Department of Chemistry, Duke University

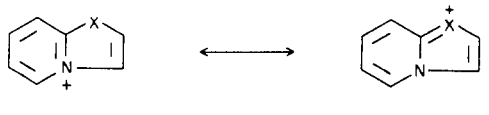
Oxazolo[3,2-*a*]pyridinium Salts (1,2)

C. K. Bradsher and Mary F. Zinn

The first synthesis of the aromatic oxazolo[3,2-*a*]pyridinium ring system has been accomplished by the cyclization of 1-acetonyl- or 1-phenacyl-2-pyridones. Through use of the analogous quinolones and 2-(*p*-bromophenacyl)-1-isoquinolone, benzologs of the new system have been prepared.

Earlier observations (3) in the imidazo[1,2-*a*]-pyridinium series (Ia) led to the prediction that there should exist a family of resonance-stabilized aromatic salts where X is an atom or group having a delocalizable pair of electrons. The synthesis of the first thiazolo[3,2-*a*]pyridinium salts (Ib) has been described recently (4).

The present communication describes the first fully aromatic oxazolo[3,2-*a*]pyridinium salts (Ic). It is known (5) that 2-alkoxypyridines react with alkyl halides to yield 1-alkylpyridones. The reaction of 2-methoxypyridine with phenacyl halides in refluxing acetone likewise appears to take place at position 1. Cyclization of 1-(*p*-bromophenacyl)-pyridone was brought about in concentrated sulfuric acid at room temperature. While the cyclization conditions are identical with those used earlier in the preparation of the thiazolo[3,2-*a*]pyridinium cation, the new cyclization reaction itself is more reminiscent of the dehydration of 1,4-diketones to yield furan derivatives (6). The cyclization product, obtained in 78% yield as the perchlorate salt, showed no significant absorption in the region of the infrared spectrum assigned to carbonyl absorptions, and gave no evidence of protons at < δ 7.50 in the proton magnetic resonance spectrum.

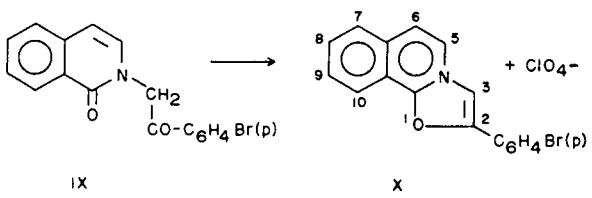


I

a, X = N-R

b, X = S

c, X = O



IX X

Results of the synthesis of oxazolo[3,2-*a*]pyridinium salts are summarized in Table I.

With sulfuric acid as the cyclizing medium, reactive aryl groups may undergo sulfonation, and this is believed to have occurred in the cyclization of the pyridones (IVb and IVc) derived from *p*-phenylphenacyl- and *p*-methoxyphenacyl bromide. Only in the latter case was it possible to obtain the sulfo betaine, presumably the betaine of 2-(4-methoxy-3-sulfophenyl)oxazolo[3,2-*a*]pyridinium hydroxide, in a state of analytical purity. Betaine formation may be avoided by the more hazardous procedure of using hot 70% perchloric acid as the cyclizing medium. In a single small scale experiment, it was shown that 1-(*p*-phenylphenacyl)-2-pyridone may be cyclized in perchloric acid in 90% yield.

The 2-methyloxazolo[3,2-*a*]pyridinium cation (Ve), although obtained in poor yield, is of interest because its spectra and reactivity would be expected to resemble closely those of the unknown parent cation (Ic).

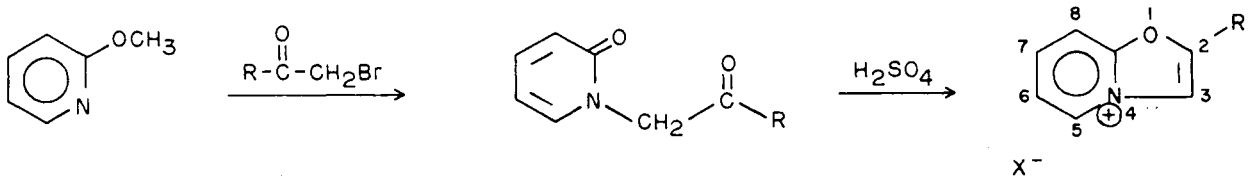
The methyloxazolopyridinium perchlorate (Ve) was less stable to 0.001 *M* sodium hydroxide solution than were the sulfur analogs (Ib) (4b) and within a few hours the characteristic absorption maximum at 262 mμ disappeared and a new one appeared at 305 mμ. The nature of the chemical change involved has not been determined.

The nuclear magnetic resonance spectrum of 2-methyloxazolo[3,2-*a*]pyridinium perchlorate in trifluoroacetic acid showed a singlet at δ 2.68 assigned to protons of the methyl group and bands assigned to the aromatic protons in the region δ 7.6-9.1 with areas in the predicted ratio of 1.00 to 1.67.

A logical sequel to the synthesis of oxazolo[3,2-*a*]-pyridinium salts was an attempt to prepare benzologs of the system (Table II). Both 2-methoxyquinoline and 2-methoxylepidine reacted with α-bromomethyl ketones; but under the conditions used for the preparations of the phenacylpyridones (IV), only low yields of the expected quinolones (VII) were obtained.

TABLE I

2-Substituted Oxazolo[3,2-*a*]pyridinium Salts



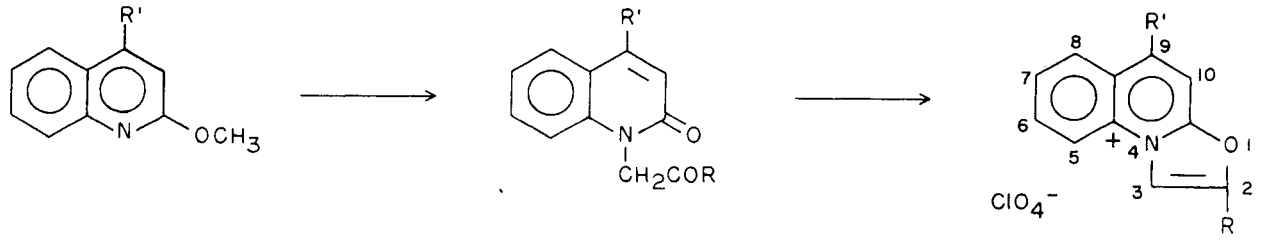
II III a-e IV a-e V a-e

	III R	IV Yield, %	Yield, %	V λ max, mμ (log ε)
a	*p*-BrC_6H_4	78 (a)	78	265 (4.20), 283sh (4.15), 294sh (4.14), 305 (4.10)
b	*p*-$C_6H_5C_6H_4$	55	90 (b)	285sh (4.25), 318 (4.45)
c	*p*-$CH_3OC_6H_4$	52	77 (c)	208 (d) (4.51), 228sh (4.16), 284sh (4.07), 320 (4.35)
d	C_6H_5	74	72	238 (3.97), 285sh (4.18), 297 (4.21)
e	CH_3	-- (e)	19	262 (4.08), 270sh (4.04), 277sh (3.91)

(a) In one experiment using 2-ethoxypyridine, only a 32% yield of IVa was obtained. (b) To avoid sulfonation, cyclization was carried out in 70% perchloric acid. (c) The product was not the expected 2-(*p*-methoxyphenyl)oxazolo[3,2-*a*]pyridinium perchlorate, but a sulfobetaine believed to be the betaine of 2-(4-methoxy-3-sulfophenyl)oxazolo[3,2-*a*]pyridinium hydroxide. (d) The ultraviolet absorption spectrum of the sulfobetaine was determined in 81% ethanol. (e) The intermediate 1-acetonyl-2-pyridone was not isolated but used directly in the cyclization reaction.

TABLE II

2-Substituted Oxazolo[3,2-*a*]quinolinium Perchlorates (VIII)



VI VII a-f VIII a-f

	R'	R	VII Yield, %	VIII Yield, %	VIII λ max, mμ (log ε)
a	H	*p*-Br-C_6H_4	17	81	210 (4.49), 220 (4.50), 228sh (4.45), 248 (4.21), 265 (4.29), 275sh (4.24), 298sh (4.01), 318sh (4.25), 332 (4.27).
b	H	C_6H_5	38	65	218sh (4.45), 228sh (4.41), 237sh (4.34), 246sh (4.31), 260sh (4.18), 268sh (4.12), 318 (4.20), 330 (4.21).
c	H	*p*-$C_6H_5C_6H_4$	9	0 (a)	
d	CH_3	*p*-BrC_6H_4	19	60	222 (4.51), 230sh (4.44), 268 (4.31), 274sh (4.29), 297sh (4.11), 318sh (4.32), 330 (4.34).
e	CH_3	C_6H_5	30	62	218sh (4.44), 230 (4.38), 245sh (4.29), 260 (4.21), 272sh (4.15), 317 (4.24), 328 (4.25).
f	CH_3	CH_3	28	94	230 (4.52), 247sh (3.82), 270sh (3.70), 282 (3.78), 308 (3.93).

(a) A very insoluble product, probably the sulfobetaine, was obtained but not in a state of analytical purity. Attempts to cyclize the quinolone in 70% perchloric acid failed.

TABLE III

Alkylation Products of Methoxy Bases

	R	M.P., °C	Crystalline Form	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
				Pyridones (IVa-d)						
a	*p*-BrC_6H_4	168-170	plates (a)	$C_{13}H_{10}BrNO_2$	53.44	53.24	3.45	3.54	4.79	4.47
b	*p*-$C_6H_5C_6H_4$	233.5-235.5	needles	$C_{19}H_{15}NO_2$	78.87	78.85	5.23	5.29	4.84	4.84
c	*p*-$CH_3OC_6H_4$	149-150.5	needles (b)	$C_{14}H_{13}NO_3$	69.12	68.81	5.39	5.36	5.76	5.85
d	C_6H_5	156-158 (c)	needles	$C_{13}H_{11}NO_2$	73.22	73.26	5.20	5.27	6.57	6.86
				Quinolones (VIIa-c, R' = H)						
a	*p*-BrC_6H_4	195-196	needles (d)	$C_{17}H_{12}BrNO_2$	59.66	59.64	3.54	3.32	4.09	4.19
b	C_6H_5	165.6-169	needles (b)	$C_{17}H_{13}NO_2$	77.55	77.24	4.98	5.02	5.32	5.42
c	*p*-$C_6H_5C_6H_4$	180-182	microcryst.	$C_{23}H_{17}NO_2$	81.39	81.88	5.05	5.19	4.13	4.10
				Quinolones (VIId-f, R' = CH_3)						
d	*p*-BrC_6H_4	230.5-233.5	plates (e)	$C_{18}H_{14}BrNO_2$	60.69	60.71	3.96	3.78	3.93	3.84
e	C_6H_5	179-180.5	prisms	$C_{18}H_{15}NO_2$	77.96	78.02	5.45	5.43	5.05	4.97
f	CH_3	156-157	needles	$C_{13}H_{13}NO_2$	72.52	72.44	6.09	6.05	6.51	6.62
				Isoquinolone (IX)						
	p-BrC_6H_4 (f)	244-249 (g)	plates	$C_{17}H_{12}BrNO_2$	59.66	59.36	3.54	3.06	4.09	4.20

(a) From methanol-ethyl acetate. (b) Ivory colored. (c) Lit. [C. Alberti, *Gazz. Chim. Ital.*, **86**, 1181 (1956)], m.p. 154-155°. (d) Orange. (e) In addition to crystallizing as square plates, m.p. 229-231°, it crystallized simultaneously as a microcrystalline powder, m.p. 219-221°. If the low-melting form was melted and allowed to resolidify, it melted at 229-232°. The analytical sample was a mixture of both forms, m.p. 224-233°, remelted at 230.5-233.5°. (f) This product was obtained from 1-methoxyisoquinoline in 8% yield. (g) Decomposition point.

TABLE IV

Sulfuric Acid Cyclizations of Alkylation Products

Oxazolo[3,2-*a*]pyridinium Perchlorates (Va-e)

	R	M.P., °C	Crystalline Form	Formula	C Calcd.	C Found	H Calcd.	H Found	V Calcd.	V Found
a	*p*-BrC_6H_4 (a)	259-262	plates	$C_{13}H_9BrClNO_5$	41.68	41.77	2.42	2.50	3.74	4.04
c	4-CH_3O-3SO_3H-C_6H_3 (b)	>350	powder	$C_{14}H_{11}NO_5S\cdot{}^1/_2H_2O$	53.59	53.57	3.85	3.48	4.46	4.71
d	C_6H_5	218-222 (c)	needles	$C_{13}H_{10}ClNO_5$	52.81	52.61	3.41	3.77	4.74	5.10
e	CH_3	130-133 (d)	plates	$C_8H_8ClNO_5$	41.13	41.42	3.45	3.68	6.00	6.20
	Oxazolo[3,2-*a*]quinolinium Perchlorates (VIIIa-b, R' = H)									
a	*p*-BrC_6H_4	253.5-256.5	needles	$C_{17}H_{11}BrClNO_5$	48.08	48.31	2.61	2.59	3.30	3.41
b	C_6H_5	272.5-275	needles	$C_{17}H_{12}ClNO_5$	59.05	59.40	3.50	3.43	4.05	4.23
	Oxazolo[3,2-*a*]quinolinium Perchlorates (VIIId-f, R' = CH_3									
d	*p*-BrC_6H_4	267-269 (e)	needles (f)	$C_{18}H_{13}BrClNO_5$	49.28	49.06	2.99	3.27	3.19	3.16
e	C_6H_5	230-235 (e)	powder (f)	$C_{18}H_{14}ClNO_5$	60.09	60.32	3.92	3.70	3.89	3.75
f	CH_3	263-268.5	needles (d)	$C_{13}H_{12}ClNO_5$	52.45	52.26	4.06	4.14	4.71	4.76
	Oxazolo[2,3-*a*]isoquinolinium Perchlorate									
	p-BrC_6H_4	274.5-277 (g)	powder (f)	$C_{17}H_{11}BrClNO_5$	48.08	48.38	2.61	2.62	3.30	3.51

(a) The nuclear magnetic resonance spectrum measured in trifluoroacetic acid showed no bands at > δ 7.50. (b) The cyclization of 1-(*p*-methoxyphenacyl)-2-pyridone (IVc) is accompanied by sulfonation to afford a betaine believed to be the betaine of 2-(4-methoxy-3-sulfophenyl)oxazolo[3,2-*a*]-pyridinium hydroxide. It was crystallized from ethanol-water. (c) The bromide, needles m.p. 197.5-199.5°, was prepared by first precipitating the tribromide salt from an aqueous solution of the perchlorate, followed by conversion of the tribromide to bromide by boiling it in an acetone-methanol mixture. *Anal.* Calcd. for $C_{13}H_{10}BrNO\cdot H_2O$: C, 53.08; H, 4.11; N 4.76. Found: C, 53.28; H, 3.96; N, 4.90. (d) From methanol-ethyl acetate. (e) Decomposes. (f) From ethanol. (g) λ max, mμ (log ε) 227 sh (4.39), 240 (4.30), 267 (4.46), 277 (4.46), 296 sh (4.18), 314 (4.30) and 336 sh (4.07).

Cyclization of the quinolones in sulfuric acid gave satisfactory yields, but as in the case of the pyridone analog (IVb), appeared to be accompanied by sulfonation where the 4-biphenylyl group was present (VIIc).

Only a single example of the oxazolo[2,3-*a*]isoquinolinium system (the 2-*p*-bromophenyl derivative, X) was prepared in 46% yield.

It is anticipated that the new oxazolo[3,2-*a*]pyridinium salts and benzologs thereof will undergo some of the interesting reactions characteristic of cationic aromatic systems.

EXPERIMENTAL

The elemental analyses were carried out by Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, West Germany and Galbraith Laboratories, Knoxville, Tennessee. Melting points were determined in capillaries with a Laboratory Devices Mel-Temp block, and are uncorrected. Unless otherwise indicated, all ultraviolet absorption spectra were measured in 95% ethanol using 1 cm silica cells in a Cary Model 14 spectrophotometer.

Methoxy Bases.

2-Methoxypyridine is available commercially (7) and the 2-methoxy- (8) and 2-methoxy-4-methylquinolines (9) were prepared as previously described from the corresponding chloro- derivatives by the action of sodium methoxide in methanol. 1-Methoxyisoquinoline was prepared by the method of Fernau (10) which involves the action of methyl iodide on the silver salt of 1-hydroxyisoquinoline.

Alkylation of Methoxypyridine, 2-Methoxyquinolines and 1-Methoxyisoquinoline.

In a typical preparation, the alkoxy base was heated under reflux for 48 hours in reagent grade acetone with one to two equivalents of the phenacyl or acetonyl bromide. The alkylation products (IV, VII, IX) were usually purified by crystallization from methanol. Experimental data for the alkylation products are summarized in Table III.

Cyclization Reactions in Sulfuric Acid.

Two hundred milligrams of the pyridone or pyridone benzolog was dissolved in 10 ml. of concentrated sulfuric acid at room temperature, and the resulting solution allowed to stand for 24 hours. The sulfuric acid solution was then cooled and poured into 300 ml. of ice-cold anhydrous ether. The precipitated solid was collected, dissolved in a minimum quantity of water and 70% perchloric acid added until there was no further precipitation. The perchlorate salt was collected and recrystallized from methanol. The results of the sulfuric acid cyclizations are summarized in Table IV.

2-(*p*-Phenylphenyl)oxazolo[3,2-*a*]pyridinium Perchlorate (Vb).

Attempted cyclization of 1-(*p*-phenylphenacyl)-2-pyridone (IVb) in concentrated sulfuric acid led to a water-insoluble product which was almost certainly a sulfo betaine. Two hundred milligrams of the pyridone (IVb) in about 10 ml. of 70% perchloric acid was heated on a steam bath (safety shield) until all of the solid had dissolved. The solution was cooled, diluted and allowed to stand at -15° for 24 hours. The precipitate was crystallized from ethanol-water to afford 137 mg. (90%) of a pale yellow solid, m.p. 268-273°, λ max, mμ (log ε), 285 sh (4.25) and 318 (4.45).

Anal. Calcd. for $C_{19}H_{14}ClNO_5$: C, 61.38; H, 3.80; N, 3.77. Found: C, 61.11; H, 3.82; N, 3.91.

Betaine of 2-(4-Hydroxy-3-sulfophenyl)oxazolo[3,2-*a*]pyridinium Hydroxide (V, R = 4-OH, 3-$SO_3HC_6H_3$-, X = OH).

To a mixture containing 1.1 ml. of concentrated hydriodic acid in approximately 1.3 ml. of glacial acetic acid, 100 mg. of the betaine of 2-(4-methoxy-3-sulfophenyl-oxazolo[3,2-*a*]pyridinium hydroxide (Vc) was added and the mixture refluxed for 24 hours. The acids were removed under vacuum, the residue washed with methanol and recrystallized from ethanol-water, yield 19 mg. (20%) of a colorless product, m.p. < 390°, λ max, mμ 81% ethanol (log ε) 208 (4.54), 228 sh (4.14), 238 sh (4.03), 283 sh (4.04) and 3.18 (4.37). Solutions of the product gave a positive phenol color test with ferric chloride.

Anal. Calcd. for $C_{13}H_9NO_5S \cdot H_2O$: C, 50.48; H, 3.59; N, 4.53. Found: C, 50.75; H, 3.40; N, 4.71.

REFERENCES

(1) This work has been made the subject of a preliminary communication: C. K. Bradsher and Mary F. Zinn, *J. Heterocyclic Chem.*, **1**, 219 (1964). The nomenclature has been revised to correspond to the practice of *Chemical Abstracts*.

(2) This research was supported by Public Health Service Grant No. H-2170 of the National Hearth Institute.

(3) C. K. Bradsher, E. F. Litzinger, Jr. and Mary F. Zinn, *J. Heterocyclic Chem.*, 2, 331 (1965).

(4a) F. S. Babichev and V. N. Bubnovskaya, *Ukr. Khim. Zh.*, 30, 848 (1964); *Chem. Abstr.*, 62, 1766c (1965). (b) C. K. Bradsher and D. F. Lohr, Jr., *Chem. Ind.* (London), 1801 (1964).

(5) L. A. Paquette and N. A. Nelson, *J. Org. Chem.*, **27**, 1085 (1962), and references there cited.

(6) R. C. Elderfield and T. N. Dodd, Jr., "Heterocyclic Compounds," R. C. Elderfield, Editor, John Wiley and Sons, Inc., New York, p. 127.

(7) Aldrich Chemical Company, Inc.

(8) P. Friedlaender and H. Ostermaier, *Ber.*, **15**, 336 (1882); T. B. Grave, *J. Am. Chem. Soc.*, **46**, 1466 (1924).

(9) L. Knorr, *Ann. Chem.*, **236**, 100 (1886).

(10) A. Fernau, *Monatsh. Chem.*, **14**, 66 (1893).

Received November 28, 1966 Durham, North Carolina 27706