(w), 2915 (w), 1599, 1492 (m), 920 (w), 820 (m), 751, 684 cm^{-1}; MS (*m/e*) 193 (parent). For **4g**: NMR δ 2.47 (s, 3 H), 7.2–7.7 (m); IR (neat) 3050 (b, w), 2920 (b, w), 1588, 1492, 1440, 1400, 1216 (w), 1117 (w), 823 (m), 750, 685 cm^{-1}; MS (*m/e*) 193 (parent).

Reaction of 4-Chloropyridine *N*-Oxide (1h) with 2. For **3h**: NMR δ 6.63 (dm, 1 H, J = 5 Hz), 7–8 (m); IR 3050 (b, w), 1563 (m), 1540 (m), 1476 (m), 1430, 1392, 1340, 1127 (m), 1013 (m), 755 (m), 739 (m), 720, 686 cm^{-1}. For **4h**: NMR δ 7.1–7.7 (m), 8.45 (d, 1 H, J = 5 Hz); IR (neat) 3050 (m), 1597 (w), 1567, 1545, 1491 (m), 1453 (m), 1381 (m), 1095 (m), 890 (m), 823 (m), 755, 685 cm^{-1}; MS (*m/e*) 213 (parent).

A picrate of **4h** had mp 165–167 °C dec from ethanol: IR (KBr) 2205 (m) 1640 cm^{-1}. Anal. Calcd for $C_{19}H_{11}N_4O_7Cl$: C, 51.53; H, 2.50. Found: C, 51.54; H, 2.74.

2-Phenylfuro[3,2-*c*]pyridine. This compound was obtained both from the aqueous and chloroform portions in the preparation of **3h**. Column chromatography yielded the furopyridine (27% yield), from the benzene eluate: mp 123.5–124 °C; NMR ($CDCl_3$) 7.0 (d, H_3, J = 1 Hz), 7.43 (m, 4 H), 7.83 (m, 2 H), 8.45 (d, H_6, J = 6 Hz), 8.90 (d, H_4, J = 1 Hz); IR (KBr) 1462 (m), 1456 (m), 1260 (m), 1011 (m), 883, 826, 752, 680 (m) cm^{-1}; MS (*m/e*) 195 (parent). Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65. Found: C, 80.52; H, 4.67.

Reaction of 4-Methoxypyridine *N*-Oxide (1i) with 2. For **3i**: NMR δ 3.4 (s, 3 H), 6.25 (dm, 1 H, J = 6 Hz), 7–8 (m); IR 3050 (w), 1580, 1475, 1437, 1365, 1207 (m), 742 (m), 718 (m), 687 (m) cm^{-1}. For **3j**: NMR δ 3.33 (s, 3 H), 6.30 (d, 1 H, J = 6 Hz), 7–7.8 (m), 8.1 (2 H); IR 3021 (b, w), 1573, 1430, 1368, 1272, 1020, 960 (m), 850 (m), 800 (m), 743, 705 ± 20 (b) cm^{-1}.

Reaction of 4-Nitropyridine *N*-Oxide (1k) with 2. In this system, the "standard" conditions were altered: The reaction was carried out in DMF as solvent at 110 °C for **3d**. The solvent was then evaporated under reduced pressure and the residue was treated with methanol and 10% aqueous potassium hydroxide at reflux temperature for 3 h. The solid was filtered and purified by chromatography; the filtrate was extracted with chloroform and subjected to the standard purification cycle yielding 2-phenylfuro[3,2-*c*]pyridine (4% yield), mp 118.5–119 °C, by column chromatography and sublimation.

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Registry No.—**1a,** 694-59-7; **1c,** 931-19-1; **1d,** 1003-73-2; **1f,** 1003-67-4; **1h,** 1121-76-2; **1i,** 1122-96-9; **1k,** 1124-33-0; **2,** 34387-64-9; **4b** picrate, 63731-36-2; **4h** picrate, 63731-37-3; 2-phenylfuro[3,2-*c*]-pyridine, 63731-38-4.

References and Notes

(1) N. Morita, J. I. Dickstein, K. Imafuku, and S. I. Miller, in preparation.
(2) (a) J. I. Dickstein and S. I. Miller, "Chemistry of the Carbon Carbon Triple Bond", S. Patai, Ed., Wiley, New York, N.Y., in press; (b) D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis,* 205 (1975); (c) C. G. Stuckwisch, *ibid.,* 469 (1973); (d) J. Bastide, J. Hamelin, F. Texier, and Y. Vo Quang, *Bull. Soc. Chim. Fr.,* 2555, 2871 (1973); (e) T. Uchida and K. Matsumoto, *Synthesis,* 209 (1976).
(3) (a) R. A. Abramovitch and I. Shinkai, *Acc. Chem. Res.,* **9,** 192 (1976); (b) R. A. Abramovitch, G. Grins, R. B. Rogers, and I. Shinkai, *J. Am. Chem. Soc.,* **98,** 5671 (1976); (c) R. A. Abramovitch and I. Shinkai, *ibid.,* **97,** 3227 (1975).
(4) (a) R. A. Abramovitch and G. M. Singer, "Pyridine and Its Derivatives: A Supplement", Part I, R. A. Abramovitch, Ed., Wiley, New York, N.Y., 1974, Chapter 1A; (b) E. Ochiai, "Aromatic Amine Oxides", Elsevier, Amsterdam, 1967.
(5) F. M. Hershenson and L. Bauer, *J. Org. Chem.,* **34,** 655 (1969). A referee "pointed out that there is a plausible alternative to the episulfonium ion mechanism", namely, one which proceeds via 2,3-dithioalkyl-2,3-dihydropyridine (R. A. Abramovitch and P. Tomasik, *J. Heterocycl. Chem.,* **12,** 501 (1975)).
(6) (a) C. K. McGill, U.S. Patent 3 045 022; *Chem. Abstr.,* **57,** 15077 (1962); (b) J. H. Blumenthal, U.S. Patent 2 874 162; *Chem. Abstr.,* **53,** 12311 (1959); (c) N. Morita, unpublished results; (d) Ch. Kaneko and T. Miyasaka, *Shika Zairyo Kenkyusho Hokoku, Tokyo Ika Shika Daigaku,* **2,** 269 (1963), cited in ref 4b, p 253; (e) T. Agawa and S. I. Miller, *J. Am. Chem. Soc.,* **83,** 449 (1961).
(7) J. C. Craig, M. D. Bergenthal, I. Fleming, and J. Harley-Mason, *Angew. Chem.,* **8,** 429 (1969).
(8) A. Steigel, J. Sauer, D. A. Kleier, and G. Binsch, *J. Am. Chem. Soc.,* **94,** 2770 (1972).
(9) M. Ogata, H. Matsumoto, and H. Kanō, *Tetrahedron,* **25,** 5217 (1969).
(10) A. R. Katritzky and A. P. Ambler, "Physical Methods in Heterocyclic Chemistry", Vol. II, A. R. Katritzky, Ed., Academic Press, New York, N.Y., 1963, Chapter 10.
(11) J. I. Dickstein and S. I. Miller, *J. Org. Chem.,* **37,** 2175 (1972).
(12) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.,* **31,** 4070 (1969).
(13) A. R. Katritzky, D. J. Short, and A. J. Boulton, *J. Chem. Soc.,* 1516 (1960).
(14) A. W. Singer and S. M. McElvain, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 740.

The Vilsmeier–Haack Aroylation of Pyrroles Reexamined

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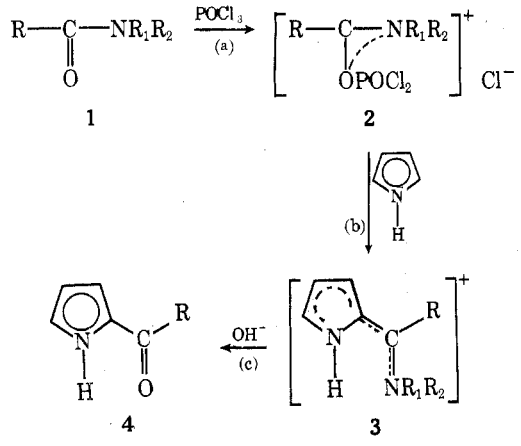
Vilsmeier–Haack formylation of pyrroles is well established, but its extension to aroylation, despite offering advantages over other methods, has not been properly exploited as no systematic study of the reaction has been reported. The latter reaction has been reexamined and a method for the aroylation of certian pyrroles on a 5–200-mmol scale in yields of 85–96% is given together with a brief discussion of the reactivity of pyrroles and carboxamides, the preparation of the amide–phosphoryl chloride complex, azafulvene formation, and general experimental conditions necessary for efficient reaction. The preparation of 2-benzoylpyrrole is described to illustrate the improvements, and several new aroylpyrroles are reported.

The Vilsmeier–Haack reaction[1] (Scheme I[2]) is well established[3] as a means of formylating pyrroles (Scheme I, R = H) and the experimental procedure widely used is that of Silverstein et al.[4] The reaction offers the advantages of monoformylation,[5] virtually exclusive attack[6] at the α position of unsubstituted pyrroles lacking bulky N substituents[7] and consistently high yields.

The reaction was later extended to include the acylation[8] (Scheme I, R = alkyl) and aroylation[9] (Scheme I, R = aryl) of pyrroles. While retaining the other advantages of the formylation reaction, the extended processes usually gave poorer yields. Consequently, aroylation by the Vilsmeier–Haack method, notwithstanding occasional reported yields of 80% or more,[10,11] appears to have fallen into disfavor and to have been supplanted by other procedures,[12] themselves often severely limited in their application to pyrrolic substrates.

Despite recognition[13] that "the conditions employed in the Vilsmeier–Haack condensation can be critical", no systematic investigation of the experimental conditions necessary for efficient aroylation by this procedure has yet been reported. Consequently, the conditions commonly employed are those reported for the formylation of pyrrole,[4] which are, in fact, unnecessarily harsh and unsuitable for the aroylation of pyrroles.

Scheme I



Accordingly, we undertook a thorough investigation[14] of the aroylation of pyrroles by the Vilsmeier–Haack procedure and wish to report those results which bear directly on the use of the reaction as an efficient method for the preparation of aroyl pyrroles.

The Amide. Despite the widespread use of *N,N*-dimethylamides (1, R_1, R_2 = CH_3) in reported Vilsmeier–Haack procedures, it was found that morpholides (1, R_1R_2 = $-CH_2CH_2OCH_2CH_2-$) were better reagents except when the phenyl nucleus carried a strongly electron withdrawing group such as a nitro group which rendered reaction with phosphoryl chloride incomplete. In such cases, the dimethylamide analogues gave better results.

Morpholides formed complexes (2, R_1R_2 = $-CH_2CH_2OCH_2CH_2-$) with phosphoryl chloride which were eight to ten times more reactive than the corresponding *N,N*-dimethylamide complexes. This may be ascribed to enhancement of the activating effect of the morpholine oxygen atom by coordination of that atom with the excess phosphoryl chloride used in the present procedure.

Thiobenzamide–phosphoryl chloride complexes,[15] although readily formed, are unreactive toward pyrrole and appear to be of little synthetic utility.

Formation of the Vilsmeier–Haack Reagent (Scheme I, Step a). A report that amide–phosphoryl chloride complex formation (2, R = aryl) is best carried out in the absence of solvent[10] was confirmed and it was further shown that such reaction could readily be followed by NMR spectrometry using the neat complex. The progress of the reaction was apparent from the relative intensity of new signals 0.7 to 1 ppm downfield of the original signals due to the nitrogen-substituent protons and ca. 0.3 ppm downfield of the original aromatic proton resonances. Following complex formation was necessary, as complete reaction prior to admixture with the pyrrole proved essential.

By custom, complex formation is carried out by treating the amide with no more than 1 equiv of phosphoryl chloride, often in the presence of halogenated hydrocarbons.[4,11] In fact, an excess of 1 to 10 equiv of phosphoryl chloride had no adverse effect on the Vilsmeier–Haack reaction itself and was beneficial during complex formation not only because of a reduction in viscosity which assisted monitoring by NMR spectrometry but also because the rate of complex formation was increased thereby.[16] The optimum quantity of phosphoryl chloride was found to be 2 to 2.5 equiv, and the presence of halogenated solvents during complex formation was avoided as these solvents promoted dissociation of the complex.

The rate of complex formation was found to be dependent on the electron density at the carbonyl oxygen of the amide, the reaction being retarded by the presence of groups that are electron withdrawing in the presence of phosphoryl chloride. When morpholides formed complexes very slowly or incompletely, the use of *N,N*-dimethylamides was satisfactory.

Although complex formation could be accelerated by gentle warming, temperatures above 40 °C were best avoided because of partial dissociation of the complex. Subsequently, cooling did, however, permit the reaction to go to completion. This effect was most marked in the case of slowly formed amide–phosphoryl chloride complexes for which the temperature range of 25 to 35 °C was found to be satisfactory.

The Vilsmeier–Haack Reaction (Scheme I, Step b). Azafulvenes (3, R = aryl) were formed by treating the amide–phosphoryl chloride complex with the pyrrole in anhydrous 1,2-dichloroethane within the temperature range of 20 to 35 °C. The reaction was followed by UV spectrophotometry by measuring the increase in absorption in the 350- to 400-nm region.

The presence of 1,2-dichloroethane at this stage had no adverse effect, as dissociation of the amide complex was considerably slower than azafulvene formation. The use of *strictly* anhydrous 1,2-dichloroethane was essential, however, as traces of water not only led to lower yields and products of poorer quality, but also retarded the reaction appreciably.[17] Although slightly higher reaction temperatures could be used, both yield and product quality suffered at temperatures above 40 °C. Reactions carried out under the conditions described were clean, and notwithstanding the presence of excess phosphoryl chloride the reaction mixtures could be allowed to stand for long periods without side reactions occurring. Consequently, sluggish reactions such as those involving *N*-methylpyrrole (reaction time ca. 28 days) also proceeded in high yield.

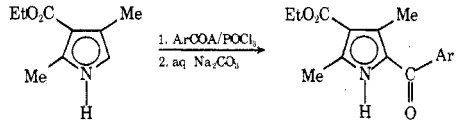
The Pyrrole. Pyrrole and a number of substituted pyrroles were investigated. In no case, where both α and β positions were vacant, was evidence of attack in the β position found. The reaction proved effective in the presence of C-alkyl substituents and a 4-alkoxycarbonyl group (relative to attack in the 2 position), but not so when a 4-acetyl group was present.

Steric retardation of the reaction due to an adjacent C-methyl group was more than offset by its activating electronic effect. An *N*-methyl substituent, however, markedly reduced the rate of aroylation. Thus, *N*-methyl pyrrole reacted at approximately one hundredth of the rate of pyrrole itself. The inference that this was due to a steric factor arising from a specific orientation in the transition state is supported by the fact that *N*-methylpyrrole undergoes formylation by the Vilsmeier–Haack procedure more rapidly than pyrrole.[18] *N*-methyl-2-aroylpyrroles are therefore best prepared by introducing the *N*-methyl group after aroylation. Such alkylation was performed to good effect by way of the thallium(I) intermediate.[19]

Hydrolysis (Scheme I, Step c). Hydrolysis of the azafulvene was carried out using aqueous sodium carbonate solution at room temperature followed by heating for 45 min. This period of heating was often far in excess of requirement for full hydrolysis but was convenient and did not lead to a reduction in yield. Monitoring of the hydrolysis was not attempted because the reaction mixtures were heterogeneous. The products were isolated by conventional means and were obtained in satisfactory purity after one recrystallization.

Yields. Yields, physical constants, and some reaction times are given in Tables I and II and are reproducible for preparations on the scale of 5 to 200 mmol (ca. 1 to 34 g of 2-benzoylpyrrole). Ethyl 2,4-dimethylpyrrole-3-carboxylate was chosen as the principal substrate for studying changes in experimental procedures aimed at improving yields as it was also suitable as a reference compound for the rate studies which were concurrently under way.[14] For the same reason most of the reactions were carried out at 35 °C. However, in those

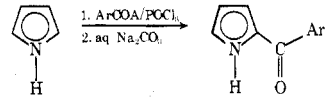
Table I



Registry no.	Ar	A	Complex formation[a]	Azafulvene formation,[b] h (λ_{max}, nm)	% Yield[c]	Mp °C[d,e]
63833-34-1	4-Methoxyphenyl	Morpholide	60 min	10.8 (376)	90 (96)	148.5–149.5
63833-35-2	4-Tolyl	Morpholide	120 min	7.0 (379)	85 (92)	133–134
63833-46-5	Phenyl	Morpholide	160 min	3.1 (379)	92 (99)	109–110[f]
63833-36-3	4-Chlorophenyl	Morpholide	10 h	2.3 (386)	87 (95)	174–174.5
	4-Chlorophenyl	Dimethylamide	55 min	18.2 (374)	90 (93)	174–174.5
63833-37-4	3-Chlorophenyl	Dimethylamide	85 min	7.8 (374)	88 (94)	135–136
63833-38-5	4-Nitrophenyl	Dimethylamide	4 h	1.9 (388)	96 (*g*)	173–175
63833-39-6	3-Nitrophenyl	Dimethylamide	7 h	3.2 (381)	87 (90)	180–181
63833-40-9	3,5-Dinitrophenyl	Dimethylamide	None			
63833-41-0	2-Pyrrolyl	Dimethylamide	<4 min	178 (~374)	86 (*g*)	188–189
63833-42-1	2-Furyl	Dimethylamide	50 min	1.8 (391)	80 (87)	110–111
63833-43-2	2-Thienyl	Dimethylamide	90 min	2.7 (385)	86 (88)	107.5–108.5
63833-45-4	3-Pyridyl	Diethylamide	120 min	8.7 (388)	85 (97)	155–156.5[h]

[a] At 35 °C using 2.16 equiv of $POCl_3$, minimum time for full formation. [b] At 35 °C, 0.2 M in 1,2-dichloroethane, 10-mmol scale. [c] First crop only from petroleum ether (60–65 °C) or toluene/petroleum ether. Second figure gives yield by spectrophotometric assay. [d] Satisfactory analyses (±0.2% for C, H and N) were reported for all new compounds listed. [e] All compounds gave satisfactory NMR and IR spectra. Keto carbonyl absorptions were all in the region 1590–1621 cm^{-1}. [f] In agreement with literature value, ref 9. [g] Product crystallized before assay could be performed. [h] In agreement with literature value, ref 20.

Table II



Registry no.	Ar	A	% yield[a]	Mp, °C
63833-47-6	4-Nitrophenyl	Dimethylamide	91	160–162 (160–161[b])
13169-71-6	4-Chlorophenyl	Morpholide	87	118.5–119.5 (114–115[b])
	Phenyl	Morpholide	86	77.5–78 (79[c])
55895-62-0	4-Tolyl	Morpholide	86	118–119 (119[b])
11963-43-5	4-Methoxyphenyl	Morpholide	88	112.5–113.5 (110–112[b])

[a] First crop only. Prepared on a 20-mmol scale at 25 °C using a 0.2 M solution in 1,2-dichloroethane. Pyrrole reacted at approximately half the rate of ethyl 2,4-dimethylpyrrole-3-carboxylate. [b] Reference 21. [c] Reference 22.

cases where reactions were repeated at 25 °C the yields rose by 2–3%.

To establish that the improved procedure was appropriate to an acid-sensitive substrate, several of the aroylations were repeated using pyrrole. These reactions also went in good yield, indicating that the experimental procedure here reported is not limited to very stable pyrroles only.

Experimental Section

Pyrrole was redistilled and stored, under argon, at 0 °C. Ethyl 2,4-dimethylpyrrole-3-carboxylate[23] was sublimed[24] before use. Phosphoryl chloride was twice redistilled at atmospheric pressure and stored, under argon, in sealed ampules. Anhydrous 1,2-dichloroethane was obtained by distillation from phosphorus pentoxide. All other solvents and reagents were of good commercial quality and were used without further purification.

Dimethylamides were prepared in high yield by treatment of the appropriate acid chloride (0.5 M in toluene) with anhydrous dimethylamine and were recrystallized from petroleum ether (60–65 °C) or toluene/petroleum ether. Morpholides were prepared in the same way using an equimolecular mixture of morpholine and triethylamine which facilitated the removal of the amine salt.

Melting points (Kofler hot stage) are uncorrected.

General Prodedure. The appropriate amide was dissolved in phosphoryl chloride (0.2 mL/mmol of amide), and the solution, protected from moisture, was allowed to stand until NMR spectrometry showed complex formation to be complete. A solution (0.2 M) of the pyrrole (1 equiv relative to amide) in anhydrous 1,2-dichloroethane was added in one batch to the syrupy complex. After thorough mixing, the homogeneous solution, protected from moisture, was allowed to stand until azafulvene formation was complete as shown by UV spectrophotometry using 1,2-dichloroethane for dilution of the samples drawn. The reaction mixture was poured, with stirring, into 10% aqueous sodium carbonate solution (25 mL/mL of $POCl_3$), stirred at room temperature for 15 min, and then for 45 min at reflux temperature. After cooling, the product was isolated from the dichloroethane layer and recrystallized from petroleum ether (60–65 °C) or toluene/petroleum ether.

2-Benzoylpyrrole (Representative Example). A mixture of *N*-benzoylmorpholine (2.96 g, 20 mmol) and phosphoryl chloride (4.0 mL, 43.2 mmol) was kept at 25 °C for 6 h. A solution of pyrrole (1.38 mL, 20 mmol) in anhydrous 1,2-dichloroethane (100 mL) was added and, after swirling, the reaction mixture was left at ca. 25 °C for 14 h. After hydrolysis with 10% aqueous sodium carbonate solution (100 mL), the organic layer was separated and the aqueous layer was washed with 1,2-dichloroethane (two 20-mL portions). The combined organic layers were dried (Na_2CO_3), the solvent was removed, and the residue was recrystallized (charcoal) from petroleum ether (60–65 °C) to give the desired ketone as colorless needles (2.95 g, 86%), mp 77.5–78 °C (lit.[22] mp 79 °C).

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Registry No.—$ArCONMe_2$ (Ar = 4-ClC_6H_4), 14062-80-7; $ArCONMe_2$ (Ar = 3-ClC_6H_4), 24167-52-0; $ArCONMe_2$ (Ar = 4-$O_2NC_6H_4$), 7291-01-2; $ArCONMe_2$ (Ar = 3-$O_2NC_6H_4$), 7291-02-3; $ArCONMe_2$ (Ar = 3,5-di$O_2NC_6H_3$), 2782-45-8; $ArCONMe_2$ (Ar = 2-pyrrolyl), 7126-47-8; $ArCONMe_2$ (Ar = 2-furyl), 13156-75-7; $ArCONMe_2$ (Ar = 2-thienyl), 30717-57-8; *N*-(4-methoxybenzoyl)morpholine, 7504-58-7; *N*-(4-methylbenzoyl)morpholine, 63833-44-3; *N*-(4-chlorobenzoyl)morpholine, 19202-04-1; ethyl 2,4-dimethylpyrrole-3-carboxylate, 2199-51-1; phosphoryl chloride, 10025-87-3; 2-benzoylpyrrole, 7697-46-3; *N*-benzoylmorpholine, 1468-28-6; *N,N*-diethyl-3-pyridinecarboxamide, 59-26-7; pyrrole, 109-97-7; 4-nitro-*N,N*-dimethylbenzamide, 7291-01-2.

References and Notes

(1) A. Vilsmeier and A. Haack, *Chem. Ber.*, **60**, 119 (1927).
(2) The exact structure of the amide–$POCl_3$ complex (**2**) is uncertain; see, for example, G. Jugie, J. A. Smith, and G. J. Martin, *J. Chem. Soc., Perkin Trans. 2*, 925 (1975), and references cited therein. For complexes generated and used in situ we favor the structure shown.
(3) Early reports include M. A. T. Rogers, *J. Chem. Soc.*, 596 (1943); A. H. Cook and J. R. Majer, *J. Chem. Soc.*, 482 (1944).
(4) R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1967, p 831.
(5) P. E. Sonnett, *J. Org. Chem.*, **37**, 925 (1972), has shown that the intermediate azafulvene (**3**, R = H) does not react further with Vilsmeier–Haack reagents.
(6) H. J. Anderson and H. Nagy, *Can. J. Chem.*, **50**, 1961 (1972), in a footnote report a 0.5% yield of the 3-aldehyde in a large-scale preparation of 2-formylpyrrole.
(7) C. F. Candy, R. A. Jones, and P. H. Wright, *J. Chem. Soc. C*, 2563 (1970); however, J. K. Chakrabarti and D. E. Turner, *J. Heterocycl. Chem.*, **11**, 417 (1974), report formation of 5% of the 3-aldehyde on formylation of *N*-methylpyrrole.
(8) E. Ghigi and A. Drusiani, *Atti Accad. Sci. Ist. Bologna, Cl. Sci. Fis., Rend.*, **5**, 56 (1957–1958); *Chem. Abstr.*, **54**, 5613i (1960). See also W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).
(9) G. G. Kleinspehn and A. E. Briod, *J. Org. Chem.*, **26**, 1652 (1961).
(10) J. A. Ballantine, A. H. Jackson, G. W. Kenner, and G. McGillivray, *Tetrahedron, Suppl.* **7**, 241 (1966).
(11) L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, **37**, 3691 (1972).
(12) See, for example, J. M. Patterson, *Synthesis*, 281 (1976).
(13) A. Ermili, A. J. Castro, and P. A. Westfall, *J. Org. Chem.*, **30**, 339 (1965).
(14) Results dealing with the effect of substituents and reaction conditions on the rate of reaction will be published in the appropriate journal.
(15) J. G. Dingwall, D. H. Reid, and K. Wade, *J. Chem. Soc. C*, 913 (1969), reported that *N,N*-dimethylthioformamide is more effective than *N,N*-dimethylformamide in the formylation of certain compounds.
(16) S. Alunni, P. Linda, G. Marino, S. Santini, and G. Savelli, *J. Chem. Soc., Perkin Trans. 2*, 2070 (1972).
(17) The presence of 0.05% water in the reaction mixture approximately halved the rate and reduced the yield by one seventh.
(18) S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc., Chem. Commun.*, 427 (1972).
(19) M. Beyers, J. White, and G. McGillivray, unpublished results. The method is a modification of that of C. F. Candy and R. A. Jones, *J. Org. Chem.*, **36**, 3993 (1971).
(20) M. Strell and E. Kopp, *Chem. Ber.*, **91**, 1621 (1958).
(21) M. K. A. Khan and K. J. Morgan, *J. Chem. Soc.*, 2579 (1964).
(22) H. Fischer and H. Orth, "Die Chemie de Pyrroles", Vol. I, Johnson Reprint Corp., New York, N.Y., 1968, p 204.
(23) Reference 22, p 247.
(24) Strictly speaking, the purification was by low-pressure distillation onto a cold-finger condenser. When quite pure, this compound is stable indefinitely at room temperature. See, however, A. H. Corwin and K. W. Doak, *J. Am. Chem. Soc.*, **77**, 464 (1955).

N-Nitroaziridines: Synthesis, Thermal Stability, and Solvolytic Reactivity

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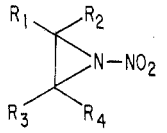
The syntheses of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane (**5**) and 10-methyl-1,9-(*N*-nitroaziridino)decalin (**6**), the first known *N*-nitroaziridines, are described. Their thermal rearrangements and their reactivity in the presence of protic solvents are also examined.

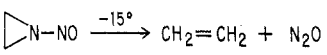
Synthetic and naturally occurring aziridines and nitro-substituted heterocycles are rich sources of important pharmaceuticals, veterinary medicines, and agrichemicals.[1] *N*-Nitroaziridines (**1**) are representative of both classes, but until



1

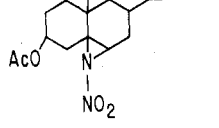
R_1, R_2, R_3, R_4 = H or ALKYL

now were unknown. Research in this area may have been inhibited by the impression that these aziridines would be too unstable to isolate, since *N*-nitrosoaziridines are known to decompose spontaneously at −15 °C, giving nitrous oxide and olefin.[2]

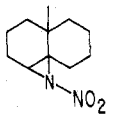


2 **3** **4**

We now wish to report the synthesis of two stable *N*-nitroaziridines (**5** and **6**) by a novel route. Both compounds are



5



6

stable at room temperature, but undergo unique thermal rearrangements at elevated temperatures.

Synthesis

The synthesis of *N*-nitroaziridine **5** began with nitration of cholesteryl acetate (**7**) to give 6-nitrocholesteryl acetate (**8**) (Scheme I). This reaction proved quite capricious with yields from 20 to 50% even under identical conditions, probably because of variations in quality of the sodium nitrite and nitric acid. Conversion to the chlorooxime **9** was effected with dry hydrogen chloride in ether.[3] Direct addition of nitrosyl chloride to cholesteryl acetate, followed by acidic isomerization to chlorooxime **9**, was an unacceptable alternative because steroidal olefins give chloronitro derivatives rather than the