They were soluble in DMF, pyridine, ethyl acetate, benzene, toluene, chloroform, acetone, and other common solvents for polymeric esters even in the presence of a protic solvent, such as alcohol. Solutions gelled on standing over an extended period of time finally resulting in separation of the corresponding polysaccharides or polyvinyl alcohol. On addition of mineral acid, the regenerated polymer separated immediately. The nitrite esters were analyzed by suspending the moist fibrous material in water, acidifying with sulfuric acid, and keeping the mixture in a closed Erlenmeyer flask with occasional shaking. After about 1 hr, a portion of the sample was neutralized with sodium hydroxide and the nitrite titrated with permanganate solution. The nitrate formed during titration was precipitated and identified as nitron nitrate.[9] The other portion was poured slowly and with agitation into 3–4 volumes of isopropyl alcohol to precipitate the polysaccharide and the precipitate was removed, dried in vacuo over P_2O_5 at 60°, and weighed.

Registry No.—Cellulose nitrite, 57255-90-0; starch nitrite, 57255-91-1; quar gum nitrite, 57108-91-5; locust bean gum nitrite, 57108-95-9; alginic acid nitrite, 57108-92-6; hemicellulose nitrite, 57108-93-7; polyvinyl alcohol nitrite, 57108-94-8; dinitrogen tetroxide, 10544-72-6; nitrosyl chloride, 2696-92-6.

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Selective Chlorinations in Sulfuric Acid. Synthesis of Some 2-Amino-5-chloro-, 2-Amino-3-chloro-, and 2-Amino-3,5-dichloropyridines

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A convenient and general process is described for the selective monochlorination of 2-aminopyridine and a number of methyl-substituted 2-aminopyridines. The chlorination of 2-aminopyridine at various sulfuric acid concentrations and the distribution of chlorinated products has been studied in detail. The results show that with increasing acidity dichlorination decreases, and in 72% sulfuric acid only traces of dichlorination occur. The selectivity of the chlorination reaction is ascribed to differences in the rate of chlorination of protonated vs. nonprotonated substrates.

We wish to report a convenient and general process for the selective monochlorination of 2-aminopyridine and a number of methyl-substituted 2-aminopyridines.

Several procedures for the chlorination of 2-aminopyridine have appeared in the literature. Chichibabin[1] reported the chlorination of 2-aminopyridine in ethanol. Later workers,[2,3] unable to duplicate the literature results, utilized 20% aqueous sulfuric acid at 25° as the solvent. However, in each of these procedures the desired monochlorinated product was found to be contaminated with significant amounts of 2-amino-3,5-dichloropyridine. A 70% yield of 2-amino-5-chloropyridine, with only slight formation of dichlorinated product, was obtained by treating 2-aminopyridine in concentrated hydrochloric acid with hydrogen peroxide.[4] These results on the chlorination of 2-aminopyridine in highly acidic media, and the varied selectivity reported in the halogenation of other aminopyridines,[5,6] led us to undertake a systematic investigation of this reaction.

Results

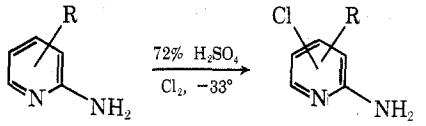
Chlorination of 2-Aminopyridine. Reaction of 2-aminopyridine (1) with a 2 molar excess of chlorine gas at various sulfuric acid concentrations gave the products listed in Table I. The distribution clearly shows that with increasing acidity dichlorination decreases, and in 72% sulfuric acid only traces of 2-amino-3,5-dichloropyridine (1c) are formed. Under optimum conditions (see Table II) the crude product 2-amino-5-chloropyridine (1b) had 99% purity and was obtained in 82–85% yield (98% based on recovered 1).

Table I
Chlorination of 2-Aminopyridine in Sulfuric Acid

Sulfuric acid concn		% product distribution	
Wt %	H_0	5-Chloro-	3,5-Dichloro-
17	−0.8	50	50
30	−1.5	52	48
45	−2.7	77	23
55	−3.7	92	8
72	−5.8	98	2

Chlorination of Substituted 2-Aminopyridines. The generality of the chlorination process and the specificity toward monochlorination were demonstrated by chlorination of the compounds listed in Table II. As one might anticipate, the methyl groups facilitate 3 substitution. The combined effect of the methyl group on product distribution in the case of the 2-amino-4-methyl- and 2-amino-6-methylpyridines (3 and 5) when compared with 2-amino-4,6-dimethylpyridine (6) was very close to an average. The structure of each chlorinated product was easily determined by ^1H NMR spectroscopy except in the case of 2-amino-6-methylpyridine (5). Each monochloro derivative of 5 displayed an AB system for the aromatic protons, and the spectra were almost identical. A literature search revealed that Parker and Shive had prepared the nitro derivative (9) of 2-amino-3-chloro-6-methylpyridine by an alternate route.[7] Using their procedure we nitrated 5 and separated the mononitro products (7 and 8), and subsequent

Table II
Selective Chlorination in Sulfuric Acid

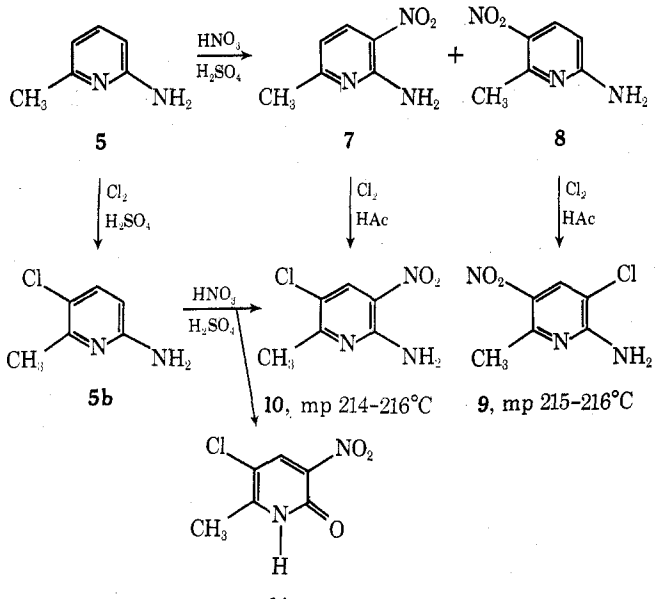


(1)

No.	Starting material	pK_a[a]	% product distribution[b] a, 3-Chloro	b, 5-Chloro	c, 3,5-Dichloro	% yield[c]
1	2-Aminopyridine	6.14	0	98	Tr	85 (98)
2	2-Amino-3-methylpyridine	6.52	0	99	0	92 (98)
3	2-Amino-4-methylpyridine	6.76	58	41	Tr	90 (99)
4	2-Amino-5-methylpyridine	6.50	87	0	0	14 (16)
5	2-Amino-6-methylpyridine	6.69	12	88	Tr	85 (99)
6	2-Amino-4,6-dimethylpyridine	7.12	39	59	2	67 (82)
1b	2-Amino-5-chloropyridine	4.71	0	97	3	3 (99)

[a] The pK_a data were taken from W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, 31, 1295 (1966), except for 1b which was from P. J. Brignell, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc. B*, 117 (1970). [b] Product distribution was determined by GLC on the entire product mixture. [c] Yields in parentheses are based on recovered starting material.

Scheme I



chlorination of the individual isomers afforded respectively the known 2-amino-3-chloro-5-nitro-6-methylpyridine (**9**) and the new chloro derivative **10** (Scheme I). The major monochlorinated isomer from **5**, which consisted of 88% of the product, was nitrated and gave two products, one of which was a *mononitro* derivative identical in all respects with **10**. A mixture melting point with **10** was not depressed, although one with **9** was depressed. Thus the structure of the major monochlorinated product from **5** was **5b**. The other product from nitration of **5b** was identified as 3-nitro-5-chloro-6-methyl-2-pyridone (**14**), formed by hydrolysis of the 2-amino moiety.

To determine the specificity and relative reactivity of the aminopyridine nucleus for monochlorination, the compounds listed in Table III were treated with 2 mol of chlorine in 72% sulfuric acid. 2-Amino-5-chloropyridine (**1b**) completely resisted further chlorination and the results were identical with the reaction with 1 mol of chlorine. Selective monochlorination was lost with **3**, **5**, and **6** owing to the enhanced activity caused by the methyl group(s). It is interesting to note that while both the 4-methyl- (**3**) and 6-methyl- (**5**) pyridines form 3-chloro derivatives with 1 mol of chlorine, treatment with a second mole of chlorine converts these isomers completely to the 3,5-dichloro derivatives, while the 5-monochloro isomers survive.

Table III
Chlorination with 2 Mol of Chlorine in 72% Sulfuric Acid

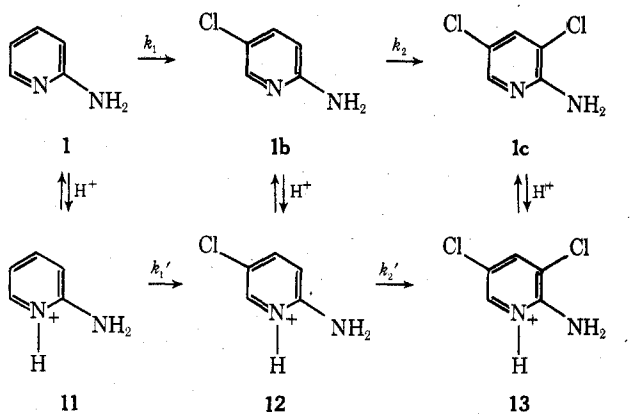
No.	Starting material	% product distribution[a] a, 3-Cl	b, 5-Cl	c, 3,5-DiCl	% yield[b]
1	2-Aminopyridine	0	98	Tr	85 (98)
3	2-Amino-4-methylpyridine	36	31	33	95 (99)
5	2-Amino-6-methylpyridine	Tr	52	48	95 (98)
6	2-Amino-4,6-dimethylpyridine	Tr	8	92	83 (92)

[a] Product distribution was determined by VPC. [b] Yields in parentheses are based on recovered starting material.

Discussion

We have interpreted our results on these chlorination reactions with respect to the equilibria shown for 2-aminopyridine in Scheme II. Katritzky and co-workers[8] determined

Scheme II



the rate of bromination of **1b** in dilute sulfuric acid at 20° and showed that it decreased rapidly with increasing acidity. Therefore, at very high acidities (≥72% sulfuric acid) both **1** and **1b** are predominantly protonated and reaction with chlorine would be largely limited to **11** and **12**. One plausible explanation of our results with these 2-aminopyridines is (cf. Tables II and III) that k_1' is much greater

Table IV
Properties of Some Chloro-2-aminopyridines

No.	Compd	Mp, °C	Proton chemical shifts, τ[a] 3	4	5	6	Anal.[b]
1b	2-Amino-5-chloropyridine	136–137	H 3.54 (d)	H 2.65 (dd)		H 2.13 (d)	
1c	2-Amino-3,5-dichloropyridine	85–86		H 2.34 (d)		H 2.04 (d)	
2b	2-Amino-3-methyl-5-chloropyridine	67–68	CH_3 7.91	H 2.77 (d)		H 2.14 (d)	C, H, N, Cl
3a	2-Amino-3-chloro-4-methylpyridine[c]	96–98		CH_3 7.70	H 3.49 (d)	H 2.18 (d)	C, H, N
3b	2-Amino-4-methyl-5-chloropyridine[c]	149–151	H 3.65 (s)	CH_3 7.75		H 2.07 (s)	C, H, N, Cl
3c	2-Amino-3,5-dichloro-4-methylpyridine[c]	124–126				H 2.03 (s)	C, H, N, Cl
4a	2-Amino-3-chloro-5-methylpyridine	61–62		H 2.70 (d)	CH_3 7.83	H 2.20 (br)	C, H, N, Cl
5a	2-Amino-3-chloro-6-methylpyridine[c]	63–66		H 2.68 (d)	H 3.79 (d)	CH_3 7.94	C, H, N, Cl
5b	2-Amino-5-chloro-6-methylpyridine	73–74	H 3.73 (d)	H 2.68 (d)		CH_3 7.94	C, H, N, Cl
5c	2-Amino-3,5-dichloro-6-methylpyridine	133–135		H 2.59 (s)		CH_3 7.90	C, H, N, Cl
6a	2-Amino-3-chloro-4,6-dimethylpyridine[c]	110–113		CH_3 7.77	H 3.60 (s)	CH_3 7.77	C, H, N
6b	2-Amino-5-chloro-4,6-dimethylpyridine	123–124	H 3.77 (s)	CH_3 7.71		CH_3 7.57	C, H, N, Cl
6c	2-Amino-3,5-dichloro-4,6-dimethylpyridine	151–152		CH_3 7.60		CH_3 7.57	C, H, N, Cl

[a] Compounds **1b** and **1c** were run in Me_2SO, and all others were done in $CDCl_3$. The coupling constants, where applicable, were $J_{3,4}$ and $J_{4,5} \simeq 8$, $J_{4,6} \simeq 2$, and $J_{5,6} \simeq 5$ Hz. [b] The analytical data were acceptable within 0.3% for all elements. [c] These substances were separated by preparative silica gel chromatography (3:2 chloroform–dioxane), and purified by sublimation.

than k_2', and this difference is what allows selective chlorination to proceed.

Experimental Section

^1H NMR spectra were determined on a Varian T-60 spectrometer. The high-resolution mass spectra were determined on a Model 21-110 Consolidated Electrodyne Corp. spectrometer. Other mass spectra were determined on a Hitachi RMU-6E spectrometer. Melting points were run on a Thomas-Hoover apparatus and were corrected. The gas chromatographic analyses were done by Mr. M. Yager and Mr. C. Hartlage on a 6-ft column packed with 2% Carbowax 20M on Chromosorb G (80–100 mesh) with a He flow rate of 25 ml/min at 140°C. Elemental analyses were performed by Mr. G. Maciak and associates of Eli Lilly and Co.

General Chlorination Procedure [e.g., Synthesis of 2-Amino-5-chloropyridine (1b)]. To a 1-l. flask equipped with a stirrer, thermometer, gas addition tube, and dry ice condenser was added 470 ml of 72% aqueous sulfuric acid. With external cooling, 94.1 g (1.0 mol) of 2-aminopyridine (1) was added in portions to maintain an internal temperature of 25° or below. The ice bath was removed and precondensed chlorine gas (71 g, 45.5 ml, 1.0 mol) was allowed to evaporate over a 2-hr period through the gas inlet tube beneath the surface of the reaction mixture. The temperature dropped slowly to −30°, and after completion of the chlorine addition, the mixture was stirred for an additional 90 min with a chlorine reflux. The dry ice condenser was removed, and the solution was allowed to come to room temperature. The solution was poured into 1 kg of ice and the pH adjusted to 10 with 50% aqueous sodium hydroxide. The resulting chilled slurry was filtered and the solid was washed with cold water and afforded after drying (2 hr, 50°, in vacuo) 105.3 g (82%) of **1b**, mp 135–137° (lit. 135–137°), GLC analysis showed 0.2% **1**, and 1.1% **1c**. The filtrate and washes were extracted with chloroform (3 × 100 ml), and the combined extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness in vacuo, affording 18.0 g of tan, crystalline solid; GLC analysis showed 64.5% (11.6 g) **1**, 7.3% (1.3 g) **1c**, and 28.2% (5.1 g) **1b**.

The chloro-2-aminopyridines described in Tables II and III were prepared by the general chlorination procedure and in most cases the scale was 0.2–0.25 mol per run. Unless indicated otherwise in Table IV, when a mixture was obtained, the individual isomers were separated and purified by chormatography on silica gel and eluted with ethyl acetate. Some properties of the chloro-2-aminopyridines are listed in Table IV.

2-Amino-3-chloro-5-nitro-6-methylpyridine (9). To compound **8** (1.53 g, 10 mmol, mp 188–190° [7]) in 40 ml of glacial acetic acid at 25° was added chlorine gas beneath the surface from 0.45 ml (10 mmol) of liquid chlorine. The mixture was stirred for 12 hr and poured into 40 ml of water, and the resulting solid was washed with water and dried, affording 0.5 g of a yellow-orange powder, mp 195–200°. Two crystallizations from ethanol gave needles, mp 211–214° (lit.[7] mp 215–216°). A mixture melting point of **9** with **10** made from **5b** was depressed (mp 180–190°). TLC, methylene chloride–silica gel, showed R_f **9** 0.40 and R_f **10** 0.54.

2-Amino-3-nitro-5-chloro-6-methylpyridine (10). A. Preparation from 7. To compound **7** (1.53 g, 10 mmol, mp 154–155° [7]) in 40 ml of glacial acetic acid at 25° was added chlorine gas beneath the surface from 0.45 ml (10 mmol) of liquid chlorine. The mixture was stirred for 2 hr and poured into 40 ml of water, and the yellow solid was washed with water and dried, affording 1.3 g (70%). Crystallization from ethanol gave **10**, 1.2 g of yellow needles, mp 214–216°. A mixture melting point of this sample with **10** made from **5b** was not depressed (mmp 213–216°). The two samples were identical by TLC and VPC.

B. Preparation from 5b. To 3 ml of concentrated sulfuric acid (*d* 1.84) at 5° was added 1.42 g (10 mmol) of **5b**, followed by 2 ml of a 1:1 mixture of nitric acid (*d* 1.42) and sulfuric acid (*d* 1.84). The mixture was slowly heated to 50° when an exotherm occurred to 70° and rapidly subsided. Heating at 50–60° was continued for 2 hr, and the solution was cooled to 25° and poured on 10 g of ice, affording a yellow solid which was filtered, washed with water, and dried. The crude yellow powder (1.0 g) was a 1:1 mixture of TLC. Two crystallizations from ethanol and one from acetone gave yellow plates (0.4 g), mp 210–214°, identical with **10** from **7** by TLC, VPC, and mixture melting point. A mixture melting point of **10** with **9** was depressed.

Isolation of 3-Nitro-5-chloro-6-methyl-2-pyridone (14). The combined ethanol filtrates from the crystallization of **10** were shown by TLC to contain the other spot found in the crude prod-

uct. Crystallization from benzene gave gold needles, mp 216–218°. The high-resolution mass spectrum gave the empirical formula $C_6H_5N_2O_3Cl$, and revealed the replacement of NH_2 by O, the presence of Cl, and NO_2: ir ($CHCl_3$) 1690 cm^{-1} (C=O).

Supplementary Material Available. GC–mass spectral data for product mixtures from chlorination of **3**, **5**, and **6** (6 pp) will appear following these pages in the microfilm edition of this volume of the journal.

Registry No.—**1**, 504-29-0; **1b**, 1072-98-6; **1c**, 4214-74-8; **2b**, 20712-16-7; **3a**, 56960-76-0; **3b**, 36936-27-3; **3c**, 31430-47-4; **4a**, 31430-41-8; **5a**, 56960-77-1; **5b**, 36936-23-9; **5c**, 22137-52-6; **6a**, 56960-78-2; **6b**, 56960-79-3; **6c**, 56960-80-6; **7**, 21901-29-1; **8**, 22280-62-2; **9**, 56960-81-7; **10**, 56960-82-8; **14**, 56960-83-9.

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Pivaloylnitrene. Reactions with Olefins and Dichloromethane Solvent Effect

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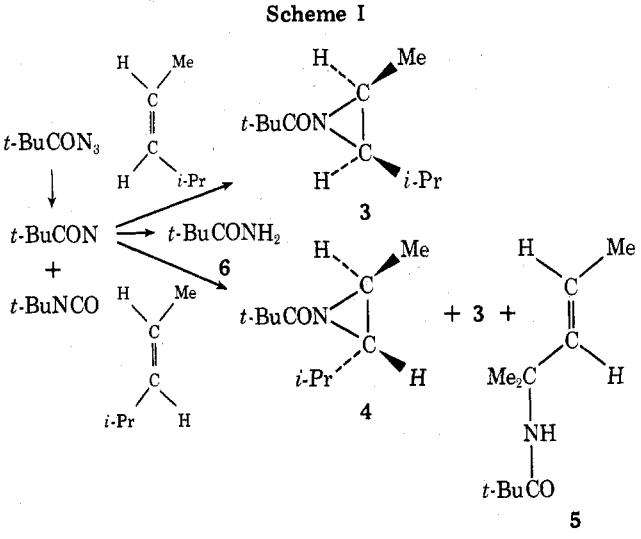
Pivaloylnitrene, generated photolytically from pivaloyl azide, adds to olefins stereospecifically in its singlet state and stereoselectively in its triplet state. Dichloromethane solvates and stabilizes the singlet nitrene without markedly decreasing its reactivity. Hydrocarbon solvents did not show such a stabilizing effect.

The photolysis of pivaloyl azide, *t*-BuCON$_3$ (**1**), generates pivaloylnitrene, *t*-BuCON (**2**), in about 50% yield, together with about the same yield of *tert*-butyl isocyanate. The latter is formed by an independent, parallel, concerted path[2,3]—the nitrene does not rearrange to *t*-BuNCO at an appreciable rate.[4–6] Of the pivaloylnitrene formed, most can be intercepted by cyclohexene; we obtained a 45% yield of 7-pivaloyl-7-azabicyclo[4.1.0]heptane plus minor yields of other nitrene products by trapping *t*-BuCON with cyclohexene.[2] Including the 41% yield of *t*-BuNCO, the material balance is in the order of 90%. Thus, pivaloylnitrene seemed to be a suitable as well as a representative[2,3] carbonylnitrene for the study of solvent effects and stereochemistry in reactions of singlet and triplet carbonylnitrenes with olefins. Such a study is reported here. A part of our results forms part of a communication,[7] and a small part overlaps with Swern's[6] work on the photolysis (with 254-nm light) of pivaloyl azide in neat *cis*- and *trans*-4-methyl-2-pentene. The results of the few duplicated experiments agree with those of Swern.

Scheme I



Results and Discussion

Photolysis of pivaloyl azide by 254-nm light in the presence of *cis*-4-methyl-2-pentene gave the cis aziridine **3** and traces of pivalamide (**6**). Under the same conditions, *trans*-4-methyl-2-pentene gave both aziridine stereoisomers, **3** and **4**, some **6**, and also the apparent allylic C–H insertion product **5**. The structures of the products **3**, **4**, **5**, and **6** were confirmed by their comparison with authentic samples. Table I shows the yields of the products. The apparent tertiary allylic C–H insertion product **5** was formed only from the trans olefin, and no analogous cis product was found in photolyses in cis olefin or its solutions. This might be due to the greater reactivity of the cis double bond (see below), which intercepts all the nitrene. It could also be due to steric hindrance of the approaching nitrene by the methyl group in the cis olefin, or both factors could combine to render the C–H insertion on C-4 unobservable in the case of the *cis*-4-methyl-2-pentene. Reactions analogous to the formation of the aziridines and of **5** have been observed earlier with cyclohexene as the substrate.[2]

Table I shows some regularities. The cis olefin gives only cis aziridine, while the trans olefin gives trans and cis aziridines and **5**. Furthermore, the yield of the trans aziridine increases with decreasing olefin concentration, while the yields of **5** and of cis aziridine are nearly constant in the photolyses of trans olefin in various concentrations in dichloromethane solutions. However, caution is in order owing to the photolability of *N*-pivaloylaziridines when using 254-nm light.[2] The aziridines **3** and **4** absorb significantly at 254 nm: **4** has ϵ 414 at 254 nm (λ_{max} 244 nm, ϵ 483) and **3** has ϵ 473 at 254 nm (λ_{max} 247 nm, ϵ 514). With the absorption coefficient of the azide **1** being only about 100 at 254 nm, the danger of photodecomposition of products exists, even when the photolyses are not carried to the point of quantitative nitrogen evolution. Therefore, all subsequent photolyses were carried out using fluorescent uv lamps which emit 83% of their light between 280 and 450