ether gave pure **1a** (30 mg, 15%): mp 188–189 °C; NMR[7] (acetone-d_6 + D_2O) δ 3.04 (s, 3, CH_3), 4.38 (d of q, 1, H_3), 4.78 (d, 1, H_4), 6.08 (d of d, 1, H_2), 7.25–8.25 (m, 7, H_1 and aromatic), 8.73 (s, 1, H_{12}); $J_{1,2}$ = 10, $J_{2,3}$ = 3, $J_{3,4}$ = 12 Hz.

***trans*-3,4-Dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydro-7-methylbenz[*a*]anthracene (2).** A solution of **1a** (23 mg, 0.083 mmol) and *m*-chloroperbenzoic acid (230 mg) in 25 mL of dry THF was stirred under N_2 for 2 h at room temperature. The solution was diluted with ether, washed twice with 10% aqueous NaOH solution and water, and dried. Evaporation of the solvent (avoiding heating), followed by trituration with ether, gave **2** (13 mg, 57%) as a white solid: mp 183–185 °C; NMR (acetone-d_6 + D_2O) 270 MHz δ 3.0 (s, 3, CH_3), 4.13 (q, 1, H_2), 4.31 (q, 1, H_3), 4.88 (d, 1, H_4), 5.40 (d, 1, H_1), 7.38–8.41 (m, 6, aromatic), 8.85 (s, 1, H_{12}); $J_{1,2}$ = 4.7, $J_{3,4}$ = 8.0, $J_{2,3}$ = 1.5 Hz.

***trans*-1,2-Dihydroxy-*anti*-3,4-epoxy-1,2,3,4-tetrahydro-7-methylbenz[*a*]anthracene (4a).** Epoxidation of **3a** (23 mg, 0.08 mmol) was carried out by the procedure employed for the analogous reactions of **1a**. Evaporation of the solvent (avoiding heating) gave crude **4a** (20 mg, 74%) which showed one major peak (80%) on LC on a Dupont Sil column (THF–heptane, 45:55). The major peak was collected and identified as **3a**: NMR (acetone-d_6 + D_2O) 270 MHz, δ 3.14 (s, 3, CH_3), 4.03 (d, 1, H_3), 4.28 (d, 1, H_4), 4.72 (br s, 1, H_2), 5.42 (apparent s, 1, H_1), 7.53–7.59 (m, 2, $H_{9,10}$), 7.75 (d, 1, H_5), 8.17 (d, 1, H_{11}), 8.37 (d, 1, H_8), 8.42 (d, 1, H_6), 8.82 (s, 1, H_{12}); $J_{1,2} \simeq 1$, $J_{2,3}$ = 0.98, $J_{3,4}$ = 3.73, $J_{5,6}$ = 8.96, $J_{8,9}$ = 8.11, $J_{10,11}$ = 8.63 Hz.

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Registry No. **1a**, 64521-14-8; **1b**, 71988-88-0; **2**, 64625-66-7; **3a**, 64521-13-7; **3b**, 71988-89-1; **5**, 72016-70-7; **6a**, 71988-90-4; **6b**, 71988-91-5; **6c**, 71988-92-6; **6d**, 71988-93-7; **7**, 71988-94-8; **8a**, 71988-95-9; **9a**, 71988-96-0; **9b**, 71988-97-1; **10**, 71964-75-5; **11**, 71964-76-6; **12**, 71964-77-7; **13**, 71988-98-2; **14a**, 71988-99-3; **14b**, 71989-00-9; **14c**, 71989-01-0; **15**, 71989-02-1; **16**, 71989-03-2; **17a**, 71989-04-3; **17b**, 71989-05-4; 3,4,7,12-tetrahydro-7-methylbenz[*a*]anthracene, 71989-06-5; 1,2,7,12-tetrahydro-7-methylbenz[*a*]anthracene, 72016-71-8; 2-acetoxy-3,4-dihydro-7-methylbenz[*a*]anthracene, 72016-72-9; 7-methylbenz[*a*]anthracene, 2541-69-7; benz[*a*]anthracene, 56-55-3; 7-bromobenz[*a*]anthracene, 32795-84-9.

Hydride Transfer from 1,4-Dihydropyridines to sp^3-Hybridized Carbon in Sulfonium Salts and Activated Halides. Studies with NAD(P)H Models[1]

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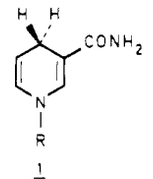
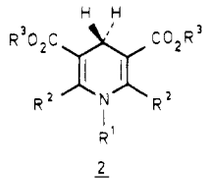
The reactions of 1,2,6-trimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (**2a**), 1-methyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (**2b**), and 1-benzyl-3-acetamido-1,4-dihydropyridine (**1**) with various sulfonium salts have been investigated. On thermal (60 °C) activation **2a,b** react with, for example, methylphenacylphenylsulfonium tetrafluoroborate (**3b**) to give the respective pyridinium salts, acetophenone, and phenyl methyl sulfide. There is some competing isomerization of the 1,4-dihydropyridines to their (nonreactive) 1,2-dihydro isomers, this being catalyzed by the pyridinium salt formed on reduction of the sulfonium salt. Phenacyl-, acetonyl-, and in some cases benzylsulfonium salts can be reduced. The group to which hydride transfer takes place should be electron deficient. These reductions can be initiated at room temperature with visible light (at room temperature pyridinium salt induced isomerization of the 1,4-dihydropyridine to its 1,2 isomer occurs only over a period of several days). The effect of visible light can be enhanced greatly by adding small amounts of dyes to the reaction mixtures. Eosin sodium salt, tetraphenylporphine, and $Ru^{II}(2,2'\text{-bpy})_3Cl_2$ are all capable of increasing the rate of reduction; the last dye is by far the most effective. The results of mechanistic investigations are consistent with the hypothesis that the light-induced reductions are one-electron transfer reactions. In some cases there appears to be a separate thermal mechanism not sensitive to either light or sensitizers. Some sulfonium salts react with dihydropyridines to give the pyridinium salt and sulfide in less than quantitative yield and no reduction products from the sulfonium salt. As determined for the case of the reaction of bromomalonitrile with **1**, and presumably also for other reactions, alkylation of an enamine carbon in the dihydropyridine is involved; the resulting iminium salt has been trapped by methanol and characterized.

The recognition that a 1,4-dihydronicotinamide (**1**) is the chemically active component of NAD(P)H[3] caused a surge of interest in 1,4-dihydropyridines in general. Derivatives of **1** are the most closely related in structure to the coenzyme. However, application of the tool of structural modification for mechanistic investigation is somewhat hampered for derivatives of **1**, owing to serious synthetic difficulties in obtaining such compounds.[4] A partial solution to this problem is found with the symmetrically substituted "Hantzsch esters" (**2**), which are readily synthesized with considerable variation in structure.



1

a) $CH_2C_6H_5$



2

a) $R^1 = R^2 = CH_3$; $R^3 = C_2H_5$

b) $R^1 = R^3 = CH_3$; $R^2 = H$

(1) Part 9 on the chemistry of dihydropyridines. For part 7 see R. H. van der Veen, R. M. Kellogg, A. Vos, and T. J. van Bergen, *J. Chem. Soc., Chem. Commun.*, 923 (1978); for part 8 see J. G. de Vries and R. M. Kellogg, *J. Am. Chem. Soc.*, **101**, 2759 (1979).

(2) (a) The Dow Chemical Co., Terneuzen, The Netherlands; (b) Undergraduate Exchange Student from Hope College, Holland, Michigan.

(3) Reviews of original literature: (a) H. Sund, H. Diekmann, and K. Wallenfels, *Adv. Enzymol. Relat. Subj. Biochem.*, **26**, 115 (1964); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. 2, W. A. Benjamin, New York, 1966, p 301.

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Table I. Reductions by 1,4-Dihydropyridines (DHP)

1,4-DHP	substrate $R^1S^+R^2R^3,BF_4^-$ R^1	R^2	R^3	compd no.	% pyridinium salt	% reduction prod R^1H	% reduction prod R^2SR^3	% 1,2-DHP	% unreacted 3	temp, °C
2a[a]	$C_6H_5COCH_2$	CH_3	CH_3	3a	40	33	33	53	57	60
	$C_6H_5COCH_2$	CH_3	C_6H_5	3b	37	34	38	52	57	60
	$4\text{-}CH_3OC_6H_4COCH_2$	C_6H_5	C_6H_5	3c	60	*b*	60		33	60
	$4\text{-}CH_3OC_6H_4COCH_2$	C_6H_5	CH_3	3d	40	*b*	33		65	60
	$3\text{-}CH_3OC_6H_4COCH_2$	C_6H_5	CH_3	3e	25	20[c]	44	53	56	60
	$2\text{-}CH_3OC_6H_4COCH_2$	C_6H_5	CH_3	3f	47	<5[c]	60	42	40	60
	$4\text{-}NO_2C_6H_4COCH_2$	C_6H_5	CH_3	3g	90	90	100	<5	<5	20
	$3\text{-}NO_2C_6H_4COCH_2$	C_6H_5	CH_3	3h	70	45	80	10	20	20
	$2\text{-}NO_2C_6H_4COCH_2$	C_6H_5	CH_3	3i	61	<5[c]	50	23	50	20
	CH_3COCH_2	C_6H_5	CH_3	3j	13	10	14	70	75	60
	CH_3	C_6H_5	C_6H_5	3k	18	<5	20	86	86	60
	$C_6H_5CH_2$	CH_3	CH_3	3l	4	4	4	86	93	60
	$C_6H_5CH_2$	C_6H_5	CH_3	3m	42	11[c]	82	11	8	60
	$C_6H_5CH_2$	C_6H_5	C_6H_5	3n	54	3[c]	100	<5	<5	60
2b[a]	$C_6H_5COCH_2$	C_6H_5	CH_3	3b	60	60	60	*d*	40	60
		alkyl halides								
2a[a]	$BrCH_2COC_6H_5$				39	35		35	71	20
	$BrCH(CN)_2$				63	70		>5	>5	20

[a] Solvent CD_3COCD_3. [b] Not found. [c] Apparently alkylation of the dihydropyridine occurs. See text. [d] A mixture of 1,2- and 1,4-dihydropyridines is formed; the transformation is reversible in this case.[17b]

Derivatives of 1 and 2, in the absence of catalysts, are not especially potent reductors. However, the *estimated* (in nonaqueous solution) reduction potential of 1 (R = $C_6H_5CH_2$) is E_0 = −361 mV and for 2 (R^1 = R^2 = H; R^3 = C_2H_5) E_0 = −370 mV, both values exceeding that for NADH (in aqueous solution), E_0 = −315 mV.[5] The potential for hydride transfer is present; the challenge is to find proper substrates and to develop suitable catalysts for the reactions.

The mechanisms by which reductions by 1 and 2 can occur are becoming clearer.[6] Catalysis of reductions of carbonyl compounds has been achieved by polarizing the carbonyl group with the aid of a proton or metal ion, especially magnesium or zinc.[7,8] Working along this general line, we recently described 1,4-dihydropyridine-containing "crown ethers" designed to contain both a metal ion and a substrate.[9]

Regardless of the finer mechanistic details, all such reactions involve the formal transfer of hydride from a 1,4-dihydropyridine to an acceptor atom, which in the case of carbonyl compounds and derivatives thereof is sp^2 hybridized. There is no reason to think that this apparent hybridization restriction to trigonal carbon is absolute. Examples of the reduction of sp^3-hybridized carbon atoms suggest themselves in several biochemical systems, an example being the in vivo (overall) reductive methylation of unactivated double bonds in fatty acids[10] by *S*-adenosylmethionine (the reaction involves initial methylation and subsequent reduction). Similar processes occur in steroids.[11-13] The presqualene alcohol pyrophosphate–squalene interconversion[14a,b] and related models of monoterpene biosynthesis provide other possible examples.[14c]

On considering this background, we decided to investigate the feasibility of the transformation depicted in eq 1. Of the various possibilities for the leaving group X, a

(1)

sulfide was predicted to be a likely candidate. This line of thought derived in part from the readiness of a dialkyl

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(6) For pertinent examples, see: (a) J. Hajdu and D. S. Sigman, *J. Am. Chem. Soc.*, **98**, 6060 (1976); (b) D. J. Creighton, J. Hajdu, and D. S. Sigman, *ibid.*, **98**, 4619 (1976); (c) J. Hajdu and D. S. Sigman, *ibid.*, **97**, 3524 (1975); (d) D. J. Creighton, J. Hajdu, C. Mooser, and D. S. Sigman, *ibid.*, **95**, 6855 (1973); (e) J. J. Steffens and D. M. Chipman, *ibid.*, **93**, 6694 (1971).

(7) For examples of this and other recent approaches, see: (a) S. S. Shinkai and T. C. Bruice, *Biochemistry*, **12**, 1750 (1973); (b) U. K. Pandit and F. R. MasCrabé, *J. Chem. Soc. D*, 552 (1971); (c) U. K. Pandit, F. R. MasCrabé, R. A. Gase, and M. J. de Nie-Sarink, *J. Chem. Soc., Chem. Commun.*, 627 (1974); (d) U. K. Pandit, R. A. Gase, F. R. MasCrabé, and M. J. de Nie-Sarink, *ibid.*, 211 (1975); (e) R. A. Gase, G. Boxhoorn, and U. K. Pandit, *Tetrahedron Lett.*, 2889 (1976); (f) D. C. Dittmer, A. Lombardo, F. H. Batzold, and C. S. Greene, *J. Org. Chem.*, **41**, 2976 (1976); (g) Y. Ohnishi, M. Kagami, and A. Ohno, *J. Am. Chem. Soc.*, **97**, 4766 (1975); (h) Y. Ohnishi, M. Kagami, and A. Ohno, *Tetrahedron Lett.*, 2437 (1975); (i) Y. Ohnishi, T. Numakunai, and A. Ohno, *ibid.*, 3831 (1975); (j) Y. Ohnishi, T. Numakunai, T. Kimura, and A. Ohno, *ibid.*, 2699 (1976); (k) D. J. Creighton and D. S. Sigman, *J. Am. Chem. Soc.*, **93**, 6314 (1971); (l) R. A. Gase, G. Boxhoorn, and U. K. Pandit, *Tetrahedron Lett.*, 2889 (1976); (m) U. K. Pandit, P. C. Keijzer, and R. A. Gase, *J. Chem. Soc., Chem. Commun.*, 493 (1976); (n) U. K. Pandit, H. van Dam, and J. B. Steevens, *Tetrahedron Lett.*, 913 (1977); (o) A. Ohno, T. Kimura, H. Yamamoto, S. G. Kim, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Jpn.*, **50**, 1535 (1977); (p) A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, *J. Chem. Soc., Chem. Commun.*, 328 (1978); (q) Y. Ohnishi, M. Kagami, T. Numakunai, and A. Ohno, *Chem. Lett.*, 915 (1976); (r) T. Endo, Y. Hayashi, and M. Okawara, *ibid.*, 391 (1977); (s) Y. Ohnishi and M. Kitami, *Tetrahedron Lett.*, 4033, 4035 (1978); (t) A. Ohno, T. Kimura, S. G. Kim, H. Yamamoto, S. Oka, and Y. Ohnishi, *Bioorg. Chem.*, **6**, 21 (1977); (u) A. Ohno, H. Yamamoto, T. Okamoto, S. Oka, and Y. Ohnishi, *Chem. Lett.*, 65 (1968); (v) A. Ohno, S. Yasui, H. Yamamoto, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Jpn.*, **50**, 294 (1978); (w) N. Baba, Y. Matsumara, and T. Sugimoto, *Tetrahedron Lett.*, 4281 (1978); (x) K. Nakamura, A. Ohno, S. Yasui, and S. Oka, *ibid.*, 4815 (1978); (y) T. Endo, H. Kawasaki, and M. Okawara, *ibid.*, 23 (1979).

(8) For a review of the applications of NADH itself for synthetic and mechanistic purposes, see J. B. Jones and J. F. Beck, *Tech. Chem. (N.Y.)*, **10**, 107 (1976).

(9) (a) T. J. van Bergen and R. M. Kellogg, *J. Chem. Soc., Chem. Commun.*, 964 (1976); (b) T. J. van Bergen and R. M. Kellogg, *J. Am. Chem. Soc.*, **99**, 3882 (1977).

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

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

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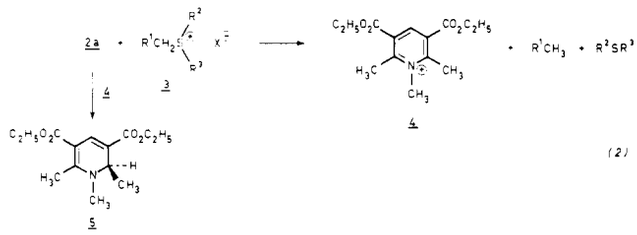
(14) (a) W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, **245**, 4597 (1970); (b) J. W. Cornforth, *Chem. Soc. Rev.*, **2**, 1 (1973); (c) B. M. Trost, P. Conway, and J. Stanley, *J. Chem. Soc., Chem. Commun.*, 1639 (1971).

sulfide to serve as a leaving group in the reactions of *S*-adenosylmethionine.[15]

Results and Discussion

A. Reaction Scope and Structure–Reactivity Considerations. For the most part the readily available Hantzsch ester **2a** was used; the reactions of **2b** and **1** were also examined but not in as much detail.[16] The anticipated reduction indeed occurred, usually at 60 °C, in a number of cases. In all cases reactions reached completion in 48 h.

The normal course for the reaction is illustrated in eq 2 for the case of **2a**. The results of the reduction of a



(2)

number of sulfonium salts are collected in Table I. Note that in these initial experiments no effort was made to exclude room light (vide infra). There was no evidence of reduction of the carbonyl group of, for example, **3b** nor could any phenyloxirane (reduction of carbonyl followed by elimination of sulfide) be detected.

The isomerization of **2a** to the unreactive 1,2-dihydro isomer **5** is an unavoidable side reaction under these conditions that becomes particularly serious for the case of sluggishly reactive sulfonium salts. The isomer **5** arises by reduction of pyridinium salt **4** by **2a** (eq 2); as soon as any reduction of **3** has occurred, isomerization catalyzed by **4** sets in and cannot be suppressed.[17] A temperature of reaction was sought which provided a workable compromise between the rates of reduction and isomerization.

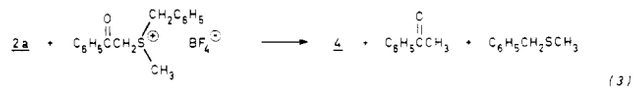
A combination of ^{1}H NMR spectroscopy and GLC was used to determine product compositions. Those products and reactants that had nonoverlapping absorptions in the ^{1}H NMR spectrum were identified by peak enhancement with authentic materials, and yields were determined by repeated integrations using 1,1,2,2-tetrachloroethane as an internal standard. For those products that could not be determined quantitatively by ^{1}H NMR spectroscopy, recourse was taken in GLC using appropriate internal standards. Control experiments were performed to ensure that observed product peaks did not arise through pyrolysis of the sulfonium salt in the injector port. This problem can be serious if appreciable amounts of sulfonium salt are still present in the reaction mixture.

Many of the reductions of the sulfonium salts listed in Table I proceed smoothly and quantitatively. A good example is the reaction of methylphenacylphenylsulfonium tetrafluoroborate (**3b**) with **2c** for which the rate of reduction is comparable to that of isomerization. The reaction stops before **3b** has been entirely consumed because the 1,4-dihydropyridine **2a** has been isomerized to its unreactive 1,2 isomer **5**. All the reactants can be accounted for nearly quantitatively. In other cases the rate of reduction is very high, for example **3g**, and little isomerization occurs. Note that this reduction proceeds well at 20 °C whereas the reduction of **3b** goes at a reasonable rate only at 60 °C.

Comparison of the reduction of *benzyl*sulfonium salt **3l** with that of *phenacyl*sulfonium salt **3a**, the leaving group being $(CH_3)_2S$ in both cases, reveals that electron deficiency in the group to be reduced is necessary for significant reduction. The benzyl salt is unmistakably, but sluggishly, reduced to toluene. The general order of reactivity toward reduction for the sulfonium salts is phenacyl > acetonyl > benzyl. We found that **2a** was a better reducing agent than **2b**; reductions proceeded very slowly or not at all with the latter. The reduction of **3b** (Table I) by **2b** was very clean, however. For the phenacylsulfonium salts the substitution of the electron-withdrawing nitro group at the 4-position enhances the tendency toward reduction whereas substitution with electron-donating groups such as methoxy leads to bad material balances. As seen from Table I, in the latter case sulfide is formed, but little, if any, reduction product can be isolated. A fair amount of 1,4-dihydropyridine is also unaccounted for. No other characterizable products could be found. We return to the case of the poor material balances in section B.

Although the rationale for examining the reactions of sulfonium salts with 1,4-dihydropyridines (eq 1, X = R_2S^+) in retrospect seems justified, later investigation showed that various electron-deficient, but uncharged, alkyl halides also react as seen from the entries for phenacyl bromide and bromomalonitrile in Table I. By far the most reactive substrate investigated is bromomalonitrile, which is consumed by reaction with **2a** within a matter of seconds after mixing.

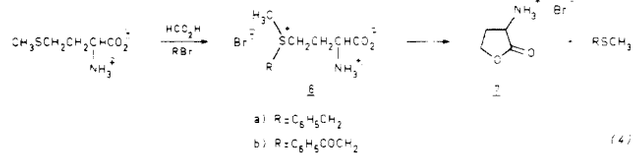
The higher reactivity toward reduction of *phenacyl* compared to *benzyl* was also nicely illustrated with benzylmethylphenacylsulfonium tetrafluoroborate (**3o**) in its reaction with **2a** (eq 3). At room temperature under



(3)

normal lighting reduction of **3o** proceeded slowly to give over 2 days 62% acetophenone and *no detectable amounts* of toluene. The salt **3o** is also slowly consumed by rearrangement to a nonpolar component (probably a Stevens rearrangement product[18] although this point was not explored).

The reductions of sulfonium salts derived from methionine were also accomplished. An attempt to use the sulfonium bromides **6b** failed, owing to the rapid formation of lactone **7** at the temperatures required for reduction (eq 4).[19] To avoid this problem, we protected (racemic) me-



(4)

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(16) A portion of these results has appeared as preliminary communications: T. J. van Bergen and R. M. Kellogg, *J. Am. Chem. Soc.*, **98**, 1962 (1976); D. M. Hedstrand, W. H. Kruizinga, and R. M. Kellogg, *Tetrahedron Lett.*, 1255 (1978).

(17) The scope and mechanism of these reactions has been examined: (a) T. J. van Bergen, T. Mulder, and R. M. Kellogg, *J. Am. Chem. Soc.*, **98**, 1960 (1976); (b) T. J. Bergen, T. Mulder, R. A. van der Veen, and R. M. Kellogg, *Tetrahedron*, **34**, 2377 (1978).

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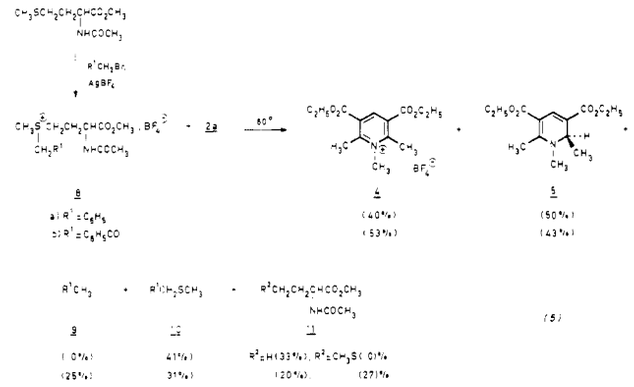
(19) A mixture of the diastereomeric sulfonium bromides from free *dl*-methionine was prepared by the method of (a) T. Hashimoto, H. Kitano, and K. Fukui, *Nippon Kagaku Zasshi*, **89**, 810 (1968); *Chem. Abstr.*, **70**, 28546 (1969). The spontaneous decomposition is known; see, for example: (b) T. F. Lavine, N. F. Floyl, and M. S. Cammaroti, *J. Biol. Chem.*, **207**, 107 (1954); (c) F. Schlenk and J. L. Damko, *Radiat. Res.*, **16**, 327 (1962).

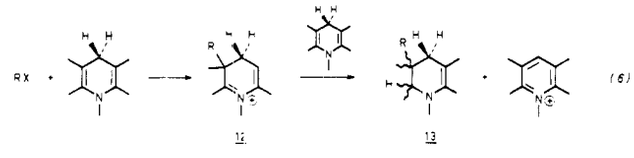
thionine by esterification and acylation on nitrogen; subsequent alkylation gave the sulfonium salts **8a,b** as mixtures of diastereomers, which reacted smoothly with **2c** with the results shown in eq 5. Under the conditions used



(CD_3COCD_3 solvent, 65 °C) the reductions go more smoothly and cleanly than might have been anticipated on consideration of the results of Table I. Quite unexpected was the exclusive reduction at the *methionine* carbon with salt **8a**; only homoalanine and benzyl methyl sulfide are formed; no toluene could be detected. A convincing explanation of this positional selectivity is not obvious.

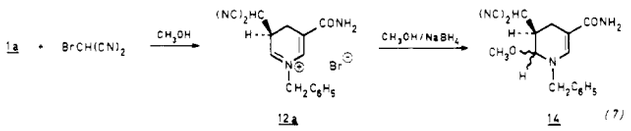
The reactions of several other potential substrates with **2a** were also investigated, but with little success, by using thermal activation (see, however, part C). Triphenylsulfonium perchlorate gave no observable reaction, and under the conditions used here trimethylphenacylammonium perchlorate gave only unidentified products with **2a**; a similar result was obtained with phenacyltriphenylphosphonium bromide. Trimethyl phosphate and benzyldiphenylphosphine failed to react with **2a**.

B. Alkylations of 1,4-Dihydropyridines. In some reductions by **2a**, sulfonium salt and dihydropyridine are consumed without the production of a reduction product outside of the sulfide from the consumed sulfonium salt. This problem was especially acute with 1-benzyl-1,4-dihydronicotinamide (1). We suspected that the competing reaction was alkylation of an enamine carbon of the 1,4-dihydropyridine, leading to the reaction course shown in eq 6.[20] This would result in consumption of substrate (alkylating agent) and dihydropyridine.



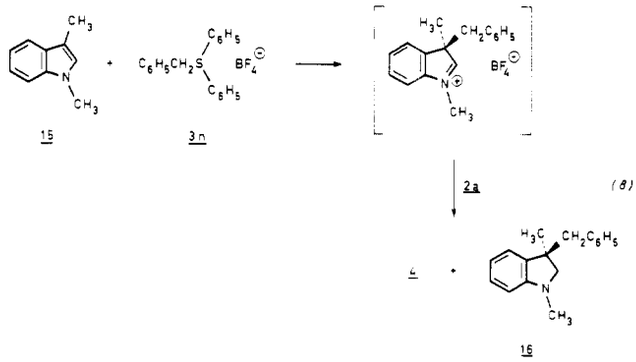
The tetrahydropyridine **13** formed on reduction of the iminium salt **12** could undergo a second alkylation, producing saturated compounds with several asymmetric centers; characterization of such products would be difficult.

To test this hypothesis, we examined the reaction of **1** with the very reactive bromomalonitrile (eq 7). Directly after **1** and bromomalonitrile were mixed in methanol, $NaBH_4$ was added with the intention of reducing the iminium salt **12a**. However, the iminium salt is trapped more rapidly by methanol, and $NaBH_4$ acts only as a base to neutralize HBr and to release the isolated product **14**. Compound **14** appears to be a single diastereomer of undetermined stereochemistry.



The structure of **14** follows from analytical and spectral data (see Experimental Section). Particularly informative is the UV spectrum, which in CH_3OH shows λ 284 nm (log ε 4.25), which is characteristic for β-aminocrotonamide chromophores.[21] The ^{13}C NMR spectrum has absorptions having the anticipated multiplicity for sp^3-hybridized carbons at 89.3 (C-2), 44.1 (C-3), and 26.3 (C-4) ppm (from Me_4Si) and for sp^2-hybridized carbons at 138.5 (C-5) and 139.3 (C-6) ppm. The remaining absorptions are readily assigned to the substituent carbon atoms.

Equation 6 is based on the assumption that a 1,4-dihydropyridine will reduce an iminium salt intermediate. There is good precedent for this.[7] However, to obtain additional support for this assumption, we carried out the reaction of eq 8. The benzylated and reduced product **16**



was isolated in 46% yield and pyridinium salt **4** in 60% yield. The alkylation of **15**[22] clearly proceeds more rapidly than that of **2a**, which now fulfils the function of reducing agent for the iminium salt.

C. Mechanism of Reduction. Light-Induced Reactions. The reaction of methylphenacylphenylsulfonium tetrafluoroborate (**3b**) with **2a** was chosen for further mechanistic investigation. An attempt to measure the kinetics of reduction by UV spectroscopy led to the unanticipated observation that no reduction occurred *in* the ultraviolet spectrometer whereas the reaction proceeded smoothly at the same temperature *outside* of the spectrometer. This obviously points to an effect of room lighting. Indeed, at 25 °C (compared with 60 °C in Table I) in CD_3COCD_3 under irradiation by a light bulb, **3b** is reduced quantitatively to acetophenone and phenyl methyl sulfide with no trace of isomerization of **2a** to the 1,2-dihydro isomer **5** (a reaction that is slow at room temperature). There is precedent[23] for light reductions by 1,4-dihydropyridines but hardly at the low levels involved here.

(20) For representative literature, 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, *J. Chem. Soc., Chem. Commun.*, 478 (1970); (f) C. S. Giam and S. D. Abbott, *J. Am. Chem. Soc.*, **93**, 1294 (1971).

(21) J. W. Cornforth, G. Ryback, G. Popjak, C. Donniger, and G. Schroepfer, Jr., *Biochem. Biophys. Res. Commun.*, **9**, 371 (1962).

(22) For alkylations of indole see, for example, W. C. Sumpter and F. M. Miller, *Chem. Heterocycl. Compd.*, **8**, 1–65 (1954).

(23) (a) J. A. Berson and E. Brown, *J. Am. Chem. Soc.*, **77**, 450 (1955); (b) J. L. Kurz, R. Hutton, and F. H. Westheimer, *ibid.*, **83**, 584 (1961); (c) W. R. Frisnell and C. G. Mackenzie, *Proc. Natl. Acad. Sci. U.S.A.*, **45**, 1568 (1969); (d) A. A. Krasnovskii, G. P. Brin, and N. N. Drozdova, *Dokl. Akad. Nauk SSSR*, **150**, 1157 (1963); *Chem. Abstr.*, **59**, 8994e (1963); (e) R. J. Kill and D. A. Widdowson, *J. Chem. Soc., Chem. Commun.*, 755 (1976).

Table II

$$2a^c + 3b^c \xrightarrow[CD_3CN]{CD_3COCD_3} 4 + C_6H_5COCH_3 + C_6H_5SCH_3 + 5$$

conditions	$t_{1/2}$, h	yield, % 4	$C_6H_5COCH_3$	$C_6H_5SCH_3$	5
A. 70 °C, dark[a]	10	<5	<5	<5	>95
B. 25 °C, dark	72	<5	<5	<5	<5
C. 25 °C, room light	48	100	100	100	0
D. 25 °C, room light, 1,4-dinitrobenzene (0.1 M)	*b*	<5	<5	<5	<5
E. 25 °C, room light, TPP	3	100	100	100	0
F. 25 °C, room light, eosin	1	100	100	100	0
G. 25 °C, room light, $Ru^{II}(bpy)_3Cl_2$	0.3	100	100	100	0
H. 25 °C, room light, $Ru^{II}(bpy)_3Cl_2$, 1,4-dinitrobenzene	*b*	<5	<5	<5	0

[a] A small amount of reduction occures, accounting for the isomerization to 1,2-dihydropyridine 5. In contrast to the results reported in Table I, these reactions were carried out by taking all precautions possible to exclude visible and ultraviolet light. [b] No detectable amount of reaction. [c] In 1 M concentration.

1,4-Dihydropyridines have a tail in the UV absorption spectrum that runs just into the visible region (most 1,4-dihydropyridines are light yellow).[24] Examination of the UV spectra of mixtures of **2a** and **3b** revealed no new bands in the visible region. Hence only the short-wavelength portion of the visible-light spectrum can be involved in accelerating the reaction. It is clear that greater enhancements might be achieved if a broader portion of the visible spectrum were to be absorbed by a colored compound, the excited state of which could induce the reduction reaction by energy transfer or chemical reaction. In accord with this line of thought addition of small amounts of tetraphenylporphine (TTP) indeed led to a large increase in the rate of reduction. An even larger acceleration was produced on using the disodium salt of eosin. By far the most spectacular effect, however, was that produced by ruthenium(II) tris(2,2′-bipyridine) dichloride ($Ru^{II}(bpy)_3Cl_2$).[25] Qualitative results are given in Table II. The concentration of the sensitizers was ca. 10^{-3} M whereas that of **2a** and **3a** was 0.1 M. The reactions in the presence of the dyes, especially $Ru^{II}(bpy)_3Cl_2$, are characterized by their cleanness, high reaction rates, and lack of competing rearrangement of 1,4-dihydropyridine.

In terms of mechanism the most revealing hints come from entries D and H in Table II and eq 9. The light reactions, with or without sensitizer, are stopped completely by 10^{-1} M 1,4-dinitrobenzene, which is a good electron acceptor known to be capable of interrupting one-electron-transfer chains.[26] Converse reasoning implies that the reactions under study have one-electron-transfer steps.

All evidence now in hand indicates that there is no fundamental mechanistic difference between these light-induced reactions and the "thermally induced" reactions reported in Table I (the results in Table I were accumulated before the effect of light was discovered). The point has not been checked for all the entries in Table I, but in many cases very low light levels may have initiated the reactions, which were normally carried out in Pyrex tubes wrapped in aluminum foil and held in an oven or water bath at the desired temperature. For the reaction of **2a** and **3b** at room temperature no reaction takes place if shorter wavelength visible light is eliminated by working under red light. At 60 °C the amount of reduction varies with the conditions used; the results reported in Table I generally represent the maximum amount of reduction found by working under normal but not stringent conditions to exclude light. There may be, however, at least for some reactions, a separate thermal path. A good case is the reduction of methionine sulfonium salt **8b** by **2a**; we were unable to demonstrate that either visible or ultraviolet light affected the rate of reduction, and we could not observe any inhibition of the rate of reduction by 1,4-dinitrobenzene.

Table III. Rates of Light-Induced Reductions of Sulfonium Salts with and without Added $Ru^{II}(bpy)_3Cl_2$[a]

sulfonium salt	dihydropyridine	$t_{1/2}$, h[b]
3b	**2a**	0.16 (4)
	2b	0.25 (3.5)
	1	<0.16 (6)[c]
3a	**2a**	0.67 (326)[c]
$C_6H_5COCH_2S(C_6H_5)_2$-BF_4 (**3p**)	**2a**	2.5 (48)[d]
3j	**2a**	70[c] (360)[c]
	2b	10[c] (48)[c]
	1	1.5 (8)[e]
$CH_3O_2CCH_2S(C_6H_5)$-CH_3BF_4 (**3q**)	**2a**	1 (144)
3m	**2a**	8 (192)[c]
	2b	9[c] (60)[c]
	1	1.5 (9)[c]
$(CH_3)_3SBF_4$ (**3r**)	**2a**	no reaction[f]

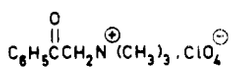
[a] Solutions were at 25 °C and were 0.1 M in both dihydropyridine and sulfonium salt (in CD_3CN with 10^{-3} M $Ru(bpy)_3Cl_2$). Irradiated in Pyrex NMR tubes held 30 cm from a fluorescent lamp. [b] Values in parentheses refer to light-induced reactions without $Ru^{II}(bpy)_3Cl_2$. For reactions with half-lives of >1 day significant (10–30%) isomerization of 1,4-dihydropyridine occurred. [c] Approximately 50% reduction and 50% alkylation. [d] Chiefly alkylation. [e] About 70% reduction and 30% alkylation. [f] Total reaction time 168 h.

In Table III the results are listed of a semiquantitative investigation of structure–reactivity correlations for both 1,4-dihydropyridines and sulfonium salts. Light-induced reductions both with and without $Ru^{II}(bpy)_3Cl_2$ were investigated. The indicated half-lives refer to the rate of disappearance of dihydropyridine and depend, of course, on the light source. One obvious conclusion from Table III is that alkylation by reactive sulfonium salts is suppressed relative to reduction in the presence of $Ru^{II}(bpy)_3Cl_2$. For example, approximately 50% reduction of **3b** can be achieved with 1-benzyl-1,4-dihydronicotinamide (**1**) whereas in dark reactions only alkylation is found. One

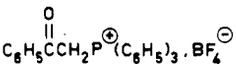
(24) See, for example, W. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).
(25) F. H. Burstall, *J. Chem. Soc.*, 173 (1938).
(26) (a) R. C. Kerber, G. W. Urry, and N. Kornblum, *J. Am. Chem. Soc.*, **86**, 3904 (1964); **87**, 4529 (1965); (b) R. L. Ward, *J. Chem. Phys.*, **32**, 410 (1960); (c) M. T. Jones and S. I. Weissman, *J. Am. Chem. Soc.*, **84**, 4269 (1962).

can also conclude from Table III that the order of reactivity of the sulfonium salts lies in the order $C_6H_5COCH_2$ > $CH_3O_2CCH_2$ > CH_3COCH_2 > CH_3 in close analogy with the order derived from Table I.

In separate experiments we found that salts **17** and **18**,



17



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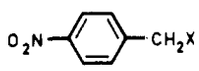

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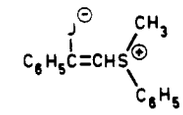
a) X = Br
b) X = Cl



20

neither of which give characterizable products in thermal reactions with **2a** (part A), are reduced to acetophenone in 60 and 16% yield, respectively, on irradiation in the presence of $Ru^{II}(bpy)_3Cl_2$. Likewise, the 4-nitrobenzyl halides **19a,b** are reduced smoothly by **2a** with light and $Ru^{II}(bpy)_3Cl_2$ to 4-nitrotoluene. The corresponding benzyl halides are unreactive. The halides **19a,b** are known to be good substrates for one-electron reductions.[26]

The ylide **20** derived from **3b** failed to react with **2a** with or without light and/or sensitizers; **20** can therefore reasonably be eliminated as a possible intermediate.

The reaction of **2a** with **3b** can have chain character as demonstrated by a *dark* reaction at 55 °C (little spontaneous reaction occurs under these circumstances) in the presence of azobis(isobutyronitrile) (AIBN). The chain length (moles of acetophenone produced per atom of initiator) is approximately 10.

Reactions in the presence of $Ru^{II}(bpy)_3Cl_2$ lend themselves well to study, owing to the remarkable properties of this inorganic sensitizer,[27] which in CH_3CN has a charge-transfer absorption at 450 nm and, moreover, is luminescent. The excited state derived from absorption in this band can donate an electron to electron-deficient substrates or accept an electron (or hydrogen atom) from electron-rich substrates. Both processes can be monitored by quenching of the luminescence of the complex. Much to our surprise we found that in carefully degassed CH_3CN solutions neither **3b**, an electron-deficient potential quencher, nor **2a**, an electron-rich potential quencher, had any effect on the luminescence of $Ru^{II}(bpy)_3Cl_2$ (Figure 1). Because the reaction of **2a** with **3b** has characteristics of a one-electron-transfer reaction, we had expected that the one-electron transfer of $Ru^{II}(bpy)_3Cl_2$ would be involved in the acceleration of this reaction.

A possible solution to this dilemma was found in the following observation. After removal of the solvent after completion of the reaction of **2a** with **3b** in the presence of $Ru^{II}(bpy)_3Cl_2$, a very tiny nitrile absorption was observed in the infrared spectrum at 2250 cm^{-1}.

Careful GLC and ^1H NMR analysis revealed that this absorption was due to a trace amount of succinonitrile. On

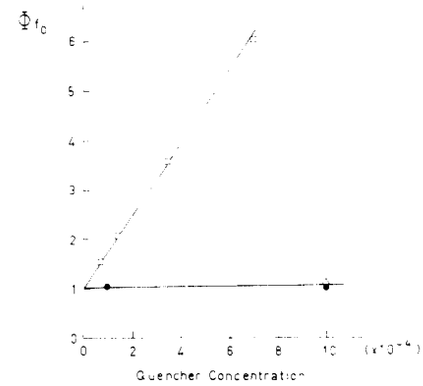
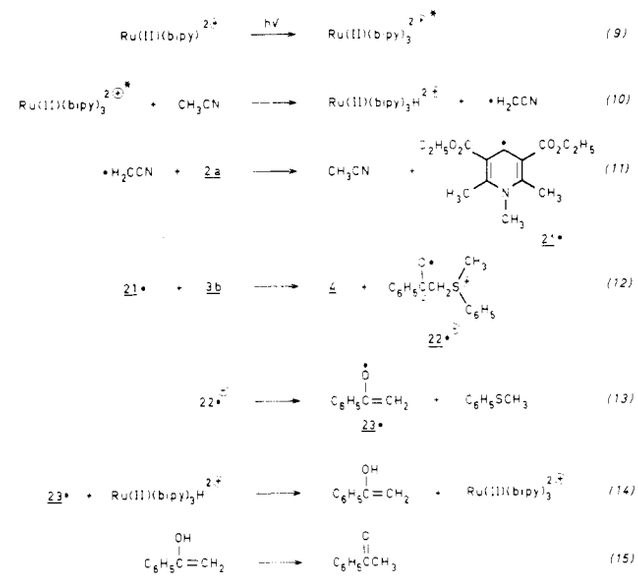


Figure 1. Quenching of $Ru^{II}(bpy)_3^{2+}$ luminescence: □ = 1,4-dinitrobenzene, $k_q = 8.8 \times 10^9$ L mol^{-1} s^{-1} with $\tau_0 = 0.88 \times 10^{-6}$ s for $Ru^{II}(bpy)_3^{2+}$ (lit.[27f] $k_q = 6.56 \times 10^9$ L mol^{-1} s^{-1} in degassed CH_3CN); ● = **3b**; △ = **2a**.

irradiation of $Ru^{II}(bpy)_3Cl_2$[28] alone in CH_3CN for several hours larger quantities (roughly 1 equiv of succinonitrile/equiv of sensitizer) were found. Succinonitrile has also been reported to be a trace product in the photochemical reactions of a derivative of $Ru^{II}(bpy)_3^{2+}$ with triethylamine in acetonitrile.[28b] One possible interpretation of our observations is that an excited but nonluminescent state of $Ru^{II}(bpy)_3^{2+}$ abstracts a hydrogen atom from acetonitrile, and the radical $\cdot CH_2CN$, like the radical $(CH_3)_2\dot{C}CN$ from AIBN, initiates the reaction of **2a** with **3b**, most likely by hydrogen atom abstraction from the 4-position of **2a**.

In eq 9–15 a working hypothesis is given for the mechanism of the reaction.[29] The precise timing of the various



reaction steps is not known, and modification of some of the suggested reaction steps may later prove necessary. The general mechanism proposed bears a clear resemblance to that proposed for nucleophilic substitution at (tertiary) carbon in electron-deficient benzyl halides or for certain examples of aromatic nucleophilic substitution.[30]

(27) For a discussion of recent developments with $Ru^{II}(bpy)_3^{2+}$ and derivatives thereof, see: (a) G. Sprintschnik, H. W. Sprintschnik, P. P. Kirsch, and D. G. Whitten, *J. Am. Chem. Soc.*, **99**, 4947 (1977); (b) J. N. Demas and A. W. Adamson, *ibid.*, **95**, 5159 (1973); (c) G. Navon and N. Sutin, *Inorg. Chem.*, **13**, 2159 (1974); (d) G. S. Lawrence and V. Balzani, *ibid.*, **13**, 2976 (1974); (e) C. R. Bock, T. J. Meyer, and D. G. Whitten, *J. Am. Chem. Soc.*, **96**, 4710 (1974); (f) C. R. Bock, T. J. Meyer, and D. G. Whitten, *ibid.*, **97**, 2909 (1975).

(28) For a recent summary of the literature on electron-transfer reactions of the excited state of $Ru^{II}(bpy)_3^{2+}$ and other inorganic complexes, see: (a) R. C. Young, J. K. Nagle, T. J. Meyer, and D. G. Whitten, *J. Am. Chem. Soc.*, **100**, 4773 (1978); (b) P. J. DeLaive, J. T. Lee, H. W. Sprintschink, H. Abruña, T. J. Meyer, and D. G. Whitten, *ibid.*, **99**, 7094 (1977).

(29) In the absence of dye the dihydropyridine must be the light absorber. The excited state of dihydropyridine could either transfer electronic energy or an electron to **3b** to initiate the reaction.

(30) J. F. Bunnett, *Acc. Chem. Res.*, **11**, 414 (1978).

In eq 7–15 steps involving chain character have not been included. Chain character is readily realized if **23**· abstracts a proton from **2a** rather than from $Ru^{II}(bpy)_3H^{2+}$ (step 14); this produces acetophenone and radical **21**·, which can participate again in step 12, leading to chain character. Reliable quantum-yield measurements supported by isotopic-labeling studies are needed to verify whether the reaction has chain character. Note also that at this time the postulation of hydrogen atom transfer steps, as opposed to electron-transfer steps, is entirely heuristic. Again more information is needed to make a distinction between these two possibilities.

Conclusions

The reductions of various electron-deficient sulfonium salts and alkyl halides by 1,4-dihydropyridines can be rapid and quantitative when carried out under the proper conditions, i.e., ambient or lower temperature and initiation by visible light with added sensitizers. The competing reactions of alkylation of an enamine carbon of the dihydropyridine and isomerization of the dihydropyridine are suppressed under these conditions.

Some questions remain unanswered. One-electron pathways account for many of the reductions, but the exact sequence of steps is a matter of speculation at this time. It is not known whether the mechanism for alkylation is related to or independent of the reduction mechanisms. It is also unclear whether all reductions are one-electron-transfer processes. It will be difficult to obtain answers to these questions.[6-8]

We do feel that our results, at this stage chiefly descriptive, expand significantly the scope and mechanistic knowledge of reductions by 1,4-dihydropyridines. Such information aids in the design of new synthetic systems[31] and providing essential information for the mechanisms of NAD(P)H-catalyzed reductions.[32]

Experimental Section

Melting points were determined either on a melting point block or on an automatic Mettler apparatus and were not corrected in either case. Spectral measurements were made on usual laboratory instruments. Compounds cited without reference were either commercially available or were prepared by literature methods. Fluorescence quenching experiments were done on samples degassed by five freeze–thaw cycles. All dihydropyridines and sulfonium salts were carefully stored in the dark to avoid decomposition.

1,2,6-Trimethyl-3,5-bis(ethoxycarbonyl)-1,4-dihydropyridine (2a) was prepared from 1,2,6-trimethyl-3,5-bis(ethoxycarbonyl)pyridinium perchlorate[33] by following a literature procedure.[34] A similar procedure was followed for the preparation of **2b**.

1,2,6-Trimethyl-3,5-bis(ethoxycarbonyl)-1,2-dihydropyridine (5) was prepared by following a literature procedure.[33]

1-Benzyl-1,4-dihydronicotinamide (1) was prepared from 1-benzylnicotinium chloride[35] as described in the literature.[36]

Dimethylphenacylsulfonium perchlorate (3a) was prepared by stirring a solution of 8.5 g (0.042 mol) of phenacyl bromide and 5.0 g (6 mL, 0.08 mol) of dimethyl sulfide in 50 mL of benzene for 24 h. The precipitated sulfonium bromide[37] was collected by filtration and was dissolved in 100 mL of H_2O. The solution was filtered, a saturated aqueous sodium perchlorate solution was added, and 6.0 g (0.021 mol, 50% yield) of **3a** was collected by filtration: mp 185–187 °C (recrystallized from ethanol/acetonitrile); IR (KBr) 1680 (C=O), 1080 cm^{-1} (ClO_4); ^1H NMR (C_3D_6O) δ 3.20 (s, 6 H, 2 CH_3), 5.58 (s, 2 H, CH_2), 7.50–8.25 (m, 5 H, aryl H).

Anal. Calcd for $C_{10}H_{13}ClO_5S$: C, 42.79; H, 4.67; Cl, 12.63. Found: C, 42.84; H, 4.60; Cl, 12.60.

Methylphenacylphenylsulfonium tetrafluoroborate (3b) was prepared by adding 8.8 g (0.042 mol) of silver tetrafluoroborate portionwise to a well-stirred solution of 8.5 g (0.042 mol) of phenacyl bromide and 8.7 g (0.070 mol) of thioanisole in 75 mL of methylene chloride. Stirring at ambient temperature was continued for 20 h, and the insoluble salts were removed by filtration. The filtrate was evaporated, and the residue was crystallized by stirring it with 25 mL of acetonitrile, giving 11.6 g (0.034 mol, 83% yield) of **3b**: mp 120–122 °C (recrystallized from absolute C_2H_5OH); IR (KBr) 1680 (C=O), 1050 cm^{-1} (BF_4^-); ^1H NMR (C_3D_6O) δ 3.56 (s, 3 H, CH_3), 5.96 (s, 2 H, CH_2), 7.50–8.50 (m, 10 H, aryl H).

Anal. Calcd for $C_{15}H_{15}BF_4OS$: C, 54.57; H, 4.58; S, 9.71. Found: C, 54.59; H, 4.57; S, 9.67.

(4-Methoxyphenacyl)diphenylsulfonium tetrafluoroborate (3c) was prepared by adding a mixture of 4-methoxyphenacyl bromide (14.0 g, 0.061 mol) and diphenyl sulfide (27 g, 0.145 mol) over 30 min to $AgBF_4$ (0.057 mol) in 50 mL of methylene chloride. The reaction mixture was allowed to stir another 12 h, the AgBr was removed by filtration, and the solvent was removed to leave a heavy oil, which was taken up in 100 mL of diethyl ether. Two layers were formed: the lower gray-brown layer was separated and was dissolved in a warm petroleum ether (40–60 °C)/benzene (1:1) mixture, and the insoluble material was filtered off. On cooling (11 g, 0.0261 mol, 46% yield) of the sulfonium salt **3c** precipitated as white crystals: mp 132–133 °C; ^1H NMR (CD_3COCD_3) δ 3.95 (s, 3 H, CH_3O), 6.50 (s, 2 H, CH_2), 7.0–8.3 (complex, 8 H, aromatic).

Anal. Calcd for $C_{20}H_{19}BF_4O_2S$: C, 59.76; H, 4.54; S, 7.59; F, 17.99. Found: C, 59.87; H, 4.54; S, 7.63; F, 17.87.

(4-Methoxyphenacyl)methylphenylsulfonium tetrafluoroborate (3d) was prepared from $AgBF_4$ (6.0 g, 0.031 mol), 4-methoxyphenacyl bromide (7.1 g, 0.031 mol), and thioanisole (9.0 g, 0.073 mol) as described above. There was obtained 10.0 g (0.0278 mol, 90% yield) of **3d**: mp 140–141 °C; ^1H NMR (CD_3COCD_3) δ 3.53 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3O), 5.87 (s, 2 H, CH_2), 6.9–8.3 (complex, 9 H, aromatic).

Anal. Calcd for $C_{16}H_{17}BF_4O_2S$: C, 53.65; H, 4.76; S, 8.91; F, 21.10. Found: C, 53.23; H, 4.81; S, 8.88; F, 20.85.

(3-Methoxyphenacyl)methylphenylsulfonium tetrafluoroborate (3e) was prepared from $AgBF_4$ (4 g, 0.0205 mol), 3-methoxyphenacyl bromide (4.7 g, 0.205 mol), and thioanisole (7.5 g, 0.06 mol). There was obtained 4.3 g (0.012 mol, 58% yield) of **3e**: mp 119.5–120 °C; ^1H NMR (CD_3COCD_3) δ 3.54 (s, 3 H, CH_3S), 3.83 (s, 3 H, CH_3O), 5.95 (s, 2 H, CH_2), 7.3–8.4 (complex, 9 H, aromatic).

Anal. Calcd for $C_{16}H_{17}BF_4O_2S$: C, 53.26; H, 4.76; S, 8.91; F, 21.10. Found: C, 53.39; H, 4.74; S, 8.93; F, 21.25.

(2-Methoxyphenacyl)methylphenylsulfonium tetrafluoroborate (3f) was prepared from $AgBF_4$ (2.5 g, 0.013 mol), 2-methoxyphenacyl bromide (2.94 g, 0.13 mol), and thioanisole (5 g, 0.04 mol). There was obtained 2.8 g (0.008 mol, 61% yield) of **3f**: mp 144.5–145 °C; ^1H NMR (CD_3COCD_3) δ 3.52 (s, 3 H, CH_3O), 4.03 (s, 3 H, CH_3O), 5.82 (s, 2 H, CH_2), 6.9–8.4 (complex, 9 H, aromatic).

Anal. Calcd for $C_{16}H_{17}BF_4O_2S$: C, 53.36; H, 4.76; S, 8.91; F, 21.10. Found: C, 53.28; H, 4.82; S, 9.01; F, 21.31.

(4-Nitrophenacyl)methylphenylsulfonium tetrafluoroborate (3g) was prepared as described above from $AgBF_4$ (4.0 g, 0.0205 mol), 4-nitrophenacyl bromide (5.0 g, 0.0206 mol), and

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thioanisole (7.5 g, 0.06 mol). The AgBr and the sulfonium salt were isolated from CH_2Cl_2 by filtration with a P4 glass filter, and the precipitate was taken up in warm CH_3OH. The AgBr was removed by filtration. When the CH_3OH solution was cooled, the sulfonium salt separated. After several recrystallizations there was obtained 2.5 g (0.0067 mol, 32% yield) of product: mp 180–181.5 °C; ^1H NMR (CD_3COCD_3) δ 3.58 (s, 3 H, CH_3), 6.06 (s, 2 H, CH_2), 7.5–8.4 (complex, 9 H, aromatic).

Anal. Calcd for $C_{15}H_{14}BF_4NO_3S$: C, 48.02; H, 3.76; N, 3.74; F, 20.25. Found: C, 48.12; H, 3.74; N, 3.82; F, 20.40.

(3-Nitrophenacyl)methylphenylsulfonium tetrafluoroborate (3h) was prepared from $AgBF_4$ (2.25 g, 0.011 mol), 3-nitrophenacyl bromide (2.8 g, 0.011 mol), and thioanisole (4.5 g, 0.038 mol). There was obtained 3.2 g (0.0086 mol, 86% yield) of **3h**: mp 123.5–125 °C; ^1H NMR (CD_3COCD_3) δ 3.61 (s, 3 H, CH_3S), 6.06 (s, 2 H, CH_2), 7.6–8.6 (complex, 9 H, aromatic).

Anal. Calcd for $C_{15}H_{14}BF_4NO_3S$: C, 48.02; H, 3.76; N, 3.74. Found: C, 48.02; H, 3.71; N, 3.83.

(2-Nitrophenacyl)methylphenylsulfonium tetrafluoroborate (3i) was prepared from $AgBF_4$ (1.3 g, 0.0065 mol), 2-nitrophenacyl bromide (1.6 g, 0.0065 mol), and thioanisole (2.5 g, 0.02 mol). Isolation was complicated by the precipitation of the sulfonium salt with AgBr. The combined precipitate was taken up in CH_3OH, the AgBr was filtered off, and the salt **3i**, was allowed to crystallize out. The material in the CH_2Cl_2 filtrate was isolated by removal of CH_2Cl_2, addition of 50 mL of $(C_2H_5)_2O$, removal of the heavy brown insoluble oil, and recrystallization of this material from CH_3OH. The samples of **3i** were combined and recrystallized several times from CH_3OH to give 0.7 g (0.0021 mol, 33% yield) of **3i**: mp 171.0–172.5 °C; ^1H NMR (CD_3COCD_3) δ 3.25 (s, 3 H, CH_3S), 5.16 (s, 2 H, CH_2), 7.45–8.3 (complex, 9 H, aromatic).

Anal. Calcd for $C_{15}H_{14}BF_4NO_3S$: C, 48.62; H, 3.76; N, 3.75. Found: C, 47.65; H, 3.67; N, 3.78.

Methyldiphenylsulfonium perchlorate (3k) was prepared by adding dropwise a solution of 6.84 g (0.06 mol) of methyl fluorosulfonate in 30 mL of methylene chloride to a stirred and ice-cooled solution of 11.16 g (0.06 mol) of diphenyl sulfide also in 30 mL of the same solvent. After a 16-h reaction time the solvent was evaporated, and the residue was dissolved in 50 mL of water. A solution of 70% aqueous perchloric acid was added dropwise until all the **3k** had precipitated. Filtration followed by recrystallization from 90 mL of a 1:1 methanol/ethanol mixture afforded 8.29 g (0.03 mol, 45% yield) of **3k**: mp 69.5–73 °C (lit.[38] mp 73–74 °C); ^1H NMR (CD_3OD) δ 3.88 (s, 3 H, CH_3), 7.90–8.50 (m, 10 H, aryl H).

Benzyldimethylsulfonium tetrafluoroborate (3l) was prepared by adding 11.3 g (0.058 mol) of silver tetrafluoroborate portionwise to a well-stirred and ice-cooled solution of benzyl bromide (10 g, 0.058 mol) and dimethyl sulfide (6 mL, 0.08 mol) in 50 mL of methylene chloride. After a 16-h reaction period, followed by filtration and evaporation, a residue was obtained that was recrystallized from 2-propanol to yield 8.6 g (0.036 mol, 62% yield) of **3l**: mp 99–101 °C; ^1H NMR (CD_3OD) δ 2.78 (s, 6 H, 2 CH_3), 4.58 (s, 2 H, CH_2), 7.46 (s, 5 H, aryl H).

Anal. Calcd for $C_9H_{13}BF_4S$: C, 45.02; H, 5.46; S, 13.35. Found: C, 45.27; H, 5.42; S, 13.37.

Benzylmethylphenylsulfonium tetrafluoroborate (3m) was prepared by adding silver tetrafluoroborate (8.8 g, 0.042 mol) portionwise to a stirred, ice-cooled mixture of excess benzyl bromide (30 g, 0.174 mol) and thioanisole (10.02 g, 0.042 mol). After a 20-h reaction period 50 mL of methylene chloride was added, followed by filtration and evaporation, giving a residue that solidified on stirring with 100 mL of ether. Filtration gave 7.7 g (0.025 mol, 60% yield) of **3m**: mp 121–122 °C (recrystallized from ether/acetonitrile); ^1H NMR (C_3D_6O) δ 3.42 (s, 3 H, CH_3), 4.98 and 5.26 (d, J = 13 Hz, 2 H, CH_2), 7.35 (s, 5 H, aryl H), 7.60–8.10 (m, 5 H, aryl H).

Anal. Calcd for $C_{14}H_{15}BF_4S$: C, 55.65; H, 5.00; S, 10.61. Found: C, 55.62; H, 5.12; S, 10.68.

Benzyldiphenylsulfonium tetrafluoroborate (3n) was prepared from diphenyl sulfide (10.2 g, 0.054 mol), excess benzyl bromide (50 g), and silver tetrafluoroborate (10.5 g, 0.054 mol) via a literature procedure.[38] There was obtained 7.3 g (0.020 mol, 37% yield) of **3n**, mp 105–108 °C (lit.[38] mp 105–106 °C).

Benzylphenacylphenylsulfonium perchlorate was prepared from phenacyl phenyl sulfide (4 g, 17.5 mol), benzyl bromide (3.1 g, 18.2 mol), and $AgClO_4$ (3.7 g, 17.8 mmol) in 25 mL of CH_2Cl_2. The yellow precipitate was filtered off and washed with CH_2Cl_2. The combined CH_2Cl_2 solutions were evaporated, the solid residue was dissolved in 50 mL of CH_2Cl_2 (<30 °C), and 200 mL of ether was rapidly added to give the white precipitate **3o** (2.8 g, 7.03 mmol, 40% yield): mp 135.5–136 °C (recrystallized from $CH_2Cl_2/(C_2H_5)_2O$); ^1H NMR (CD_3COCD_3) δ 5.22 (d, J = 15 Hz, 1 H, $CHHC_6H_5$), 5.50 (d, J = 15 Hz, 1 H, $CHHC_6H_5$), 6.11 (s, 2 H, CH_2CO), 7.40–8.40 (complex, 10 H, aromatic). A satisfactory elemental analysis was not obtained.

Phenacyldiphenylsulfonium tetrafluoroborate (3p) was prepared by adding to a solution of $AgBF_4$ (9 g, 0.046 mol) in 50 mL of CH_2Cl_2 a mixture of phenacyl bromide (9 g, 0.045 mol) and diphenyl sulfide (20 g, 0.107 mol) in 50 mL of CH_2Cl_2 over 30 min and allowing the mixture to stand for 12 h. Removal of the AgBr by filtration followed by removal of solvent left a residue that was taken up in 100 mL of diethyl ether. The dirty gray oil, insoluble in ether, was separated and dissolved in warm ethanol. When the solution was cooled, there was formed 10.3 g (0.0264 mol, 58% yield) of **3p**: mp 164–165 °C; ^1H NMR (CD_3COCD_3) δ 6.51 (s, 2 H, CH_2), 7.8–8.4 (complex, 10 H, aromatic).

[(Methoxycarbonyl)methyl]methylphenylsulfonium tetrafluoroborate (3q) was prepared from thioanisole (8.7 g, 0.07 mol) and iodoacetic acid methyl ester (10.0 g, 0.05 mol) in 75 mL of methylene chloride by adding portionwise 9.8 g (0.05 mol) of silver tetrafluoroborate to the stirred solution. After a 20-h period the inorganic materials were removed by filtration, and the solvent was evaporated. The viscous residue was dissolved in 10 mL of dimethoxyethane, was filtered, and was subsequently poured into 100 mL of ether. The supernatant was decanted, leaving 7.80 g (0.027 mol, 55% yield) of pure, viscous **3q**, which failed to become crystalline: IR 1740 cm^{-1} (C=O); ^1H NMR (C_3D_6O) δ 3.57 (s, 3 H, SCH_3), 3.78 (s, 3 H, OCH_3), 5.03 (s, 2 H, CH_2), 7.70–8.40 (m, 5 H, aryl H); mass spectrum, a fragmentation peak at m/e 182.0394 (calcd for $C_9H_{10}O_2S$, m/e 182.0401). Owing to crystallization problems, an acceptable elemental analysis could not be obained.

(3-Amino-3-carboxypropyl)benzylmethylsulfonium bromide (6a) was prepared according to the literature[39] by stirring *dl*-methionine (25 g, 0.17 mol) and benzyl bromide (29 g, 0.17 mol) in a mixture of 250 mL of methylene chloride and 100 mL of formic acid at ambient temperature for 2 days. Removal of the solvent left a viscous residue that crystallized from a 1:1 methanol/acetone solvent mixture, giving 20.0 g (0.062 mol, 37% yield) of **6a**: dec 126–130 °C (lit.[19a] dec 113–114 °C); IR (KBr) 3500 (NH_2), 2500 (CO_2H), 1630 cm^{-1} (C=O); ^1H NMR (D_2O) δ 2.28 (m, 2 H, CH_2), 2.76 (s, 3 H, CH_3), 3.35 (m, 2 H, SCH_2), 3.76 (t, 1 H, CH), 4.62 (AB, J = 12 Hz, 2 H, SCH_2), 7.48 (s, 5 H, aryl H).

(3-Amino-3-carboxypropyl)methylphenacylsulfonium bromide (6b) was prepared by stirring 12.5 g (0.085 mol) of *dl*-methionine and 17.0 g (0.085 mol) of phenacyl bromide in 100 mL of formic acid for 20 h. The mixture was poured into 750 mL of ether, and, after the precipitate had settled out, the supernatant was decanted. The residue was redissolved in 100 mL of acetonitrile, and the above procedure was repeated with 400 mL of ether. Thereafter the product was precipitated from 100 mL of methanolic solution, yielding 17 g of **6b** (0.049 mol, 57% yield): dec 122–126 °C (lit.[39] dec 113–114 °C); IR (KBr) 3500 (NH_2), 2500 (CO_2H), 1680 cm^{-1} (C=O); ^1H NMR (D_2O) δ 2.52 (m, 2 H, CH_2), 3.10 (s, 3 H, SCH_3), 3.66 (m, 2 H, SCH_2), 7.40–8.05, (m, 5 H, aryl H); the phenacyl methylene could not be observed owing to H/D exchange.

***dl*-*N*-Acetylmethionine methyl ester** was prepared by suspending *dl*-methionine (35 g, 0.3 mol) in 90 mL of absolute methanol and adding dropwise with ice cooling over a 20-min period 36 g (0.3 mol) of freshly distilled thionyl chloride.[40] The

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mixture was stored at 2–5 °C for 2 days. The solvent was removed on a rotary evaporator, 20 g of ice was added, the pH was adjusted to 8 with ammonia, and the solution was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered, and concentrated. The residue afforded, after vacuum distillation, 31.0 g (0.19 mol, 63% yield) of methionine methyl ester [bp 83–95 °C (0.08 mm)].

The ester (16.0 g, 0.098 mol) was allowed to react with 12.5 g (0.122 mol) of acetic anhydride in 60 mL of dry pyridine for 20 h. The solution was poured into 300 mL of saturated aqueous NaCl solution, and the product was extracted with methylene chloride. The extracts were dried ($MgSO_4$), filtered, and evaporated, leaving a residue that on recrystallization from a cyclohexane/benzene mixture yielded 17.8 g (0.087 mol, 89% yield) of *dl* product, mp 80–81.5 °C (lit.[41] mp 82.6–83.2 °C).

[3-(Acetylamino)-3-(methoxycarbonyl)propyl]benzylmethylsulfonium tetrafluoroborate (8a) was prepared from the protected ester described above (4.5 g, 0.022 mol) and benzyl bromide (3.8 g, 0.022 mol) in 50 mL of methylene chloride by adding to this stirred solution 4.3 g (0.022 mol) of silver tetrafluoroborate portionwise. After a 24-h reaction period the inorganic salts were removed from the reaction mixture by filtration, and the solvent was thereafter removed on a rotary evaporator. The residue was redissolved in 20 mL of acetonitrile and poured into 50 mL of ether. The solution was allowed to settle, and the supernatant was decanted. The residue was then dried under vacuum, leaving 6.4 g (0.017 mol, 76% yield) of glassy **8a** as a mixture of diastereomers which failed to become crystalline: IR 3350 (NH), 1740 and 1660 (C=O), 1050 cm^{-1} (BF_4^-); ^1H NMR (C_3D_6O) δ 2.10 (s, 3 H, CH_3), 2.30 (m, 2 H, CH_2), 2.97 (s, 3 H, SCH_3), 3.50 (d, 2 H, SCH_2), 3.70 (s, 3 H, OCH_3), 4.67 (m, 1 H, NH), 4.85 (s, 2 H, SCH_2), 7.52 (m, 5 H, aryl H), 9.00 (d, J = 4 Hz, 1 H, NH); mass spectrum, no parent peak. An acceptable elemental analysis was not obtained.

[3-(Acetylamino)-3-(methoxycarbonyl)propyl]methylphenacylsulfonium tetrafluoroborate (8b) was prepared from the *dl* protected methionine ester (4.5 g, 0.022 mol) and phenacyl bromide (4.3 g, 0.022 mol) with silver tetrafluoroborate (4.3 g, 0.022 mol) as described for **8a**. There was obtained 5.8 g (0.014 mol, 64% yield) of a glassy mixture of diastereomers of **8b**, which failed to crystallize: IR 3350 (NH), 1740, 1680 and 1660 (C=O), 1050 cm^{-1} (BF_4^-); ^1H NMR (C_3D_6O) δ 1.95 (s, 3 H, CH_3), 2.50 (m, 2 H, CH_2), 3.16 (s, 3 H, SCH_3), 3.60 (m, 2 H, CH_2), 3.66 (s, 3 H, OCH_3), 4.55 (m, 1 H, CH), 5.53 (s, 2 H, SCH_2), 7.35–8.15 (m, 6 H, 5 aryl H and NH); mass spectrum, no parent peak, fragment ion at m/e 310.1113 (calcd for $C_{15}H_{20}NO_4S$, m/e 310.1061). An acceptable elemental analysis could not be obtained.

1-Benzyl-3-(dicyanomethyl)-2-methoxy-1,2,3,4-tetrahydronicotinamide was prepared by adding dropwise 1.3 g (0.009 mol) of bromomalonitrile[42] in 20 mL of methanol to a stirred and ice cooled solution of **1** (2.0 g, 0.009 mol) in 25 mL of methanol. Thirty minutes after the addition was completed, excess sodium borohydride (760 mg, 0.02 mol) was added portionwise to remove the generated hydrogen bromide. Stirring was continued for ca. 2 h, and the mixture was poured into 200 mL of water, followed by methylene chloride extraction. The extracts were dried (Na_2SO_4), filtered, and concentrated. Preparative TLC (silica gel and a 5:1 ether/methanol mixture) afforded 1.36 g (4.9 mmol, 55% yield) of **14** as a glass, which after repeated attempts solidified in acetone. Product **14** is rather unstable and has a pronounced tendency to polymerize: dec 112–114 °C; IR (KBr) 3330 (NH_2), 2200 (CN), 1640 (C=O), 1160 cm^{-1} (CO); UV (methanol) λ_{max} 284 nm (log ϵ 4.25); ^1H NMR (C_3D_6O) δ 7.25 (m, 6 H, 5 H, aryl and 1-vinyl H), 6.10 (br s, 2 H, NH_2), 4.42 (s, 2 H, NCH_2), 4.38 (m, 2 H, OCH–N and dicyanomethyl H), 3.32 (s, 3 H, OCH_3), 3.17–2.40 (1 H, CH), 2.75 (m, 2 H, allyl CH_2); ^{13}C NMR (C_3D_6O; ppm from Me_4Si) 26.3 (allylic CH_2, t, J = 126 Hz), 44.1 (CH, d, J = 160 Hz), 56.1 (OCH_3, q, J = 148 Hz), 58.0 (NCH_2, t, J = 138 Hz), 59.6 (CH, d, J = 140 Hz), 89.3 (OCH, d, J = 160 Hz), 98.8 (s, CN), 128.4, 128.7, 129.2, and 138.5 (phenyl and 5-pyridyl C, m), 139.3 (6-pyridyl C, d, J = 170 Hz), 170.4 (s, CO); mass spectrum, fragment ion at m/e 176.1045 (calcd for $C_{16}H_{12}N_4O$, m/e 276.1011), loss of CH_4 and H_2O.

Reaction of 1,3-Dimethylindole, Phenacyldiphenylsulfonium Tetrafluoroborate (3a), and Hantzsch Ester 2a. A mixture of 1,3-dimethylindole (400 mg, 2.75 mmol), **3a** (1 g, 2.75 mmol), and **2a** (735 mg, 2.75 mmol) was dissolved in 20 mL of dry CH_2Cl_2 and allowed to stand with stirring at room temperature for 24 h. The solvent was removed. Analysis of the ^1H NMR spectrum of the crude residue indicated that 60% of the theoretical amount of pyridinium salt **4** had been formed. The crude product was chromatographed over a silica gel column using CH_2Cl_2 as eluent to give 3-benzyl-1,3-dimethyl-2,3-dihydroindole (**16**; 300 mg, 1.27 mmol, 46% yield): ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H, CH_3), 2.72 (s, 3 H, NCH_3), 2.84 (s, 2 H, $CH_2C_6H_5$), 2.78 (d, J = 9 Hz, 1 H, CHHN), 3.30 (d, J = 9 Hz, 1 H, CHHN), 6.4–7.4 (complex, 9 H, aromatic); exact mass, calcd m/e 237.150, found m/e 237.150 (parent).

Anal. Calcd for $C_{17}H_{18}N$: C, 86.3; H, 8.08; N, 5.90. Found: C, 85.61; H, 8.09; N, 5.90.

Methylphenylsulfonium phenacylide (20) was prepared from phenacylphenylmethylsulfonium perchlorate (1500 mg, 4.38 mmol) dissolved in 25 mL of $CHCl_3$ at 0 °C. To this solution was slowly added aqueous NaOH solution (1.5 g of NaOH in 10 mL of H_2O). Stirring was continued until all the solid had dissolved. The organic layer was separated, and the aqueous layer was extracted with 25 mL of $CHCl_3$. The organic layers were combined and dried over Na_2SO_4. Removal of the solvent followed by recrystallization from C_6H_6 gave **20** (600 mg, 2.65 mmol, 60% yield), mp 112–115 °C (lit.[43] mp 113–114 °C).

General Procedure for Reductions with 1,4-Dihydropyridines. Solutions in the appropriate solvent were made 0.1 M in both sulfonium salt (or other substrate) and dihydropyridine. The reactions reported in Table I were carried out for the most part in NMR tubes enclosed in aluminum foil and held in a water bath or oven at the desired temperature. ^1H NMR spectra were taken regularly to monitor the course of the reaction. Usually the reaction mixtures were allowed to stand 48 h at the desired temperature to ensure that the reaction had gone to completion. Identification and quantitative determination of the products and unconsumed starting materials were carried out by the procedures discussed in the text.

Light-induced reductions were again for the most part carried out in Pyrex NMR tubes. Reactions on a larger scale were done in Pyrex flasks. The data in Table II were obtained by using a closed but ventilated box containing a holder for the NMR tube and a fluorescent lamp placed 30 cm from the sample holder. Reaction rates are of course dependent on the distance of the lamp from the sample tubes and the intensity of the lamp. Sensitizer concentrations were 10^{-3} M. Degassing (except for fluorescence-quenching experiments with $Ru^{II}(bpy)_3Cl_2$) had no appreciable effect on light-induced reductions.

Reaction of 2a and 3b in the Presence of AIBN. The 1,4-dihydropyridine **2a** (27 mg, 0.1 mmol) and sulfonium salt **3b** (as the perchlorate, 34 mg, 0.1 mmol) were dissolved in 0.5 mL of CD_3COCD_3, and the mixture was placed in an NMR tube, which was wrapped carefully in aluminum foil. Azobis(isobutyronitrile) (0.5 mg, 0.0029 mmol) was added, and the tube was heated at 55 °C for 20 h. Analysis of the ^1H NMR spectrum indicated that 0.06 mmol of pyridinium salt **4**, 0.04 mmol of 1,2-dihydropyridine **5**, and 0.055 mmol each of acetophenone and phenyl methyl sulfide had been formed. No **2a** remained. Assuming that two initiator fragments are formed from each AIBN molecule, the chain length is calculated to be 9.9.

A blank reaction carried out without AIBN indicated that little spontaneous reduction occurred although **2a** was partially isomerized in **5**.

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Notes

Vacuum Liquid Chromatography: An Alternative to Common Chromatographic Methods

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There is a constant need in organic chemistry to separate both large and small quantities of mixtures efficiently, rapidly, and inexpensively. Unfortunately, it is seldom that all three of these requirements are satisfied in the commonly used chromatographic techniques. Efforts to improve these methods include the use of multibore columns,[1] flash chromatography,[2] automated systems,[3] and dry-column chromatography.[4] We wish to report the development of vacuum liquid chromatography (VLC), a method which we feel possesses all of the desirable characteristics mentioned above. VLC has become the major method for separation of steroids and marine natural products in our laboratory.

The development of this method arose from the need to have a simple inexpensive chromatographic system at the bench, capable of producing good resolution in a short time. A previous attempt to achieve this goal utilized a sintered-glass Büchner funnel, partially filled with TLC grade sorbent, under vacuum as a "column".[5,6] This afforded resolution comparable to that of gravity column chromatography (70–230 mesh sorbent) but in a much shorter time period. The major drawbacks to this very simple system were channeling, caused by the necessary intermittent breaking of the vacuum, uneven sample application, and limited resolution due to the shortness of the column. VLC overcomes these drawbacks.

Channeling was eliminated by developing a system in which the column was kept under vacuum continuously. Sample application problems were overcome by (a) decreasing the ratio of column cross section to the quantity of the sorbent (use of a longer, narrower column) and (b) by the use of a preabsorbent layer of celite such as that used on some TLC plates. Resolution was increased greatly by an increase in column length relative to cross-sectional area.

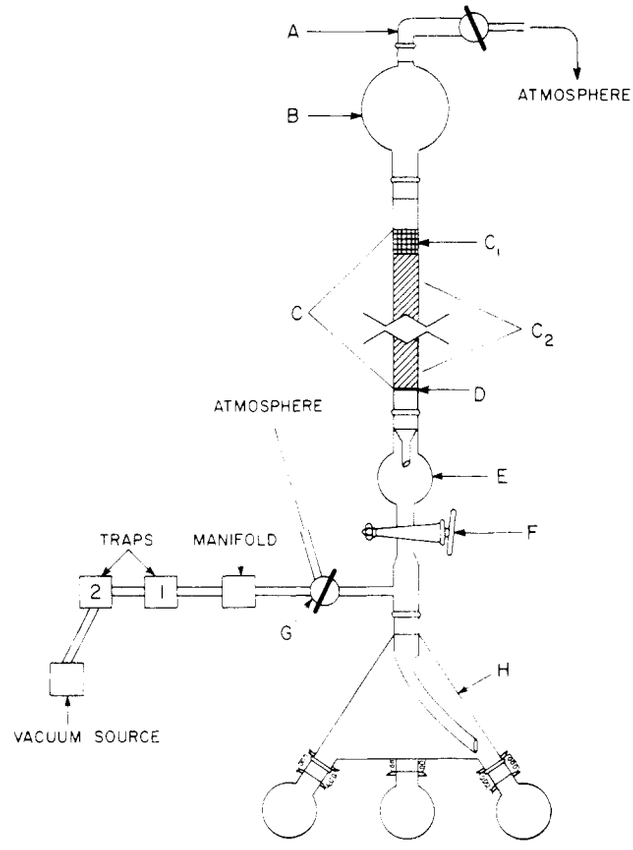

Figure 1. VLC apparatus and some specifications: A, stopcock/stopper; B, solvent reservoir (2 L); C, column; C_1, preabsorbent layer (diatomaceous earth, celite, filter aid or equivalent); C_2, sorbent (TLC grade, 10–40 μm); D, sintered glass frit (10–20 μm pore size); E, eluent reservoir (250 mL); F, column isolation stopcock; G, vacuum/atmosphere stopcock; H, receiver head; trap 1, 250 mL; trap 2, 50 mL; vacuum, mechanical pump.

The apparatus shown in Figure 1 consists of the column C fitted with standard taper joints at upper and lower ends

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