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.

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Reactions of Perhaloacetones with Dihydropyridines and Other Electron Donors

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Received February 18, 1976

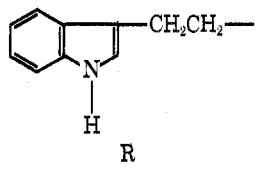
The kinetics of the reduction of hexachloroacetone by 3-substituted 1-benzyl-1,4-dihydropyridines is first order in each reactant. The rate of reduction is sensitive to the electron-withdrawing power of the 3 substituent. Attachment of an indole moiety at either the 3 or the 1 position of the dihydropyridine 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

Table I. Rate Constants for the Reduction of Hexachloroacetone (1×10^{-2} M) by Substituted Dihydropyridines[a] in Acetonitrile at 26.6 °C



R

Registry no.	1-Subst	3-Subst	k_{obsd},[b] s^{-1}
59547-43-2	$PhCH_2$	$CON(CH_3)_2$	2.34×10^{-2}
952-92-1	$PhCH_2$	$CONH_2$	2.71×10^{-3}
	$PhCH_2$	$CONH_2$	3.69×10^{-3} c
	$PhCH_2$	$CONH_2$	5.06×10^{-3} d
	$PhCH_2$	$CONH_2$	6.75×10^{-3} e
	$PhCH_2$	$CONH_2$	1.68×10^{-3} f
	$PhCH_2$	$CONH_2$	3.55×10^{-4} g
	$PhCH_2$	$CONH_2$	8.21×10^{-5} h
19350-64-2	$PhCH_2$	$COCH_3$	4.65×10^{-4}
37589-77-8	$PhCH_2$	CN	4.76×10^{-5}
59547-44-3	CH_3	$CONHCH_3$	7.53×10^{-3} i
59547-45-4	CH_3 (1)	CONHR	6.33×10^{-3} i
59547-46-5	R (2)	$CONH_2$	7.29×10^{-3} i

[a] Concentrations in 10^{-4} M range. [b] Pseudo-first-order constant. [c] Ketone concentration 1.5×10^{-2} M. [d] Ketone concentration 2.0×10^{-2} M. [e] Ketone concentration 2.5×10^{-2} M. [f] 4,4-d_2; ketone concentration 2.55×10^{-2} M. [g] In presence of 5×10^{-3} M $ZnCl_2$. [h] In benzene solvent. [i] 26.1 ± 0.2 °C.

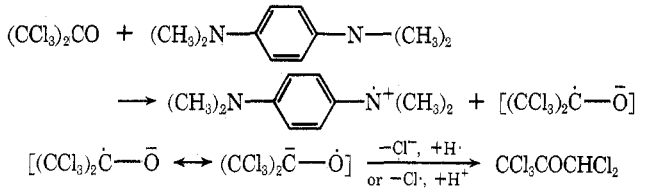
pseudo-first-order kinetics was observed. The rate constant, however, showed first-order dependence on the halo ketone concentration. Table I summarizes the rate data. The rate constant varies by more than 2×10^8 on going from a 3-*N,N*-dimethylcarbamoyl to a 3-cyano substituent. Attachment of an indole moiety to the dihydronicotinamide results, at most, in an 18% decrease in the rate constant from that of 1-methyl-3-methylcarbamoyl-1,4-dihydropyridine. The interpretation of such a small effect is difficult: it may be caused by a steric effect of the bulky indolylethyl substituent, by a small, electron-withdrawing effect of that group, or by complexation of the dihydropyridine with the indole ring. That an interaction can occur between the pyridine and indole rings is indicated by fluorescent emission at 430 nm from the dihydropyridine ring of **1** when the indole chromophore is excited at 300 nm. A similar behavior of **2** was reported by Shifrin a number of years ago.[15] Charge-transfer complexation frequently affects rates; for example, the rate of reaction of pyridine with 3,5-dinitrophthalic anhydride is reduced (ca. 15–50%) by the electron donor, acenaphthene, which stabilizes the anhydride.[16]

Data on the effect of solvents are limited. Protic solvents are unsatisfactory because they react with hexachloroacetone. The reduction proceeds 33 times faster in acetonitrile than in benzene, a reasonable finding in view of the formation of charged molecules from neutral ones. The experimental energies of activation in acetonitrile are 5.2 and 7.2 ± 0.6 kcal mol^{-1}, respectively, for the 3-carbamoyl- and 3-cyano-1,4-dihydropyridines. Entropies of activation are −45.5 and −47.2 ± 0.2 eu, respectively. These activation energies are low compared with those for the reduction of aliphatic ketones by sodium borohydride (9.3–14.9 kcal mol^{-1}).[17] Reduction of riboflavin by 1-*n*-propyl-1,4-dihydronicotinamide has a low activation energy, which prompted the suggestion of complex formation prior to reduction.[18] While experimental energies of activation may be lowered by complex formation,[19] the low activation energies encountered in the reductions of hexachloroacetone may be a consequence of the negative entropies of activation attendant the formation of charged species in an aprotic solvent.[20]

The product isotope effect, k_H/k_D, for the reduction of hexachloroacetone, pentachloroacetone, and *sym*-tetrachloroacetone by 1-benzyl-1,4-dihydronicotinamide is 3.7 ± 0.2, 3.8 ± 0.2, and 3.7 ± 0.2, respectively. The isotope effect was obtained by determination of the amount of deuterium in the alcohol formed by reduction of the ketone by the 4-monodeuteriodihydronicotinamide. The kinetic isotope effect obtained from the comparison of the rates of 1-benzyl-4,4-dideuterio-1,4-dihydronicotinamide with the undeuterated isomer was ca. 4.0 (k_{HH}/k_{DD} = 3.96 ± 0.28), essentially the same as the product isotope effect. The magnitude of the product isotope effect is coincidentally almost the same as that reported (3.8 ± 0.3) for the reduction of trifluoroacetophenone by 1-benzyl- or 1-*n*-propyl-1,4-dihydronicotinamide.[2e]

Effect of Zinc(II) Ions. Zinc ions (5×10^{-3} M) decrease (by a factor of ca. 7) the rate of reduction of hexachloroacetone (1×10^{-2} M) in acetonitrile by 1-benzyl-1,4-dihydronicotinamide (1.5×10^{-4} M), in contrast to the zinc ion accelerated reductions of other carbonyl compounds,[5-7] because of complexation of the zinc with the nicotinamide derivative. The zinc ions not only cause a bathochromic shift from the normal absorption for the dihydro compound at 348 nm but also cause an increase in the absorbance of about 50%. These changes seem too large to be accounted for by a change in solvent polarity on addition of the small amount of zinc chloride. Difference spectra of solutions of the dihydronicotinamide and zinc chloride indicate that the complex has absorption at 389 nm. Because of the closeness of the absorption maxima for complexed and uncomplexed substrate, the equilibrium constant could not be determined accurately. If the rate of reaction of the complexed species is assumed to be small relative to the rate of the uncomplexed species, a dissociation constant of 0.136 is obtained from kinetics.[21] Complexation may occur through the amide group,[22] or it may be of the charge transfer type. Complexation of the electropositive zinc ion with the dihydronicotinamide would be expected to decrease its reducing power in the same manner as attachment of a more electron-withdrawing substituent group.

Reactions with Tetramethyl-*p*-phenylenediamine and with 1,4,4-Trimethyl-1,4-dihydropyridine. Treatment of hexachloroacetone or hexafluoroacetone with *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine in acetonitrile gives a deep blue color, identified as Würster's blue by its ultraviolet absorption spectrum at 568 and 617 nm[23] and by electron spin resonance.[24] The ketyl radical (below in brackets) was not observed by ESR; in any case, its lifetime is short.[25] Pentachloroacetone is formed in about 30% yield; chloride ions were detected by silver nitrate. Tetrachloroacetone (15%) also was obtained.



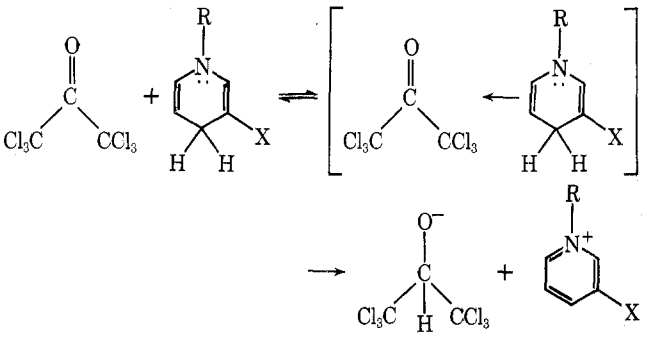
When hexafluoroacetone and the diamine are mixed, a transient, instantaneously produced absorption at 402 nm was observed before the appearance of the blue color of the cation radical of the diamine. An orange color was seen which within a few seconds gave way to the blue of the cation radical. In cyclohexane, the mixture of diamine and hexafluoroacetone showed a broad, new absorption centered at 400 nm and no further change was observed. It seems that a solvent more polar than cyclohexane is required for the electron transfer, which produces ions. The new absorption band may be caused

by formation of a charge-transfer complex. For example, absorption at 843 nm not attributable to any other reactant or product was suggested as being caused by a charge-transfer complex of the diamine and chloranil.[23c]

Just after hexachloroacetone and 1-benzyl-1,4-dihydronicotinamide are mixed in acetonitrile, a transient absorption is observed at higher wavelength (ca. 380 nm) than the absorption for the dihydro compound alone.[26] When 1,4,4-trimethyl-1,4-dihydropyridine, which cannot transfer hydrogen because there is none at the 4 position, is treated with hexachloroacetone in acetonitrile, the solution became yellow at first and then purple. New absorptions appeared at 384 and 540 nm. A purple solution (λ_{max} 586, 720 nm) also appeared when the trimethyldihydropyridine was treated with chloranil. An amorphous, purple solid was obtained from this solution, but the solid was unable to be characterized. Its broad and featureless infrared spectrum and its lack of solubility in both polar and nonpolar solvents suggest a polymer. The new absorptions produced when dihydropyridines are mixed with halo ketones may indicate formation of either a complex, a radical intermediate, or an adduct. No ESR signals could be observed in either hexane or acetonitrile when the reactants were mixed in a special cell immediately prior to the ESR measurement. The trimethyldihydropyridine has been reported to form a charge-transfer complex with maleic anhydride.[27]

Discussion

Charge transfer complexation and one-electron transfers involving hexachloro- or hexafluoroacetone are possibilities which must be considered when examining reductions of these ketones by models for the pyridine nucleotide coenzymes. Previous observations have indicated that free-radical inhibitors do not affect the reduction of the carbonyl group, but one-electron transfers within complexes cannot be ruled out.[2b] The requirement of an obligatory intermediate to explain isotope effects in the reduction of trifluoroacetophenone supports a more complex mechanism than a simple, one-step hydride ion transfer.[2e] Our finding that the kinetic isotope effect with hexachloroacetone and 1-benzyl-4,4-dideuterio-1,4-dihydronicotinamide is essentially the same as the product isotope effect contrasts with the studies on trifluoroacetophenone for which the two isotope effects differed. This result is consistent both with a mechanism of hydrogen transfer involving an intermediate complex (provided the same reasonable assumptions are made concerning the magnitudes of rate constants as was made in the trifluoroacetophenone work)[2e] and with a mechanism involving no intermediates. The significant involvement of charge-transfer complexation in the photoreduction of trifluoroacetophenone[12] lends credence to the suggestion of intermediate complexes, probably of the donor–acceptor type. As mentioned previously, the regioselectivity of reactions of an unsymmetrically substituted perhaloacetone with a dihydropyridine derivative may be interpreted on the basis of an oriented, intermediate complex.[14] Oriented complexes or transition states have been suggested to explain the stereospecificity of certain dehydrogenase enzymic reductions,[13,28] and preliminary, stereospecific complexation may occur in the recently reported zinc-catalyzed reduction of α-keto esters by chiral NADH models.[7] Complexation may be especially important for highly electron-deficient substrates, and the spectroscopic observations with perhaloacetones and 1,4,4-trimethyl-1,4-dihydropyridine and 1-benzyl-1,4-dihydronicotinamide may be considered as indications of complex formation although, as indicated above, other possibilities, or combinations of them, may explain the results. The scheme for the reduction of hexachloroacetone via a complex is illustrated:



Experimental Section[29]

Materials. Acetonitrile (Matheson Coleman and Bell, Spectroquality) was refluxed over calcium hydride for 2 h and distilled from the hydride. The halo ketones were obtained commercially and were purified by distillation. Hexafluoroacetone was used as obtained. 1-Benzyl-3-carbamoyl-1,4-dihydropyridine and its mono-4-deuterio analogue were prepared as previously described.[30] *N,N,N′,N′*-Tetramethyl-*p*-phenylenediamine was prepared from the dihydrochloride.[31] 1,4,4-Trimethyl-1,4-dihydropyridine was prepared as described previously.[27] 1-(β-Ethyl-3-indolyl)-3-carbonyl-1,4-dihydropyridine[15] was prepared as described previously. 1-Benzyl-4,4-dideuterio-1,4-dihydronicotinamide was prepared according to the directions of Mauzerall and Westheimer[32] by reduction of 1-benzyl-3-carbamoyl-4-deuteriopyridinium chloride in D_2O. ^1H NMR analysis of the intermediate, methyl 4-deuterionicotinate, showed only 2–3% of protium at the 4 position.

1-Benzyl-3-acetyl-1,4-dihydropyridine. Reduction of 1-benzyl-3-acetylpyridinium chloride by sodium dithionite was done as described previously.[2b,33] A better yield was obtained when the reduction was done at 0 °C for 7 h, during which time the dihydropyridine precipitated. Precipitation was encouraged by refrigeration of the reaction mixture overnight. Recrystallization from ethanol provides off-white crystals (85% yield), mp 64–66 °C dec (lit.[33] mp 61–67 °C).

1-Benzyl-3-cyano-1,4-dihydropyridine. 3-Cyanopyridine (30 g, 0.288 mol) and benzyl chloride (36.5 g, 0.288 mol) were refluxed for 22 h in 150 ml of absolute ethanol in a 300-ml, one-necked, round-bottomed flask equipped with a condenser and drying tube. No precipitation of product was observed upon cooling even at freezer temperatures. A small amount of the solution (ca. 2 ml) was placed in a test tube, and anhydrous ether was added. A white precipitate formed and these crystals were used to seed the main body of the reaction solution. Precipitation then occurred rapidly to give white 1-benzyl-3-cyanopyridinium chloride (41 g, 62%). The material starts to darken in color at ca. 185 °C and becomes red just before melting: mp 207–209 °C dec; ir (KBr) 2250 (w), 1640 (s), 1580 (w), 1490 cm^{-1} (s); uv (methanol) 268 nm (ϵ 3900); NMR (D_2O) δ 9.4 (s, 1 H), 9.15 (complex doublet, 1 H), 8.8 (complex doublet, 1 H), 8.26 (quartet, 1 H), 7.31 (complex multiplet, 5 H), 5.8 (s, 2 H).

Anal. Calcd for $C_{13}H_{11}ClN_2$: C, 67.7; H, 4.77; N, 12.1. Found: C, 67.8; H, 5.05; N, 12.1.

Sodium dithionite (34.8 g, 0.2 mol) and sodium carbonate (17.7 g, 0.167 mol) were dissolved in 250 ml of distilled water in a 500-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer and a 60-ml addition funnel. 1-Benzyl-3-cyanopyridinium chloride (11.5 g, 0.05 mol) dissolved in 50 ml of distilled water was added dropwise to the vigorously stirred solution by means of the addition funnel. The solution immediately became yellow but no precipitation occurred throughout the entire addition of the salt which took 30 min. After ca. 90 min more, a yellow precipitate formed. Stirring was halted when it appeared that precipitation had been completed. The solid was collected by filtration and recrystallized from ethanol–water (no heating). Bright yellow needles (7 g, 71%) were obtained and dried in a vacuum oven for 1 h at 35–40 °C: mp 52–53 °C dec; ir (KBr) 2200 (s), 1680 (s), 1610 (s), 1495 cm^{-1} (m); uv (CH_3CN) 340 nm (ϵ 5600); NMR ($CDCl_3$) δ 7.31 (s, 5 H), 6.51 (d, $J_{2,6}$ = 1.5 Hz, 1 H), 5.68 (pair of quartets, 1 H), 4.58 (pair of triplets, 1 H), 4.18 (s, 2 H), 3.02 (broad quartet, 2 H).

Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.51; H, 6.12; N, 14.28. Found: C, 79.38; H, 6.02; N, 14.45.

1-Benzyl-3-(*N,N*-dimethylcarbamoyl)-1,4-dihydropyridine. *N,N*-Dimethylnicotinamide (25 g, 0.17 mol) and benzyl chloride (21.5 g, 0.17 mol) were refluxed for 8 h in 100 ml of ethanol in a 200-ml, round-bottomed, one-necked flask equipped with a condenser and

drying tube. No precipitation occurred upon cooling. Because of the hygroscopicity of the salt no attempt was made to obtain the 1-benzyl-3-(*N,N*-dimethylcarbamoyl)pyridinium chloride as a solid, and 100 ml of water was added to the oil obtained by evaporation of solvent. The yield of salt was estimated to be ca. 35 g (75%). A NMR spectrum of the water solution was consistent with the presence of a pyridinium salt: δ 9.26 (s, 1 H), 9.16 (d, 1 H), 8.70 (d, 1 H), 8.24 (quartet, 1 H), 7.44 (broad singlet, 5 H), 5.9 (s, 2 H), 3.05 (s, 3 H), 2.95 (s, 3 H).

The reduction was carried out directly on half of the aqueous solution of pyridinium salt (ca. 17 g, 0.062 mol) at 0 °C. Sodium dithionite (41.8 g, 0.24 mol) and sodium carbonate (21.2 g, 0.20 mol) were dissolved in 200 ml of distilled water in a 500-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer and a 60-ml addition funnel. To this vigorously stirred solution, the salt solution was added dropwise over a period of 1 h. The solution turned yellow immediately, and 1 h after the salt addition had been completed, a yellow precipitate formed. The reaction was put under nitrogen to prevent decomposition of the dihydro compound. The reaction was allowed to proceed for a total of 6 h. The solid was collected by filtration under nitrogen, crude mp 38–50 °C. This compound decomposed very quickly in air to give a dark brown oil. Purification was accomplished by eight recrystallizations (material dissolved in ethanol without heating, water added to the cloud point, then cooling). The yield after all recrystallizations was 4 g (37%): mp 56–58 °C; ir ($CHCl_3$) 1675 (s), 1600 (vs), 1490 cm^{-1} (s); uv (ethanol) 345 nm (ε 4300); NMR ($CDCl_3$) δ 7.3 (s, 5 H), 6.23 (d, $J_{2,6}$ = 1.5 Hz, 1 H), 4.59 (pair of triplets, 1 H), 4.22 (s, 2 H), 3.17 (broad doublet, 2 H), 2.97 (s, 6 H).

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.39; H, 7.44; N, 11.58. Found: C, 74.21; H, 7.08; N, 11.36.

1-Methyl-3-(*N*-methylcarbamoyl)-1,4-dihydropyridine. Sodium carbonate (21.2 g, 0.20 mol) and 1-methyl-3-(*N*-methylcarbamoyl)pyridinium iodide[34] (6.8 g, 0.0274 mol) were dissolved in water (150 ml). The solution was cooled to 4 °C and sodium dithionite (13.0 g, 0.07 mol) was added. The mixture was stirred at 4 °C for 3 h and the solid was removed by filtration. Recrystallization of the solid from hot water (60–70 °C) gave a light yellow solid (2.1 g, 0.0138 mol, 50.4%): mp 77–79 °C; uv (CH_3CN) 347 nm (ε 5485); NMR ($CDCl_3$) δ 2.75 (s, 3 H), 2.90 (s, 3 H), 3.06 (m, 2 H), 3.33 (s, 1 H), 4.63 (m, 1 H), 5.70 (m, 1 H), 6.86 (m, 1 H).

1-Methyl-3-(*N*-β-ethyl-3-indolyl)carbamoylpyridinium Iodide. Nicotinic acid tryptamide[35] (2.50 g, 0.009 mol) and methyl iodide (5.11 g, 0.036 mol) were dissolved in absolute ethanol (50 ml). The mixture was refluxed for 20 h and cooled. Ethyl ether was added to the cloud point, and cooling to −20 °C precipitated the yellow product (2.0 g, 0.0049 mol, 54%): mp 204–206 °C; NMR (Me_2SO-d_6) δ 2.9–3.18 (m, 2 H), 3.45–3.70 (m, 2 H), 3.78 (m, 1 H), 4.41 (s, 3 H), 6.83–7.67 (m, 5 H), 8.08–8.33 (m, 1 H), 8.81–8.95 (m, 1 H), 9.05–9.15 (m, 1 H), 9.38 (m, 1 H).

Anal. Calcd for $C_{17}H_{18}IN_3O$: C, 50.12; H, 4.42; N, 10.31. Found: C, 50.38; H, 4.41; N, 10.13.

1-Methyl-3-(*N*-β-ethyl-3-indolyl)carbamoyl-1,4-dihydropyridine. Sodium carbonate (0.636 g, 0.006 mol) and 1-methyl-3-(*N*-β-ethyl-3-indolyl)carbamoylpyridinium iodide were dissolved with stirring in water (350 ml) in an atmosphere of nitrogen. Sodium dithionite (1.74 g, 0.01 mol) was added in several portions and the solution became bright yellow. Stirring was continued for 1 h and the solution was extracted with methylene chloride (3 × 100 ml). Drying ($NaSO_4$) and removal of the solvent at reduced pressure gave an amorphous yellow solid (0.58 g, 0.0021 mol, 68.8%): mp 197–201 °C; NMR (CD_3CN) δ 2.81 (s, 3 H), 2.98 (m, 4 H), 3.50 (m, 2 H), 5.66 (m, 1 H), 6.08 (m, 1 H), 6.86–7.66 (m, 6 H); uv (CH_3CN) 347 nm (ε 5850). An analysis was not performed because the compound is extremely sensitive to air and heat: the material turns to an oil and becomes progressively dark red.

Table II. Variation of k_{obsd} with Temperature for the Reduction of Hexachloroacetone[a] by 1-Benzyl-3- carbamoyl-1,4-dihydropyridine[b] in Acetonitrile

Temp, K	$10^3\ k_{obsd}\ s^{-1}$
299.6	2.52
309.6	3.32
319.6	4.41

[a] 1.00 × 10^{-2} M. [b] 1.08 × 10^{-4} M.

Table III. Interactions of *N,N,N',N'*-Tetramethyl-*p*-phenylenediamine and 1,4,4-Trimethyl-1,4-dihydropyridine with Electron Acceptors in CH_3CN

Donor[a]	Registry no.	Acceptor[b]	Registry no.	ESR signal	Color	λ_{max}, nm
TMPD	100-21-1	HFA	684-16-2	Yes	Blue	402,[c] 568, 617
TMPD		HCA			Blue	404, 568, 620
TMPD		HFA				380–450[d]
TMPD		DDQ	84-58-2		Blue	430, 568, 611
TMPD		CA	118-75-2		Blue	450, 568, 620
TDP	59547-47-6	HCA	116-16-5	No	Blue-red	540[e]
TDP		CA		No	Purple	586, 720

[a] TMPD = *N,N,N',N'*-tetramethyl-*p*-phenylenediamine; TDP = 1,4,4-trimethyl-1,4-dihydropyridine. [b] HFA = hexafluoroacetone; HCA = hexachloroacetone; DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; CA = chloranil. [c] Disappears after 10 min as absorption at 568 and 617 nm reaches maximum intensity. [d] Hexane solvent; broad, weak absorption. [e] New absorption first appears at 382 nm slowly giving way to the absorption at 540 nm.

Kinetics and Isotope Effects. Spectrophotometric measurements were done on a Perkin-Elmer ultraviolet–visible spectrophotometer, Model 202, equipped with a controlled temperature cell mount and a time-drive accessory with interchangeable motors.

The dihydro compound was weighed out on a Cahn ratio balance and was transferred to a volumetric flask, and the flask was filled to the mark with acetonitrile. The halo ketone was weighed directly into a volumetric flask and the flask was then filled to the mark with solvent.

In a typical run the sample and reference cells were placed in the thermostated cell mount which was maintained at 26.6 ± 0.05 °C. The time-drive accessory was locked on the wavelength of maximum absorption of the dihydropyridine. The reference cell contained pure solvent. Products of the reaction, the pyridinium ion and the alkoxide ion, were not needed in the reference cell at the concentrations used since they did not interfere with the band being followed. A syringe equipped with a Chaney adapter was used to deliver 2 ml of the halo ketone solution into the sample cell. The same syringe was then washed and dried thoroughly and used to deliver 2 ml of the dihydropyridine solution into the halo ketone solution in the sample cell. Mixing was instantaneous; the cell compartment cover was closed quickly and locked, and the time drive motor was started. The speed of the time drive motor used was chosen on the basis of a length of time sufficient to allow 65% or more reaction to occur. Control experiments showed that solvent evaporation was negligible for periods up to 1 h.

The infinity values of the absorbance (A_∞) were obtained in two ways. At the conclusion of a run the reaction solution was transferred from the sample cell to a 10-ml volumetric flask. The flask was sealed and placed in a constant-temperature bath for the required time (ca. 20 half-lives). At the end of that time the solution was returned to the sample cell and its spectrum was recorded. The other method used was to mix equal volumes of the reaction solutions in a 10-ml volumetric flask which was then sealed and placed in a thermostated bath. After the required time, the t_∞ spectrum of the solution was recorded.

Rate constants (pseudo-first-order) were calculated from the slope of the line obtained by plotting log ($A_t - A_\infty$) against time, where A_t is the absorbance at time t. The absorption of the dihydropyridines obeys Beer's law. Table II gives the data from which the experimental energies and entropies of activation were obtained.

The NMR spectrum taken immediately after mixing chloroform-*d*

solutions (room temperature) of 1-benzyl-1,4-dihydronicotinamide and hexachloroacetone showed the absence of absorption at δ 3.10 for the methylene protons at the 4 position of the dihydro compound and appearance of absorption at δ 4.81 for the 2 proton of 1,1,1,3,3,3-hexachloro-2-propanol.[36] Protons for the formation of hexachloro-2-propanol from the alkoxide presumably are donated by solvent or by the amide group.

The rate of reaction of hexachloroacetone with 1-benzyl-1,4-dihydronicotinamide in the absence of atmospheric oxygen was determined spectrophotometrically in a Pyrex ultraviolet cell equipped with a side bulb and an attached joint for evacuation of the cell and side arm by means of a high vacuum system. A solution of the halo ketone was placed in the cell and a solution of the dihydronicotinamide was placed in the side bulb. The solutions were frozen in a bath of dry ice–trichloroethylene and the system was degassed ($<10^{-3}$ mm). The observed rate constant for a reaction mixture 1.0×10^{-2} M in halo ketone and 1.0×10^{-4} M in dihydronicotinamide at 26.6 °C was 2.58×10^{-3} s^{-1}, in satisfactory agreement with the average value of 2.71×10^{-3} s^{-1} obtained when no precautions were taken to exclude air.

The halo-2-propanols were isolated from reactions in acetonitrile of 1-benzyl-4-deuterio-1,4-dihydronicotinamide with hexachloroacetone, pentachloroacetone, and *sym*-tetrachloroacetone. Control experiments show that exchange of deuterium from the alcohol does not occur either during workup or under the conditions of reduction (e.g., 2-deuteriohexachloro-2-propanol does not lose its deuterium when it was put through the workup procedure consisting of evaporation of the acetonitrile solution and chromatography of the residue on Florisil with elution by 2:1 hexane–ether or when it was added to a mixture of *sym*-tetrachloroacetone and 1-benzyl-1,4-dihydronicotinamide in acetonitrile.) Deuterium analysis was done on the acetates of the alcohols (prepared by treating the alcohol with acetic anhydride plus 2 drops of concentrated sulfuric acid) by mass spectrometry (with the exception of pentachloroisopropyl alcohol, which was analyzed without conversion to an acetate). The values of k_H/k_D thus obtained were 3.7, 3.8, and 3.7, respectively. A sample of 1,1,3,3-tetrachloro-2-propyl acetate also was analyzed by the combustion–falling drop technique[37] to give a value of k_H/k_D of 3.9, within experimental error (0.2) of the values obtained by mass spectrometry.

Interaction of *N,N,N',N'*-Tetramethyl-*p*-phenylenediamine and 1,4,4-Trimethyl-1,4-dihydropyridine with Halo Ketones. The observations are summarized in Table III. Gas chromatography [on a 5 ft × 0.25 in. glass column of 20% Dow-Corning Silicone Oil 550 on Chromosorb P (80/100 mesh)] of the reaction of diamine and hexachloroacetone showed the formation of pentachloroacetone whose infrared spectrum (of an isolated sample) was identical with that of an authentic sample. Tetrachloroacetone and unreacted hexachloroacetone also were detected. In a comparison of the gas chromatographic behavior of the reaction mixture with that of a mixture of authentic hexachloroacetone, pentachloroacetone, and tetrachloroacetone, one can estimate that the reaction mixture contained roughly 15% hexachloroacetone, 25% pentachloroacetone, and 15% tetrachloroacetone. Water (20 ml) was added to the reaction mixture and nonpolar organic compounds were extracted with ether (20 ml) twice. The aqueous solution was acidified and addition of aqueous silver nitrate gave an immediate precipitate of silver chloride (ca. 1 mol of chloride ions were produced per mole of hexachloroacetone).

A purple, amorphous product was obtained from the reaction of chloranil with 1,4,4-trimethyl-1,4-dihydropyridine: ir, broad and featureless; NMR (Me_2SO-d_6) δ 1.23 (m), 2.20 (s), 2.60 (s), 2.90 (m), 3.60 (m).

Spectroscopic Observations on Mixtures of Halo Ketones and 1-Benzyl-1,4-dihydronicotinamide. Alone, hexachloroacetone and hexafluoroacetone each have an absorption maximum in acetonitrile at 296 and 290 nm, respectively. Solutions of halo ketone and 1-benzyl-1,4-dihydronicotinamide in acetonitrile were mixed, and the ultraviolet spectrum was immediately taken in the region above 330 nm. The absorbance (beyond 350 nm) of the mixture was always greater than the sum of the absorbances of the reactants. The concentration of halo ketone was much greater than the concentration of dihydropyridine. A 1 M solution of hexachloroacetone and a 10^{-4} M solution of 1-benzyl-1,4-dihydronicotinamide showed new absorption (difference spectrum) at 382 nm.[26] This absorption disappears as the reduction proceeds. Pentachloroacetone and *sym*-tetrachloroacetone (both 5×10^{-2} M) with 10^{-4} M dihydro compound gave new maxima in the difference spectra at 371 and 362 nm, respectively. 1,1,1-Trichloroacetone (50% by volume) and chloroacetone (neat) showed no change in the ultraviolet spectrum when mixed with a 10^{-4} or 10^{-3} M solution of 1-benzyl-1,4-dihydronicotinamide.

Acknowledgments. We are grateful to the National Institute of Arthritis and Metabolic Diseases, Grant AM07770, for partial support of this work. We also thank Bristol Laboratories for donation of a proton magnetic resonance spectrometer to the Department of Chemistry which enabled the NMR spectra reported in this paper to be obtained.

Registry No.—3-Cyanopyridine, 100-54-9; benzyl chloride, 100-44-7; 1-benzyl-3-cyanopyridinium chloride, 14535-08-1; *N,N*-dimethylnicotinamide, 6972-69-6; 1-benzyl-3-(*N,N*-dimethylcarbamoyl)pyridinium chloride, 58287-39-1; 1-methyl-3-(*N*-methylcarbamoyl)pyridinium iodide, 58287-40-4; 1-methyl-3-(*N*-β-ethyl-3-indolyl) carbamoylpyridinium iodide, 59547-48-7; nicotinic acid, 59-67-6; tryptamide, 61-54-1.

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Alkyl Nitrate Nitration of Active Methylene Compounds. Nitration of Arylidene and of Alkylidene Phenylhydrazines[1]

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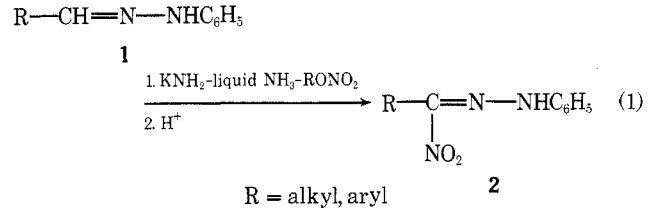
Received March 31, 1976

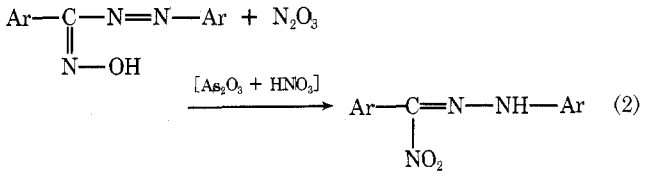
The alkyl nitrate nitration of arylidene and alkylidene phenylhydrazines affords the corresponding α-nitroarylidene and α-nitroalkylidene phenylhydrazines. Exclusive nitration on carbon is observed. This is in contrast to alkylation and acylation reactions which occur on nitrogen. The NMR spectra of the nitro compounds show the presence of both the *Z* and *E* isomers. The ratio of the isomers varies with the polarity of the solvent, the *Z* configuration predominating in nonpolar media owing to intramolecular hydrogen bonding.

In continuation[2] of our studies of the alkyl nitration, we are now reporting on its application to the synthesis of α-nitroarylidene and α-nitroalkylidene phenylhydrazines (eq 1).



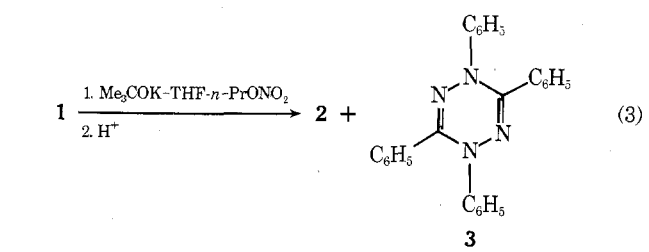
(1)

Previously, the only available method for preparing these compounds involved the coupling of diazonium compounds with salts of primary nitro compounds.[3,4] The method has afforded moderate yields and suffered because substituted arylnitromethanes are not readily available. α-Nitroarylidene phenylhydrazines have also been obtained in low yields from the oxidation of arylazoaldoximes[5] (eq 2).



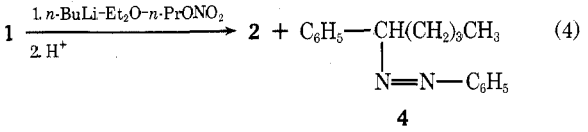
(2)

The nitration reaction in eq 1 was studied in several base–solvent systems with 1 (R = C_6H_5) as the model compound; the results are summarized in Table I. Highest yields (91%) of α-nitrobenzylidene phenylhydrazine (**2**) (R = C_6H_5) were obtained in the potassium amide–liquid ammonia system when the molar ratio of 1 to base to nitrating agent was 1:1:2. In the potassium *tert*-butoxide–tetrahydrofuran (THF) system, the yield of **2** was 80% but the reaction was accompanied by the formation of 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (**3**) (eq 3). It is very likely that **2** is the precursor in the formation of **3** for **2** was converted into **3** on heating in ethanolic potassium hydroxide or methanolic sodium methoxide.[6]



(3)

When the nitration of **1** was carried out in the *n*-butyllithium–ethyl ether system, 1-phenylazo-1-phenylpentane (**4**) was the major product (40%) and **2** the minor product (30%) (eq 4). Compound **4** arose from a nucleophilic attack of *n*-butyllithium on the azomethine carbon of **1**, followed by air oxidation, a reaction which is well documented.[7]



(4)

The generality of the reaction in the potassium amide–liquid ammonia system was established by its application to a variety of compounds **1** including those derived from heterocyclic carboxaldehydes. As indicated by the data shown in Table II, the yields of some of the nitro compounds were substantially higher when reactions were carried out in a more concentrated medium. For instance, the yield of α-nitroethylidene phenylhydrazine (**5**) was increased by 53% when the concentration of potassium amide was increased from 0.3 to 0.7 M. This phenomenon was previously observed in the nitration of alkylsulfonate esters[8] and alkyl-substituted heterocyclics.[9]

However, nitrations in a more concentrated medium did not improve the yields of α-nitro-1-naphthylidene phenylhydrazine and α-nitro-3-picolylidene phenylhydrazine.

The low yields of compounds **2** (R = alkyl), with the exception of compound **5**, are very likely due to the instability of the starting materials.

Spectra of Compounds 2. A detailed study of the NMR spectra of compounds **2** indicated that in solution, both *E* and *Z* isomers were present. In relatively nonpolar solvents, the *Z* isomer predominated. This can be explained on the basis of its increased stability due to intramolecular hydrogen bonding. For example, the spectrum of **2** (R = C_6H_5) in $CDCl_3$ showed two NH absorptions at δ 12.0 and 8.0, which integrated to a value of 0.7 and 0.3 protons, respectively. The signals at δ 12.0 and 8.0 were assigned to the *Z* and *E* isomers, respectively. In a recent NMR study of these compounds, the authors reported only one NH signal in $CDCl_3$ at δ 11.73–11.89 and assigned it to the *Z* isomer.[10] The absorption peak at 12.0