bicarbonate and once with brine, dried (Na_2SO_4), and evaporated. The resulting oil was dissolved in methanol and treated with sodium borohydride as described earlier for the preparation of **14**. Chromatography on 10 g of silica gel eluting with 4% ether–petroleum ether (bp 30–60°) afforded 114 mg (38%) of **14**-d_3. Further purification was accomplished by preparative glc (5 ft, 20% SE 30, 125°): deuterium distribution (ms); 7.4% d_0, 12.0% d_1, 23.8% d_2, 49.3% d_3, 8.0% d_4, average of 2.4 deuterium atoms; τ 2.82–3.17 (m, 4 ArH), 4.39 (br s, $H_{1/2}$ = 6.0 Hz, 1.34 H, mainly H_5), 6.98 (t, J = 5.5 Hz, 2 H, H_2), 7.15 (NCH_3, 3 H), 7.94 (br t, $J \sim$ 5.5 Hz, 1.7 H, H_3), average of 2.6 deuterium atoms.

N-**Methyl-1,2,3,4-tetrahydroquinoline-**d_x (**23-***2,4,4-d*$_3$). A solution of 243 mg (1.67 mmol) of **18** in 1.0 ml of dimethyl-d_6 sulfoxide was treated with 0.20 ml (0.24 mmol) of 1.2 *M* potassium *tert*-butoxide (in dimethyl-d_6 sulfoxide). After 82 hr at room temperature, the product was isolated and reduced using the above procedure for the preparation of **14**-d_3 yielding 198 mg (79%) of **23**-d_3. This product was purified further by preparative glpc (5 ft, 20% SE 30, 115°): deuterium distribution (ms) 15.0% d_2, 84.7% d_3, 0.4% d_4, average of 3.0 deuterium atoms; τ 2.80–3.63 (m, 4 H), 6.85 (tt, J_{HD} = 1.5 Hz, 1.1 H), 7.18 (s, 3 H), 8.18 (br d, $J_{2,3}$ = 6.0 Hz, 2 H); average of 2.8 deuterium atoms.

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N,N-Disubstituted Aminomethyllithium Compounds

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Abstract: Five members of a novel class of heteroatom-substituted organometallic compounds, $RR'NCH_2Li$, have been conveniently prepared by a transmetalation reaction between the appropriate (N,N-disubstituted aminomethyl)tributyltin and *n*-butyllithium. The stabilities of these organolithium compounds varied with substitution at nitrogen. For example, in mixed tetrahydrofuran–hexane solvent, *N,N*-dimethylaminomethyllithium (**1′**) decomposed *ca.* 50% during 18 hr at 45°, while *N*-methyl-*N*-phenylaminomethyllithium decomposed completely within 4 hr at 25°. **1′** was found to be significantly less reactive than *n*-butyllithium as a metalating agent which thereby demonstrates that the *N,N*-dimethylamino substituent, relative to an alkyl group, has an overall stabilizing effect on a carbon–lithium bond. In addition to its obvious synthetic utility, **1′** proved useful as an intermediate for the conversion of benzophenone to $(CH_3)_2NCH{=}C(C_6H_5)_2$ and $(C_6H_5)_2CHCHO$.

Within the past few years several new types of heteroatom-substituted organometallic compounds have been prepared in which the heteroatom bears no formal charge. Included in this list of useful synthetic intermediates are sulfur-, phosphorus-, silicon-, and oxygen-substituted methyllithium compounds. The first two organometallic compounds are

$$ZCH_2Li$$

$$Z = RS, R_2P, R_3Si, RO$$

readily obtained by metalation of the corresponding weakly acidic methanes,[1-3] while the last compound has been realized in acceptable yield from the reaction of an α-halomethyl ether with lithium.[4] Silylmethyllithium compounds have been obtained by both types of reactions.[5-7] As reported in a recent preliminary communication,[8] this series of heteroatom-substituted organometallic compounds has been extended to include the parent nitrogen carbanion, *N,N*-dimethylaminomethyllithium, by yet a third method, *i.e.*, a transmetalation reaction between *n*-butyllithium·TMEDA (*N,N,N′,N′*-tetramethylethylenediamine) and (*N,N*-dimethylaminomethyl)tributyltin. The transmetalation route is far superior to the direct metalation method[9] for preparing the aminomethyllithium compound in that the former is rapid and essentially quantitative in contrast to the latter reaction which is very slow and affords the desired compound in low yield.

We now report the synthesis of some additional nitrogen-substituted methyllithium compounds by the transmetalation reaction, variations of the method, and initial findings pertaining to the chemical behavior of these novel organolithium compounds.

Transmetalation reactions between *n*-butyllithium and (N,N-disubstituted aminomethyl)tributyltin compounds, **1–3**, occurred quantitatively within a few minutes in hexane at 0°, while the presence of a small amount of tetrahydrofuran was required to achieve similar results with **4** and **5**. Ether was intermediate to

$$\underset{\textbf{1–5}}{RR'NCH_2Sn(C_4H_9\text{-}n)_3} + n\text{-}C_4H_9Li \xrightarrow{0°} RR'NCH_2Li + (n\text{-}C_4H_9)_4Sn$$

$$\textbf{1′–5′}$$

1, **1′**, R,R′ = CH_3
2, **2′**, R,R′ = $(-CH_2-)_5$
3, **3′**, R,R′ = $-H_2CCH_2OCH_2CH_2-$
4, **4′**, R = CH_3; R′ = C_6H_5
5, **5′**, R,R′ = C_6H_5

tetrahydrofuran and hexane in its ability to facilitate the reaction. TMEDA, as used in the initial[8] generation of

(1) D. J. Peterson, *J. Org. Chem.*, **32**, 1717 (1967).
(2) E. J. Corey and D. Seebach, *ibid.*, **31**, 4097 (1966).
(3) D. J. Peterson, *J. Organometal. Chem.*, **8**, 199 (1967).
(4) U. Schöllkopf, H. Küpers, H.-J. Traencker, and W. Pitteroff, *Justus Liebigs Ann. Chem.*, **704**, 120 (1967).
(5) J. W. Connolly and G. Urry, *Inorg. Chem.*, **2**, 645 (1963).
(6) D. J. Peterson, *J. Organometal. Chem.*, **9**, 373 (1967).
(7) D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968).
(8) D. J. Peterson, *J. Organometal. Chem.*, **21**, P63 (1970).
(9) D. J. Peterson and H. R. Hays, *J. Org. Chem.*, **30**, 1939 (1965).

1′, is undoubtedly even more effective than tetrahydrofuran, but its use is not required owing to the rapidity of the transmetalation reaction. The resulting aminomethyllithium compounds are only slightly soluble in hexane, but moderately soluble in tetrahydrofuran. Indeed, the separation of **1′** from hexane-soluble tetrabutyltin, for example, was effected quite simply by filtration of the transmetalation reaction mixture. However, tetrabutyltin is relatively unreactive and need not be removed prior to utilization of the nitrogen-substituted carbanions.

For the purpose of determining the yields of **1′–5′**, the transmetalation reaction mixtures were treated with benzaldehyde to form the corresponding α-aminomethylbenzyl alcohols. With the exception of the morpholino derivative **3′** the alcohols were isolated in

$$\underset{\mathbf{1'\text{–}5'}}{RR'NCH_2Li} + C_6H_5CHO \xrightarrow{H^+} RR'NCH_2CH(OH)C_6H_5$$

70–80% yields (based on starting **1**, **2**, **4**, and **5**). These results clearly show the value of the transmetalation method for preparing nitrogen-substituted carbanions. The reaction of **3** with *n*-butyllithium was similarly quantitative, *i.e.*, all of **3** was consumed and tetrabutyltin was formed in 70% yield, but only 33% of the alcohol derivative was obtained. This suggests that **3′** decomposed quite rapidly since derivatization with benzaldehyde was carried out within 0.5 hr after its generation by the transmetalation reaction. Another possibility is that **3** did not react with *n*-butyllithium exclusively by transmetalation. Variations in solvent composition (presence or absence of THF) and temperature had little effect on the overall yield of **3′**.

The precursory **1–5** were obtained by aminomethylating tributyltinlithium with either the appropriate *N,S*-acetals and/or sodium N,N-disubstituted aminomethane sulfonates. Both of these aminomethylating agents, which are formed from readily available secondary amines, formaldehyde, and benzenethiol or so-

$$\left.\begin{matrix} RR'NCH_2SC_6H_5 \\ \text{or} \\ RR'NCH_2SO_3Na \end{matrix}\right\} \xrightarrow{(n\text{-}C_4H_9)_3SnLi} \mathbf{1'\text{–}5'}\ (50\text{–}75\%)$$

dium bisulfite, are known to undergo similar reactions with various carbanions.[10,11]

Any special utility that heteroatom-substituted organometallic compounds may possess above that of the more classical types of organometallic compounds results from their bifunctionality, *i.e.*, the carbanionic and heteroatomic parts of the molecules provide centers of high and moderate nucleophilicity (sulfur, phosphorus) or electrophilicity (silicon), respectively. Consequently, subsequent to the normal organometallic reaction of the carbanion, additional operations can be performed on the heteroatom to effect its removal or to convert it to a higher oxididation state derivative. For example, in reactions of ZCH_2Li with carbonyl compounds, the following transformations can be effected.

$$ZCH_2Li + \begin{matrix} \diagdown \\ \diagup \end{matrix}\!\!C{=}O \longrightarrow ZCH_2\underset{\diagdown}{\overset{\diagup}{C}}OLi$$

(10) I. E. Pollak and G. F. Grillot, *J. Org. Chem.*, **32**, 2892 (1967).
(11) H. E. Zaugg and R. J. Michaels, *ibid.*, **33**, 2167 (1968).

$$ZCH_2COLi \xrightarrow{Z = R_3Si} H_2C{=}C(Z)- + R_3SiOLi^{7,12}$$

$$ZCH_2COLi \xrightarrow{CH_3I} CH_3\overset{+}{Z}CH_2COLi\ I^- \xrightarrow{Z = R_2P} H_2C{=}C(Z)- + CH_3P(O)R_2^{3}$$

$$CH_3\overset{+}{Z}CH_2COLi\ I^- \xrightarrow{Z = RS} H_2C\text{—}C(Z)\text{(O)} + CH_3SR^{13}$$

To demonstrate the feasibility of this type of reaction for nitrogen-substituted organolithium compounds, **1′** was treated with triphenylphosphine oxide to give the expected[14] lithiated phosphine oxide **6**. Hydrolysis of

$$\mathbf{1'} + (C_6H_5)_3PO \longrightarrow (C_6H_5)_2P(O)CHLiN(CH_3)_2\ (\mathbf{6}) + C_6H_6$$

$$\mathbf{6} \xrightarrow{H_3{}^+O} (C_6H_5)_2P(O)CH_2N(CH_3)_2\ (64\%)$$

$$\mathbf{6} \xrightarrow{(C_6H_5)_2CO} (C_6H_5)CHCHO \longleftarrow (C_6H_5)_2C{=}CHN(CH_3)_2 + (C_6H_5)_2P(O)OLi$$

6 afforded (*N,N*-dimethylaminomethyl)diphenylphosphine oxide. Treatment of **6** with benzophenone resulted in the immediate formation of the corresponding enamine by a "Horner type" reaction.[15] Finally, the dimethylamino moiety was removed by hydrolysis of the enamine to give diphenylacetaldehyde in an overall yield of 44%. This reaction therefore provides a method for preparing "homologated" enamines (with respect to normal enamine syntheses) and converting ketones to the corresponding "homologated" aldehydes. The latter conversion represents a new example of a recently studied[16] class of reactions referred to as nucleophilic acylations.

Of obvious interest when considering any of the heteroatom-substituted organolithium compounds is the effect of the heteroatom on the chemical behavior of the carbanion to which it is attached. The second row heteroatoms, silicon, phosphorus, and sulfur, appear to stabilize the carbanion by d-orbital resonance which exceeds any opposing destabilizing forces. This interaction rationalizes the ease with which the parent heteroatom-substituted methanes undergo metalation[1–3,6,7] and base-catalyzed exchange.[17] By way of contrast, the first row elements, oxygen and nitrogen, lack low-lying d orbitals and the overall effect of these heteroatoms on the carbanions reduces to an interplay of inductive and repulsion factors. In the simplest sense, the electronegative oxygen and nitrogen substituents would be expected to inductively stabilize a carbanion, while repulsion between the nonbonding pairs of electrons of the heteroatoms and carbanions (polarized carbon–lithium bond) should result in destabilization. In the absence of a donor solvent, heteroatom–lithium complexation would enhance the ionic character of the carbon–lithium bond, but concurrently

(12) T. H. Chan, E. Chang, and E. Vinokuv, *Tetrahedron Lett.*, 1137 (1970).
(13) See, for example, A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, Chapter 9.
(14) D. Seyferth, D. E. Welch, and J. K. Heeren, *J. Amer. Chem. Soc.*, **86**, 1100 (1964).
(15) See ref 13, Chapter 5.
(16) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969).
(17) E. A. Yakovleva, E. N. Tsvetkov, D. I. Lobanov, M. I. Kabachnik, and A. I. Shatenshtein, *Tetrahedron Lett.*, 4161 (1966).

create an opposing stabilizing partial positive charge on the heteroatom in the sense, $^{-}CH_2Z^{+}Li$.

One indication of the chemical reactivity of an organometallic compound is its ability to function as a base in a metalation reaction. Accordingly, to gain some insight into the reactivity of aminomethyllithium com-

$$ZCH_2Li + \text{—CH} \longrightarrow ZCH_3 + \text{—CLi}$$

pounds, **1′** was chosen as a model for study and was treated with the weak hydrocarbon acid, benzene. In hexane as solvent, **1′** did not metalate benzene during 16 hr at 25°, while in mixed hexane–ether solvent phenyllithium was formed in *ca.* 6% yield during 18 hr at 45°. The addition of 1 equiv of TMEDA to a **1′**–benzene reaction mixture in hexane solvent resulted in some increase in rate of metalation in that phenyllithium was formed in 8% during 3 hr at room temperature.

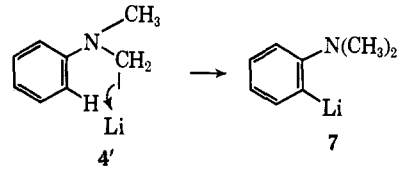
To put these findings into perspective, attention is called to metalations of benzene by *n*-butyllithium to the extent of 5% in refluxing ether (undisclosed time)[18] and to the extent of 50% during 3 hr at room temperature in hexane when the *n*-butyllithium was potentiated with TMEDA.[19]

A comparison of those reactions in which TMEDA was involved allows the tentative conclusion to be made that, relative to a propyl group, an *N,N*-dimethylamino substituent has a slight but significant stabilizing effect on a lithiated methylene moiety ($-CH_2Li$), *i.e.*, **1′**·TMEDA is less reactive than *n*-butyllithium·TMEDA. Indeed, if the reasonable assumption is made that **1** and tetrabutyltin possess similar thermodynamic ground state energies, the conclusion that **1′** is less reactive than *n*-butyllithium finds some support by the very occurrence of the transmetalation reaction between *n*-butyllithium and **1** to form **1′**. Within the time limits of the experiments (<18 hr) there was no evidence which indicated the existence of an equilibrium between reactants and products. Equilibrium situations have been established for organotin–organolithium transmetalation reactions in which the exchanging groups were

$$\mathbf{1} + n\text{-}C_4H_9Li \rightleftharpoons \mathbf{1'} + (n\text{-}C_4H_9)_4Sn$$

quite similar, *e.g.*, phenyl and vinyl.[20] Further, it is known[20] that *n*-butyllithium does not displace simple alkyl groups, such as 3-butenyllithium,[21] from 3-butenyltri-*n*-butyltin.

Several examples of rearrangements of organometallic compounds to thermodynamically more stable isomers have recently been disclosed. Since the ring-lithiated isomer of **4′**, *o*-lithio-*N,N*-dimethylaniline (**7**), is known[22] to be a stable compound, it appeared of interest to determine whether **4′** would rearrange to **7**. Accordingly, a mixed hexane–tetrahydrofuran solution



4′ **7**

of **4′** was allowed to stand for 4 hr and subsequently treated with benzaldehyde. α-(*N*-Methyl,*N*-phenylaminomethyl)benzyl alcohol was not obtained from this reaction which proved the disappearance of **4′**. Surprisingly, however, neither was any alcohol resulting from **7** realized. The only nitrogen-containing products isolated were dimethylaniline (~20%), methylaniline (~5%), and a high-boiling material that resisted characterization. The dimethylaniline probably resulted from the attack of **4** on tetrahydrofuran, but the main decomposition pathway is not apparent at this time.

Interestingly, **1′** was found to be considerably more stable than **4′**. Thus, subsequent to benzaldehyde derivatization, α-(*N,N*-dimethylaminomethyl)benzyl alcohol was obtained in 50% yield from a solution of **1′** in mixed hexane–tetrahydrofuran solvent that had stood at room temperature for 18 hr. It is therefore apparent that *ca.* only 50% **1′** was consumed by reaction with tetrahydrofuran and/or by an unknown decomposition pathway.

Experimental Section

General. All reactions involving organometallic compounds were conducted under an atmosphere of oxygen-free argon. The organotin compounds, **1–5**, were stored under argon in ampoules fitted with ground glass stopcocks. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride just prior to use. Glpc analyses were performed on 5-ft columns of SE-30 and Carbowax as stationary phases.

Materials. Tributyltinlithium was prepared by a reported[23] procedure but with one important variation, *i.e.*, the reaction mixture was cooled in an ice bath to maintain the temperature below 10° during the reaction, rather than allowing it to reflux. In our hands heat promoted the formation of significant quantities of tetrabutyltin which hampered purification of the desired **1–5**. By either method some hexabutylditin (~15–20%) always remained uncleaved by lithium wire containing 1% sodium. Lithium dispersion afforded similar results. Attempts to effect complete cleavage of the hexabutylditin by promoting the reaction with "electron transport agents" such as naphthalene and biphenyl were unsuccessful. *N,N*-Dimethylaminomethyl phenyl sulfide,[24] *N*-piperidinomethyl phenyl sulfide,[25] and *N,N*-diphenylaminomethyl phenyl sulfide were prepared in greater than 80% yield by reported procedures. Sodium *N*-phenyl,*N*-methylaminomethane sulfonate, mp >360°, was prepared in a similar manner but with sodium bisulfite replacing benzene thiol. *Anal.* Calcd for $C_8H_{10}NNaO_3S$: C, 43.0; H, 4.5; N, 6.3. Found: C, 42.8; H, 4.5; N, 6.2. Infrared and proton nmr spectral data were in accord with the structure assignment.

The **1** was synthesized in *ca.* 75% yield as described in the prior communication[8] with the variation that tributyltinlithium was prepared as discussed above.

The α-(N,N-disubstituted aminomethyl)benzyl alcohols all exhibited distinguishing ABX patterns in their ^1H nmr spectra corresponding to the $\geq NCH_AH_BCH_X$ portions of the molecules. Only the spectrum of α-(*N,N*-dimethylaminomethyl)benzyl alcohol was analyzed in detail.[8]

Preparation of (*N*-Methyl,*N*-phenylaminomethyl)tributyltin (4). A solution of tributyltinlithium in THF, prepared by reaction of

(18) H. Gilman and J. W. Morton, *Org. React.*, **8**, 258 (1954).

(19) M. D. Rausch and D. J. Ciappenelli [*J. Organometal. Chem.*, **10**, 127 (1967)] report quantitative metalation of benzene by *n*-butyllithium·TMEDA within 3 hr when both reactants were present in higher concentration than in our experiment.

(20) D. Seyferth and M. A. Weiner, *J. Amer. Chem. Soc.*, **84**, 361 (1962).

(21) The 3-butenyl group can be considered comparable to an alkyl group in this reaction since the carbon–carbon double bond would not significantly influence the stability of the carbanion.

(22) D. W. Slocum, G. Brook, and C. A. Jennings, *Tetrahedron Lett.*, 3443 (1970).

(23) C. Tamborski, F. E. Ford, and E. J. Solaski, *J. Org. Chem.*, **28**, 237 (1963).

(24) G. F. Grillot and H. G. Thompson, *ibid.*, **22**, 706 (1957).

(25) G. F. Grillot, H. R. Felton, B. R. Garrett, H. Greenberg, R. Green, R. Clementi, and M. Moskowitz, *J. Amer. Chem. Soc.*, **76**, 3969 (1954).

81 g (0.25 mol) of tributyltin chloride with excess lithium at ±10°, was added to a prewarmed (60°) suspension of 56 g (0.27 mol) of sodium *N*-methyl,*N*-phenylaminomethane sulfonate in 100 ml of THF. After *ca.* 2 hr, the reaction mixture was hydrolyzed, the organic layer was separated, dried, concentrated, and distilled to give a mixture, bp 139–160° (0.07 mm), of 43.8 g (43%) of **4** and 10.0 g of hexabutylditin. Chromatography of the mixture on Woelm neutral alumina (activity grade I) resulted in a separation of the two organotin compounds with hexabutylditin being eluted by hexane, while diethyl ether was required to elute **4**. *Anal.* Calcd for $C_{20}H_{37}NSn$: C, 58.5; H, 9.0; N, 3.4. Found: C, 58.0; H, 9.2; N, 3.2. The ^1H nmr spectrum of **4** in $CDCl_3$ confirmed the structure assignment with the distinguishing $>NCH_2Sn<$ signal centered at τ 6.74 [$J(CH_2$-$^{117,119}Sn)$ *ca.* 11 Hz, not resolved] and N-CH_3 signal at τ 7.1.

Preparation of (*N*-Piperidinomethyl)tributyltin (2). In a manner described for the synthesis of **1**, **2**, bp 119–125° (0.2 mm), was prepared in 46% yield from the reaction of tributyltinlithium with *N*-piperidinomethyl phenyl sulfide. The ^1H nmr absorption of $>NCH_2Sn<$ in $CDCl_3$ was centered at τ 7.45 [$J(CH_2$-$^{117,119}Sn)$ *ca.* 21 Hz, not resolved]. The methiodide salt of this compound melted at 154.5–156°. *Anal.* Calcd for $C_{19}H_{42}INSn$: C, 43.0; H, 7.9; N, 2.6. Found: C, 43.1; H, 8.1; N, 2.4.

Preparation of (*N*,*N*-Diphenylaminomethyl)tributyltin (5). In a manner described for the synthesis of **1**, **5**, bp 165–173° (0.05 mm), was prepared in 50% yield from the reaction of tributyltinlithium with *N*,*N*-diphenylaminomethyl phenyl sulfide. The ^1H nmr absorption of $>NCH_2Sn<$ in $CDCl_3$ was centered at τ 6.4 [J-(CH_2-$^{117,119}Sb$) *ca.* 15 Hz, not resolved]. *Anal.* Calcd for C_{25}-$H_{39}NSn$: C, 63.5; H, 8.3; N, 3.0. Found: C, 63.3; H, 7.9; N, 2.5.

Preparation of (*N*-Morpholinomethyl)tributyltin (3). In a manner similar to the procedure described for the preparation of **1**, **3**, bp 130–135° (0.2 mm), was obtained in 17% yield from the reaction of tributyltinlithium with *N*-morpholinomethyl phenyl sulfide. The ^1H nmr signal for $>NCH_2Sn<$ (in $CDCl_3$) was centered at τ 7.6 [$J(CH_2$-$^{117,119}Sn)$ *ca.* 12 Hz, not resolved]. The methiodide salt of **3** melted at 191°. *Anal.* Calcd for $C_{18}H_{40}INO\cdot Sn$: C, 40.6; H, 7.5; N, 2.6. Found: C, 40.7; H, 7.8; N, 2.5.

Preparation and Characterization of *N*-Methyl-*N*-phenylaminomethyllithium (4′). To a chilled (*ca.* 0°) solution of 8.2 g (0.02 mol) of **4** in 7 ml of THF there was added 15 ml of 1.5 *M n*-butyllithium in hexane which resulted in a temperature rise of 20°. After the addition and 10 min of stirring, an aliquot was removed from the reaction mixture, hydrolyzed, and analyzed by glpc. No starting amine was detected, while tetrabutyltin was shown to be present. Derivatization of **4′** was then effected by the addition of 2.3 g (0.022 mol) of benzaldehyde. After 0.5 hr of stirring at 20°, the reaction mixture was poured into dilute sulfuric acid and the organic layer was extracted with ether. Distillation of the concentrate of this layer gave 5.6 g (81%) of tetrabutyltin, bp 81° (0.04 mm). The aqueous layer was made basic and extracted with ether. Distillation of the concentrate afforded 3.6 g (79.5%) of α-(*N*-methylanilinomethyl)benzyl alcohol, bp 137–142° (0.04 mm) [lit.[26] bp 160° (1 mm)]. A ^1H nmr spectrum of the alcohol of $CDCl_3$ exhibited signals centered at τ 7.2 (NCH_3), 6.6 (N-CH_2), and 5.16 (HOC–H) in the correct area ratios. There were no peaks in the spectrum which would result from the ring isomer, α-(*o*-dimethylaminophenyl)benzyl alcohol. Also, the absence of the ring isomer in the distillate was demonstrated by glpc analysis. A methiodide salt of the alcohol melted at 173° (lit.[26] mp 154.5°). *Anal.* Calcd for $C_{16}H_{20}INO$: C, 52.0; H, 5.6; N, 3.9. Found: C, 51.7; H, 5.5; N, 3.8. Mass spectral data obtained for the alcohol were consistent with the structure assignment.

Preparation and Characterization of *N*,*N*-Dimethylaminomethyllithium (1′). To a chilled (*ca.* 0°) solution of 10.4 g (0.03 mol) of **1** in 10 ml of hexane there was added 20 ml of 1.5 *M n*-butyllithium in hexane which resulted in the immediate formation of a precipitate of **1′**. Glpc analysis of a hydrolyzed aliquot of the reaction mixture showed **1** to be absent, while tetrabutyltin was detected. Benzaldehyde (3.2 g; 0.03 mol) and a few milliliters of THF were then added to derivatize **1′**. Subsequent to *ca.* 0.5 hr of stirring, the reaction was poured into dilute sulfuric acid and worked up as described for the preparation of **4′** to give 3.8 g (73%) of α-(*N*,*N*-dimethylaminomethyl)benzyl alcohol,[8] bp 75–85° (0.5 mm). Data obtained from ir, ^1H nmr, and glpc analyses were identical with those obtained from an authentic sample.

(26) W. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 1385 (1963).

Preparation and Characterization of *N*-Piperidinomethyllithium (2′). In the same manner as described for **1′**, **2′** was prepared from the reaction of 11.6 g (0.03 mol) of **2** with 20 ml of 1.5 *M n*-butyllithium and derivatized with 3.2 g (0.03 mol) of benzaldehyde to give 8.6 g (85%) of tetrabutyltin and 4.2 g (68%) of α-(*N*-piperidinomethyl)benzyl alcohol, mp 69–71° (lit.[27] mp 69–71°). Elemental and ^1H nmr spectral analyses confirmed the structure assignment. Also, the hydrochloride salt of the alcohol melted at 196.5–197.5° (lit.[27] mp 201–203°).

Preparation and Characterization of *N*-Morpholinomethyllithium (3′). In the same manner as described for **1′**, **3′** was prepared from the reaction of 7.8 g (0.02 mol) of **3** with 13.3 ml of 1.5 *M n*-butyllithium and derivatized with 2.2 g (0.02 mol) of benzaldehyde to give 4.7 g (68%) of tetrabutyltin and 1.4 g (33%) of α-(*N*-morpholinomethyl)benzyl alcohol, mp 81–82° (lit.[27] mp 80–81°). A ^1H nmr spectral analysis confirmed the structure assignment.

Preparation and Characterization of *N*,*N*-Diphenylaminomethyllithium (5′). To a chilled (0°) solution of 0.02 mol of *n*-butyllithium in 20 ml of hexane there was added 9.5 g (0.02 mol) of **5** and 5 ml of THF. The reaction mixture became increasingly orange with time and a precipitate had formed within 0.5 hr. The transmetalation reaction was complete within 1.25 hr as evidenced by the disappearance of **5** by glpc analysis. Subsequently, **5′** was treated with 0.022 mol of benzaldehyde and the reaction mixture was hydrolyzed with aqueous NH_4Cl. Work-up and distillation gave 6.5 g (93%) of tetrabutyltin, bp 80–85° (0.05 mm), and 4.8 g (83%) of α-(*N*,*N*-diphenylaminomethyl)benzyl alcohol, bp ~175° (0.05 mm). On standing in chilled hexane the alcohol crystallized, mp 63–65°. A ^1H nmr spectrum of the compound in $CDCl_3$ exhibited distinguishing signals centered at 6.2 (>NCH_2–) and 5.15 (HOC$<H$). *Anal.* Calcd for $C_{20}H_{19}NO$: C, 83.0; H, 6.6; N, 4.8. Found: C, 82.8; H, 6.4; N, 4.5.

Preparation of α-[(*o*-Dimethylamino)phenyl]benzyl Alcohol. A solution of 24.2 g (0.2 mol) of *N*,*N*-dimethylaniline in 200 ml of hexane was treated overnight with 125 ml of 1.6 *M n*-butyllithium complexed with 0.2 mol of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. The reaction mixture was then treated with 21.2 g (0.2 mol) of benzaldehyde while moderating the temperature with an ice bath. The usual work-up and distillation afforded the desired product, bp 130–150° (0.03 mm). The compound crystallized on standing and was twice recrystallized from hexane to give 30.8 g of alcohol (66%), mp 69–71.5°. *Anal.* Calcd for $C_{15}H_{17}NO$: C, 79.3; H, 7.5; N, 6.2. Found: C, 79.6; H, 7.8; N, 6.1. A ^1H nmr spectrum of the alcohol in $CDCl_3$ confirmed the structure assignment with singlet peaks centered at τ 7.5 (NCH_3) and 4.0 (–C–H). In $CD_3S(O)D_3$ solvent, the –OH and –C–H ^1H nmr peaks were split into the expected doublets.

Reaction of *N*,*N*-Dimethylaminomethyllithium with Benzene. A dispersion of **1′** in hexane, prepared from 7.0 g (0.02 mol) of **1**, was treated with 2 ml of benzene and allowed to stir for 16 hr at room temperature. Subsequent to this time, the organolithium compounds were derivatized with 3.25 g (0.03 mol) of trimethylchlorosilane (THF was added to facilitate the coupling reaction). The reaction mixture was hydrolyzed with dilute aqueous base and the organic materials were extracted with ether. The ether concentrate was distilled to give (*N*,*N*-dimethylaminomethyl)trimethylsilane which was converted to the corresponding methiodide salt: 2.5 g (46%), mp 235° (lit.[28] mp 242°). A ^1H nmr spectral analysis of the compound confirmed the structure assignment. The distillation residue was shown not to contain phenyltrimethylsilane by ^1H nmr spectral and glpc analyses.

In Ether–Hexane. A cloudy solution of **1′** in 20 ml of hexane and 30 ml of diethyl ether, prepared from 10.5 g (0.03 mol) of **1**, was treated with 4 ml of benzene and stirred for 18 hr at 40°. Subsequently, the clear reaction mixture was treated with 3.5 g (0.033 mol) of benzaldehyde and hydrolyzed with dilute acid. The acid layer ultimately afforded 2.0 g (40.5%) of α-(*N*,*N*-dimethylaminomethyl)benzyl alcohol that was identical in all respects with authentic compound.[8] The neutral layer extract was dried, concentrated, and distilled to give a mixture of 0.33 g (6%) of benzhydrol and 8.7 g (84%) of tetrabutyltin as determined by a quantitative glpc analysis. The presence of benzhydrol in the distillate was further confirmed by ^1H nmr analysis.

In Hexane and TMEDA. A solution of **1′**·TMEDA in 30 ml of hexane, prepared from 10.5 g (0.03 mol) of **1** and 0.03 mol of

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n-butyllithium TMEDA complex at 0°, was treated with 5.2 ml of benzene and stirred at room temperature for 3 hr. Subsequently, the reaction mixture was treated with 3.5 g (0.033 mol) of benzaldehyde and worked up as described above to give 3.3 g (67%) of α-(*N*,*N*-dimethylaminomethyl)benzyl alcohol, bp 50–52° (0.03 mm), 0.8 g (12%) of $(CH_3)_2NCH_2CH_2N(CH_3)CH_2CH(OH)C_6H_5$, bp ~100° (0.03 mm), 10.2 g of tetrabutyltin, and ~0.4 g (8%) of benzhydrol.

Reaction of Triphenylphosphine Oxide with 1′. Treatment of a suspension of 5.56 g (0.02 mol) of triphenylphosphine oxide in 50 ml of anhydrous ether with a suspension of 0.02 mol of **1′** in 20 ml of hexane at 27°, followed by stirring for 2 hr, gave a deep red-brown solution. The reaction mixture was then quenched with 20 ml of water and worked up in the usual manner to afford 3.3 g (64%) of (*N*,*N*-dimethylaminomethyl)diphenylphosphine oxide, mp 180–182° (lit.[29] mp 185–187°) and 6.0 g (87%) of tetrabutyltin, bp 91–94° (0.1 mm). Subsequent recrystallization of the phosphine oxide from benzene–hexane afforded 3.15 g of compound, mp 181–182°. ^1H nmr spectral analysis of the phosphine oxide in $CDCl_3$ showed aromatic protons (10, m) at τ 2.5, methylene protons (2, d, *J* = Hz) at 6.7, and methyl protons (6, s) at 7.6.

Preparation of *N*-(2,2-Diphenylethylidine)-*N*,*N*-dimethylamine and Diphenylacetaldehyde. A solution of 3.62 g (0.02 mol) of benzophenone in 15 ml of anhydrous ether was added to 0.02 mol of [α-lithio-α-(*N*,*N*-dimethylamino)methyl]diphenylphosphine oxide (prepared as described above). The reaction mixture rapidly lost color and was mildly exothermic. After 1.5 hr stirring at 27°, the reaction mixture was hydrolyzed with 40 ml of a 10% sulfuric acid solution. The reaction mixture was filtered and extracted with ether, and the organic layer washed to neutrality. Removal of the solvent *in vacuo* afforded 12.8 g of a two-phase oil. Distillation gave 1.75 g (44%) of diphenylacetaldehyde, bp 91–100° (0.05 mm), and 6.0 g (87%) of tetrabutyltin. The aldehyde was identified by comparison of its ^1H nmr spectrum and glpc data with that of an authentic sample.

In a separate experiment, the enamine intermediate was isolated and characterized in the following way. Prior to the hydrolysis step, the reaction mixture was taken up in ether, washed quickly with water (three 40-ml portions), dried, and solvent removed *in vacuo* to afford a two-phase oil. Glpc analysis showed that the mixture contained tetrabutyltin, unreacted benzophenone, and the enamine. The enamine was collected by glpc and characterized by ^1H nmr spectral analysis (in $CDCl_3$) with aromatic protons (10, d, *J* = 14 Hz) at 2.9, vinyl proton (1, s) at 3.7, and methyl protons (6, s) at 7.5. A mass spectral analysis of the compound was consistent with the structure assignment.

Stability of 1′ in Mixed Hexane–Tetrahydrofuran Solvent. A solution of 0.03 mol of **1′** in 30 ml of hexane and 5 ml of THF was allowed to stand for 18 hr at room temperature and then treated with 3.5 g (0.033 mol) of benzaldehyde. The usual work-up gave 2.5 g (50%) of α-(*N*,*N*-dimethylaminomethyl)benzyl alcohol, bp 52–56° (0.1 mm). A higher boiling fraction was also obtained, but not characterized. No attempt was made to isolate the neutral product(s) of the reaction.

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Proton Magnetic Resonance Study of the Indole N*H* Resonances of Lysozyme. Assignment, Deuterium Exchange Kinetics, and Inhibitor Binding

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Abstract: Resonances of the indole N*H* protons of the six component tryptophan residues of hen egg white lysozyme are coincident in the denatured form of the protein. Five of six indole N*H* protons are resolved in the 220-MHz pmr spectrum of the protein in the native conformation. Chemical modification, deuterium exchange kinetics, and inhibitor perturbation studies, in combination with published X-ray results, permit identification of these resonances with specific tryptophan residues.

Concomitant with improvements in instrumention, a number of laboratories have undertaken over the past few years studies by proton magnetic resonance (pmr) spectroscopy of the structures of proteins in solution. As was to be expected, because of the large number of structurally and environmentally nonequivalent protons, the pmr spectra of proteins are exceedingly complex and by no means competely resolved even at the highest resonance field presently available on commercial spectrometers.

In spite of this complexity, it is clear that the maximal and probably unique contributions of pmr spectroscopy to the elucidation of structural and dynamic processes of proteins in solution will depend on the extent to which resolved resonances can be uniquely identified with specific protons of the protein. Over the past few years there has been a good deal of progress in this direction. Resonances of the C-2 protons of the four histidine residues of bovine ribonuclease have been resolved and assigned.[2a] Resolved resonances in the high-field portion of the pmr spectrum of HEW lysozyme have been attributed to methyl protons of, principally, valine, leucine, and isoleucine residues perturbed by ring-current field effects.[2b,3,4] Resonances

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