, a point on which we will elaborate in the following section.

Pmr Results.—The 60-MHz spectrum of "menthyllithium" is shown in Figure 1. The proton (H^α) bonded at the same carbon as the metal atom appears at τ 10.50 in aliphatic and aromatic hydrocarbon solvents and consists of a multiplet which bears a strong resemblance to α-methinyl proton resonances of various menthyl derivatives (Figure 2). The latter are characterized by multiplets[15,16] with widths at half-height of *ca.* 26 cps, while the corresponding resonances for the neomenthyl epimers are virtual singlets with widths of *ca.* 8 cps. The width of the menthyllithium resonance in hydrocarbon solutions is *ca.* 22 cps and, significantly, *does not change over the temperature range +40 to −85°.* Moreover, the addition or diethyl ether at 0° or below merely shifts the resonance to τ 11.00 without altering its structure.[14] The 100-MHz spectrum of the H_α proton is superimposable with the 60-MHz resonance. Moreover, we have not observed any alteration of the spectrum over a period of several hours after changing the temperature as much as ±50° in hydrocarbon solvents.

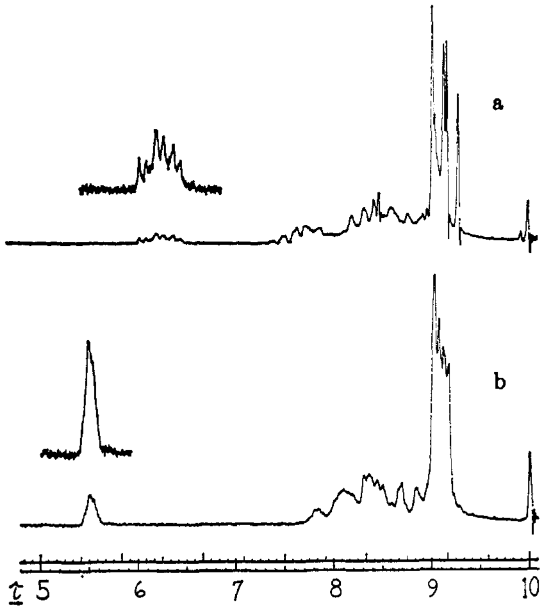

Figure 2.—(a) Pmr spectra of menthyl chloride (Ia), ordinate expansion illustrating the α-methinyl proton resonance; (b) neomenthyl chloride (IIa).

These results are in agreement with the carbonation data of the previous section which suggest the presence of only one organolithium compound in any significant amounts. Furthermore, we propose that a rapid equilibrium (1) may be ruled out by a consideration of

$$\mathrm{Ic} \rightleftharpoons \mathrm{IIc} \quad \text{(fast)} \qquad (1)$$

the present data and other similar data in the literature.

In the limit of rapid interconversion the over-all rate constants for eq 1 should be much larger than $\Delta\delta$, the chemical shift difference for the α-methinyl protons in I and II in the slow exchange limit (*ca.* 50 cps). If the temperature dependence of the rate constant for equation 1 can be written as $k = A\ \exp(-E^*/RT)$, then upper limits for E^*, the inversion barrier, may be calculated for various values of A. For A values of 10^{14}–10^{10} sec^{-1} (corresponding to Eyring ΔS^* values of *ca.* 6 and −12 eu, respectively), the value of E^* must be *much less* than 12 kcal/mol. Such a low inversion barrier is entirely inconsistent with other information regarding the stability of carbon–lithium aggregates. It seems reasonable that in order for inversion to occur the very stable alkyllithium oligomer must be destroyed, probably by the formation of monomeric units. An elegant argument has been presented by Brown[17]

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[14] Diethyl ether, tetrahydrofuran, and 1,2-dimethoxyethane are rapidly cleaved by menthyllithium at room temperature and above. *Caution!*

[15] The characteristic patterns for α-methinyl protons of menthyl and neomenthyl derivatives have been computer synthesized utilizing the LOCOON program.[16] We shall report on this subject in more detail at a later date.

[16] S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

[17] T. L. Brown, *J. Organometal. Chem.*, **5**, 188 (1966).

which suggests that such a process must require approximately 35 kcal/mol. Even the dissociation of the ethyllithium hexamer into a tetramer and a dimer requires approximately 18 kcal/mol according to Li^7 nmr data from Brown's laboratories.[18] We suggest that an inversion barrier for menthyllithium of much less than 12 kcal/mol represents a highly improbable circumstance in view of the aforementioned data. A much more consistent conclusion is that menthyllithium is entirely rigid in hydrocarbon solution, and that its inversion barrier is of the order of 35 kcal/mol.

It is true that cyclic secondary amines, which are isoelectronic with carbanions, invert very rapidly even at −85°.[19] However, inversion of cycloalkyllithiums *via* the carbanion must first involve dissociation of the C–Li bond, a process involving considerable activation energy, as mentioned above. Moreover, the inversion of a carbanion–cation pair is not comparable to inversion of a cyclic amined, such as piperidine. The inverting nonbonded electron pair must overcome the attraction of the counterion, thus adding several kilocalories to the inversion barrier. It is significant to note that Miller, *et al.*,[20] have estimated the inversion barriers of several carbanions to be higher than for the corresponding amines without considering the electrostatic factor mentioned above.

In view of previous data in the literature, the slow rate of interconversion of methyllithiums in hydrocarbon solvents may not be particularly surprising. However, it has generally been assumed that donor solvents such as ethers promote the dissociation of the carbon-metal bond, suggesting that inversion of Ic should occur with greater facility in such solvents. On the other hand, it has been reported[21] that neohexyllithium inverts rapidly only above 0° in diethyl ether. This is consistent with our results which indicate that menthyllithium is also stable in diethyl ether below 0°.

The pmr spectrum of Ic in dimethyl ether also shows the α-methinyl resonance at τ 10.95, virtually the same value as in diethyl ether (Figure 1); the width at half-height is 22 cps. However, a second resonance is observed at τ 10–13 whose width is only 8 cps. Although the integration of this second peak is difficult on our A-60 due to the nearness of other stronger peaks, our best values indicate a 25:75 ratio of the τ 10.13:10.95 peaks at −40°. Unfortunately, we are unable to increase the temperature significantly owing to solvent cleavage.[22,23] Carbonation of the contents of the nmr tube yields a 70:30 ratio of acids Ib/IIb. We conclude that the low-field resonance is due to neomenthyllithium which is slowly interconverting (on the nmr time scale) with menthyllithium. Further measurements are in progress to determine the precise rate of the interconversion process in dimethyl ether.

Experimental Section

Materials.—Phillips Petroleum Co. pure grade *n*-pentane, benzene, and cyclopentane were redistilled from $LiAlH_4$. Anhydrous grade diethyl ether was treated similarly. Dimethyl ether was obtained from Matheson Co. and used directly from the cylinder. Lithium metal rod with 1% Na content was obtained from the Lithium Corp. of America. (−)-Menthol was obtained from Aldrich Chemical Co., $[\alpha]^{25}\text{D}$ −54.8° (*c* 2.88, *n*-pentane). (−)-Menthyl chloride was prepared by the method of Smith and Wright,[24] bp 98° (21 torr), $[\alpha]^{25}\text{D}$ −48.5° (*c* 5.02, *n*-pentane). (+)-Neomenthyl chloride was prepared by the method of Horner, *et al.*,[25] bp 91° (15 torr), $[\alpha]^{25}\text{D}$ +53.7° (*c* 1.27, *n*-octane). The chlorides were shown to be >95% pure by glpc (column A).

Analytical Methods.—Gas chromatographic separations were performed on four columns: (A) Cyanosilicone XF-1150 (20% on 60–80 mesh Chromosorb P), 10 ft × 0.25 in. Al tubing; (B) Carbowax 4000 (10% on 30–60 mesh Chromosorb W), 8 ft × 0.25 in. Al tubing; (C) polypropylene glycol (15% on 30–60 mesh Chromosorb W), 10 ft × 0.25 in. Al tubing: (C) Carbowax K-1540 Golay column, 100 ft × 0.01 in. Proton magnetic resonance spectra were obtained on Varian A-60, A-60-A, and HA-100 spectrometers. Optical rotations were obtained on a Rudolf Model 80 polarimeter with sodium lamp. Lithium alkyl concentrations were determined by the modified Gilman double titration procedure.[26]

Menthyllithium.—Lithium sand (0.7 mol) was prepared by vigorously shaking molten metal in hot mineral oil. The sand was quickly filtered, washed with pentane, and transferred to a 500-ml three-neck round bottom flask along with *ca.* 200 ml of dry pentane. The flask was previously purged with prepurified argon; it was equipped with a Hirschberg stirrer which operates through a 24/40 Asco Teflon stirring gland, a pressure-equalized dropping funnel, and a Friedrichs reflux condenser to which an argon inlet was connected. The dropping funnel contained a solution of (−)-menthyl chloride (0.25 mol) in 125 ml of pentane. The contents of the flask were rapidly stirred under an argon blanker and brought to gentle reflux with a heating mantle. Approximately 10% of the halide was added to initiate the reaction. After initiation some pieces of metal settled to the bottom of the flask with a purple coloration, and the reflux rate increased. The heating was diminished at this point and the remainder of the halide added over a period of 3–4 hr. Reflux was usually maintained by the heat of reaction. After all of the halide was added, the reaction mixture was stirred for 1 additional hr at reflux and for 2 additional hr at room temperature.

The preparation of menthyllithium from (+)-neomenthyl chloride followed the same procedure as given above, with slightly lower yields.

The reaction vessel was stoppered and taken into a glove box where the contents were filtered through a medium porosity frit. The clear, pale yellow solution contained from 0.12 to 0.15 mol of alkyllithium based on the double titration procedure[26] (48–60% yield).

The alkyllithium was crystallized by removing most of the pentane *in vacuo*. The crystalline menthyllithium usually contained some *p*-menthenes which were removed by carefully washing with a minimum of cold pentane. The yield of crystalline product was diminished due to its solubility in the menthene by-products. With care we have isolated 10 g of the crude product from a typical 0.25-mol preparation (28% yield). The material may be recrystallized from cold pentane.

The optical rotation of the recrystallized alkyllithium compound was carefully measured in a 1-dm. tube which was fitted with stoppers and with Teflon washers sealing the end plates. Since *p*-menthenes are strongly dextrorotatory, several samples were measured using freshly recrystallized material. The olefin content was determined by glpc (column B) immediately after the optical rotation was measured. Only rotation data on solutions of negligible olefin content were accepted: $[\alpha]^{25}\text{D}$ +45 ± 5° (*c*, *n*-octane).

Carbonation Results.—Pentane solutions of the alkyllithium compound were carbonated by pouring over Dry Ice–pentane slurries in an argon-flushed polyethylene glove bag. The excess

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[18] T. L. Brown, D. W. Dickerhoof, and D. A. Bafus, *J. Amer. Chem. Soc.*, **84**, 1371 (1962).

[19] J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *ibid.*, **89**, 3761 (1967).

[20] G. W. Koeppl, D. S. Sagatys, G. S. Krishnamurthy, and S. I. Miller, *ibid.*, **89**, 3396 (1967).

[21] J. D. Roberts, private communication reported in "Fundamentals of Carbanion Chemistry," D. J. Cram, Academic Press Inc., New York, N. Y., 1965, p 128.

[22] Reaction of alkyllithiums with dimethyl ether yields methoxymethyllithium, which may insert a methylene group as follows: $RLi + CH_3OCH_2Li \rightarrow RCH_2Li + CH_3OLi$.[23] We find no evidence for these reactions below −20°.

[23] K. Ziegler and H. G. Gellert, *Ann.*, **567**, 185 (1950).

[24] J. G. Smith and G. F. Wright, *J. Org. Chem.*, **17**, 1116 (1952).

[25] L. Horner, H. Oedinger, and H. Hoffmann, *Ann. Chim.*, **626**, 26 (1959).

[26] H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964).

carbon dioxide was allowed to evolve, and the mixture was acidified with dilute hydrochloric acid. The aqueous layer was separated and washed with diethyl ether repeatedly. The combined organic layers were dried over anhydrous magnesium sulfate. The crude carboxylic acid was obtained in very high yield (>90%) by evaporation of the solvent: mp 62–65°, $[\alpha]^{25}D$ −56.1° (*c* 5.2, EtOH); lit. values for 3-*p*-menthanecarboxylic acid (Ib), mp 60–63°, $[\alpha]^{20}D$ −42.6°.[24] More often the acid was converted to its methyl ester without isolation of the free acid. The method of Moore and Reed[27] for the preparation of diazomethane was followed. Glpc of the ester product with columns C or D yielded in every case a preponderance of one epimer, which proved to be methyl 3-*p*-menthanecarboxylate (I, R = COOMe). The ester was isolated in high yields by distillation: bp 93.5–94° (3 torr), $[\alpha]^{25}D$ −39.7° (*c* 5.0, pentane). The identity of the ester was confirmed by 100-MHz pmr measurements which showed the characteristic splitting for the α-methinyl proton (H_α) in the axial position (τ 7.67). The resonance could not be identified unequivocally in the 60-MHz spectrum. The methyl ester of the neomenthyl acid was collected by preparative glpc and shown to have the correct infrared and pmr spectrum. The α-methninyl proton was observed at τ 7.12 with a width of 8 cps. The ester was present in quantities of less than 5% of the menthyl ester except when dimethyl ether was the solvent for the alkyllithium compound (cases H and I in Table I).

Dimethyl ether solutions were prepared in a two-necked flask, one neck of which was fitted with a 2-mm bore stopcock for connection to a vacuum line. The flask was loaded in the drybox with crystalline lithium compound, both necks were stoppered, and the flask was transferred to the vacuum line outside the box. Dimethyl ether was distilled into the flask which was cooled with a Dry Ice–acetone bath. The flask was allowed to equilibrate in a bath at the desired temperature under a pressure of argon gas. Excess gas pressure was vented through a 2-cm Hg-filled U-tube so that the pressure inside the flask would not exceed atmospheric pressure appreciably. The flask was then transferred in its thermostat bath to the polyethylene glove bag where it was carbonated by quickly pouring into a Dry Ice–pentane slurry. The work-up beyond this point was very similar to that described above.

In one case an nmr tube containing menthyllithium in dimethyl ether at −40° was broken under a pentane–Dry Ice slurry and worked up as usual. The ratio of acids Ib/IIb was found to be 70:30 by glpc after esterification.

Carbonation of hydrocarbon solutions at room temperature were carried out in a three-necked, round-bottom flask into which the organometallic solution was loaded in the drybox. The flask was properly sealed and transferred outside the box. The flask was fitted with a reflux condenser the exit of which was connected to an argon tank through a T-joint, the other arm of which was joined to a Hg-filled U-tube to maintain only slight positive pressure inside the flask. Into another neck of the flask was fitted a gas dispersion tube through which carbon dioxide gas was bubbled. The flow of gas through the solution was continued until no carbon-bound lithium could be detected. The work-up proceeded as described above.

To determine if neomenthyllithium was insoluble in *n*-pentane and might have been discarded with the lithium chloride byproduct, the residue from one preparation (case A) was carbonated as a slurry with Dry Ice. Only a trace of ester was detected after work-up, it being the methyl ester of Ib.

Pmr Spectra.—Most of the measurements were made on an A-60 in our laboratories which was carefully calibrated with tetramethylsilane and chloroform. The variable temperature accessory was calibrated with methanol intermittently while obtaining sample spectra. Measurements below −60° were made on an A-60-A at Texas Woman's University.[28] Spectra at 100 MHz were obtained at Texas Christian University.[28] Sample tubes were loaded with solutions in the drybox and sealed with pressure caps obtained from NMR Specialties, Inc. No oxidation was observed while spectra were being obtained. In some cases the tubes were sealed with rubber septa so that diethyl ether could be added to the tube later. Dimethyl ether solutions were prepared on a vacuum line. A joint (14/35) was sealed to the nmr tube. The tube was loaded with crystalline material in the drybox and a stopcock adapter fitted into the joint. The tube was transferred to a vacuum line outside the box and evacuated. Dimethyl ether was distilled into the tube to a convenient level while cooling with liquid nitrogen. The tube was then sealed off with a torch, transferred to a thermostat bath at the desired temperature, and shaken periodically to dissolve the lithium alkyl. The tube was transferred to the spectrometer which was previously set at the proper temperature. Silicone stopcock grease was rigorously excluded from all apparatus when dimethyl ether solutions were prepared.

Several internal reference standards were used including tetramethylsilane, cyclopentane, toluene, and benzene. Chemical shifts were corrected to tetramethylsilane standard.

Registry No.—Ia, 16052-42-9; Ib, 16052-40-7; Ic, 16052-41-8; I (R = COOMe), 16052-43-0; IIa, 13371-12-5.

Acknowledgment.—We are grateful to The Robert A. Welch Foundation for generous support of this work.

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[27] J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

[28] We are grateful to Dr. A. Pronay and Dr. W. B. Smith at Texas Woman's University and Texas Christian University, respectively, and to Dr. B. A. Shoulders at the University of Texas at Austin for their cooperation in this work.