To this was added 40 mL of dry ether and 5.71 g (52.6 mmol) of trimethylchlorosilane and the mixture stored at -25 °C overnight. Ether was removed by rotary evaporation (to 0 °C) and the residue short-path distilled to give 5.33 g (61%) of water-white material: bp 34 °C (11 mm); NMR analysis indicated the presence of 3% hexamethyldisiloxane as the only significant contaminant; NMR δ 0.23 (s, 9 H), 2.24 (s, 3 H); IR 1617 (C=N), 1253 ($SiMe_3$) cm^{-1}. Anal. Calcd for $C_5H_{12}ClNOSi$: C, 36.24; H, 7.30. Found: C, 35.96; H, 7.49.

Conversion of 3a,b into Isoxazolines 4a,b. The generation of nitrile oxides from both **3a** and **3b**[6] is typified by the following procedure for the preparation of **4a** (R^1 = H, R^2 = n-C_6H_{13}). A flask with an open side arm was charged with a magnetic stirrer and 1.16 g (20 mmol) of potassium fluoride. KF was dried by heating the flask for several minutes with a flame while under nitrogen flow. After cooling, 6 mL of dry acetonitrile, 0.71 mL (0.51 g, 4.5 mmol) of 1-octene, and 0.75 g (4.5 mmol) of **3a** were added, the side arm was septum sealed and the flask stoppered and sealed with Parafilm. After stirring for 28 h at 25 °C, pentane and water were added, the pentane layer dried ($MgSO_4$) and concentrated, and the residue evaporatively distilled to give 0.53 g (70%) of 3-methyl-5-n-hexyl-Δ^2-isoxazoline: bp 50 °C (0.1 mm); NMR δ 0.68-1.83 (m, 13 H), 1.95 (t, 3 H, J = 1 Hz), 2.25-3.30 (m, 2 H), 4.2-4.8 (m, 1 H); IR 1613 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31. Found: C, 71.09; H, 11.19.

Runs that generated isoxazolines of possibly significant water solubility (Table I, entries 4-6, 8, and 9) were worked up by filtration of the crude reaction mixture, followed by distillation.

The thermal generation of acetonitrile oxide from **3a** was shown to occur by refluxing a mixture of 0.51 g (4.5 mmol) of 1-octene, 0.75 g (4.5 mmol) of **3a**, and 6 mL of dry toluene under nitrogen for 43 h. Distillation afforded 0.44 g (57%) of the isoxazoline.

Other new isoxazolines (**4a,b**) reported here are listed in the following entries of Table I.

Entry 7: bp 90 °C (0.6 mm); NMR δ 0.9-1.7 (m, 6 H), 1.89 (t, 3 H, J = 1 Hz), 2.35 (br s, 1 H), 2.49 (br s, 1 H), 2.96 (d, 1 H, J = 8 Hz), 4.40 (d, 1 H, J = 8 Hz); IR 1620 cm^{-1}. Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67. Found: C, 71.26; H, 8.99.

Entry 8: bp 45 °C (0.5 mm); NMR δ 1.04 (d, 3 H, J = 7 Hz), 1.23 (d, 3 H, J = 6.5 Hz), 1.93 (s, 3 H), 3.04 (m, 1 H), 4.62 (AB q, 1 H, J = 6.5, 9.5 Hz); IR 1627 (w), 1462 (sh), 1445 (s), 1387 (s), 1324 (m), 1310 (sh), 1060 (m), 1025 (m), 985 (m), 890 (s), 863 (s), 770 (w), 729 (w), 636 (m) cm^{-1}. Anal. Calcd for $C_6H_{11}NO$: C, 63.69; H, 9.80. Found: C, 63.47; H, 9.79.

Entry 9: bp 45 °C (0.25 mm); NMR δ 1.16 (d, 3 H, J = 7 Hz), 1.32 (d, 3 H, J = 6 Hz), 1.90 (d, 3 H, J = 1 Hz), 2.74 (m, 1 H), 4.12 (AB q, 1 H, J = 6, 9 Hz); IR 1624 (s), 1460 (sh), 1440 (s), 1385 (s), 1328 (m), 1090 (w), 1056 (m), 1010 (m), 978 (w), 890 (s), 870 (s), 843 (m), 788 (w), 717 (w) cm^{-1}. Anal. Calcd for $C_6H_{11}NO$: C, 63.69; H, 9.80. Found: C, 63.26; H, 9.97.

Entry 11: mp 51.6-52.0 °C (from hexane-ether); NMR δ 0.65-2.1 (m, 13 H), 2.90 (*ABX* pattern, 1 H, J = 8.5, 16.5 Hz), 3.38 (*ABX* pattern, 1 H, J = 10, 16.5 Hz), 4.43-5.0 (m, 1 H), 7.22-7.90 (m, 5 H); IR 1690 (w), 1660 (w), 855 (s), 790 (s) cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO$: C, 77.88; H, 9.15. Found: C, 77.70; H, 8.90.

Registry No. **3a**, 86260-81-3; **3b**, 69054-15-5; **4a** (R^1 = H; R^2 = n-C_6H_{13}), 83670-86-4; **4a** (R^1 = H; R^2 = $SiMe_3$), 78847-14-0; **4a** (R^1 = H; R^2 = Ph), 7064-06-4; **4a** (R^1 = H; R^2 = OCH_2CH_3), 86260-82-4; **4a** (R^1 = H; R^2 = CO_2Me), 55134-82-2; **4a** (R^1 = H; R^2 = CN), 86260-83-5; **4a** (R^1, R^2 = bicyclo[2.2.1]heptane-2,3-diyl, 83670-87-5; *cis*-**4a** (R^1 = R^2 = CH_3), 82150-07-0; *trans*-**4a** (R^1 = R^2 = CH_3), 82150-02-5; **4a** (R^1, R^2 = cyclohexane-1,2-diyl), 24010-91-1; **4b** (R^1 = H; R^2 = n-C_6H_{13}), 84965-95-7; **4b** (R^1 = H; R^2 = OCH_2CH_3), 86260-84-6; **4b** (R^1 = H; R^2 = CN), 1011-38-7; n-$C_6H_{13}CH{=}CH_2$, 111-66-0; $Me_3SiCH{=}CH_2$, 754-05-2; $PhCH{=}CH_2$, 100-42-5; $C_2H_5OCH{=}CH_2$, 109-92-2; $MeO_2CCH{=}CH_2$, 96-33-3; $NCCH{=}CH_2$, 107-13-1; *c*-$CH_3CH{=}CHCH_3$, 590-18-1; *t*-$CH_3CH{=}CHCH_3$, 624-64-6; acetonitrile oxide, 7063-95-8; trimethylchlorosilane, 75-77-4; norbornene, 498-66-8; cyclohexene, 110-83-8; benzonitrile oxide, 873-67-6.

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Synthesis of Trisubstituted Vinyl Chlorides[1]

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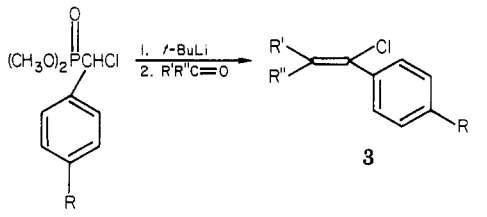
We have previously shown that 1,2-diarylvinyl chlorides can be synthesized from diphenyl (1-chlorobenzyl)-phosphonates, base, and aryl aldehydes in a Horner-Emmons type fashion.[2] Savignac et al.[3] have since devised an appealing method for the synthesis of 1-chlorobenzylphosphonates and obtained greater yields of the vinyl chlorides. Trisubstituted vinyl chlorides have eluded this synthetic procedure since success with a ketone in a reaction with the α-heterosubstituted phosphonate carbanion has been achieved only with cyclohexanone.[3]

We now report the expansion of this method to include more sterically hindered ketones such as benzophenone. By decreasing the bulk of the phosphonate moiety by using methyl instead of phenyl esters and utilizing more vigorous reaction conditions, good yields of trisubstituted vinyl chlorides were obtained. Thus, lithium dimethyl (1-chlorobenzyl)phosphonate was refluxed in THF for 24-48 h with the appropriate ketone to yield the corresponding 1-chloro-2,2-disubstituted-1-phenylethene (**3**; Table I; eq 1).



(1)

3

2a, R = H
b, R = OCH_3

The position of the olefinic double bond and the chlorine atom are not in doubt; various functional groups are not affected by this reaction; and the carbonyl compound may contain a double or triple bond.[2] ^{13}C NMR spectra were taken of a representative number of the trisubstituted vinyl chlorides from asymmetric ketones including those of **3f** and **3h**. In Figures 1 and 2 the peaks of the methyl groups of the ^{13}C NMR spectra of **3f** and **3h** are given. The larger of the two peaks is assigned to the least hindered E isomers. The ratio between the two peaks indicates the E/Z ratio. The exhibited spectra were in full agreement with the proposed structures for those compounds. The stereochemistry of the products seems to be readily explainable on the basis of steric hinderance. In all these compounds, **3e**, **3f**, and **3h**, practically only one isomer, the one with the large (in comparison to the alkyl groups) phenyl groups on opposite sides of the double bond, was obtained. With groups of comparable sizes, e.g., **3c**, the E and Z isomers were formed in virtually the same amounts. In addition to the stereochemistry the yields of the vinyl chlorides also seem to be governed by steric effects. The readily available starting materials and the ease of this reaction make this a simple and general method for the

(1) This paper is part 13 of the series Synthesis with α-Heterosubstituted Phosphonates. Part 12: Crenshaw, M. D.; Schmolka, S. J.; Zimmer, H.; Whittle, R.; Elder, R. C. *J. Org. Chem.* **1982**, *47*, 101.

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Table I

ketone	phosphonate	product	yield,[a] %
benzophenone	2a	3a	58
9-fluorenone	2a	3b	50
4-[2-(diethylamino)ethoxy]-benzophenone	2a	3c[b]	66
1,3-diphenyl-2-propanone	2a	3d	42
acetophenone	2a	3e[c]	77
propiophenone	2a	3f[d]	58
3,3'-dinitrobenzophenone	2a	3g	42
4-cyanoacetophenone	2a	3h[c]	71
4,4'-dimethoxybenzophenone	2b	3i	43

[a] In all cases the unreacted ketone could be recovered, but no attempt was made to determine the fate of the phosphonate that did not yield the vinyl chloride. [b] *Z/E* ratio 47/53 determined by HPLC. [c] *Z/E* ratio 94/6 determined by ^1H and ^{13}C NMR. [d] *Z/E* ratio 93/7 determined by ^{13}C NMR.

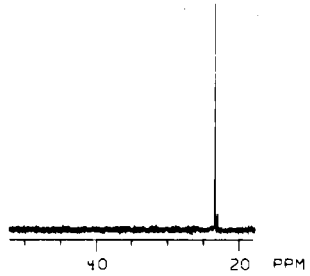

Figure 1. ^{13}C NMR spectrum of CH_3 group of **3h** (H decoupled).

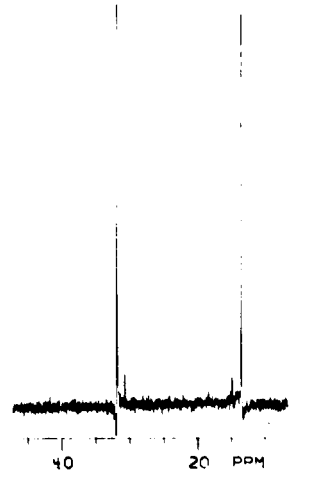

Figure 2. ^{13}C NMR spectrum of CH_3 and CH_2 groups of **3f** (H decoupled).

synthesis of trisubstituted vinyl chlorides.

This method was applied to the synthesis of clomiphene (**3c**; gonad-stimulating principle)[4,5] and chlorotrianisene (**3i**; estrogen),[6,7] which are normally synthesized via a Grignard reaction.[8,9] However, the Grignard reaction is not compatible with many functional groups such as carbonyl, halogeno, cyano, and nitro groups. Thus, our procedure allows 1,1,2-trisubstituted vinyl chlorides including analogues of clomiphene and chlorotrianisene to be synthesized that were unobtainable by the hitherto known methods.

Experimental Section

General Methods. Ultraviolet spectra (UV) were recorded by a Norelco Unicam Model 6P800A spectrometer. Wavelengths, λ_{max}, are reported in millimicrons (mμm). Infrared spectra (IR) were recorded by a Perkin-Elmer Model 599 instrument. Mass spectral data were obtained on a Perkin-Elmer RUM-7 or a Kratos MS-80 mass spectrometer.

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded by a Varian T-60 instrument or a Nicolet 300-MHz spectrometer. ^{13}C NMR spectra were recorded by the Nicolet spectrometer. Chemical shifts are expressed in δ units relative to 1% tetramethylsilane as an internal standard; coupling constants are given in hertz (Hz). Liquids were analyzed by exact mass spectrometry ($\pm 4 \times 10^{-3}$ mass units) and solids by combustion analysis (C, H: ±0.4%). Combustion analyses were performed at M-H-W Laboratories, Phoenix, Az. Melting points were determined with a Mel-Temp melting point apparatus and are uncorrected as are boiling points.

Tetrahydrofuran (THF) was purified by continuous distillation under argon from benzophenone and sodium metal. Standardized solutions of *tert*-butyllithium were a gift from Lithium Corp. of America. 3,3'-Dinitrobenzophenone was synthesized according to Barnett and Matthews.[10] 4-[2-(Diethylamino)ethoxy]benzophenone was prepared from 4-hydroxybenzophenone and 2-chloro-*N*,*N*-diethylethylamine.[8a] All other reagents were commercially available from Aldrich Chemical Co., Matheson Coleman and Bell, Fisher Scientific Co., and/or Eastman Kodak Co. All reagents were purified by recrystallization or distillation prior to use. The reported yields are of isolated, purified materials.

Dimethyl Benzylphosphonate (1a). Equimolar amounts of trimethyl phosphite and benzyl chloride were refluxed under a nitrogen atmosphere for 20 h and purified by distillation; $C_9H_{13}O_3P$, bp 85 °C (0.15 mm) [lit.[11] bp 100 °C (0.7 mm)]; ^1H NMR (CCl_4) δ 3.0 (d, 2H, J = 22 Hz), 3.55 (d, 6H, J = 10 Hz), 7.2 (s, 5H). Yield 72%.

Dimethyl (4-methoxybenzyl)phosphonate (1b): prepared in the same manner as **1a** from trimethyl phosphite and 4-anisyl chloride;[12] $C_{10}H_{15}O_4P$, clear oil, bp 141 °C (0.45 mm) [lit.[13] bp 175–6 °C (3.3 mm)]; ^1H NMR was identical with published spectral data;[13] yield 59%.

Dimethyl 1-Chloro-1-phenylmethanephosphonate (2a). Chlorination of **1a** was achieved by the method of Petrova et al.,[3] but *tert*-butyllithium was used in place of *n*-butyllithium; $C_9H_{12}ClO_3P$, clear oil, bp 137 °C (0.7 mm) [lit.[14] bp 105 °C (0.07 mm)]; ^1H NMR was identical with published spectral data; yield 96%.

Dimethyl 1-chloro-1-(4-methoxyphenyl)methanephosphonate (2b): prepared in the same manner as **2a** except that a methanol liquid nitrogen bath was used (−100 °C); clear oil, bp 150 °C (0.50 mm); ^1H NMR ($CDCl_3$) δ 3.60 (d, 3 H, *J* = Hz), 3.79 (s, 3 H), 3.81 (d, 3 H, *J* = 10 Hz), 4.90 (d, 1 H, *J* = 14 Hz), 6.90 (d, 2 H, *J* = 8 Hz), 7.50 (dd, 2 H, *J* = 8 Hz, *J'* = 2 Hz); mass spectrum, *m/e* (relative intensity) 264 [M^+ (^{35}Cl), 17.6], 266 [M^+ (^{37}Cl), 6.3].

1-Chloro-1,2,2-triphenylethene (3a). Typical Procedure. To a stirred solution of 0.01 mol of **2** in 65 mL of anhydrous THF at −78 °C was added 1.1 equiv of *tert*-butyllithium in pentane. After 30 min, 1.1 equiv of benzophenone in 10 mL of anhydrous

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THF was added dropwise. The reaction mixture was warmed to room temperature and refluxed for 30 h. Water was then added and the mixture extracted with carbon tetrachloride. Following drying of the combined organic layers over $MgSO_4$ and evaporation of the solvent, the remainder, an oily solid, was purified by column chromatography; $C_{20}H_{15}Cl$, colorless needles, mp 117.5–119 °C (95% ethanol) [lit.[15] mp 117.3–118.9 °C]; ^1H NMR (CCl_4) δ 6.8–7.45 (m); mass spectrum, *m/e* (relative intensity) 290 [M^+ (^{35}Cl), 100], 292 [M^+ (^{37}Cl), 33.5].

(α-Chlorobenzylidene)fluorene (3b): $C_{20}H_{13}Cl$, yellow plates, mp 123–124.5 °C (95% ethanol) [lit.[16] mp 120–122 °C]; ^1H NMR (CCl_4) δ 6.2–7.7 (m); mass spectrum, *m/e* (relative intensity) 288 [M^+ (^{35}Cl), 79.6], 290 [M^+ (^{37}Cl) 28.7].

Clomiphene A and B (as free base; **3c**): pale yellow oil, bp 215 °C (0.55 mm); ^1H NMR ($CDCl_3$) δ 1.05 (m, 6 H) 2.68 (m, 6 H), 4.03 (m, 2 H), 6.6–8.0 (m, 14 H); UV (MeOH) λ_{max} 234, 241;[17] mass spectrum, *m/e* (relative intensity) 405 [M^+ (^{35}Cl), 13.5], 407 [M^+ (^{37}Cl), 4.5]; exact mass calcd for $C_{26}H_{28}ClNO$ *m/e* 405.1861, found *m/e* 405.1859.

1-Chloro-1,3-diphenyl-2-(phenylmethyl)propene (3d): colorless needles, mp 91–92 °C (95% ethanol); ^1H NMR (CCl_4) δ 3.35 (s, 2 H), 3.70 (s, 2 H), 7.0–7.55 (m, 15 H); mass spectrum, *m/e* (relative intensity) 318 [M^+ (^{35}Cl), 43.4], 320 [M^+ (^{37}Cl), 16.3]. Anal. Calcd for $C_{22}H_{19}Cl$: C, 82.87; H, 5.91. Found: C, 83.00; H, 6.05.

1-Chloro-1,2-diphenylpropene (3e): colorless oil, bp 115 °C (0.55 mm); NMR (CCl_4) δ 2.35 (s, 3 H), 6.80–7.25 (m, 10 H); mass spectrum, *m/e* (relative intensity) 228 [M^+ (^{35}Cl), 100.0], 230 [M^+ (^{37}Cl), 30.1]; exact mass calcd for $C_{15}H_{13}Cl$ *m/e* 228.0707, found *m/e* 228.0695.

1-Chloro-1,2-diphenyl-1-butene (3f): colorless oil, bp 123 °C (1.30 mm); ^1H NMR (CCl_4) δ 1.05 (t, 3 H, *J* = 8 Hz), 2.85 (q, 2 H, *J* = 8 Hz), 6.9–7.40 (m, 10 H); mass spectrum, *m/e* (relative intensity) 242 [M^+ (^{35}Cl), 93.1], 244 [M^+ (^{37}Cl), 30.7]; exact mass calcd for $C_{16}H_{15}Cl$ *m/e* 242.0864, found *m/e* 242.0848.

1-Chloro-2,2-bis(3-nitrophenyl)-1-phenylethene (3g): colorless powder, mp 126–127.5 °C [sublimed at 60 °C (0.5 mm)]; ^1H NMR ($CDCl_3$) δ 7.3–8.4 (m); mass spectrum, *m/e* (relative intensity) 380 [M^+ (^{35}Cl), 100], 382 [M^+ (^{37}Cl), 39]. Anal. Calcd for $C_{20}H_{13}ClN_2O_4$: C, 63.08; H, 3.44. Found: C, 62.72; H, 3.66.

1-Chloro-2-(4-cyanophenyl)-1-phenylpropene (3h): colorless powder, mp 74–79 °C, bp 151 °C (0.55 mm); ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 7.1–7.7 (m, 9 H); IR (neat) 2235 cm^{-1}; mass spectrum, *m/e* (relative intensity) 253 [M^+ (^{35}Cl), 98.8], 255 [M^+ (^{37}Cl), 30.7]; exact mass calcd for $C_{16}H_{12}CN$ *m/e* 253.0660, found *m/e* 253.0658. Anal. Calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77. Found: C, 75.72; H, 4.83.

Chlorotrianisene (3i): colorless powder, mp 114–5 °C (MeOH) [lit.[9] mp 113–114 °C]; NMR ($CDCl_3$) δ 3.70 (s, 3 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 6.90 (m, 12 H); mass spectrum, *m/e* (relative intensity) 380 [M^+ (^{35}Cl), 100], 382 [M^+ (^{37}Cl), 38].

Acknowledgment. We acknowledge the assistance of Mr. Frank P. Palopoli of Merrell-Dow for the determination of the *E/Z* content of the isomeric mixture of clomiphene A and B prepared by our method. This investigation was supported in part by an Institutional Grant of the American Cancer Society and a grant by the University of Cincinnati Research Council.

Registry No. **1a**, 773-47-7; **1b**, 17105-65-6; **2a**, 16965-75-6; **2b**, 86457-76-3; **3a**, 18084-97-4; **3b**, 86457-77-4; (*Z*)-**3c**, 15690-55-8; (*E*)-**3c**, 15690-57-0; **3d**, 61507-95-7; (*Z*)-**3e**, 65787-74-8; (*E*)-**3e**, 65787-75-9; (*Z*)-**3f**, 69967-86-8; (*E*)-**3f**, 69967-85-7; **3g**, 86457-78-5; (*Z*)-**3h**, 86457-79-6; (*E*)-**3h**, 86457-80-9; **3i**, 569-57-3; trimethyl phosphite, 121-45-9; benzyl chloride, 100-44-7; 4-anisyl chloride, 824-94-2; benzophenone, 119-61-9; 9-fluorenone, 486-25-9; 4-[2-(diethylamino)ethoxy]benzophenone, 796-77-0; 1,3-diphenyl-2-propanone, 102-04-5; acetophenone, 98-86-2; propiophenone, 93-55-0; 3,3′-dinitrobenzophenone, 21222-05-9; 4-cyanoacetophenone, 1443-80-7; 4,4′-dimethoxybenzophenone, 90-96-0.

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(17) Clomiphene A and B as HCl salt: λ_{max} (MeOH) 230 and 239 mμm. See ref 8b.

Communications

Interaction of Sulfur Dioxide with 1-Benzyl-1,4-dihydronicotinamide

Summary: Anhydrous sulfur dioxide reacts rapidly with 1-benzyl-1,4-dihydronicotinamide to give a reduced species of sulfur dioxide, possibly HSO_2^-, which can be trapped by reaction with Michael acceptors to give sulfones.

Sir: The ubiquity of sulfur dioxide as an undesirable pollutant is reason for investigation of its interaction with biologically important molecules. Although considerable information is available about the interaction of models for the coenzyme, NAD^+ (nicotinamide adenine dinucleotide), with reduced species of sulfur dioxide such as dithionite[1] or sulfite,[2-4] no studies exist on the interaction of anhydrous sulfur dioxide with dihydronicotinamide models for the reduced coenzyme, NADH, although a reaction with the hypothetical sulfurous acid is described.[4] Removal of water from aqueous solutions of sulfur dioxide regenerates the gas[5] so that in biological systems of low water content the free sulfur dioxide may be an important contributor to the overall toxic effects.

In a recent investigation of the mechanism of the reduction of analogues of NAD^+ by dithionite, evidence was presented for the reaction proceeding via hydride transfer from the sulfoxylate anion, HSO_2^-, to the pyridinium salt to give the 1,4-dihydropyridine and sulfur dioxide.[1] The reverse reaction of sulfur dioxide with the dihydropyridine was excluded.[1] Although this may be true in aqueous media in which these studies were done, where sulfur dioxide is hydrated, we have found to the contrary that sulfur dioxide in essentially anhydrous media reacts rapidly and apparently quantitatively with 1-benzyl-1,4-dihydronicotinamide, an analogue of NADH, to give a yellow pyridinium salt, **1**, whose anion is one or more reduced species of sulfur dioxide. The salt obtained in liquid sulfur dioxide shows a maximum in the UV spectrum at 265 nm (95%

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