of thiobenzophenone in the presence of oxygen has been treated by G. Oster, L. Citarel, and M. Goodman, *J. Am. Chem. Soc.*, **84**, 703 (1962); no dark reaction was reported.
(4) Thiobenzophenone *S*-oxide has been reported to be slightly green: B. Zwanenburg, L. Thijs, and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **86**, 577 (1967).
(5) W. F. Linke, "Solubilities of Inorganic and Metalorganic Compounds", Vol. II, 4th ed, American Chemical Society, Washington, D.C., 1965, p 1228.
(6) A similar intermediate arising from singlet oxygen and certain sulfides has been trapped and characterized kinetically by C. S. Foote and J. W. Peters, *J. Am. Chem. Soc.*, **93**, 3795 (1971).
(7) A. Battaglia, A. Dondoni, P. Giorgianni, G. Maccagnani, and G. Mazzanti, *J. Chem. Soc. B*, 1547 (1971).
(8) S. Searles and H. R. Hays, *J. Org. Chem.*, **23**, 2028 (1958).
(9) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis", 3d ed, Macmillan, New York, N.Y., 1975, p 585.

Mass Spectra of Some Isomeric Monosubstituted Pyridines. Participation of the Ring Nitrogen in the Fragmentation of the 2 Isomers

Paul H. Chen

Philip Morris USA, Research Center, Richmond, Virginia 23261

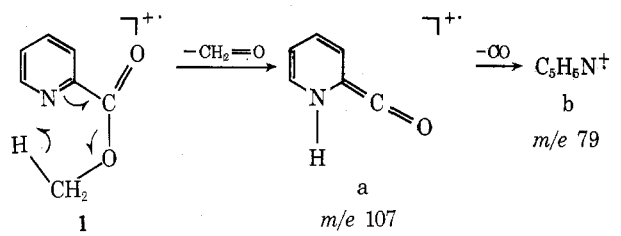
Received March 30, 1976

The mass spectra of several isomeric monosubstituted pyridines were investigated. The compounds studied include methyl and ethyl esters of isomeric pyridinecarboxylic acids, pyridinecarboxamides, pyridylacetic acids, and pyridylacrylic acids. The mass spectra of 2-substituted pyridine compounds reported in this study are different from those of their corresponding 3 or 4 isomers. The differences are attributable to the interaction of the side chain in the 2 isomers with the ring nitrogen. This interaction generally results in a hydrogen transfer to the ring nitrogen and elimination of a neutral molecule. The hydrogen transfer can be a six-membered as well as five- or seven-membered transition state.

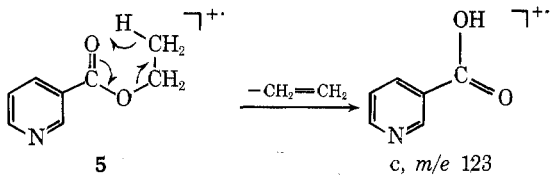
It is often difficult to differentiate between isomers from their mass spectra. In a number of benzenoid aromatic isomers, however, the differentiation can be made as a result of ortho effects[1] or peri effects.[2] In the case of isomeric monosubstituted pyridine derivatives, distinction is sometimes possible due to the interaction of the 2-substituted side chain with the pyridine ring nitrogen.[3-5] In the present study the mass spectra of several sets of isomeric pyridine compounds were investigated to determine if the ring nitrogen is involved in the electron impact induced fragmentation. The participation of the ring nitrogen may be useful for identification purposes in differentiating the 2 isomer from the 3 and 4 isomers.

Methyl Esters of Pyridinecarboxylic Acids. The mass spectra of methyl picolinate (**1**), methyl nicotinate (**2**), and methyl isonicotinate (**3**) are shown in Figure 1. While mass spectra of **2** and **3** are very similar, large differences are observed between the mass spectrum of **1** and those of **2** and **3**. The 3- and 4-substituted pyridines exhibit strong molecular ion peaks and strong fragment ion peaks due to simple bond cleavage α to the carbonyl. In contrast, the mass spectrum of the 2 isomer shows that the molecular ion and an ion due to α-cleavage (*m/e* 106) are weak. Cooks and co-workers[3] also reported very low molecular ion abundances for the 2-substituted pyridines.

The formation of a relatively strong ion at *m/e* 107 in the spectrum of the 2 isomer is likely initiated by the interaction of the ring nitrogen with the substituent at the 2 position. The similar reaction product ion is absent or insignificant in the spectra of the 3 and 4 isomers. The relatively weak *m/e* 107 ion in the spectra of these two isomers is essentially attributed to the natural isotope abundance of the strong *m/e* 106 ion. The formation of the *m/e* 107 ion from the ionized 2 isomer **1** can be explained by a transfer of a methyl hydrogen to the ring nitrogen and elimination of formaldehyde to give an ion a in a McLafferty rearrangement. Similar elimination of formaldehyde has been shown in the spectrum of 2-methoxycarbonylimidazole.[6] Ion a further loses a CO to yield a very strong ion b (*m/e* 79) which is very weak in the spectra of the 3 and 4 isomers. The elemental compositions of ions a and b have been substantiated by high-resolution mass measurements. The fragmentations from *m/e* 137 to *m/e* 107 and *m/e* 107 to *m/e* 79 as well as other major fragmentation pathways shown in Figure 1 were confirmed by the presence of an appropriate metastable peak (denoted by an asterisk) determined by scanning in the metastable mode (see the Experimental Section).



Ethyl Esters of Pyridinecarboxylic Acids. The mass spectra of ethyl picolinate (**4**), ethyl nicotinate (**5**), and ethyl isonicotinate (**6**) are shown in Figure 2. As in their methyl ester homologues, the mass spectra of the 3- and 4-pyridine isomers are very similar, whereas striking differences are observed between the spectrum of the 2-pyridine compound and those of the 3 and 4 isomers. High-resolution mass measurements show that the strong *m/e* 123 peak in the spectra of the 3 and 4 isomers is due to the McLafferty rearrangement ion c by elimination of an ethylene molecule from the molecular ion **5**. Similar elimination of ethylene from the molecular ion is not in operation in the spectrum of the 2-pyridine compound. Instead, a McLafferty rearrangement involving a hydrogen



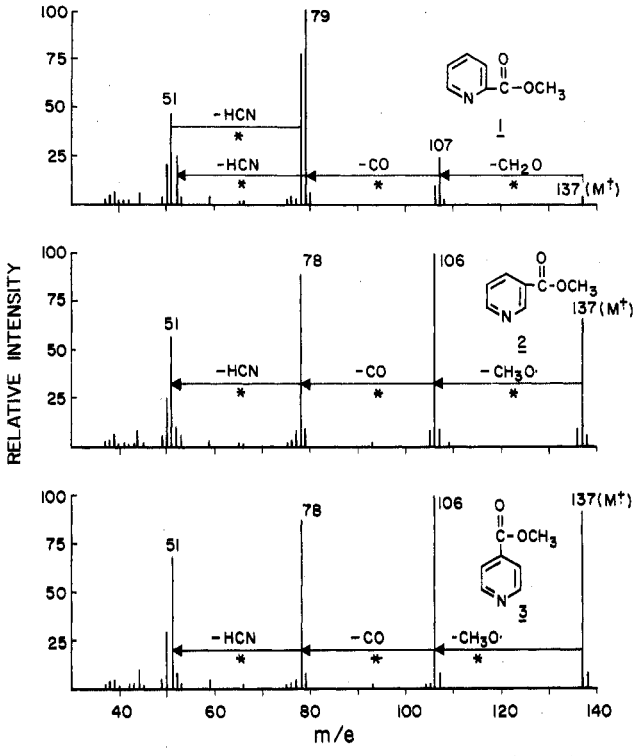


Figure 1. Mass spectra (70 eV) of methyl picolinate (1), methyl nicotinate (2), and methyl isonicotinate (3).

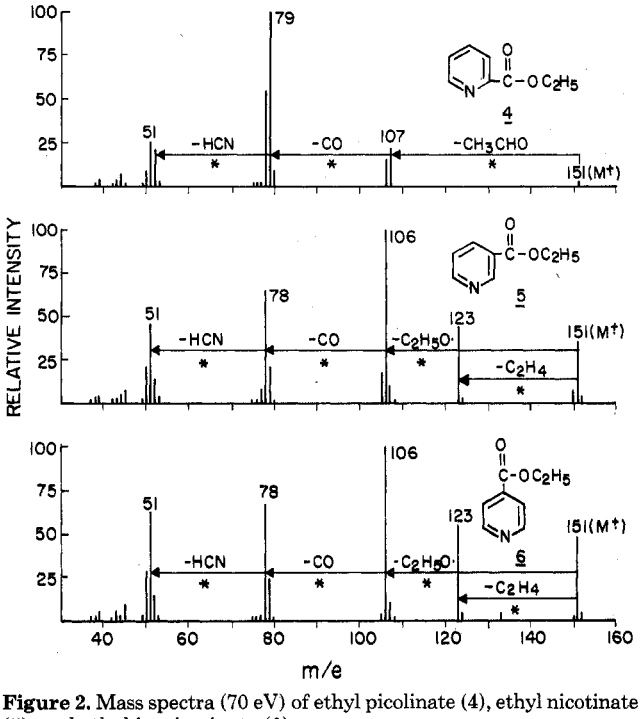
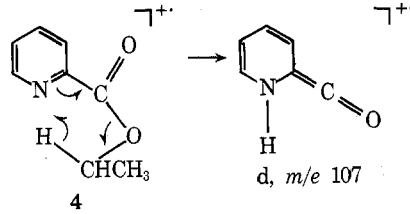


Figure 2. Mass spectra (70 eV) of ethyl picolinate (4), ethyl nicotinate (5), and ethyl isonicotinate (6).

transfer to the ring nitrogen yielding ion d (*m/e* 107) is observed in the spectrum of the 2-pyridine compound **4**. Similar McLafferty rearrangements with a hydrogen transfer from



4 d, *m/e* 107

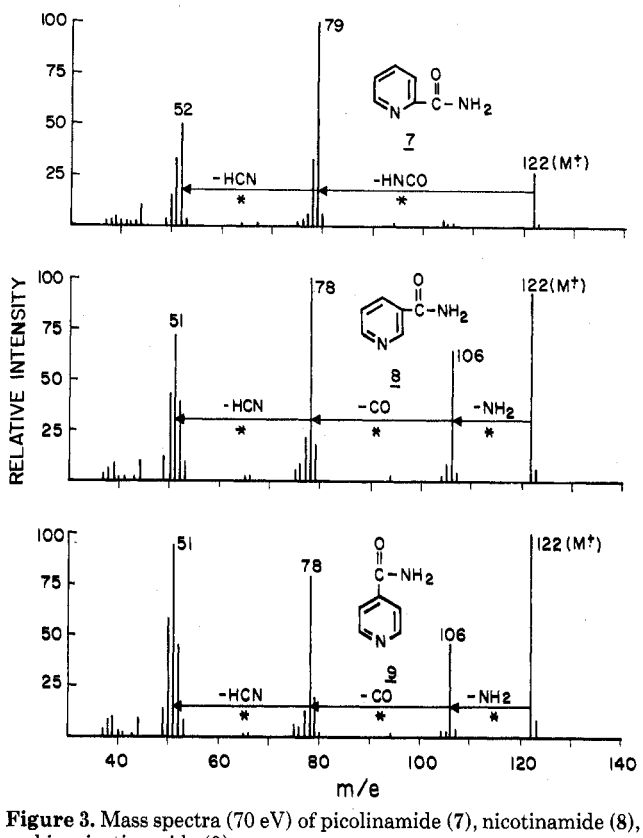
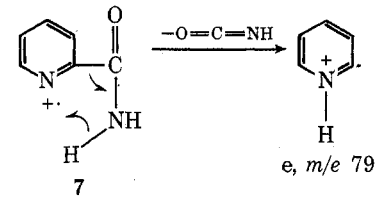


Figure 3. Mass spectra (70 eV) of picolinamide (7), nicotinamide (8), and isonicotinamide (9).

the 2-substituted side chain to the pyridine ring nitrogen have been reported by Cooks et al.,[3] Tomer and Djerassi,[4] Moser and Brown,[7a] and Lightner et al.[8] Deuterium labeling of the methylene hydrogens of compound **4** confirmed that the hydrogen which transfers to the ring nitrogen originates from the α hydrogens of the ethoxy group. The transfer of this hydrogen is facilitated by a six-membered transition state in addition to being a secondary hydrogen.

The mass spectrum of the 2-pyridyl ethyl ester **4** exhibits a base peak at *m/e* 79. The spectra of the 2-pyridyl methyl ester **1** (see Figure 1) and several other 2-substituted pyridine compounds investigated in this study also show a base peak or a strong peak at *m/e* 79. A strong peak at *m/e* 79 generally results from a hydrogen transfer from the 2 substituent to the ring nitrogen followed by a cleavage of the bond attached to the 2 position. The presence of a strong peak at *m/e* 79 and a weak molecular ion peak may be of diagnostic value in identifying the 2-substituted pyridine compounds.

Picolinamide, Nicotinamide, and Isonicotinamide. As shown in Figure 3, the difference between the spectrum of picolinamide (**7**) and those of nicotinamide (**8**) and isonicotinamide (**9**) is evident. The difference is primarily due to the interaction of the ring nitrogen with the side chain in picolinamide. This interaction results in a hydrogen transfer to the ring nitrogen in a five-membered transition state and elimi-



7 e, *m/e* 79

nation of isocyanic acid to yield the base peak ion e (*m/e* 79). The expulsion of isocyanic acid from **7** is analogous to the loss of CO_2 from 2-pyridinecarboxylic acids.[7] The other major

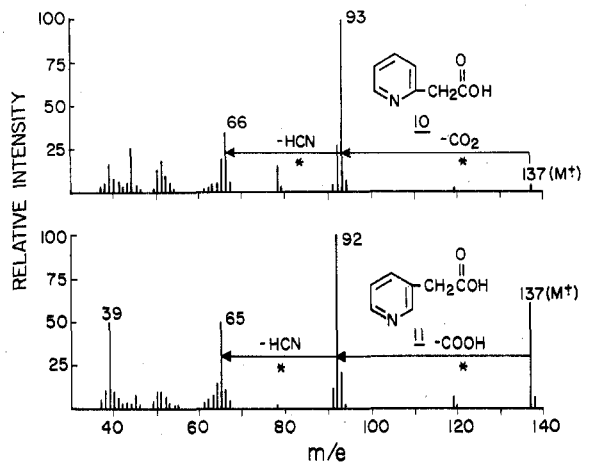


Figure 4. Mass spectra (70 eV) of 2-pyridylacetic acid (**10**) and 3-pyridylacetic acid (**11**).

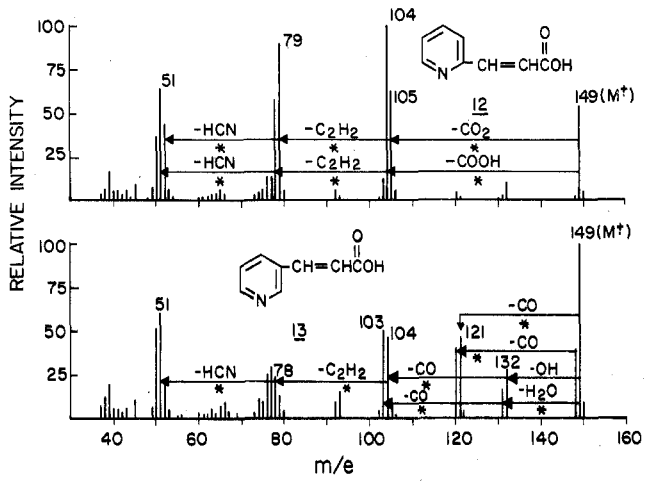
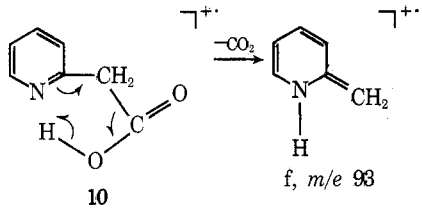


Figure 5. Mass spectra (70 eV) of 2-pyridylacrylic acid (**12**) and 3-pyridylacrylic acid (**13**).

fragmentations are shown in Figure 3. The spectra of nicotinamide and methyl nicotinate have been reported elsewhere.[9]

Pyridylacetic Acids. The striking differences between the mass spectra (Figure 4) of 2-pyridylacetic acid (**10**) and 3-pyridylacetic acid (**11**) are the following: **10** has a very weak molecular ion and a very strong M − CO_2 ion (*m/e* 93), whereas **11** has a strong molecular ion and a very strong M − COOH ion (*m/e* 92). The weak molecular ion and the facile loss of carbon dioxide from the molecular ion in the spectrum of **10** are attributed to the interaction of the substituent at the



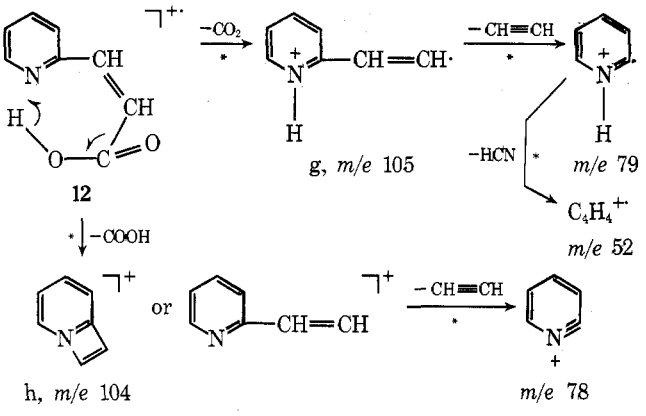
2 position with the ring nitrogen. The interaction is initiated by a transfer of the carboxylic hydrogen to the ring nitrogen in a six-membered ring transition state and expulsion of carbon dioxide yielding ion f (*m/e* 93). Moser and Brown[7] have reported earlier the loss of carbon dioxide from a number of substituted 2-pyridinecarboxylic acid molecular ions and attributed this loss to an interaction of the ring nitrogen and the carboxyl group.

A metastable peak measured by scanning in the metastable mode was observed for the transition from *m/e* 137 (M) to *m/e* 93 (M − CO_2) for compound **10.** This indicates that at least part of M − CO_2 is due to electron impact. The chemical ionization mass spectrum of **10** shows an intense M + 1 peak at *m/e* 138. This suggests that at least a substantial part of **10** is not thermally decomposed prior to ionization.

Pyridylacrylic Acids. The mass spectra of 2-pyridylacrylic acid (**12**) and 3-pyridylacrylic acid (**13**) are shown in Figure 5. Again differences are evident between the spectra of the two isomers. The major fragmentation pathways of **12** are illustrated in Scheme I. Note that the elimination of CO_2 to yield a strong ion g (*m/e* 105) is initiated by a seven-membered ring hydrogen transfer to the pyridine nitrogen. The corresponding peak (*m/e* 105) is weak in the spectrum of **13.** The possible involvement of the side chain in the cyclization to the ring nitrogen to give an ion h (see Scheme I) may contribute to the formation of a very strong ion at *m/e* 104 (M − COOH).

The mass spectrum of 3-pyridylacrylic acid displays two strong peaks at *m/e* 121 and 120 corresponding to the loss of

Scheme I



CO and HCO from the molecular ion, respectively. The elemental compositions of these two ions have been substantiated by high-resolution mass measurements. Other fragmentation pathways are shown in Figure 5.

In summary, mass spectra of 2-substituted pyridine compounds investigated in this study are different from those of their corresponding 3 or 4 isomers. The differences are attributable to the participation of the ring nitrogen in the fragmentation of the 2 isomers.

Experimental Section

All the compounds except methyl picolinate, picolinamide, and 2-pyridylacrylic acid were purchased from Aldrich Chemical Co. Methyl picolinate and picolinamide were obtained from Chemicals Procurement Laboratories. 2-Pyridylacrylic acid was purchased from Research Organic/Inorganic Chemical Corp. 2-Pyridylacetic acid was obtained as its hydrochloride salt. It was converted to free base and its mass spectrum was obtained without storage of sample. Ethyl-*1,1-d*$_2$ picolinate was prepared from ethyl-*1,1-d*$_2$ alcohol and picolinic acid by a method similar to the procedure used by Badgett et al.[10] for octyl nicotinate. The purity of samples was checked by GC, ir, or NMR. In the cases where impurities were found, the samples were purified by either recrystallization or gas chromatography.

Mass spectra were obtained on a CEC 21-104 mass spectrometer at 70 eV, 10 μA, and 2400 V ion accelerating voltage. Samples were introduced via the direct insertion probe. The accurate mass measurements were done on a CEC 21-110B mass spectrometer with a resolution of about 10 000. The metastable peaks were measured by the accelerating voltage scan method similar to the one used by Schulze and Burlingame.[11] The chemical ionization mass spectrum was obtained on a Du Pont 21-490 mass spectrometer using isobutane as the reagent gas.

Registry No.—**1**, 2459-07-6; **2**, 93-60-7; **3**, 2459-09-8; **4**, 2524-52-9; **5**, 614-18-6; **6**, 1570-45-2; **7**, 1452-77-3; **8**, 98-92-0; **9**, 1453-82-3; **10**, 13115-43-0; **11**, 501-81-5; **12**, 7340-22-9; **13**, 1126-74-5; 2-pyridylacetic acid HCl, 16179-97-8.

References and Notes

(1) (a) H. Budzikiewicz, D. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, pp 197, 220, 352, 516; (b) G. G. Still, *Org. Mass Spectrom.*, **5**, 977 (1971).
(2) (a) J. H. Bowie, P. J. Hoffmann, and P. Y. White, *Tetrahedron*, **26**, 1163 (1970); (b) P. H. Chen and D. C. Kleinfelter, *J. Org. Chem.*, **38**, 3015 (1973).
(3) R. G. Cooks, R. N. McDonald, P. T. Cranor, H. E. Petty, and N. L. Wolfe, *J. Org. Chem.*, **38**, 1114 (1973).
(4) K. B. Tomer and C. Djerassi, *J. Org. Chem.*, **38**, 4152 (1973).
(5) (a) C. S. Barnes, R. J. Goldrack, E. J. Halbert, J. G. Wilson, R. J. Lyall, and S. Middleton, *Tetrahedron Lett.*, 705 (1972); (b) D. F. Glenn and W. B. Edwards, III, *Org. Mass Spectrom.*, **10**, 913 (1975); (c) Z. Zaretskii, A. Ben-Bassat, and D. Lavie, *J. Heterocycl. Chem.*, **12**, 837 (1975).
(6) J. H. Bowie, R. G. Cooks, S. O. Lawesson, and G. Schroll, *Aust. J. Chem.*, **20**, 1613 (1967).
(7) (a) R. J. Moser and E. V. Brown, *Org. Mass Spectrom.*, **4**, 555 (1970); (b) E. V. Brown and R. J. Moser, *J. Heterocycl. Chem.*, **8**, 189 (1971).
(8) D. A. Lightner, R. Nicoletti, G. B. Quistad, and E. Irwin, *Org. Mass Spectrom.*, **4**, 571 (1970).
(9) G. R. Waller, Ed., "Biochemical Applications of Mass Spectrometry", Wiley-Interscience, New York, N.Y., 1972, pp 524, 525.
(10) C. O. Badgett, R. C. Provost, Jr., C. L. Ogg, and C. F. Woodward, *J. Am. Chem. Soc.*, **67**, 1135 (1945).
(11) P. Schulze and A. L. Burlingame, *J. Chem. Phys.*, **49**, 483 (1968).

Reactions of Perhaloacetones with Dihydropyridines and Other Electron Donors

Donald C. Dittmer,* Anthony Lombardo, Frederick H. Batzold, and Charles S. Greene

Department of Chemistry, Syracuse University, Syracuse, New York 13210

Received February 18, 1976

The kinetics of the reduction of hexachloroacetone by 3-substituted 1-benzyl-1,4-dihydropyridines is first order in each reactant. The rate of reduction is sensitive to the electron-withdrawing power of the 3 substituent. Attachment of an indole moiety at either the 3 or the 1 position of the dihydropyridine ring resulted at most in a small decrease in the rate. Activation energies for reduction by the 3-carbamoyl- and 3-cyanodihydropyridines are low (5–7 kcal mol^{-1}) and the entropies of activation are very negative (−46, −47 eu). Reduction by the 3-carbamoyl derivative proceeds 33 times more rapidly in acetonitrile than in benzene. The isotope effect (k_H/k_D) in the product-forming step in reactions of hexachloroacetone, pentachloroacetone, and *sym*-tetrachloroacetone with 1-benzyl-3-carbamoyl-1,4-dihydropyridine-4-*d* is essentially invariant with the nature of the halo ketone. Changes in the ultraviolet–visible spectra are observed when dihydropyridines and halo ketones are mixed, suggesting the possible intervention of intermediate complexes in the reduction. Although electron spin resonance studies indicated the lack of detectable radicals in these reactions, one-electron transfer occurs from *N,N,N',N'*-tetramethyl-*p*-phenylenediamine to hexafluoroacetone to yield the cation radical of the amine. Pentachloroacetone is the product from hexachloroacetone and the diamine. 1,4,4-Trimethyl-1,4-dihydropyridine in acetonitrile gives highly colored solutions when mixed either with hexachloroacetone or chloranil. It was not possible to identify products from these reactions.

The efficient, nonenzymic reductions of thiobenzophenones[1] and halo ketones[2] by 1-substituted 1,4-dihydronicotinamides are approximations to the biological reductions of simple carbonyl groups by the coenzyme, NADH. Electronegative halogen atoms enhance the ease of reduction of the carbonyl group in the halo ketones, a finding consistent with the increase in the rate of reduction of the thiocarbonyl groups in thiobenzophenones when electron-withdrawing substituents are present[1] and in the reduction of electron-deficient nitro and nitroso groups by NADH models.[3,4] Recently, Creighton and Sigman found that complexation of the carbonyl group of 1,10-phenanthroline-2-carboxaldehyde by zinc ions allows its efficient reduction by 1-*n*-propyl-1,4-dihydronicotinamide.[5] Metal ions also facilitate the reduction of pyridoxal phosphate,[6] the reduction of α-hydroxy ketones, and the stereoselective reduction of esters of pyruvic and benzoylformic acids[7] by NADH models. In none of the model systems for the biological reduction of a carbonyl group by dihydronicotinamides has a simple, unactivated carbonyl group been reduced efficiently: metal ions or highly electronegative carbonyl compounds are required.

These above examples involve hydrogen transfers from NADH models to a substrate. The NADH models are capable also of electron donation,[8] and one-electron transfers to tetracyanoethylene,[9] quinones,[10] *N*-methylphenazinium methosulfate,[11] and pyocyanine[11] have been observed. The kinetic isotope effects in the reduction of trifluoroacetophenone by various 1-substituted 1,4-dihydronicotinamides have been explained on the basis of an intermediate, possibly of the charge transfer type, in which partial electron transfer may have occurred.[2e] Charge transfer interactions of trifluoroacetophenone with aromatic electron donors are especially important in the photoreductions of that ketone as compared with acetophenone.[12] The possible intervention of charge transfer complexes in hydrogen transfers from NADH has been suggested,[13] and the possible involvement of the halo ketones in such complexes prior to their reduction by NADH models has been noted.[2b] An oriented complex has been suggested to account for the regioselectivity of the addition of a halomethyl anion produced in a haloform-like cleavage of the product of reduction of 1,1,3-trichloro-1,3,3-trifluoro-2-propanone by 1-benzyl-3-cyano-1,4-dihydropyridine.[14]

Reduction of Hexachloroacetone by Dihydropyridines. The reduction of hexachloroacetone in acetonitrile by 1-benzyl-1,4-dihydronicotinamide is first order in both reactants, the kinetics being followed by noting the decrease in absorbance of the dihydro compound. No change in rate was observed when the reaction was done in a degassed cell; and the addition of *tert*-butylcatechol, a free-radical inhibitor, had little effect. For convenience, excess ketone was used so that