order rate constants varied less than 10% on doubling or halving the concentrations of **2**.
(16) F. Hommes and R. W. Estabrook, *Biophys. Res. Commun.*, 11, 1 (1963).
(17) Data now in hand indicate less than a 10% change in reaction rate constant on changing from polar to nonpolar solvents.
(18) J. Kuthan, N. V. Koshirma, and M. Ferles, *Collect. Czech. Chem. Commun.*, **35**, 3825 (1970).
(19) (a) R. F. Williams, S. Shinkai, and T. C. Bruice, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 1763 (1975); (b) T. C. Bruice and Y. Yano, *J. Am. Chem. Soc.*, **97**, 5263 (1975).

T. J. van Bergen, Titi Mulder, Richard M. Kellogg*
Department of Organic Chemistry, University of Groningen
Zernikelaan, Groningen, The Netherlands
Received December 18, 1975

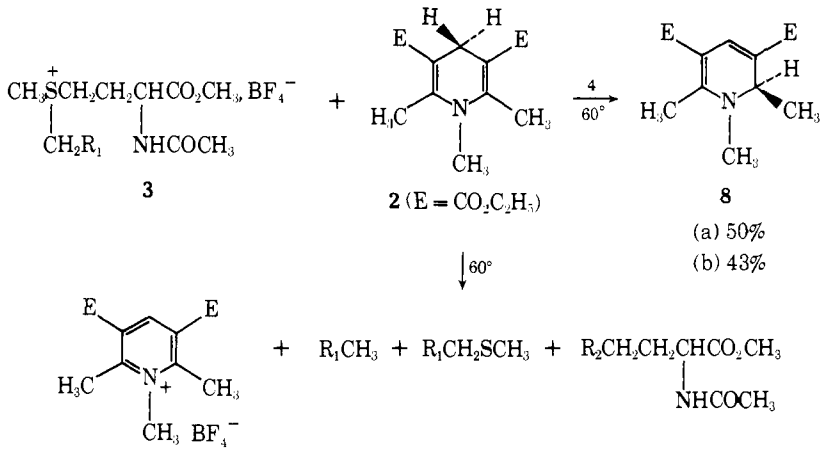
Hydride Transfer from NADH Models to sp^3-Hybridized Carbon. Competition with Enamine Alkylation

Sir:

Following the initial recognition that reactions of simple 1,4-dihydropyridines,[1] including the readily accessible Hantzsch esters,[2,3] can be used to mimic certain aspects of hydride transfer from NAD(P)H, an avalanche of examples has accumulated in the literature.[4] Conspicuously absent (to the best of our knowledge) among these many reactions is any demonstration of reduction of a sp^3-hybridized carbon via (formal) nucleophilic displacement by hydride derived from the dihydropyridine. We report here the discovery of examples of such reactions using either sulfonium salts or activated halides as substrates. For several important biological processes NAD(P)H reduction of sp^3-carbon provided with a good leaving group may reasonably be postulated (direct reduction of a free carbonium ion being less likely). Examples suggest themselves in the in vivo (overall) methylations by *S*-adenosylmethionine (**1**)[5] of unactivated double bonds in fatty acids (the reaction, however, involves initial methylation and subsequent reduction)[6a,b] and steroids[7,8] as well as the presqualene alcoholpyrophosphate–squalene interconversion[9] and related models of monoterpene biosynthesis.[10]

When **2** was allowed to react in C_3D_6O at 60° with the protected methionine sulfonium salts (**3a, b**),[11,12] a quantitative reaction ensued with the results shown in Scheme I.[13] The desired reduction is clearly taking place. With benzyl sulfonium salt (**3a**), hydride incorporation is (surprisingly)

Scheme I



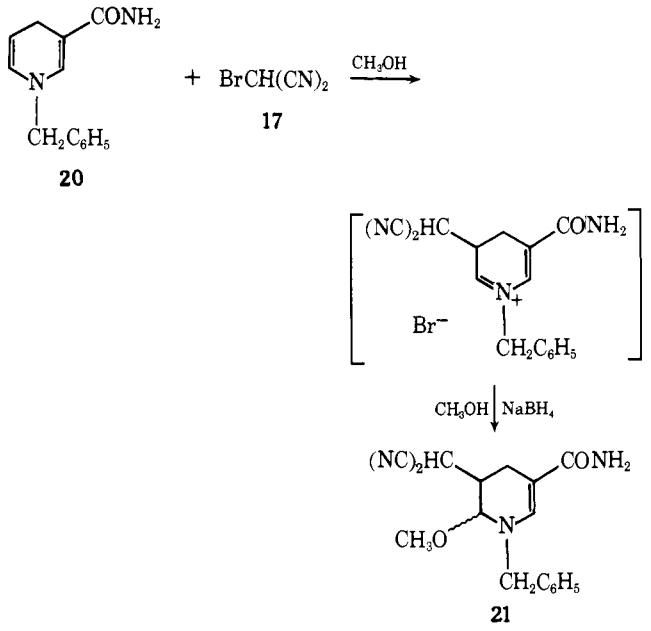
		4	**5**	**6**	**7**	
(**3a**)	$R_1 = C_6H_5$	(40%)	(0%)	(41%)	$R_2 = H$[14] (33%)	$R_2 = CH_3S$ (0%)
(**3b**)	$R_1 = C_6H_5CO$—	(53%)	(25%)	(31%)	(26%)	(27%)

Table I. Reductions by 3,5-Dicarboethoxy-1,2,6-trimethyl-1,4-dihydropyridines (**2**)[13]

	Sulfonium salt $R_1S^+R_2R_3$				% reduction products		% transhydrogenation[4c]		
	R_1	R_2	R_3	% oxidation product **4**	R_1H	R_2–S–R_3	1,2-DHP	**8**	Unreacted substrate
9	$C_6H_5COCH_2$	CH_3	CH_3 X^- [a]	40	33	33	53	**9**	57
10	$C_6H_5COCH_2$	CH_3	C_6H_5 Y^-	37	34	38	52	**10**	57
11	$CH_2CO_2CH_3$	CH_3	C_6H_5 Y^-	13	10	14	70[b]	**11**	75
12	CH_3	C_6H_5	C_6H_5 X^-	18	[c]	20	86	**12**	86
13	$C_6H_5CH_2$	CH_3	CH_3 Y^-	3–5	3–5[d]	3–5	86[e]	**13**	93
14	$C_6H_5CH_2$	CH_3	C_6H_5 Y^-	42	11[d]	82	11	**14**	8
15[g]	$C_6H_5CH_2$	C_6H_5	C_6H_5 Y^-	54	3[d]	100	[f]	**15**	[f]
Alkyl halides									
16[g]	$BrCH_2COC_6H_5$			39	35 (**5b**)		35[h]	**16**	71
17[g]	$BrCH(CN)_2$			63	70[i] (**18**)		[f]	**17**	[f]

[a] $X^- = ClO_4^-$, $Y^- = BF_4^-$, solvent C_3D_6O, temp 60°. [b] **2** remained in 11% yield. [c] No attempts were made to detect methane. [d] The radical coupling product, bibenzyl, was not present. [e] **2** remained in 10% yield. [f] Not detectable. [g] Carried out at room temperature. [h] **2** remained in 26% yield. [i] Lower limit for yield.

Scheme II



exclusively at a methionine carbon whereas with phenacyl salt (**3b**) both the methionine and phenacyl methylenes accept hydride. Reduction is prevented from proceeding to completion by the previously discovered competing transhydrogenation of **2** to **8** catalyzed by product **4**;[4c] this reaction is irreversible and **8** also fails to react with the sulfonium salts, which are recovered unchanged in yields equivalent to that of **8.** The isomerization proceeds, of course, with a steadily increasing rate as the concentration of **4** increases with progress of the reaction.

The sulfonium salts **9–13**[15] listed in Table I also react cleanly and essentially quantitatively as shown. One notes that the presence of electron withdrawing groups on the carbon to be reduced enhances the hydride accepting ability but this is not an absolute requirement as witnessed by **12** and **13,** wherein the sp^3 carbon is inefficiently but unmistakably reduced. In a departure in pattern, **14** and **15** give poor material balances (note that the sum of **4** + **8** is much less than 100%) and indeed intractable material is formed. We believe this to be an alkylation product of **2,** the contention of which is supported by further results (see below).

Phenacyl bromide (**16**) reacts smoothly but not too rapidly with **2** whereas the better activated halide, bromomalonitrile (**17**),[16] is consumed completely within the time of mixing giving in good yield malonitrile (**18**).[17] This observation coupled with the fact that **9–11** fail to exchange protons for deuterium in deuterated acetone[18] makes unlikely that either a sulfur ylide (or an enol in carbonyl activated substrates) participates in the reaction.

Structural changes in the 1,4-dihydropyridine affect the mode of reaction. Removal of the *N*-methyl group of **2** and replacement by hydrogen leads to initial reduction of, for example, **10,** but thereafter side reactions ensue owing to the protons being released to the medium.[19] With 1-benzyl-1,4-dihydronicotinamide (**20**), presumably a better NADH mimic,[2] total consumption of **20** and the substrates **10, 12, 14,** and **15** is seen but no reduction products can be detected.[19] Working on the hypothesis that this is due to alkylation of C-5 of **20**,[20] we allowed **17,** the most reactive substrate, to react with **20** in methanolic solution; sodium borohydride (which acts as a base) was then added. Workup gave **21** in 48% yield, mp 112–114 °C, apparently a single diastereomer of undetermined stereochemistry.[21] In contrast to the reaction with **2,** no malonitrile could be detected in this case. The reaction course must surely be that shown in Scheme II.

In summary, we have uncovered a variety of previously unrecognized examples of reduction by 1,4-dihydropyridines and some of the structural factors governing the efficiency and type of reaction involved have been revealed.[22] Further investigations of the scope and mechanism (direct hydride displacement or initial electron transfer)[23] are underway.

Acknowledgment. The Netherlands Organization for the Advancement of Pure Research (Z.W.O.) administered through the Office for Chemical Research in the Netherlands (S.O.N.) has provided a fellowship for T.J.v.B.

References and Notes

(1) (a) P. Karrer, B. H. Ringier, J. Büchi, H. Fritzsche, and U. Solmssen, *Helv. Chim. Acta,* **20,** 55 (1937), and succeeding papers; (b) G. W. Rafter and S. P. Colowich, *J. Biol. Chem.,* **209,** 773 (1954); (c) R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *J. Am. Chem. Soc.,* **79,** 712 (1957).

(2) D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.,* 77, 2261 (1955).

(3) Review of dihydropyridine chemistry: U. Eisner and J. Kuthan, *Chem. Rev.,* **72,** 1 (1972).

(4) Reviews: (a) H. Sund, H. Diekmann, and K. Wallenfels, *Adv. Enzymol.,* **26,** 115 (1964); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. 2, W. A. Benjamin, New York, N.Y., 1966, p 301; (c) also T. J. van Bergen, T. Mulder, and R. M. Kellogg, preceding paper in this issue.

(5) (a) G. De La Haba, G. A. Jamieson, S. H. Mudd, and H. H. Richards, *J. Am. Chem. Soc.,* **81,** 3975 (1959); (b) A. Kjaer, *Tetrahedron,* **30,** 1551 (1974); (c) G. A. Maw, *Sulfur Org. Inorg. Chem.,* **2,** 137 (1972).

(6) (a) J. H. Law, *Acc. Chem. Res.,* **4,** 199 (1971); (b) Y. Akamatsu and J. H. Law, *J. Biol. Chem.,* **245,** 701 (1970).

(7) (a) E. Lederer, *Experientia,* **20,** 473 (1964); (b) E. Lederer, *Q. Rev., Chem. Soc.,* **23,** 453 (1969).

(8) Mechanisms of methylation and NAD(P)H involvement: (a) S. Pohl, J. H. Law, and R. Ryhage, *Biochim. Biophys. Acta,* **70,** 583 (1963); (b) G. Jaurégulberry, J. H. Law, J. A. McCloskey, and E. Lederer, *Biochemistry,* **4,** 347 (1965); (c) also T. Cohen, G. Herman, T. M. Chapman, and D. Kuhn, *J. Am. Chem. Soc.,* **96,** 5627 (1974).

(9) (a) W. W. Epstein and H. C. Rilling, *J. Biol. Chem.,* **245,** 4597 (1970); (b) J. W. Cornforth, *Chem. Soc. Rev.,* **2,** 1 (1973).

(10) B. M. Trost, P. Conway, and J. Stanley, *Chem. Commun.,* 1639 (1971).

(11) From (*dl*)-*N*-acetylmethionine methyl ester and the respective halide following the method of V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.,* **94,** 2942 (1961). The mixture of diastereomers was used.

(12) The analogous salts from free (*dl*)-methionine (method of H. Tsugio, K. Hisao, and F. Kenichi, *Chem. Abstr.,* **70,** 28546b (1969)) undergo, under the reaction conditions, an intramolecular cyclization to (*dl*)-α-amino-α-butyrolactone and sulfide. See also (a) T. F. Lavine, N. F. Floyl, and M. S. Cammaroti, *J. Biol. Chem.,* **207,** 107 (1954); (b) F. Schlenk and J. L. Damko, *Radiat. Res.,* **16,** 327 (1962).

(13) Correct elemental analyses or exact mass spectral measurements in accord with theory were obtained for all new compounds. Reactions were carried out in duplicate in the indicated solvent at 0.33 M concentration and were followed as a function of time. Description of the analytical techniques used (combined ^{1}H NMR/GLC) and of control experiments will be deferred to a full publication. Reported yields are ±5% accurate.

(14) J. B. Jones, T. Kunitake, C. Niemann, and G. E. Hein, *J. Am. Chem. Soc.,* **87,** 1777 (1965).

(15) Preparation of sulfonium salts according to ref 11 and (a) M. Takaku, Y. Hayasi, and H. Nozaki, *Tetrahedron,* **26,** 1243 (1970); (b) A. W. Johnson and R. T. Amel, *J. Org. Chem.,* **34,** 1240 (1969); (c) A. J. Speziale, C. C. Tung, K. W. Ratts, and A. Yao, *J. Am. Chem. Soc.,* **87,** 3460 (1965).

(16) P. Boldt, L. Schulz, and J. Etzemüller, *Chem. Ber.,* **100,** 1281 (1967).

(17) For hydride reductions of alkyl halides, see (a) J. E. Johnson, R. H. Blizzard, and H. W. Canhart, *J. Am. Chem. Soc.,* **70,** 3664 (1948); (b) J. Zabicky and S. Ehrlich-Rogozinski, "The Chemistry of the Carbon-Halogen Bond", Part I, Wiley, New York, N.Y., 1973, p 143.

(18) See also: H. Nozaki, K. Kondô, and M. Takaku, *Tetrahedron Lett.,* 251 (1965).

(19) This and other points will be discussed in a full publication.

(20) For pertinent literature on alkylations of dihydropyridines and related structures by sulfonium salts as well as other alkylating agents, see (a) H. R. Horton and J. W. Tucher, *J. Biol. Chem.,* **245,** 3397 (1970); (b) C. P. Heinrichs, S. Adam, and W. Arnold, *FEBS Lett.,* **33,** 181 (1973); (c) U. K. Pandit, R. A. Gase, F. R. MasCrabé, and M. J. de Nie-Sarink, *J. Chem. Soc., Chem. Commun.,* 211 (1975); (d) A. G. Anderson and G. Berkelhammer, *J. Am. Chem. Soc.,* **80,** 992 (1958); (e) C. S. Giam and J. L. Stout, *Chem. Commun.,* 478 (1970); (f) C. S. Giam and S. D. Abbott, *J. Am. Chem. Soc.,* **93,** 1294 (1971).

(21) Analytical, ^{1}H NMR, ^{13}C NMR, ir, and uv data are fully in accord with this structure.[19]

(22) Reductions of sulfonium salts by lithium aluminum hydride are known, but there is little basis for comparing the direction of cleavage with that observed by us: S. Asperger, D. Stefanovi, D. Hegedic, D. Pavlorric, and L. Klasinc, *J. Org. Chem.,* **33,** 2526 (1968).

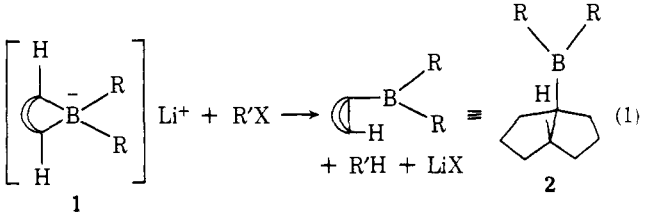
(23) (a) R. F. Williams, S. Shinkai, and T. C. Bruice, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 1763 (1975); (b) T. C. Bruice and Y. Yano, *J. Am. Chem. Soc.*, **97**, 5263 (1975).

T. J. van Bergen, Richard M. Kellogg*
Department of Organic Chemistry
University of Groningen
Zernikelaan, Groningen, The Netherlands
Received December 18, 1975

The Facile Rearrangement of Lithium Dialkyl-9-borabicyclo[3.3.1]nonane "Ate" Complexes via Hydride Transfer. A Simple Synthetic Route to *cis*-Bicyclo[3.3.0]oct-1-yldialkylboranes and Derivatives

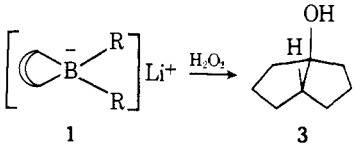
Sir:

Lithium "ate" complexes (**1**), derived from the addition of alkyllithiums to representative *B*-alkyl-9-borabicyclo-[3.3.1]nonanes (*B*-alkyl-9-BBN), react with a variety of reducible organic substances to form *cis*-bicyclo[3.3.0]oct-1-yldialkylboranes (**2**). This reaction apparently proceeds by the transfer of one of the bridgehead hydrogens on the "ate" complex to the organic substrate followed by subsequent or concurrent migration of the bridge bond from boron to carbon (eq 1). This sequence provides not only a novel means for reducing aldehydes, ketones, alkyl halides, and acid chlorides but also a remarkably simple route to the *cis*-bicyclo[3.3.0]oct-1-yl system.



1 2 (1)

Recently we noted that hydrogen peroxide oxidation of lithium dialkyl-9-BBN "ate" complexes proceeds anomalously, giving rise to a mixture containing variable quantities of *cis*-bicyclo[3.3.0]octan-1-ol (**3**) (eq 2), instead of the expected *cis*-1,5-cyclooctanediol.[1] A rearrangement with formation of a new carbon–carbon bond was evidently



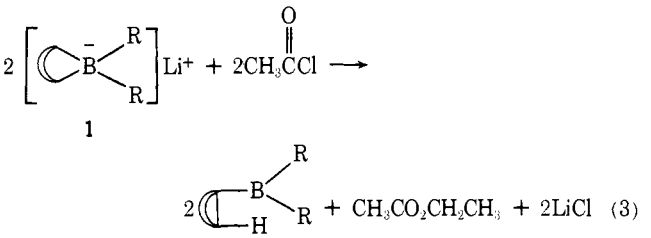
1 3 (2)

involved. We undertook to explore the possibility of achieving this rearrangement without the destruction of the postulated organoborane intermediate (**2**). Such organoboranes could provide simple routes to many compounds incorporating the *cis*-bicyclo[3.3.0]oct-1-yl moiety.[2,3]

Almost concurrently with our initial report of the anomalous oxidation of these "ate" complexes, it was reported that the same reagents were capable of reducing certain alkyl halides.[4] Consequently, we examined such halide reductions and established that the rearranged organoborane is indeed produced. Unfortunately, these reductions proceeded well only in hydrocarbon solvent. The presence of even small amounts of ethers inhibited the reaction. This became important in reactions utilizing methyllithium, soluble only in ethers. Removal of the ether to facilitate the desired reaction proved difficult.

Accordingly, another substrate was sought which would react with the "ate" complexes in the presence of ether. Simple aldehydes and ketones were reduced in hydrocarbon solvents, but the reaction was incomplete and sluggish when ether was present. An exception was chloral, which reacted rapidly even in the presence of ether.

The use of acetyl chloride as the reducible substrate offered major advantages. The reaction in hydrocarbon, as well as mixed ether–hydrocarbon solvent, was very vigorous. Analysis of the reaction mixture by GLC showed an essentially quantitative formation of the rearranged organoborane, while analysis by ^{1}H NMR indicated a high yield of ethyl acetate. Apparently 2 equiv of the "ate" complex (**1**) react with 1 equiv of acetyl chloride producing the rearranged organoborane (**2**) and lithium ethoxide. The ethoxide is then scavenged by the remaining equivalent of acetyl chloride to form the ester (eq 3).[5] This result was substantiated by the isolation of *n*-hexyl caproate from a similar reaction with hexanoyl chloride. We used this acid chloride route to examine the generality of this synthesis of *cis*-bicyclo[3.3.0]oct-1-yldialkylboranes. The results are summarized in Table I.[6]



1 (3)

The preparation of *cis*-bicyclo[3.3.0]oct-1-ylethylmethylborane is representative.[7] To an oven-dried, flamed-out, nitrogen-flushed, 50-ml flask fitted with a septum inlet, mag-

Table I. Preparation and Properties of *cis*-Bicyclo[3.3.0]oct-1-yldialkylboranes (**2**)

Alkyl groups					Physical data			
							^{11}B NMR	
R[a]	R'[b]	% yield[c] (GLC)	% yield[d] (Isolated)	% purity[e] (GLC)	bp, °C	(mmHg)	R_3B,[f] δ	"Ate" complex,[g] δ
Methyl	Methyl	96	94	93[h]	76–78	(20)	−81.9	+20
Ethyl	Methyl	99	97	97	28–32	(0.005)	−82.7	+20.4
Isopropyl	Methyl	92	97	94[h]	39–43	(0.005)	−81.3	+18.2
n-Butyl	Methyl	93	—	—	—		−82.7	+20.8
Methyl	*n*-Butyl	—	95	99	53–56	(0.005)	−82.3	+20.8
tert-Butyl	Methyl	91	97	86[h]	46–49	(0.005)	−80.3	+16.7
n-Butyl	*n*-Butyl	—[i]	94	—[i]	65–68	(0.005)	−81.8	+18.5

[a] *B*-R-9-BBN. [b] R'Li. [c] Reaction scale 4 mmol. [d] Reaction scales of 15–35 mmol. [e] ^{13}C NMR showed only one set of peaks for the bicyclooctyl ring. [f] ^{11}B NMR shift from BF_3:OEt_2 in ppm for **2**. [g] ^{11}B NMR shift from BF_3:OEt_2 for the "ate" complex precursor (**1**). [h] The major impurity appears to be the *B*-R-9-BBN. [i] The organoborane decomposes in the GLC.