1725 cm^{-1} (s, C=O); UV λ_{max} (MeOH) 240 nm (ϵ 41 000), 322 (9500); mixture melting point with material from above was 175–176 °C. Anal. Calcd for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 16.09. Found: C, 62.05; H, 3.73; N, 16.21.

2-Methylquinoxaline-3-carboxylic Acid 1-Oxide (17). Methyl 2-methyl-3-quinoxalinecarboxylate 1-oxide (5.00 g, 23.0 mmol) was suspended in aqueous 0.5 M sodium hydroxide solution (50 mL). All starting material went into solution within 10 min, and a white precipitate formed upon addition of aqueous 0.5 M hydrochloric acid solution (50 mL). The solid was collected and recrystallized from water to give 4.00 g (81%) of **17**:[4b] mp 150–151 °C; NMR (CF_3CO_2D) δ 3.10 (3, s, CH_3), 8.20–8.90 (4, m, H-5, H-6, H-7, H-8); IR (KBr) 1735 cm^{-1} (C=O); UV λ_{max} (MeOH) 244 nm (ϵ 23 800), 330 (7450); mass spectrum *m/e* 204 $(M)^+$. Several attempts to obtain an analytical sample of **17** were unsuccessful apparently owing to the thermal instability of this compound (vide infra).

2-Methylquinoxaline 1-Oxide (18). 2-Methylquinoxaline-3-carboxylic acid 1-oxide (1.00 g, 4.9 mmol) was added to toluene (10 mL). The resulting suspension was heated at 100 °C for 1.5 h, during which time all the starting material went into solution and a gas was evolved. The reaction mixture was cooled to room temperature and the toluene was removed under vacuum, leaving a colorless solid. The crude product was recrystallized from ether to afford 0.66 g (83%) of pure **18**: mp 85–87 °C; NMR ($CDCl_3$) δ 2.69 (3, s, CH_3), 7.77 (2, m, H-6, H-7), 8.16 (1, m, H-5), 8.58 (1, m, H-8), 8.71 (1, s, H-3); UV λ_{max} (MeOH) 240 nm (ϵ 43 300), 320 (10 500); mass spectrum *m/e* 160 $(M)^+$. Anal. Calcd for $C_9H_8N_2O$: C, 67.56; H, 5.04; N, 17.51. Found: C, 67.60; H, 5.15; N, 17.48.

Quinoxaline-2-carboxaldehyde 1-Oxide (19). 2-Methylquinoxaline 1-oxide (0.90 g, 5.6 mmol) was dissolved in ethyl acetate (15 mL). Selenium dioxide (0.75 g, 6.7 mmol) was added and the reaction mixture was refluxed for 5 h, during which time a black precipitate formed. The reaction mixture was filtered through Super-Cel and the filtrate was treated with activated carbon and evaporated, leaving a tan solid. The solid was recrystallized from acetone to give 0.39 g (39%) of **19**: mp 131–132 °C; NMR (CF_3CO_2D) δ 7.3–8.0 (3, m, H-5, H-6, H-7), 8.25 (1, m, H-8), 8.90 (1, s, H-3), 10.00 (1, s, CHO); IR (KBr) 1680 cm^{-1} (C=O); UV λ_{max} (MeOH) 242 nm (ϵ 38 700), 323 (8900); mass spectrum *m/e* 174 $(M)^+$. Anal. Calcd for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 16.09. Found: C, 62.01; H, 3.36; N, 16.03.

Acknowledgment. We thank Kerry Gombatz, Gloria Kostek, Richard Pezzullo, and Lawrence Vincent for their technical assistance.

Registry No.—**1**, 40016-70-4; **2**, 61522-53-0; **3**, 61528-76-5; **4**, 61522-54-1; **5**, 61522-55-2; **6**, 13297-17-1; **7**, 61522-56-3; **8**, 61522-57-4; **9**, 22059-64-9; **10**, 61522-58-5; **11**, 33578-43-7; **12**, 34907-12-5; **13**, 61522-59-6; **14**, 17626-51-6; **15**, 20492-05-1; **16**, 61522-60-9; **17**, 61522-61-0; **18**, 18916-44-4; **19**, 61522-62-1; trimethyl phosphite, 121-45-9.

References and Notes

(1) (a) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965); (b) J. W. McFarland, *J. Org. Chem.*, **36**, 1842 (1971); (c) W. Dürckheimer, *Justus Liebigs Ann. Chem.*, **756**, 145 (1972); (d) E. Abushanab, *J. Org. Chem.*, **38**, 3105 (1973); (e) M. J. Haddadin, G. E. Zahr, T. N. Rawdah, N. C. Chelhot, and C. H. Issidorides, *Tetrahedron*, **30**, 659 (1974); (f) R. A. Burrell, J. M. Cox, and E. G. Savins, *J. Chem. Soc., Perkin Trans. 1*, 2708 (1973).
(2) Mecadox (Pfizer Inc., New York, N.Y.).
(3) G. W. Thrasher, J. E. Shively, C. E. Askelson, W. E. Babcock, and R. R. Chalquest, *J. Anim. Sci.*, **31**, 333 (1970).
(4) (a) J. Francis, J. K. Landquist, A. A. Levi, J. A. Silk, and J. M. Thorp, *Biochem. J.*, **63**, 455 (1956); (b) J. R. Valenta, J. R. E. Hoover, and J. F. Pagno, *Antimicrob. Agents Chemother.*, 453 (1966).
(5) T. R. Emerson and C. W. Rees, *J. Chem. Soc.*, 1971 (1962).
(6) A. J. Boulton, A. C. G. Gray, and A. R. Katritzky, *J. Chem. Soc.*, 5958 (1965).
(7) J. Ackrell, M. Altaf-ur-Rahman, A. J. Boulton, and R. C. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1587 (1972).
(8) When this experiment was repeated using methanol or ethanol as solvent **2** was obtained in 65 and 74% yield, respectively. However, longer reaction times were required with these lower boiling solvents. As pointed out by a referee, the actual reducing agent could be a mixed phosphite derived from the corresponding alcohol solvent in the cases where ethanol or 1-propanol was used.
(9) M. J. Haddadin and A. S. Salameh, *J. Org. Chem.*, **33**, 2127 (1968).
(10) (a) M. S. Habib and C. W. Rees, *J. Chem. Soc.*, 3386 (1960); (b) T. R. Emerson and C. W. Rees, *ibid.*, 2319 (1964).
(11) E. Abushanab, *J. Am. Chem. Soc.*, **93**, 6532 (1971).
(12) C. H. Issidorides and M. J. Haddadin, British Patent 1 215 815 (1970); *Chem. Abstr.*, **74**, 141873b (1971).
(13) Unpublished observations.
(14) Previous reductions of QNO's with a large excess of sodium borohydride have been reported to give 1,2,3,4-tetrahydroquinoxalines in good yield: M. J. Haddadin, H. N. Alkaysi, and S. E. Saheb, *Tetrahedron*, **28**, 1115 (1970).
(15) W. S. Chilton and A. K. Butler, *J. Org. Chem.*, **32**, 1270 (1967).
(16) R. L. Robertson and R. V. Kasubick, U.S. Patent 3 767 657 (1973).
(17) N. A. Mufarrij, M. J. Haddadin, C. H. Issidorides, J. W. McFarland, and J. D. Johnston, *J. Chem. Soc., Perkin Trans. 1*, 969 (1972).
(18) C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.*, **31**, 4067 (1966).
(19) J. K. Landquist and J. A. Silk, *J. Chem. Soc.*, 2052 (1956).

Synthesis with Pyridine *N*-Oxides. 3.[1] Synthesis of 2-Arylisoxazolo[2,3-*a*]pyridinium Bromides via Acid-Catalyzed Rearrangements of 1-Aryl-2-(2-pyridinyl)ethanone *N*-Oxides

David T. Connor,* Patricia A. Young, and Maximillian von Strandtmann

Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey 07950

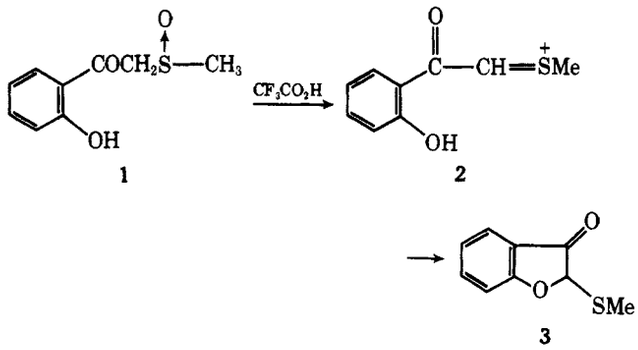
Received September 16, 1976

Reaction of 1-aryl-2-(2-pyridinyl)ethanone *N*-oxides with hydrobromic acid in acetic acid gave 2-arylisoxazolo[2,3-*a*]pyridinium bromides. Cyclization of methoxy-substituted compounds (**21**, **23**, and **31**) gave 2-(2-methoxyaryl)-isoxazolo[2,3-*a*]pyridinium bromides (**22**, **24**, and **32**), which were surprisingly refractory to demethylation. Reaction of 1-phenyl-2-pyridineethanol *N*-oxide with hydrobromic acid in acetic acid gave 2-(2-phenylethenyl)pyridine *N*-oxide hydrobromide and not 2-phenyl-2,3-dihydroisoxazolo[2,3-*a*]pyridinium bromide.

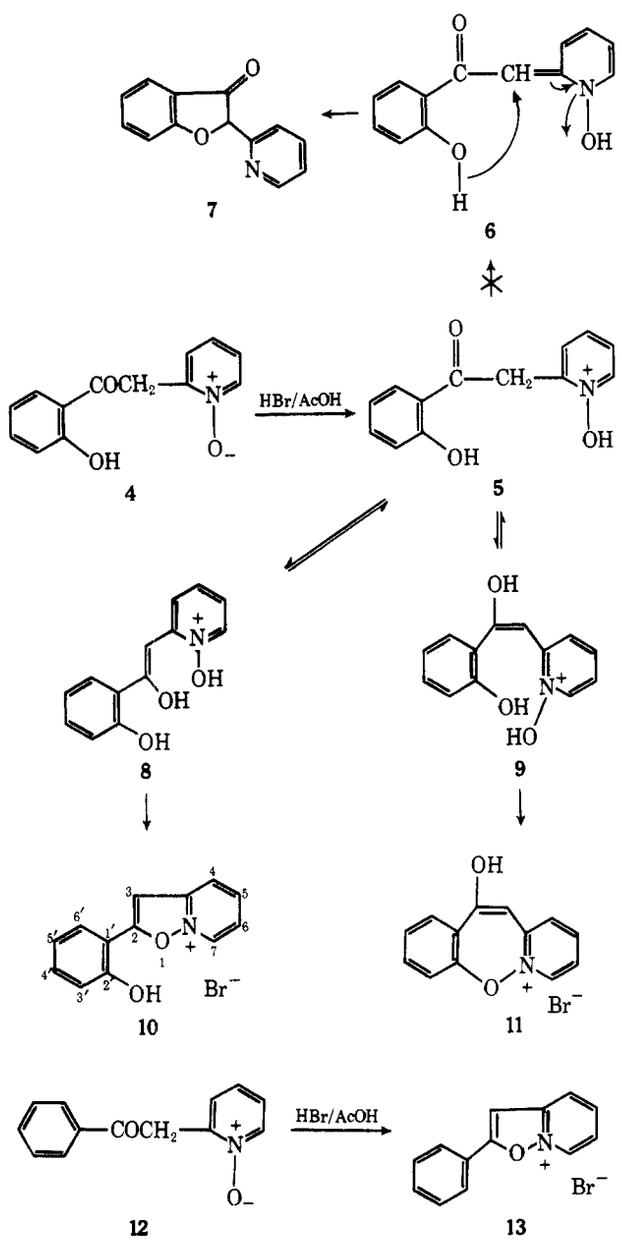
The acid-catalyzed cyclization of **1** to **3** via intramolecular nucleophilic attack on the Pummerer intermediate (**2**) was described previously.[2] 1-(2-Hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide (**4**) was prepared[3] as an intermediate for the synthesis of various heterocyclic systems.[1] As 2-picoline *N*-oxide is known to undergo a rearrangement[4-6] similar to the Pummerer rearrangement, it was expected that *N*-oxide **4** may cyclize in a manner analogous to sulfoxide **1** to give benzofuranone (**7**).

Treatment of **4** under conditions (trifluoroacetic acid in refluxing benzene) which generate **3** from **1** gave no reaction. Prolonged refluxing (24 h) also failed to give any reaction. A product with the composition expected for the HBr salt of **7** was isolated when **4** was refluxed with hydrobromic acid in acetic acid. Isoxazolo[2,3-*a*]pyridinium bromide (**10**) and 11-hydroxypyrido[1,2-*b*][1,2]benzoazepinium bromide (**11**) are other possible products arising from cyclizations of enolic intermediates **8** and **9**, respectively. The infrared spectrum

Scheme I



Scheme II



of the product showed OH bands but no carbonyl, *N*-oxide, or HBr salt bands, and the relevant features of its NMR spectrum indicated one exchangeable proton and a downfield doublet (9.87 ppm), which cannot arise from the structural features present in **7**. With acetic anhydride the product gave a monoacetate, whose NMR spectrum showed no exchangeable proton but again exhibited a downfield doublet at 9.88 ppm. These observations rule out the HBr salt of **7** as the possible product.

The reaction of *N*-oxide **12** with hydrobromic acid in refluxing acetic acid gave 2-phenylisoxazolo[2,3-*a*]pyridinium bromide (**13**). This structure is supported by analytical and spectral data, in particular the NMR spectrum, which indicates ten aromatic protons including a downfield doublet at 10.07 ppm assigned to the proton at C-7. The similarities between the UV [272 nm (ϵ 16 500) and 322 (19 800)] and NMR spectra of **13** and those of the product from the reaction of **4** with hydrobromic acid in acetic acid suggest that they have analogous structures, and thus **10** is the product formed from **4**. 1-(2-Methoxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide (**14**), which is more readily available than **4**, also gave **10** when treated under the same conditions.

This reaction represents the first general synthesis of the isoxazolo[2,3-*a*]pyridinium ring system. The compounds prepared by this method are listed in Table I. The reaction is general with the exception of compounds in which the aryl group contains basic moieties. Thus when amine **15** and pyridinyl derivative **16** are subjected to the reaction conditions, the corresponding hydrobromide salts are obtained. The only reference[7] to this ring system in the literature is the synthesis of 5-bromo-4-hydroxyisoxazolo[2,3-*a*]pyridinium bromide by a lengthy route from methyl isoxazolo-3-carboxylate. The final steps (bromination and dehydrobromination of 5-bromo-4,5,6,7-tetrahydro-6-isoxazolo[2,3-*a*]pyridinium bromide) in this synthesis limit it to the preparation of compounds containing hydroxyl and bromine substituents in the pyridinium ring.

In the majority of examples in Table I, the methoxy groups in the starting ketones are converted to hydroxy groups in the products (**10, 18, 20, 26, 28,** and **30**). Exceptions to this concomitant demethylation are **22** and **24** (which contain an halogen para to the methoxyl) and **32** (which contains a methyl group in the 7 position). Prolonged refluxing with hydrobromic acid in acetic acid fails to demethylate these compounds.

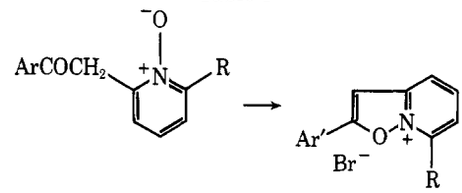
The positive charge on the nitrogen atom in the 2-arylisoxazolo[2,3-*a*]pyridinium system will lead to regions of increased electrophilicity at positions 2′, 4′, and 6′ in the aryl ring and on the 2′-methoxyl oxygen. An electron-withdrawing substituent in the 5′ position will reinforce the increased positive character at positions 2′, 4′, and 6′ and on the methoxyl oxygen. Thus protonation and demethylation at this oxygen are prevented in molecules with electron-withdrawing substituents at position 5′.

An electronic effect cannot be invoked to explain the formation of **32**. The reason for the refractory nature of the 2′-methoxy group in this molecule is not clear at this time.

An attempt was made to extend this work to the synthesis of 2-aryl-2,3-dihydroisoxazolo[2,3-*a*]pyridinium bromides. Ketone **12** was reduced to 1-phenyl-2-pyridineethanol (**33**) with sodium borohydride. The reaction of 3-(2′-pyridinyl)-propan-1-ol *N*-oxide with hydrobromic acid in acetic acid to give 2,3-dihydroisoxazolo[2,3-*a*]pyridinium bromide has been described.[8] 1-Phenyl-2-pyridineethanol *N*-oxide (**33**) was refluxed in hydrobromic acid and acetic acid in expectation that cyclization to **34** would take place; instead, 2-(2-phenylethenyl)pyridine *N*-oxide hydrobromide (**35**) was formed. The opportunity to form a system with extended conjugation by β-elimination from the carbonium ion generated from **33** is the reason for the dichotomy of product formation in these reactions. The free base of **35** had been prepared earlier[9] by the condensation of 2-picoline *N*-oxide with benzaldehyde in the presence of sodium methoxide.

Thus acid-catalyzed cyclization of (2-pyridinyl)ethanone *N*-oxides constitutes a general synthesis of the isoxazolo[2,3-*a*]pyridinium ring system, but 2-pyridineethanol *N*-oxides

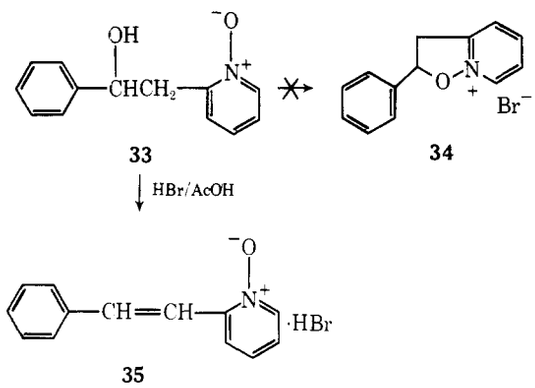
Table I[a]



R	Ar[c]	Ar'[d]	Mp,[b] °C	Yield, %	NMR C_7 H
H	Phenyl (12)	Phenyl (13)	164–165	60	10.07
H	2-Hydroxyphenyl (4)	2-Hydroxyphenyl (10)	>230 dec	86	9.87
H	2-Methoxyphenyl (14)			40	
H	2,3-Dimethoxyphenyl (17)	2,3-Dihydroxyphenyl (18)	>222 dec	72	9.88
H	2-Methoxy-5-methylphenyl (19)	2-Hydroxy-5-methylphenyl (20)	>220 dec	48	9.89
H	2-Methoxy-5-bromophenyl (21)	2-Methoxy-5-bromophenyl (22)	>202 dec	76	9.98
H	2-Methoxy-5-chlorophenyl (23)	2-Methoxy-5-chlorophenyl (24)	208–210	45	9.99
H	3,4,5-Trimethoxyphenyl (25)	3,4,5-Trihydroxyphenyl (26)	>210 dec	34	9.91
H	4-Methoxyphenyl (27)	4-Hydroxyphenyl (28)	>180 dec	59	9.89
H	3-Chloro-4-methoxyphenyl (29)	3-Chloro-4-hydroxyphenyl (30)	>215 dec	57	9.92
H	2-Aminophenyl (15)	No reaction			
H	2-Pyridinyl (16)	No reaction			C-Me
Me	2-Methoxyphenyl (31)	2-Methoxyphenyl (32)	>220 dec	37	3.04

[a] Satisfactory analytical data (±0.4% for C, H, N, Br, and Cl) were reported for all compounds listed in the table with the exceptions of **24** (C 0.55% out) and **22**. Although accurate analytical data could not be obtained for **22**, its NMR (Me_2SO-d_6) [δ 9.98 (d, 1, J = 8 Hz, C_7 H), 8.7–7.2'(m, 7, ArH), and 4.08 (s, 3, OMe)] and UV (EtOH) [274 nm (ε 13 300), 281 (13 600), 350 (15 400)] spectra were in agreement with the assigned structure. The compounds decomposed in the mass spectrometer without giving recognizable fragments. [b] The compounds were recrystallized from EtOH with the exception of **24** (from 2-propanol). [c] Registry no. are, respectively, 61395-07-1, 61395-08-2, 61436-92-8, 61395-09-3, 61395-10-6, 61395-11-7, 61395-12-8, 61395-13-9, 61395-14-0, 61395-15-1, 60928-33-8, 61395-16-2, 61395-17-3. [d] Registry no. are, respectively, 61395-18-4, 61395-19-5, 61395-20-8, 61395-21-9, 61395-22-0, 61395-23-1, 61395-24-2, 61395-25-3, 61395-26-4, 61395-27-5.

Scheme III



33 **34** **35**

are converted to the 2,3-dihydroisoxazolo[2,3-a]pyridinium system only when the C_1 substituent does not promote β-elimination.

Experimental Section

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. NMR spectra were recorded on a Perkin-Elmer R 12 B spectrometer at 60 MHz with Me_4Si as internal standard. Infrared spectra were recorded on a Beckman IR-18A spectrometer. Ultraviolet spectra were recorded on a Beckman DK-I spectrometer. Mass spectra were obtained with an AEI MS-902 instrument.

General Procedure for the Synthesis of 2-Arylisoxazolo[2,3-*a*]pyridinium Bromides. A solution of 1-aryl-2-(2-pyridinyl)ethanone N-oxide (20.0 g) in 48% hydrobromic acid (250 mL) and glacial acetic acid (250 mL) was refluxed for 5 h. The solvents were removed under reduced pressure to give crystalline products. Recrystallization (Table I) gave analytically pure material.

2-(2-Acetyloxyphenyl)isoxazolo[2,3-*a*]pyridinium Bromide. A solution of 2-(2-hydroxyphenyl)isoxazolo[2,3-a]pyridinium bromide (5.0 g) in acetic anhydride (40 mL) was refluxed for 90 min. The solvent was removed under reduce pressure to give an oil, which crystallized from ethyl acetate. Recrystallization from 2-propanol gave white crystals (4.16 g, 73%): mp 198–201 °C; λ_{max} (EtOH) 270 nm (ε 15 000), 321 (18 000); ν_{max} (Nujol) 1775 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 9.88 (d, 1, J = 8 Hz, C_7 H), 8.55–7.30 (m, 8, ArH), and 2.51 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{12}BrNO_3$: C, 53.91; H, 3.62; N, 4.19; Br, 23.91. Found: C, 53.95; H, 3.81; N, 4.18; Br, 23.83.

1-Phenyl-2-pyridineethanol *N*-Oxide (33). Sodium borohydride (1.72 g) was added to an ice-cold solution of 1-phenyl-2-(2-pyridinyl)ethanone N-oxide (10.0 g) in methanol. The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to give a solid residue, which was suspended in water, filtered, washed thoroughly with water, and dried at room temperature. Recrystallization from benzene gave white crystals (7.80 g, 77%): mp 121–123 °C; λ_{max} (EtOH) 216 nm (ε 25 200), 263 (10 100); ν_{max} (Nujol) 3260 (OH), 1250 cm^{-1} (N → O); NMR ($CDCl_3$) δ 8.35–6.80 (m, 9, ArH), 6.42 (bs, 1, OH, exchanges with D_2O), 5.14 (t, 1, J = 6 Hz, CH), and 3.37 (d, 2, J = 6 Hz, CH_2).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.56; H, 6.37; N, 6.44.

2-(2-Phenylethenyl)pyridine 1-Oxide Hydrobromide (35). A solution of 1-phenyl-2-pyridineethanol N-oxide (20 g) in 48% hydrobromic acid (200 mL) and glacial acetic acid (200 mL) was refluxed for 5 h. The solvents were removed under reduced pressure to give a crystalline product. Recrystallization from absolute ethanol gave white crystals (7.75 g, 30%): mp 187–189 °C; λ_{max} (EtOH) 231 nm (ε 11 700), 270 (21 200), 320 (24 500); ν_{max} (Nujol) 2410 (HBr salt), 1250 cm^{-1} (N → O); NMR (Me_2SO-d_6) δ 9.00–7.05 (m, 12).

Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.34; N, 5.04; Br, 28.73. Found: C, 55.99; H, 4.38; N, 4.95; Br, 28.66.

Registry No.—**33**, 61395-28-6; **35**, 61395-29-7; hydrobromic acid, 24959-67-9; 2-(2-acetyloxyphenyl)isoxazolo[2,3-a]pyridinium bromide, 61395-30-0; acetic anhydride, 108-24-7.

References and Notes

(1) Part 2: D. T. Connor, P. A. Young, and M. von Strandtmann, *J. Heterocycl. Chem.*, accepted for publication.
(2) D. T. Connor and M. von Strandtmann, *J. Org. Chem.*, **39**, 1594 (1974).
(3) Part 1: D. T. Connor, P. A. Young, and M. von Strandtmann, *J. Heterocycl. Chem.*, accepted for publication.
(4) G. Kobayashi and S. Furukawa, *Pharm. Bull.*, **1**, 347 (1953).
(5) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).
(6) O. H. Bullitt and J. T. Maynard, *J. Am. Chem. Soc.*, **76**, 1370 (1954).
(7) R. H. Good and G. Jones, *J. Chem. Soc. C*, 1196 (1971).
(8) V. Boekelheide and W. Feely, *J. Am. Chem. Soc.*, **80**, 2217 (1958).
(9) K. Ramaiah and V. R. Srinivasan, *Indian J. Chem.*, **1**, 351 (1963).