concentrated and the residue chromatographed on activity I Woelm alumina, eluting with benzene to yield 2-phenyl-5,7-dimethoxybenzofuran (**16**) (0.238 g, 88%), mp 87–90°.

(B) Photolysis of 3,3′,4,4′-Dimethylenedioxybenzoin Phthaloyl Glycinate (18). The ester **18** (0.878 g, 1.80 mmol) was irradiated in benzene solution for about 1.75 hr. Removal of the solvent afforded a brown crystalline solid which was washed several times with small quantities of ether. The ether washings were concentrated and diluted with methanol to induce crystallization of phthaloyl glycine (0.279 g, 75%), mp 192–196°, identical infrared spectrum with that of an authentic sample, and undepressed mixture melting point. The furan fraction was not investigated.

(C) Photolysis of 2,2′,3,3′-Tetramethoxybenzoin Phthaloyl Glycinate (19). The ester **19** (3.6817 g, 7.09 mmol) was irradiated in benzene solution for about 3.5 hr. The reaction mixture was concentrated until crystallization was induced. The crystalline phthaloylglycine (1.1046 g, 76%) was collected and after recrystallization from methanol–benzene had mp 195–198° and an identical infrared spectrum with that of an authentic sample. The mother liquor from the concentrated reaction mixture was diluted with ether (200 ml) and methylene chloride (100 ml), washed with 1 *N* sodium bicarbonate (two 20-ml portions) followed by water (two 25-ml portions), and dried. Removal of the solvent and chromatography of the residue on activity I Woelm alumina, eluting with benzene, afforded **2-(2′,3′-dimethoxyphenyl)-4,5-dimethoxybenzofuran** (1.384 g, 62%) which after recrystallization from *n*-hexane had: mp 72–74°; λ_{max}^{EtOH} shoulder 289 (ε 31,260), 303 (33,960), and shoulder 318 nm (23,700).

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.81; H, 5.73. Found: C, 68.86; H, 6.00.

Acknowledgment. This investigation was aided by a Public Health Service Fellowship (Grant No. 5-Fl-GM 15,948-02) to R. M. W. for which we wish to express our appreciation. An expression of appreciation is also extended to W. H. Ballard who assisted in the preparation of some of the starting materials.

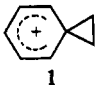
Studies of Homoconjugation in Pyridylalkyl Organometallic Compounds[1,2]

Gideon Fraenkel* and James W. Cooper

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received April 15, 1971*

Abstract: In a study of homoconjugative contributions to bonding in carbanions, a series of pyridylalkyl metallic compounds has been prepared and their nmr spectra determined. The spectra indicate that these compounds exist mainly in the open chain form. The compounds display unusual ambidentate reactivity to acylating reagents forming stable *N*-acyl derivatives of dihydropyridines which themselves are useful precursors to other organometallic compounds. Attempts to prepare the lithium compound and Grignard reagent from 3-(4-pyridyl)-3-methylbutyl chloride resulted in fragmentation with loss of ethylene to 2-(4-pyridyl)-2-metallopropanes. The latter display in their nmr spectra considerable delocalization of charge into the ring; chemically they acylate with ethyl chloroformate on *nitrogen* with formation of a stable pyridine methide–*N*-carbethoxy-4-isopropylidene-1,4-dihydropyridine. Whereas 2-(2-pyridyl)-2-methylpropylmagnesium chloride undergoes reaction at carbon with ethyl chloroformate, 2-(4-pyridyl)-2-methylpropylmetallic compounds (M = Hg, Mg, Li) acylate at *nitrogen* with ring closure to stable 1-acyl-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridines. These compounds are cleaved by organometallic compounds of sodium, magnesium, and lithium back to open chain pyridylpropyl metallic compounds which behave similarly to the reagents prepared *via* the halides. From competition experiments it is shown that ethyl chloroformate acylates pyridines faster than it reacts with alkylmagnesium halides. Thus when ethyl chloroformate is added to a mixture of pyridine and a Grignard reagent, 2-substituted *N*-carbethoxy-1,2-dihydropyridines are formed. By analogy it is proposed that the cyclization of 4-pyridylalkyl organometallic reagents by acylating agents proceeds *via* the *N*-acylpyridiniumalkyl metal species. While homoconjugative interactions are not detected from the nmr data, the failure of these pyridylalkyl metal reagents to react with excess butyllithium indicates a small degree of homoconjugative stabilization.

Phenyl participation in carbonium ion reactions is one example of many homoconjugative interactions which are thought to stabilize carbonium ions or transition states with carbonium ion character. Bridged phenylethyl cations originally proposed to accompany the solvolysis of 1-phenyl-1-methyl-2-butanol tosylate[3] have now been prepared in stable salts, and unequivocally identified by nmr spectroscopy.[4,5]



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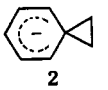
In principle the effects responsible for the stability of **1** should also apply to its negative counterpart, the as yet unknown phenanion, **2**. Species similar to **2**



2

have been suggested by Zimmerman[6] and Grovenstein[7]

(1) Presented in part at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

(2) Abstracted from the Ph.D. Thesis of J. W. Cooper, The Ohio State University, 1969.

(3) D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3863, 3875, 3883 (1949); **74**, 2159 (1952); **86**, 3767 (1964).

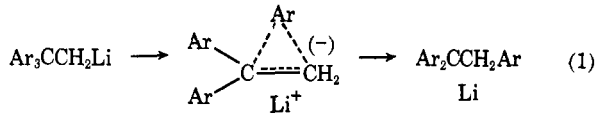
(4) L. Eberson and S. Winstein, *ibid.*, **87**, 3506 (1965).

(5) G. Olah, E. Namanworth, M. Comisarow, and B. Ramsey, *ibid.*, **89**, 711 (1967).

(6) H. E. Zimmerman and F. J. Smentowski, *ibid.*, **79**, 5455 (1957); H. E. Zimmerman and E. Zweig, *ibid.*, **83**, 1196 (1961).

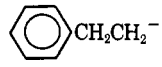
(7) E. Grovenstein, Jr., *ibid.*, **79**, 4895 (1957); E. Grovenstein, Jr., and G. Wentworth, *ibid.*, **85**, 3305 (1963); E. Grovenstein, Jr., and G.

to accompany the 1,2 rearrangement of polyarylethyllithiums, either in the transition state or as actual intermediates, *e.g.*, eq 1.



(1)

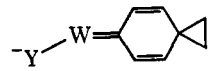
Whether or not arylethyl anions exist in the open (**3**) or the closed form (**2**) could easily be determined by



3

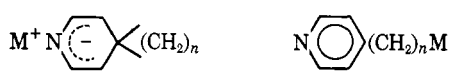
direct nmr spectroscopic observation of organometallic compounds. In general it is not possible to generate stable solutions containing free carbanions; still, the available evidence indicates the carbon–metal bonds in many organometallic compounds to be sufficiently ionic such that many of these reagents display in their physical properties features to be expected of carbanionic substances. Thus primary Grignard reagents invert at carbon bound to magnesium rapidly at room temperature.[8] Furthermore, results from proton and carbon-13 nmr and uv spectroscopic investigations of phenylmagnesium bromide reveal a strong resemblance to the data for pyridine (which is isoelectronic with the phenylanion) and quite different from what is observed for ordinary covalently substituted benzenes.[9]

So far nmr studies of β-phenylethyllithium and β-phenylethylmagnesium bromide show them to exist entirely in the open form. Most electron-withdrawing groups such as NO_2, NO, and C=O, which conjugate with negative centers and which would be expected to stabilize the bridged phenylethylanion **4**, react directly



4

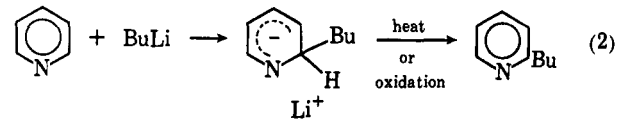
with organometallic reagents. Therefore, we have chosen to study pyridylalkyl organometallic reagents instead. The great electron-withdrawing power of the pyridine ring,[10] similar to nitrobenzene, should stabilize the spiro form of the reagent **5a** compared to the open form **5b**, and at the same time should not be susceptible



5a **5b**

to the organometallic reductions common to nitrophenyl systems.

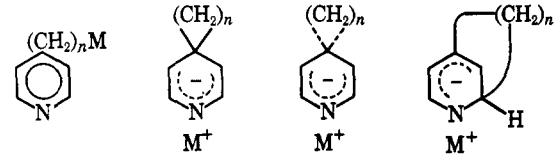
A further rationale behind the present work is based on nucleophilic substitution reactions of pyridine with organometallic reagents. Ziegler and Zeiser reported that butyllithium adds to pyridine with subsequent elimination of lithium hydride to give 2-butylpyridine, eq 2.[11] In the last 40 years an extensive literature has



(2)

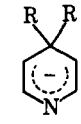
6

accumulated involving similar reactions with other organometallic reagents.[12] It has always been assumed, though never proven, that these reactions proceed *via* intermediates such as **6**. However, recent nmr studies[13] of the initial reaction product of butyllithium with pyridine at −78° clearly establish it to have the conjugated azacyclohexadienyl structure, **6**. The stability of ions such as **6** implies that pyridylalkyllithium compounds may well exist in the spiro form, **5a**. By means of nmr spectroscopy it should be readily possible to distinguish among the various forms pyridylalkyl metal compounds may assume in solution, **5a**, **5b**, **7**, and **8**. While the



5b **5a** **7** **8**

ring resonance of the open chain form will resemble ordinary pyridines the model for the spiro ion is anion **9**.



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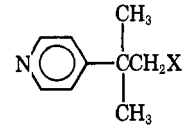
Shifts found to be intermediate between the two models will indicate structure **7**. Nmr spectroscopy will also permit identification of a 1,3 bridged species, **8**. Finally, in the event of a rapid interconversion among two or more species, rates of exchange could be obtained by use of the nmr line-shape method.

In this paper we report the results of a chemical and nmr spectral investigation of possible homoconjugation effects in pyridylalkyl metallic compounds.

Results and Discussion

Starting Materials. In a modification of the procedure of Löffler and Stietzel[14] formaldehyde was condensed with 4-isopropylpyridine to give 2-methyl-2-(4-pyridyl)-1-propanol, **10a**. The latter was converted to the chloride, 2-methyl-2-(4-pyridyl)-1-chloropropane, **10b**, using thionyl chloride. The β positions in **10b** are



10a, X = OH
10b, X = Cl

blocked to avoid polymerization by quaternization and

Wentworth, *ibid.*, **89**, 1852 (1967); E. Grovenstein and G. Wentworth, *ibid.*, **89**, 2348 (1967).

(8) See M. Witanowski and J. D. Roberts, *ibid.*, **88**, 737 (1966); G. Fraenkel and T. D. Dix, *ibid.*, **88**, 979 (1966).

(9) G. Fraenkel, D. G. Adams, and R. R. Dean, *J. Phys. Chem.*, **72**, 944 (1968); G. Fraenkel, S. Kobayashi, and S. Dayagi, *ibid.*, **72**, 953 (1968).

(10) H. L. Retcofsky and R. A. Friedel, *ibid.*, **71**, 3592 (1967).

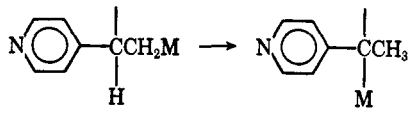
(11) K. Ziegler and H. Zeiser, *Chem. Ber.*, **63**, 1847 (1930); K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931).

(12) See R. A. Abramovitch and B. Vig, *Can. J. Chem.*, **41**, 1961 (1963).

(13) G. Fraenkel and J. W. Cooper, *Tetrahedron Lett.*, 1825 (1968).

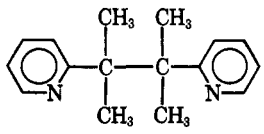
(14) K. Löffler and F. Stietzel, *Chem. Ber.*, **42**, 124 (1909).

possible proton transfer reactions in organometallic reagents, eq 3. By analogy to the method just described



(3)

2-isopropylpyridine was treated with sodamide and then trioxane in ether. Instead of the expected alcohol mainly starting material was recovered together with a solid found to be 2,3-bis(2-pyridyl)-2,3-dimethylbutane, **11**. However, under more stringent conditions 2-isopropylpyridine reacted with paraformaldehyde at 180° to give the required 2-methyl-2-(2-pyridyl)propanol, **12a**. The latter reacted smoothly in chloroform with thionyl chloride to give the expected chloride **12b**.



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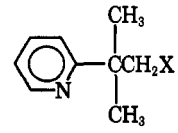
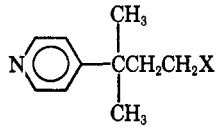


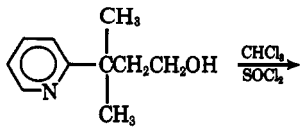
12a, X = OH
12b, X = Cl

In similar fashion to the syntheses of **10b** and **12b**, 4-isopropylpyridine was condensed with ethylene oxide in liquid ammonia with sodamide to give 3-methyl-3-(4-pyridyl)-1-butanol, **13a**, which was then converted to the chloride, **13b**, using thionyl chloride in chloroform.



13a, X = OH
13b, X = Cl

In contrast to the previous result the alcohol obtained from 2-isopropylpyridine and ethylene oxide, **14**, did not give the expected chloride on reaction with thionyl chloride in chloroform. Instead, as the result of an unusual fragmentation process (eq 4), mainly 2-isopropenylpyridine was obtained together with sulfur dioxide and ethylene. The ease with which this reaction takes place must be ascribed to a concerted decomposition of the intermediate chloro sulfite ester to 2-isopropenylpyridinium chloride and the other products (eq 5), all leaving groups being stable chemical species.



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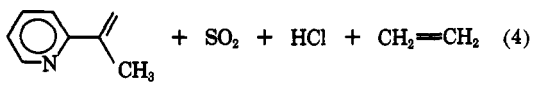
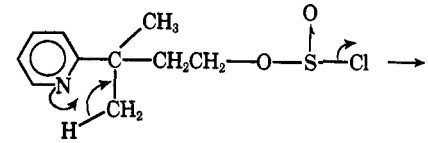
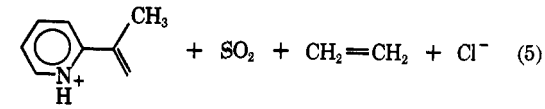


(4)

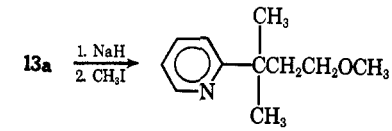
If pyridylalkyl anions are indeed homoconjugated it should be possible to generate them by ether cleavage.





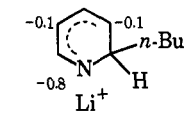
(5)

Accordingly it was decided to use methyl ether **15** as a possible organometallic precursor.



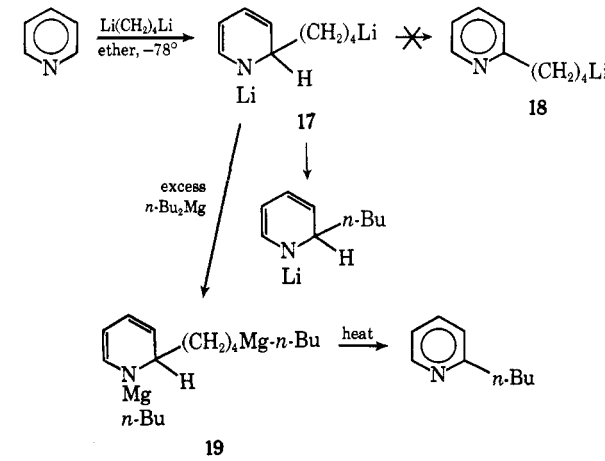
15

Generation of Organometallic Reagents. It was previously reported, from nmr measurements, that the initial adduct of butyllithium and pyridine had structure **16**.[13] A similar charge distribution has been



16

obtained from several different molecular orbital calculations—Hückel,[15] extended Hückel,[16] and CNDO/2.[17] Meanwhile a wide variety of similar adducts have been prepared,[18] and it has been found that in *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) the reaction is almost quantitative (>99%). In light of the above results a straightforward route to pyridylalkyl organometallic compounds would be the analogous addition of dilithioalkanes to pyridines. Accordingly 1,4-dilithiobutane was prepared from the dibromide and lithium wire in ether in an all-glass ball mill and then treated with pyridine at −78°. The nmr spectrum indicated >95% conversion to the adduct, **17**. This



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species remained dominant until it decomposed on standing by deprotonating the solvent and loss of lithium hydride. At no time was the desired 4-(2-pyridyl)-

(15) A. Streitweiser Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, pp 115–135.
(16) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).
(17) J. A. Pople and G. A. Segal, *ibid.*, **44**, 3289 (1966).
(18) J. W. Cooper, to be published.

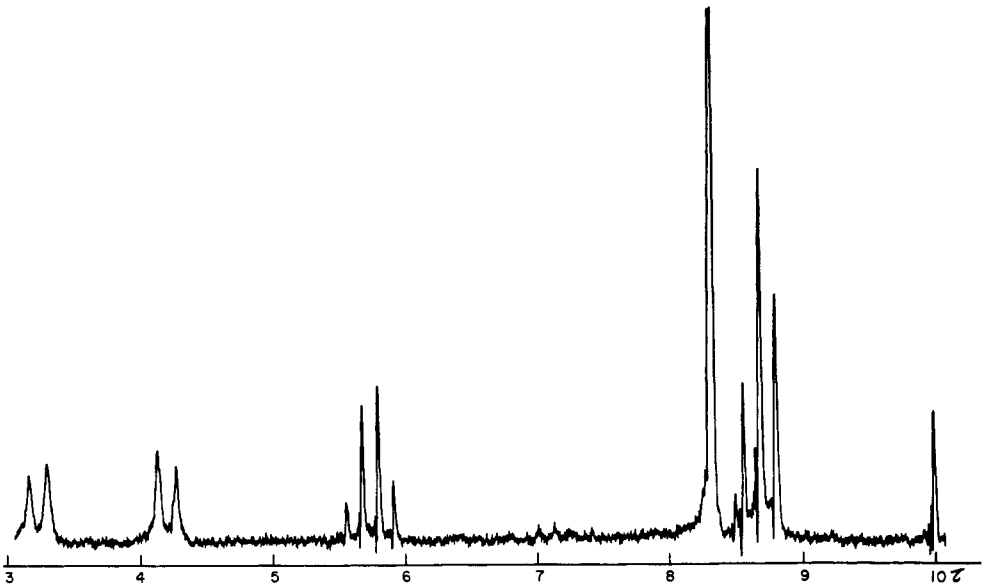
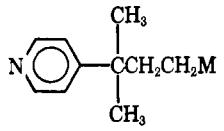


Figure 1. Nmr spectrum, 60 MHz, 1-carbethoxy-4-isopropylidene-1,4-dihydropyridine, 40° in carbon tetrachloride.

butyllithium, **18**, detected. In another experiment the initial adduct, **17**, was mixed with excess di-*n*-butylmagnesium on the assumption that the magnesium derivative **19** would be less basic than **17**. The resulting solution displayed an nmr spectrum similar to **17**. However, the magnesium derivative **19** was thermally much more stable than **17**. After heating at 100° for 30 min, **19** decomposed directly to 2-*n*-butylpyridine.

We now describe experiments to generate organometallic compounds from pyridylalkyl halides. Reaction of 3-methyl-3-(4-pyridyl)chloropropane with magnesium or lithium in ether gave, instead of the expected organometallic reagent **20**, fragmentation to ethylene and 2-(4-pyridyl)-2-lithiopropane (**21b**), or the corresponding Grignard reagent **21a**. Hydrolysis of the



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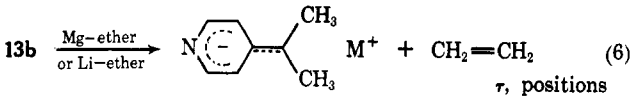
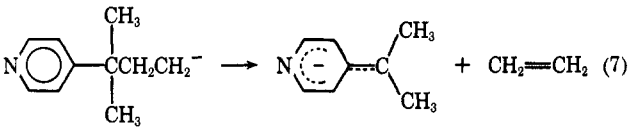


(6)

	τ, positions	
	2.6	3.5
21a, $M^+ = MgCl^+$	3.74	4.90
21b, $M^+ = Li^+$	3.50	5.74

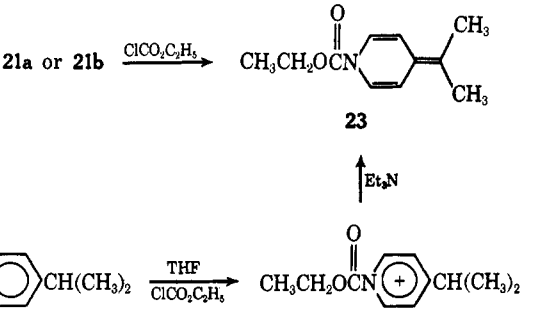
reaction mixture yielded only 4-isopropylpyridine and starting material; no 3-(4-pyridyl)-3-methylbutane was detected.[19] In the course of the fragmentation reaction the aromatic resonance in **13b** is replaced by an AA'XX' pattern *ca.* 2.0 ppm to higher field of starting material; see eq 6. These shifts are very similar to those for picolyllithium[20] and their shielding relative to pyridines is probably due to the high π-electron density around the ring. Thus, the driving force for the fragmentation of the probable intermediate **20** lies in the stability of the conjugated departing anion **22** (eq 7). An alternative mechanism might involve reduction of the pyridine ring by two electrons followed by loss of chloride ion and fragmentation.



(7)

22

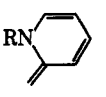
Additional evidence concerning the nature of products **21a** and **21b** comes from their chemistry. Treatment of the reaction mixture with ethyl chloroformate leads to a product with an AA'XX' nmr pattern in the vinyl proton region, tentatively assigned to be *N*-carbethoxy-4-isopropylidene-1,4-dihydropyridine, **23**. A



23

compound with identical properties to **23** was isolated from acylation of 4-isopropylpyridine with ethyl chloroformate followed by treatment with triethylamine. Mass spectral, nmr (Figure 1), and ir data are consistent with structure **23**. Evidently the acylation of **21a** and **21b** is much faster at nitrogen than carbon. For picolyllithium the opposite is the case.[20]

Compound **23** is one of the few stable pyridine methides, *e.g.*, **24**, a class of compounds which have been



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(19) G. Fraenkel and J. W. Cooper, *Tetrahedron Lett.*, 599 (1968).

(20) Chui Ho, Ohio State University, private communication.

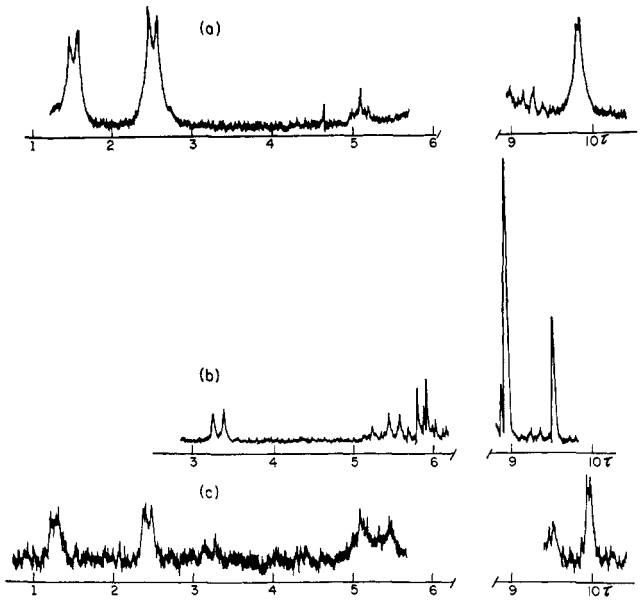
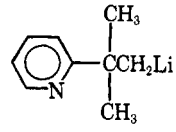


Figure 2. Nmr spectra, 60 MHz, 40°: (a) 2-(4-pyridyl)-2-methylpropylmagnesium chloride, 1.0 *M* in THF; (b) result of treating Grignard reagent in a with ethyl chloroformate; (c) result of treating 1-carbethoxy-4,4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine with butylmagnesium bromide.

postulated as reaction intermediates,[21] but only detected and isolated when the substituent is conjugated with the ring.[22] The stability of **23** must be ascribed to the amide linkage.

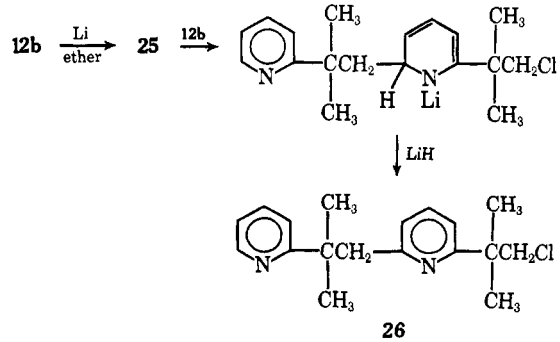
Attempts to obtain an unambiguous nmr spectrum of 2-methyl-2-(2-pyridyl)propyllithium, **25**, were unsuc-



25

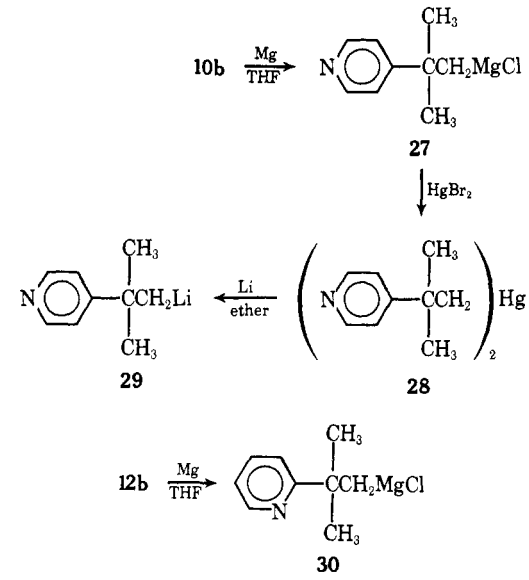
cessful. Treatment of chloride **12b** with lithium wire in ether gave, after hydrolysis, a solid (**26**) whose parent mass was determined to be 295. On the basis of the nmr and mass spectral data the course of this reaction and its product are proposed in Scheme I.

Scheme I



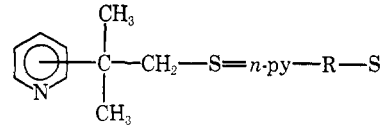
26

Both 2-(2-pyridyl)-2-methylpropyl chloride and 2-(4-pyridyl)-2-methylpropyl chloride reacted with triply sublimed magnesium in THF to give the corresponding Grignard reagents **30** and **27**. Reagent **27** was converted *via* the mercury compound **28** to the lithium compound **29**. These reagents were identified by a combination of nmr spectroscopy and chemical procedures described below.



Nmr spectral investigation (see Figure 2) gave no indication of the upfield ring proton shifts to be expected for homoconjugated carbanionic reagents. The ring proton shifts in **27**, **29**, and **30** are typical of pyridines and very similar to those for the starting chlorides; see Table I. The CH_2M proton resonances fall slightly below those for alkyl metallic compounds.

Table I. Nmr Data for Some Pyridylalkyl Metal Compounds and Their Precursors



Solvent	Compound	*n*	S	—Chemical shifts, τ— Ring (position)	CH_2
CCl_4	**12b**	2	Cl	Complex	6.23
THF	**30**	2	MgCl	Complex	10.25
CCl_4	**10b**	4	Cl	1.59 2.90 (2,6) (3,5)	6.47
THF	**27**	4	MgCl	1.66 2.50 (2,6) (3,5)	9.90
THF	**29**	4	Li	1.55 2.68 (2,6) (3,5)	9.94
CCl_4	**28**	4	Hg-R-4-py	1.61 2.91 (2,6) (3,5)	8.68

In an attempt to detect a small degree of homoconjugation the ^{13}CH coupling constant was determined for the CH_2Mg group of **27** (natural abundance). Directly bonded CH coupling constants are a measure of the s (*s*) character associated with the C–H bond orbital and of the effective nuclear charge of carbon (2s), $J \propto Z^{*2}/s$.[23] Any value larger than 125 Hz would indicate some homoconjugative interaction (cyclopropyl $J_{CH} = 167$ Hz). In fact, J_{CH} for **27** is 105 Hz, very close

(21) K. Schofield, "Hetero-Aromatic Nitrogen Compounds," Plenum Press, New York, N. Y., p 338.

(22) J. A. Berson, E. M. Evleth, and Z. Hamlet, *J. Amer. Chem. Soc.*, **87**, 2887 (1965).

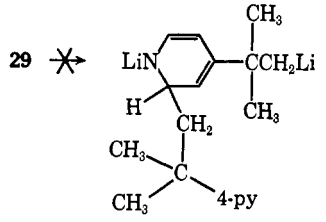
(23) D. W. Grant and W. M. Lichman, *ibid.*, **87**, 3994 (1965).

Table II. Physical Constants of 1-R-4-(1,1-Dimethylspirocyclopropyl)-1,4-dihydropyridines

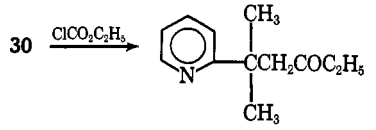
Property	R: EtOCO (32)	MeOCO (33)	C_6H_5CO (34)	MeCO (35)	Me_3Si (36)
Bp, °C (mm)	99 (0.3)	87 (0.25)	146 (0.2)	117 (0.8)	
Uv λ_{EtOH}	253	252	304	273	
			278	207	
			239		
			(197)		
	17,600	19,300	2,520	9170	
			3,740	1610	
			14,800		
			19,600		
Mass spec M^+	207	193	239	177	
Mp, °C	48–50			59–67	
Nmr shifts, τ					
vinyl 2,6	3.32	3.28	3.17	2.95, 3.46	4.07
3,5	5.57	5.54	5.48	5.41, 5.52	5.25
gem-dimethyl	8.95	8.93	8.93	8.90	9.10
cyclopropyl methylene	9.55	9.54	9.47	9.48	10.07
$J_{2,3}$, Hz	8.4	8.0	8.5	8.7	8.1

to that for primary Grignard reagents[24] indicating that homoconjugation is not detected in this experiment.

Chemistry of Pyridylalkyl Metal Compounds. The pyridylalkyl organometallic compounds which have been prepared are all stable reagents with the exception of the lithium compound **29** which slowly hydrolyzes by deprotonating the solvent. However, even over a period of several weeks at 0° there is no evidence for dimerization of **29** *via* a Ziegler–Zeiser reaction, nor is this reagent reactive to a tenfold excess of *n*-butyllithium. Since few pyridines fail to react with butyllithium[12] this result may indicate a small degree of homoconjugation in **29**.

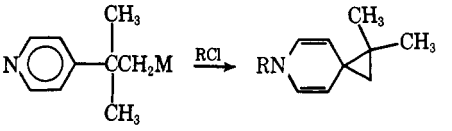


It is common practice to capture new carbanionic reagents with acid halides or trimethylsilyl chloride or hydrolyze them. As expected, reagents **27**, **29**, and **30** undergo hydrolysis to *tert*-butylpyridine, and Grignard



31

reagent **30** gives the ester **31** with ethyl chloroformate. In contrast to these results, when 2-(4-pyridyl)-2-methylpropyl metal derivatives (Mg, Li, and Hg) are treated with acid chlorides or trimethylsilyl chloride, reaction takes place at nitrogen with quantitative formation of 1-substituted-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridines, **32–36**; see Figure 2. This is one of the few examples of a nucleophilic cyclization of a pyridine, and compounds **32–36** are the first examples of stable derivatives of spirocyclopropyldihydropyridines. Due to the amide linkage these compounds are quite stable; all but the trimethylsilyl derivative were isolated and distilled. They crystallized under refrigeration and could be stored at 0° for several months. Further, eq 8 is an unusual example of nucleophilic cyclization in a mercury compound. The reaction of ethyl chloroformate with



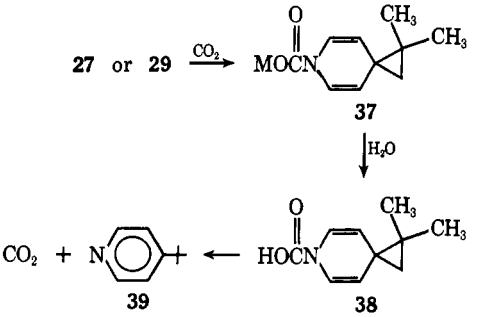
(8)

27, M = MgCl
28, M = HgR
29, M = Li

32, R = $CO_2C_2H_5$
33, R = CO_2CH_3
34, R = COC_6H_5
35, R = $COCH_3$
36, R = $(CH_3)_3Si$

bis[2-methyl-2-(4-pyridyl)propyl]mercury in THF gave quantitative conversion to **32**. This reaction also proceeded well in carbon tetrachloride. Attempts to produce a trimethylsilyl derivative from **28** were only successful in THF; it alone was not stable.

In view of the results summarized in eq 8 it is not surprising that reaction of **27** and **29** with carbon dioxide gave, on hydrolysis, 4-*tert*-butylpyridine. This result implies the intermediacy of carbamate **37** and subsequent decomposition of the carbamic acid, **38**. Consistent with these results is the finding of Eisch[25] that



reduction of the methiode of **10b** with lithium in THF results in the formation of 1-methyl-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine.

The assigned structures **32–36** are entirely consistent with the physical data: nmr, AB absorption in the vinyl region, CH_2 in the region τ 9–10, and $J(^{13}CH)$ of $^{13}CH_2$ of 162 Hz, Table II. Interestingly the cyclo-

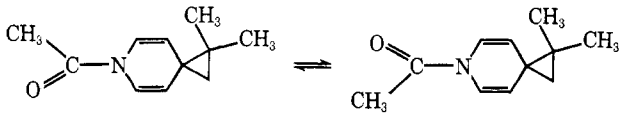
(24) G. Fraenkel, D. G. Adams, and J. Williams, *Tetrahedron Lett.*, 767 (1963).

(25) J. J. Eisch and C. A. Kovacs, *J. Organometal. Chem.*, **25**, C33 (1970).

Table III. Major Mass Spectral Fragments of the Spirocyclopropyldihydropyridines

R	M^+	Loss of CH_2	Loss of CH_3	Loss of R	4-PyC$(CH_3)_2^+$	4-PyC$(CH_2^+)(=CH_2)$	**43**	R
EtOCC (**32**)	207	193	192	134	120	118	92	
MeOCC (**33**)	193	179	178	134	120	118	92	59
C_6H_5CO (**34**)	179	225	224	134	120	118	92	105
MeCO (**35**)	177	163	162	134	120	118	92	43

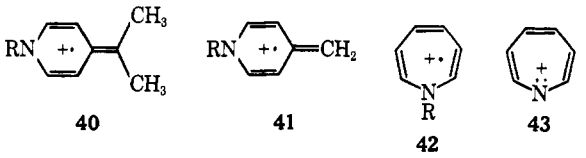
propyl proton shift is a linear function of the Hammet σ_p of R in **32–36**. The stabilization of these compounds by amide conjugation is evident from the nmr spectrum of **35**. Below −2° this compound gives two separate AB vinyl resonances of about equal intensity indicating rotation about the amide linkage to be slow (eq 9) on the nmr time scale. At higher temperatures



35a **35b** (9)

the two resonances coalesce due to faster rates of rotation. Arguing from this result it is reasonable to assume that similar stabilization must apply to the other derivatives where the shifts between the two AB resonances must be too small to measure.

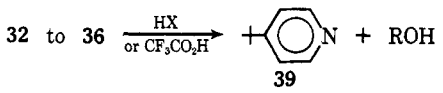
The principle features among the mass spectral data for **32–36** are peaks at M^+, $M^+ - CH_2$, **40**; $M^+ - CH_3$, $M^+ - (CH_3)_2C$, **41** or **42**; and 92, **43**, see Table III.



40 **41** **42** **43**

Although the *N*-acyl-4-spirocyclopropyl-1,4-dihydropyridines reported here are stable compounds, they are extremely labile to acids and bases.

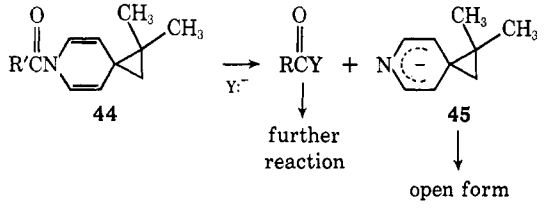
Hydrolysis of compounds **32–36** results only in 4-



39

tert-butylpyridines, protonation taking place exclusively at the methylene carbon of the three-membered ring.

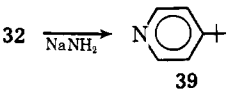
Since amides are known to be cleaved by certain nucleophiles, reaction of the acyldihydropyridines with bases presents an attractive route to generate the conjugate base of the dihydropyridine which may exist in the open or closed form, **45**. When the nucleophile is



44 **45**

an organometallic compound, cleavage of **44** should result in the generation of another metal derivative of the 2-(4-pyridyl)-2-methylpropyl system. Thus the acyl derivatives **32–35** should be useful starting materials for the generation of organometallic compounds not available from the chloride or the mercury derivative. These reagents could be investigated with nmr spectroscopy with regard to possible homoconjugative stabilization.

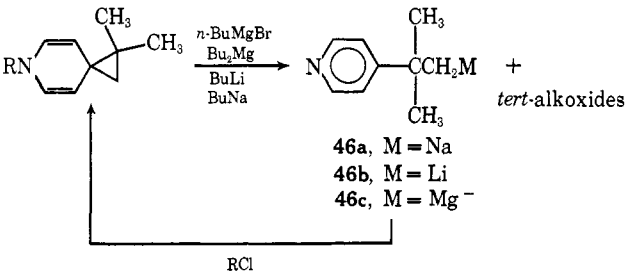
Urethane **32** was cleaved by sodamide in THF to



39

give 4-*tert*-butylpyridine. When compounds **32–35** were treated with dibutylmagnesium the vinyl and cyclopropyl resonances of starting material were replaced by a spectrum resembling that previously observed for the Grignard reagent, Figure 2c. Treatment of these new organometallic preparations with acid halides gave *N*-acylspirodihydropyridines. Similar results have been obtained with organolithium compounds and *n*-butylsodium, see Scheme II. In the latter case the re-

Scheme II



46a, M = Na
46b, M = Li
46c, M = Mg^-

R = $CO_2C_2H_5$, CO_2CH_3, $COCH_3$, COC_6H_5

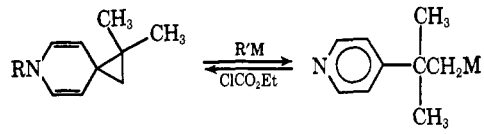
action product of the *N*-carbethoxy derivative, **32**, with *n*-butylsodium in hexane was not soluble and nmr spectra could not be obtained. However, this product reacted with methyl chloroformate to give compound **33**, thus establishing the course of the cleavage reaction. In contrast to these results **32–35** were unreactive to organozinc, -cadmium, and -aluminum compounds, even at 100°. In all cases where the organometallic product was stable in solution nmr spectra showed it to be in the open chain form, Table IV.

Due to differences in composition among the three 2-(4-pyridyl)-2-methylpropylmagnesium compounds prepared in this work it is not surprising that these reagents display slightly different chemical shifts. The products necessarily contain alkoxides and the fine structure in the CH_2Mg alkoxide resonance of these preparations indicates that exchange among organomagnesium alkoxide species is slow on the nmr time scale.[26] These effects are also evident among the nmr spectra of the lithium derivatives **29** compared to **46b**; see Tables I and IV.

The organometallic preparations **46a–c** display chemical behavior very similar to **27** and **29**. Compound **46b** is unreactive to excess butyllithium as is **29**. As in the case of **27**, **28**, and **29** the new reagents underwent

(26) H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, 32, 2481 (1967).

Table IV. 2-(4-Pyridyl)-2-methylpropylmetal Compounds by Cleavage Reactions

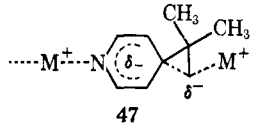


R	R'M	Solvent	Nmr product reagent— 2,6	3,5	CH_2, τ	% recyclization
EtOCO	*n*-BuLi	Ether	1.24	2.43	9.93	100
EtOCO	*n*-BuMgBr	THF	1.28	2.46	9.97	100
CH_3CO	$(n\text{-Bu})_2Mg$	THF	1.64	2.42	10.04	100
EtOCO	*n*-BuNa	Hexane	*a*			100
EtOCO	$NaNH_2$	THF	*b*			

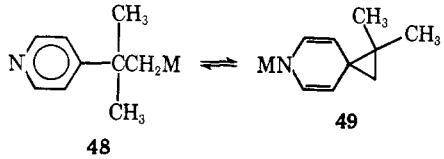
[a] Reagent insoluble. [b] Hydrolysis to 4-*tert*-butylpyridine.

acylation at nitrogen to give the spirocyclopropyldihydropyridines, **32–35**. Thus cleavage of **32–35** provides a useful path to generate certain organometallic derivatives. Spectral investigations show these to be little different from preparations *via* the chloride and mercury compound.

From the results reported here it is evident that while 2-(2-pyridyl)-2-methylpropylmagnesium chloride undergoes acylation at carbon all the 2-(4-pyridyl)-2-methylpropyl organometallic compounds *react exclusively at nitrogen*. Several effects may contribute to direct acylation at nitrogen. (1) Steric hindrance about the CH_2M part of the reagent favors acylation at nitrogen. (2) It is still possible that a small, though spectrally undetectable, degree of homoconjugation contributes to the structure of these reagents, **47**. (3) The predominant species, the open form **48**, may be in rapid equilibrium with a small amount of the closed form. The latter, **49**, acylates on nitrogen much faster than CH_2M



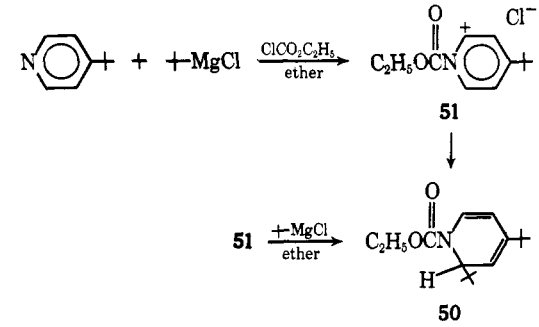
47



48 **49**

or nitrogen reacts in the open form. (4) Lastly it may be that homoconjugation is not responsible for the chemistry at all but that the nitrogen in the open form **48** is more reactive to acylation than is the CH_2M part. This last proposal has been tested with a competition experiment as described below.

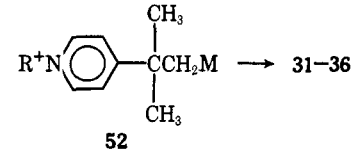
At room temperature 4-*tert*-butylpyridine does not react with Grignard reagents. In separate experiments at 25° both 4-*tert*-butylpyridine and Grignard reagents were found to react with ethyl chloroformate at rates too fast to measure. Next, a mixture of 4-*tert*-butylpyridine and *tert*-butylmagnesium chloride was treated with ethyl chloroformate. This experiment resulted in the formation of 1-carbethoxy-2,4-di-*tert*-butyl-1,2-dihydropyridine, **50**.[27] Clearly in the competition of a pyridine and a Grignard reagent for ethyl chloroformate, acylation of the pyridine is by far the faster reaction. The Grignard reagent then adds to the 2 position of the pyridinium salt, **51**. This reaction takes



51 **50**

place with many pyridines and Grignard reagents and is a useful route to prepare a wide variety of stable substituted 1-carbethoxy-1,2-dihydropyridines.[27] Furthermore the same product is obtained when the pyridinium salt is treated with the Grignard reagent.

On the basis of the results described in the preceding paragraph it would be expected that of the two sites in **46a–c** or **27–29** which can acylate, nitrogen is more reactive. Then N-acylation of the 2-(4-pyridyl)-2-methylpropyl metal compounds in the open form followed by cyclization of the *N*-carbethoxypyridinium organometallic **52**, is a sufficient mechanism to explain the formation of **32–36**. The driving force for this ring closure



52

is provided by the electron deficiency of the *N*-acylpyridinium ring. These results do not rule out homoconjugative contributions to the structure of **52**, nor do they provide positive evidence.

With regard to the structure of the pyridylalkyl metal compounds themselves it would appear that the coordination of nitrogen with metal in the system does not create enough electron deficiency in the ring such that homoconjugative interactions could be detected from the nmr spectra. On the other hand, the failure of these compounds to react with excess butyllithium implies some small homoconjugative interaction. The extreme manifestation of this effect takes place in the transition states of the cyclization reactions which result in **32–36**.

(27) G. Fraenkel, J. W. Cooper, and C. M. Fink, *Angew. Chem.*, **82**, 518 (1970).

Experimental Section

Materials and Equipment. Nmr spectra were determined on Varian nmr spectrometers, Models A60, A60A, and HA-100. Ultraviolet spectra were obtained using a Cary Model 14 spectrophotometer, and infrared data were obtained on a Perkin-Elmer Infracord.

All solvents used in the preparation of organometallic compounds were distilled from lithium aluminum hydride before use. All apparatus was flamed out under a flow of argon, and all organometallic reagents were prepared under argon, either in closed systems or under a positive argon pressure. Nmr spectra of organometallic compounds were determined from 1 *M* solutions unless otherwise specified.

Elemental analyses were carried out by Dr. A. Bernhardt of Max Planck Microanalytical Laboratory. Mass spectra were determined using an AEI MS9 mass spectrometer.

2-Methyl-2-(4-pyridyl)-1-propanol, 10a. In a modification of Löffler and Stietzel's procedure,[14] formaldehyde solution (830 ml, 10 mol) was added to a 2000-ml, round-bottomed flask containing 4-isopropylpyridine (242 g, 2.0 mol) and a magnetic stirring bar. The flask was fitted with a condenser and stirred and refluxed overnight. The solution was allowed to cool, transferred to a separatory funnel, and diluted with 250 ml of saturated NaCl solution. The mixture was extracted three times with 300-ml portions of chloroform and dried over magnesium sulfate. The chloroform was distilled off using a Newman condenser and the solution was heated until the excess formaldehyde was expelled. The remaining syrup was then distilled under vacuum: bp 150° (1.0 mm); yield, 169 g, 56%.

2-Methyl-2-(4-pyridyl)-1-chloropropane, 10b. In a 2000-ml, round-bottomed flask were combined **10a** (169 g, 1.11 mol) and 750 ml of chloroform. The flask was fitted with a condenser and drying tube and a magnetic stirrer, and immersed in an ice bath. Through a dropping funnel was added a solution of thionyl chloride (153 g, 1.30 mol) in 375 ml of chloroform. After addition was complete, the solution was refluxed for 12 hr. The product mixture was worked up by pouring over ice, neutralizing with 10% sodium hydroxide solution, extracting into chloroform, drying over magnesium sulfate, evaporating the solvent on a flash evaporator, and distilling under vacuum. The distilled product still contained nearly 50% starting material. This mixture was dissolved in chloroform (500 ml) and treated with thionyl chloride (118 g, 1.0 mol) in 250 ml of chloroform. After a second work-up, the product was still contaminated with starting material, and a third pass was made, treating the distillate dissolved in 250 ml of chloroform with thionyl chloride (116 g, 0.98 mol) added neat. The product upon work-up was found to be pure by nmr: bp 76° (0.04 mm); yield, 122.9 g, 65.2%. *Anal.* Calcd for $C_9H_{12}NCl$: C, 63.71; H, 7.13; N, 8.26; Cl, 20.40. Found: C, 63.93; H, 6.67; N, 8.50; Cl, 20.97.

Attempts to Prepare 2-Methyl-2-(2-pyridyl)propanol, 12a. Attempts to condense formaldehyde with 2-isopropylpyridine (a) by treating paraformaldehyde with the isopropylpyridine anion generated in ether with phenyllithium, (b) by refluxing with 36% formalin solution, (c) by treating 2-isopropylpyridine with sodamide and liquid ammonia and then with paraformaldehyde, or (d) trioxane, produced only starting material in the first two cases and starting material plus a high-boiling solid in the second two cases, one of which is described below.

Reaction of 2-isopropylpyridine (20 g, 0.165 mol), Fluka, with sodamide (12.5 g, 0.32 mol) in 50 ml of ether followed by addition of a solution of trioxane (14.9 g, 0.165 mol) in 25 ml of ether produced, in addition to a large amount of starting material, 1.5 g of a waxy crystalline soild which, after sublimation, softened at 85° and melted at 91°. The nmr spectrum showed multiplets at τ 1.71 and 3.12 and a singlet at τ 8.64 in the ratio of 1:3:6. Mass spectrometry showed the molecular weight to be 240 with a major fragment at 120. Elemental analysis indicated an empirical formula of $C_8H_{10}N$. No oxygen was present. These data are consistent with the dimer **11**, 3-bis(2-pyridyl)-2,3-dimethylbutane, formed by carbanion oxidation. *Anal.* Calcd for $C_{16}H_{20}N_2$: C, 79.79; H, 8.80; N, 11.66. Found: C, 79.71; H, 8.38; N, 11.48.

2-Methyl-2-(2-pyridyl)-1-propanol, 12a. Isopropylpyridine (100 g, 0.826 mol) and paraformaldehyde (140 g, 4.76 mol) were placed in a bomb of 1-l. capacity. The bomb was heated for 18 hr at 180°. The product, together with chloroform washings from the bomb, was poured into a distillation flask. The product was obtained by distillation at reduced pressure, bp 95° (10 mm). The yield was 56.1 g (44.3%). After repeated distillations, the alcohol retained a light yellow color.

2-Methyl-2-(2-pyridyl)-1-chloropropane, 12b. To a solution of 2-methyl-2-(2-pyridyl)-1-propanol, **12a** (30 g, 9.248 mol), in chloroform was added a mixture of thionyl chloride (32.5 g, 0.272 mol) in 75 ml of chloroform with stirring at 0°. The mixture was stirred overnight at room temperature and refluxed the next day. After the usual work-up the distillate (10.1 g), bp 90° (10 mm), proved to be 50% alcohol and 50% chloride. This mixture was combined with 20 g (0.166 mol) more of alcohol and treated with thionyl chloride (47.6 g, 0.40 mol) to produce 25.5 g of a mixture 80% chloride and 20% alcohol. This mixture was treated with 48 g (0.43 mol) of thionyl chloride in chloroform to produce pure chloride, bp 80° (8 mm). The yield was 22.2 g (76.0%). *Anal.* Calcd for $C_9H_{12}NCl$: C, 63.71; H, 7.13; N, 8.26; Cl, 20.90. Found: C, 63.59; H, 7.07; N, 8.14; Cl, 20.84.

3-Methyl-3-(4-pyridyl)-1-butanol, 13a. To a 2000 ml, three-necked, round-bottomed flask, jacketed with vermiculite, fitted with two Dry Ice condensers, a dropping funnel, and a mechanical stirrer, and flushed with argon, was added sodamide (32 g, 0.82 mol). Liquid ammonia (800 ml) was condensed into the flask and stirred until the sodamide was well dispersed and partially dissolved. Through the dropping funnel was added 4-isopropylpyridine (50 g, 0.413 mol). The mixture was stirred for 1.5 hr, until it turned very deep red. Ethylene oxide (36.2 g, 0.816 mol) was slowly added through the dropping funnel, and the mixture was stirred for 0.5 hr. The condensers were then removed, and a few drops of water added to neutralize any remaining 4-isopropylpyridyl anion. The ammonia was allowed to evaporate overnight. The following day, 100 ml of water was added to the flask and the slurry was stirred vigorously for 2 hr. The mixture was transferred to a large separatory funnel and extracted with several portions of chloroform. The organic layer was dried over magnesium sulfate, evaporated on a flash evaporator, and distilled: bp 133° (0.2 mm); yield, 46.7 g, 56.5%.

3-Methyl-3-(4-pyridyl)-1-chlorobutane, 13b. The same procedure and work-up were followed as given above for 2-methyl-2-(4-pyridyl)-1-chloropropane, **10b**. The alcohol, **3a** (46.7 g, 0.282 mol), was dissolved in chloroform (100 ml) and treated with thionyl chloride (40 g, 0.34 mol) in chloroform (50 ml): yield, 40.0 g, 77.4%; bp 80° (0.07 mm). *Anal.* Calcd for $C_{10}H_{14}NCl$: C, 65.39; H, 7.68; N, 7.63; Cl, 19.30. Found: C, 65.19; H, 7.47; N, 7.30; Cl, 19.43.

3-Methyl-3-(2-pyridyl)-1-butanol, 14. This compound was prepared using a procedure identical with that described for **13a**. To a suspension of sodamide (24.1 g, 0.62 mol) in liquid ammonia (350 ml) was added 2-isopropylpyridine (32 g, 0.271 mol). After stirring for 1 hr, ethylene oxide (24 g, 0.55 mmol) was added. The mixture was stirred an additional hour and worked up as above: yield, 9.1 g, 20.3%; bp 110° (5 mm). *Anal.* Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48; O, 9.68. Found: C, 72.55; H, 9.37; N, 8.20; O, 9.63.

1-Methoxy-3-methyl-3-(2-pyridyl)butane, 15. Alcohol **14** (12.3 g, 0.075 mol) was dissolved in benzene (50 ml) and stirred with sodium hydride (3.5 g, 56% in wax, 0.081 mol) under argon, for 2 hr. Methyl iodide (11.5 g, 0.815 mol) was slowly added so that the solution was maintained at a gentle reflux. The mixture was worked up by filtering off the sodium iodide and wax and extracting into chloroform. The mixture was concentrated on a flash evaporator and distilled: bp 69–70° (4 mm); yield, 9.3 g, 65.3%; nmr data, aromatic multiplets τ 1.61, 2.82, oxymethylene 6.86 (J = 7.0 Hz), methylene 8.04 (J = 7.0 Hz); *gem*-dimethyls 8.67, methoxy 6.90. *Anal.* Calcd for $C_{11}H_{17}NO$: C, 73.69; H, 9.56; N, 7.82; O, 8.93. Found: C, 73.61; H, 9.59; N, 7.88; O, 9.11.

Lithium Metal Cleavage of 3-Methyl-3-(2-pyridyl)-1-methoxybutane 15. To a 30-ml vial closed with a stopcock and flushed with argon was added a solution of **15** (0.25 g, 1.4 mmol) in THF (1.4 ml) and, under a stream of argon, small pieces of lithium wire (0.5 g, 0.13 g-atom). Several pieces of broken glass were added to scratch the lithium, and the system was closed and stirred using a magnetic stirrer. The solution rapidly became red-brown; stirring was continued overnight. The next day the solution had become yellow brown and solids had precipitated. Analysis of the hydrolysate by vpc showed only starting material present.

Attempt to Prepare 1-Lithio-2-methyl-2-(2-pyridyl)propane, 25. The reaction of 2-methyl-2-(pyridyl)-1-chloropropane, **10b** (8.5 g, 0.05 mol), with excess lithium (2.0 g, 0.7 g-atom) in THF (100 ml) and TMED (5.8 g, 0.05 mol) at 25° gave no evidence for formation of the title compound. After the mixture had been stirred for several hours, it became a very deep red. An nmr spectrum showed the presence of faint lines in the vinyl region, but none in the alkyl metal region. The solution was poured over Dry Ice (50 g) and hydrolyzed with water (30 ml). This mixture was extracted into

chloroform, dried over magnesium sulfate, and recrystallized from chloroform–petroleum ether. The mass spectrum showed that the major product had a mass of 267, and that major fragments occurred at 253, 120, and 134. The parent ion was assigned the structure **26**.

Attempt to Prepare 3-Methyl-3-(4-pyridyl)butylmagnesium Chloride. A solution of chloride **13b** (0.55 g, 3.0 mmol) in THF (1.0 ml) was slowly added with stirring to a small argon-flushed tube maintained under positive argon pressure, containing magnesium (0.50 g, 20 mmol), THF (2.0 ml), 1 drop of dibromoethane, and a magnetic stirring bar, and fitted with a condenser. After a few drops of the chloride solution was added, the mixture was heated until it turned red-brown. The chloride solution was then added slowly over a 0.5-hr period, and the resulting mixture stirred with heating an additional 0.5 hr. A sample (0.1 ml, 0.1 mmol) was removed for nmr study and injected into an argon-flushed nmr tube fitted with a serum cap. The spectrum showed, in addition to the starting material, 4-isopropylpyridylmagnesium chloride lines at τ 3.74 and 4.90 (J = 7.0 Hz) and a singlet attributed to ethylene at τ 4.75. There was no sign of any Grignard methylene multiplet in the upfield region.

Using a 10-μl syringe, ethyl chloroformate (10 μl, 0.125 mol) was added to the nmr tube. A new spectrum developed, consisting of, in addition to the isopropylpyridine anion lines, a set of doublets at τ 3.21 and 4.24 (J = 8.67 Hz). Addition of another 10 μl of ethyl chloroformate caused the anion lines to disappear and an increase in intensity of the new doublets. The chemical shifts and coupling constants of these new lines were identical with those of 1-carboethoxy-4-(isopropylidene)-1,4-dihydropyridine **23**. Attempts to isolate this compound from solution were unsuccessful.

1-Carboethoxy-4-(isopropylidene)-1,4-dihydropyridine, 23. To a 250-ml, three-necked, round-bottomed flask fitted with a condenser and dropping funnel was added 4-isopropylpyridine (10.0 g, 0.0824 mol) dissolved in THF (80 ml) while the system was maintained under positive argon pressure. While the system was stirred, using a magnetic stirrer, ethyl chloroformate (6.62 ml, 0.083 mol) was added through the dropping funnel. The solution was stirred for 0.5 hr. To the resulting slurry was added triethylamine (11.7 ml, 0.083 mol) with stirring. The solution quickly became homogeneous and stirring was continued for 1 hr. The mixture was then hydrolyzed with water (20 ml), extracted into chloroform (100 ml), dried over magnesium sulfate, concentrated on a flash evaporator, and distilled, bp 95° (0.07 mm). The liquid quickly became a white solid upon refrigeration and was found to darken rapidly in the presence of oxygen: yield, 8.30 g, 55.4%; M^+ = 193; nmr data, vinyl protons τ 3.24, 4.23 (J = 8.67 Hz); ethyl group, 5.76, 8.68 (J = 7.5 Hz); *gem*-dimethyls, 8.32.

Attempt to Prepare 1-Lithio-3-methyl-3-(4-pyridyl)butane. To a suspension of lithium (0.5 g, 0.133 g-atom) in THF (2.0 ml) in a small argon-flushed vial was added a solution of chloride **13b** in THF (1.0 ml) over a 0.5-hr period. The mixture was stirred another 4 hr, after which 90% of **13b** had fragmented to 4-isopropylpyridyllithium: nmr data, aromatic AA'BB' of starting material, τ 1.50, 2.73; AA'BB' of isopropylpyridyllithium, 3.50, 5.74.

2-Methyl-2-(4-pyridyl)-1-propylmagnesium Chloride, 27, and 2-Methyl-2-(2-pyridyl)-1-propylmagnesium Chloride, 30. Fresh DuPont THF was dried and distilled from lithium aluminum hydride into a solution of butylmagnesium bromide in THF. The THF (100 ml) was then distilled from the Grignard reagent, using a Newman condenser, into an argon-flushed three-necked, 350-ml, round-bottomed flask fitted with a dropping funnel and a magnetic stirring bar and containing excess triply sublimed magnesium (10 g, 0.042 g-atom). Part of the THF (20 ml) was withdrawn using an argon-flushed hypodermic syringe, and added to **10b** or **12b** (10.0 g, 0.059 mol) in the dropping funnel. To the solution was added 1,2-dibromoethane (0.65 g, 35 mmol), and the dropping funnel was shaken to assure thorough mixing. The THF in the flask was brought to reflux with stirring and the solution of chloride was added dropwise over a period of 1.5 hr, while the system was maintained under positive argon pressure. After one additional hour's refluxing, the solution had turned dark red.

Bis[2-methyl-2(4-pyridyl)propyl]mercury, 28. The dialkyl mercury compound was prepared from the Grignard reagent **27** in THF using the method of Fraenkel and Dix.[8] After two recrystallizations from CCl_4 the melting point was 103°. The yield, based on mercuric bromide, was 24.5%. *Anal.* Calcd for $C_{18}H_{24}HgN_2$: C, 46.10; H, 5.16; N, 5.97; Hg, 42.77. Found: C, 46.65; H, 5.56; N, 6.13; Hg, 41.59.

2-Methyl-2-(4-pyridyl)propyllithium, 29. All attempts to prepare this lithium compound from the chloride in pentane according to the methods of Applequist[28] and Gilman[29] failed. The solution had no titer and contained only starting material.

Tetrahydrofuran was used to dissolve the wax from 2 g (0.086 mol) of 30% lithium dispersion in wax in a small stopcock vial attached to a 24–40 joint. The THF solution of wax was syringed out. Fresh THF (2 ml) was distilled in from $LiAlH_4$ and a solution of bis[2-methyl-2-(4-pyridyl)propyl]mercury in 2 ml of THF was added using a syringe. The suspension was stirred with heating for 1 hr. The resulting dark red solution was filtered and sealed in an nmr tube. The CH_2Li peak appeared at τ 9.94. There was no change in the aromatic region. Titration indicated approximately 100% conversion to the lithium compound. A nmr spectrum of the hydrolyzate indicated that it was essentially all 4-*tert*-butylpyridine.

Mercury compound **28** (0.4 g, 0.9 mmol) was dissolved in 5 ml of toluene (distilled from CaH_2) and injected into a vial containing a suspension of lithium (1 g, 0.1 mol) in 2 ml of toluene. The mixture was heated for 0.5 hr and stirred for 24 hr. A light yellow solution was produced having a CH_2Li peak at τ 9.58. Titration indicated essentially complete conversion to the lithium compound.

1-Carboethoxy-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine, 32. Using a syringe flushed with argon, a 1 M solution of Grignard reagent **27** (148 ml, 0.148 mol) in THF was transferred to a dry, argon-flushed, three-necked, 500-ml, rounded-bottomed flask, fitted with a condenser, dropping funnel, and magnetic stirrer. Ethyl chloroformate (12.7 ml, 0.160 mol) was added slowly from the dropping funnel so as to maintain a gentle reflux. The mixture was stirred for 0.5 hr. To this mixture was slowly added a saturated aqueous solution of ammonium chloride (10 ml). The hydrolyzed solution was then allowed to stir until a convenient work-up time, usually overnight. The mixture was worked up by filtering off any magnesium salt slurry, extracting with chloroform, drying over magnesium sulfate, and evaporating the solvent in a flash evaporator. The resulting yellow oil was distilled, bp 99° (0.3 mm), using a short-path distillation head: yield, 15.55 g, 50.8%. *Anal.* Calcd for $C_{12}H_{17}NO_2$: C, 69.64; H, 8.27; N, 6.76; O, 15.43. Found: C, 68.56; H, 8.53; N, 6.94; O, 15.73.

Attempt to Prepare 1-Carboethoxy-2-(1,1-dimethylspirocyclopropyl)-1,2-dihydropyridine. The Grignard reagent **30** from **12b** was prepared as usual by treating **12b** (6.75 g, 40 mmol) with excess triply sublimed magnesium (approx 5 g) in THF (40 ml) using 3 drops of dibromoethane as a catalyst. After the Grignard reagent had been prepared, a solution of ethyl chloroformate (4.35 g, 40 mmol) in THF (20 ml) was added to the solution at −70°, and allowed to stand at room temperature overnight. The mixture was then poured over ice, extracted into chloroform, dried over magnesium sulfate, and distilled: yield, 4.4 g, 50%; M^+ = 207; nmr data, aromatic protons, τ 1.47, 2.66 (m) (J = 7.1 Hz); methylene 7.20; *gem*-dimethyls, 8.55. This compound was identified to be the ester **31**.

1-Carbomethoxy-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine, 33. Following the above procedure exactly, chloride **10b** (8.45 g, 50 mmol), dissolved in THF (25 ml), was used to form Grignard **27** in THF (25 ml). The Grignard solution was treated with methyl chloroformate (5.20 g, 55 mmol) forming the title compound: yield, 6.05 g, 62.2%; M^+ = 193.

1-Benzoyl-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine, 34. Following the same procedure as for **33**, Grignard reagent **27** was prepared in THF and treated with benzoyl chloride (14 ml, 0.121 mol): yield, 9.71 g, 68.7%. The mass spectral analysis indicated that two impurities were present, having molecular weights of 256.0752 and 286.0758. All attempts to separate and identify these compounds were unsuccessful. The parent ion of **35** did appear, as expected, at 239.1339. No elemental analysis could be performed.

1-Acetyl-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine, 35. Following the above procedure, Grignard **27** was prepared from chloride **10b** (8.45 g, 50 mmol) in THF (50 ml) solution. Acetyl chloride (4.74 g, 60 mmol) was added dropwise from a dropping funnel, maintaining a gentle reflux. The solution was worked up as above and distilled: bp 117° (0.8 mm); yield, 2.09 g, 23.6%; M^+ = 177.

1-Trimethylsilyl-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine, 36. Grignard reagent **27** was prepared in the usual manner from chloride **10b** (10.0 g, 59.2 mmol) and transferred away from the magnesium into another flask. Trimethylsilyl chloride

(28) D. E. Applequist and D. F. O'Brien, *J. Amer. Chem. Soc.*, **85**, 743 (1963).

(29) H. Gilman, F. W. Moore, and O. Baine, *ibid.*, **63**, 2479 (1941).

(12.7 g, 0.118 mol) was added at room temperature. All attempts at isolation of this product failed, although it was readily observed in solution in the nmr spectrum.

1-Methoxymethyl-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine. All attempts to prepare this compound, even in solution, by the addition of chlorodimethyl ether to Grignard reagent **27** were unsuccessful.

Alternate Route to 1-Carboethoxy-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine, 32. Bis(2-methyl-2-(4-pyridyl)-1-propyl)mercury **28** (0.235 g, 5 mmol) was dissolved in 1.0 ml of THF in a small closed tube, fitted with a stopcock and magnetic stirring bar, and flushed with argon. After **28** had dissolved, a small amount (0.1 ml, 0.5 mmol) was syringed into an argon-flushed nmr tube. After a spectrum of the starting material was obtained, ethyl chloroformate (8.0 μl, 0.1 mmol) was added, using a microsyringe. An immediate reaction occurred, causing the formation of a white precipitate of $HgCl_2$ and the title compound. The nmr spectrum showed 100% conversion to the spiro compound, and was identical with that taken after the addition of ethyl chloroformate to **37**. The reaction was repeated in CCl_4 using the same proportions, and the same results were obtained.

Alternate Route to 1-Trimethylsilyl-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine, 36. Mercury compound **28** was dissolved in THF as above. Chlorotrimethylsilane (8.0 μl, 6.8×10^{-5} mol) was injected into an nmr tube containing 0.1 ml of solution. A spiro compound was formed immediately, as described above. The nmr spectrum was identical with that formed in the reaction of chlorotrimethylsilane with **27**. In an attempt to observe all of the resonances of this compound, the reaction was repeated in CCl_4. There was no reaction whatever in CCl_4.

General Procedure for the Cleavage of Compound 32 with Organometallic Compounds. In a stopcock vial with a 24–40 joint was placed a small amount of **32** (0.20 g, 1 mmol) and a magnetic stir bar. The stopcock was fitted in place, and the system flamed and flushed with argon. Solvent (1.0 ml) was added, and the mixture was stirred until the **32** had dissolved. A solution of the organometallic reagent (4.0 mmol) was added and stirred for 0.5 hr at 0°, and an additional 0.5 hr at room temperature. The solution was sampled, and an nmr spectrum was obtained. The chemical shifts of the resulting cleavage mixture are reported in Table IV. The one exception to this procedure was with sodamide, which was added to the **32** solution by opening the 24–40 joint under a stream of argon. To the solution (0.2 ml, 0.2 mmol) in the nmr tube was added an excess of ethyl chloroformate (20 μl, 0.25 mmol). Addition of ethyl chloroformate returned compound **32**.

Dibutylmagnesium. Bis(*n*-butyl)mercury (7.8 g, 25 mmol) dissolved in THF (25 ml) was refluxed with stirring over triply sublimed magnesium (2.0 g, 85 mg-atoms) for 48 hr, in a closed system under argon. The titer was found to be 1.86 *M*, and the nmr spectrum showed a triplet at τ 10.70 (J = 7.9 Hz).

Butylsodium. Butylsodium was prepared by dissolving dibutylmercury (0.157 g, 0.5 mmol) in pentane (10 ml) and stirring it with excess sodium (approx 5 g, 22 mg-atoms) and broken glass in a closed stopcock tube, maintained at 0° under argon. After 1 hr, a suspension of black solid, highly reactive with water, was formed. This suspension was syringed into another tube and used immediately.

2-Methyl-2-(4-pyridyl)propylsodium, 46a. Following a similar procedure to that given above, compound **32** was dissolved in pentane (2.5 ml) and treated with butylsodium (5.0 mmol) suspended in pentane (5.0 ml). Half of the resulting red-black suspension was treated with methyl chloroformate (0.118 g, 1.25 mmol), and stirred for 0.5 hr and hydrolyzed. The solution was extracted into chloroform, dried over magnesium sulfate, and concentrated on a flash evaporator. The resulting oil was examined by nmr and vpc and found to be identical with 1-carbomethoxy-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridine, **33**. The remaining half of the suspension was hydrolyzed and worked up as above. The product was identified by nmr and vpc as 4-*tert*-butylpyridine.

Acid Cleavage of 32. Compound **32** (0.20 g, 1.0 mmol) was dissolved in trifluoroacetic acid-*1-d* (1.0 ml, 13.4 mmol) and stirred for 1 hr. The solution was then neutralized with 10% sodium hydroxide solution, extracted into chloroform, dried over magnesium sulfate, and evaporated in a flash evaporator yielding 4-*tert*-butylpyridine.

1,4-Dilithiobutane. Diethyl ether (35 ml) was syringed into a flamed out 250-ml, round-bottomed flask, sealed with a ST 24–40 joint attached to a stopcock. Under a stream of argon, lithium wire (approx 2 g, 0.7 g-atom) was cut into small pieces and dropped into the flask. This flask was then attached to the ball mill. This mill is of a new design and consists of a taped round-bottomed flask, filled with glass marbles, 1-cm diameter, attached to a flash evaporator unit, and equipped with an apparatus for adding reagents through a mercury sealed stirrer. A solution of 1,4-dibromoethane (7.0 g, 30 mmol) in ether (25 ml) was slowly added to the rapidly rotating ball mill using a hypodermic syringe. The reaction was initiated at 5°, and after it had commenced, the temperature was lowered to −5°, using an ice–salt bath. The addition was complete in about 3 hr, and the ball mill allowed to rotate an additional 1.5 hr. The suspension was transferred to a vial and centrifuged, and a sample was withdrawn into a small syringe for titration. The titer was 0.6 *M*, indicating a 92% conversion to the dilithio compound. The reagent was used immediately or stored at −70°.

Reaction of 1,4-Dilithiobutane with Pyridine and Dibutylmagnesium. To a solution of pyridine (0.147 g, 1.86 mmol) in ether (2.0 ml), maintained at −70° in a Dry Ice–acetone bath, was added dilithiobutane (2.73 ml, 3.71 mmol) prepared as above. The mixture was allowed to warm with stirring to room temperature, when it was observed to contain large amounts of solids. After stirring for 14 hr at room temperature, the solution was completely homogeneous. To this solution was added dibutylmagnesium (4.0 ml, 7.44 mmol) while stirring. The color of the mixture darkened from yellow-brown to red-brown, but nmr spectra taken before and after the addition showed no change in the spectrum of the alkyllithium–pyridine adduct. Nmr spectra were taken of samples of the solution every 24 hr for 4 days, with no noticeable change. The solution was then heated for 6 hr and the spectrum again examined. No change was detected. On extended heating in a vial at 100° the sample decomposed to 2-*n*-butylpyridine.

1-Carbethoxy-2,4-di-*tert*-butyl-1,2-dihydropyridine, 50. To a mixture of 4-*tert*-butylpyridine (1.01 g, 7.5×10^{-3} mol) with 20 ml of a 0.75 *M* solution of *tert*-butylmagnesium chloride in tetrahydrofuran (1.50×10^{-2} mol) was added ethyl chloroformate (0.81 g, 7.5×10^{-3} mol) at 0° over 10 min. The reaction mixture was hydrolyzed with 1 ml of water at 0°, the white precipitate was washed with tetrahydrofuran, and the washings were added to the organic material. After drying this with $MgSO_4$ and removing the solvent, **50** was distilled at 110°: 0.0014 mm in 55% yield; λ_{max} 2921 Å; ir at 3000, 1700, 1365, 1300–1275 cm^{-1}, respectively; mass spectrum 265 (M^{+1}), 250, 220, 208, 180, 136, 135, 120.

Addition of Butyllithium to 29. To a small stopcock vial flushed with argon was added a solution of **29** (1 *M*, 5 ml, 5 mmol) in THF, using a hypodermic syringe. Butyllithium (1.4 *M*, 7.25 ml, 10 mmol) in hexane was then added by means of another argon-flushed syringe. An nmr spectrum taken immediately after this addition, showed no change in **29**. Both the **29** and the butyllithium were clearly visible. After 4 days of standing at room temperature, this solution was again sampled and its nmr spectrum obtained. It showed no change whatever. After 1 week the butyllithium had disappeared, by deprotonating the THF, but no change had appeared in the **29**.

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