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Imidazo[1,2-a]pyridinium Salts (1)

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2-Alkylamino- or arylaminopyridines react directly with α-bromoketones to afford 1-alkyl- or 1-arylimidazo[1,2-a]pyridinium salts with substituents at position 2. Use of chloroacetaldoxime as the quaternizing agent yields (after hydrolysis) the imidazo-[1,2-a]pyridinium ion with no substituent at position 2. The earlier supposition that alkylation of imidazo[1,2-a]pyridines occurs in position 1 has been shown to be correct.

It has been pointed out that the 1-substituted imidazo[1,2-a]pyridinium system is but one of a group of aromatic heterocyclic systems isoelectronic with the quinolizinium system.

In earlier work it was shown that pyridine derivatives (I), linked in a suitable way to phenyl, could be quaternized by reaction with bromoacetone, and the quaternary salts (II) cyclized to form new tricyclic heterocyclic systems (III). Such tricyclic systems in which the linkage X is $-CH_2-$(2), -O-(3), or -S-(4) have been described. When 2-anilinopyridine (I, X = NH) is allowed to react with bromoacetone in boiling acetone the product was not the expected 1-acetonyl salt (II, X = NH) but a dehydration product having in the infrared absorption spectrum no absorption band attributable to a carbonyl group.

Since the intermediate (II, X = NH) to be expected in the quaternization reaction is a resonance hybrid in which there is an appreciable positive charge on the NH link to phenyl, it seemed unlikely that the facile cyclodehydration could involve an attack on the phenyl ring. Further evidence that there was no cyclization involving the phenyl group was the appearance of infrared absorption bonds at 695, 760 and 775 cm^{-1} suggesting the presence of an unsubstituted phenyl ring (5).

A more plausible explanation for the cyclodehydration reaction was that the attack of the carbonyl group had occurred on the anilino nitrogen atom affording the hitherto unknown 1-phenyl-2-methylimidazo[1,2-a]pyridinium cation (IVa). This theory was supported by the observation that 2-(N-methylanilino)pyridine (I, X = N - CH_3) on reaction with bromoacetone yielded the simple quaternary salt (II, X = N - CH_3) rather than a cyclodehydration product.

While the imidazo[1,2-a]pyridine structure (Va) has been recognized as an aromatic heterocyclic system since the early investigations of Tschitschibabin (6), little attention has been devoted to the 1-alkyl or aryl cations (VIa). These cations (VIa) have a resonance-stabilized 10-electron system which stands to the quinolizinium ion (VII) as indole to naphthalene. It seems probable that the group X in formula VI could be any atom or group which can furnish two electrons to the system. The first examples of the thiazolo- (VIb) (7, 8) and oxazolo-[3,2-a]pyridinium (VIc) (9) cations have been described recently.

To demonstrate the general nature of the reaction of α-haloketones with 2-alkylamino pyridines (VIII) the reactions of 2-methylamino- (R = CH_3) and 2-benzylaminopyridines (R = $C_6H_5CH_2$) have been studied. The results are summarized in Table I. The simple 1-phenyl (IVb) and 1-methylimidazo[1,2-a]pyridinium (IX, R_1 = CH_3, R_2 = R_3 = H) cations were prepared from the corresponding amines (VIII, R_1 = C_6H_5 or CH_3) by the use of chloroacetaldoxime (10) as a quaternizing agent. It was found that the cation (IX R_1 = R_2 = CH_3, R_3 = H) produced from 2-methylaminopyridine by reaction with bromoacetone was identical with that obtained by methylation of 2-methylimidazo[1,2-a]pyridine (Vb) (11). This shows the correctness of earlier conjecture (11, 12) concerning the position at which quaternization occurs in the imidazopyridine system and provides a convenient route to a variety of 1-methylimidazo-[1,2-a]pyridinium salts with substituents in the six-membered ring (Table II).

EXPERIMENTAL

The elemental analyses were carried out by Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, Germany, Dr. C. Daessle, Montreal, P. Q., Canada or by Galbraith Laboratories, Knoxville, Tennessee. The melting points were determined in capillary tubes in a Mel-Temp apparatus. Ultraviolet absorption spectra were measured in 95% ethanol using 1 cm matched silica cells in a Cary Model 14 Spectrophotometer. Infrared data were determined in potassium bromide discs, using a Perkin-Elmer Model 137 or 237 Spectrophotometer. The proton magnetic resonance data were obtained with a Varian A-60 Spectrometer. Except as noted, all products were crystallized from methanol-ethyl acetate.

1-Phenyl-2-methylimidazo[1,2-a]pyridinium Bromide (IVa).

One gram of 2-anilinopyridine (I, X = NH) and 1.61 g. of bromoacetone were refluxed for 48 hours in 25 ml. of reagent grade acetone, resulting in the formation of a precipitate. The acetone was removed under vacuum and the residue twice recrystallized. The product formed

cream-colored needles, m.p. 214-216°, yield 1.57 g. (92%); λ max, mμ (log ε) 204 (4.47) and 287 (4.06).

Anal. Calcd. for $C_{14}H_{13}BrN_2 \cdot {}^1/_4H_2O$: C, 57.25; H, 4.63; N, 9.54. Found: C, 57.45; H, 4.81; N, 9.71.

The perchlorate crystallized as colorless needles, m.p. 140-141°.

Anal. Calcd. for $C_{14}H_{13}ClN_2O_4$: C, 54.46; H, 4.24; N, 9.08. Found: C, 54.42; H, 4.36; N, 9.19.

1-Acetonyl-2-(N-methylanilino)pyridinium Bromide (II, X = NCH_3, Y = Br).

The reaction of 1 g. of 2-(N-methylanilino)pyridine (I, X = NCH_3) with 1.49 g. of bromoacetone was carried out as described for the preparation of IVa. The product was light yellow crystals, m.p. 142-143°, yield 0.44 g. (25%).

Anal. Calcd. for $C_{15}H_{17}BrN_2O$: C, 56.08; H, 5.34; N, 8.72. Found: C, 55.76; H, 5.31; N, 8.63.

The perchlorate crystallized as light yellow needles, m.p. 118-120°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_5$: C, 52.86; H, 5.03; N, 8.22. Found: C, 52.80; H, 5.07; N, 7.90.

2-(N-Methylsulfonamidophenyl)pyridine.

Crude 2-(methylamino)pyridine (14) was purified by conversion to the benzenesulfonamide derivative. By reaction of the amine with benzenesulfonyl chloride in the presence of excess 10% sodium hydroxide solution, and crystallization of the product from benzene-ligroin, the sulfonamide was obtained as colorless needles, m.p. 65.5-66.5°, yield 27%.

2-(Methylamino)pyridine.

Hydrolysis of the 2-(N-methylsulfonamidophenyl)pyridine was carried

TABLE I

Imidazo[1,2-a]pyridinium Salts from Alkylaminopyridines

	IX			Reaction Time,		Yield,	
	R_1	R_2	R_3	Hours	Temp.	%	λ max, mμ (log ε)
a	CH_3	-	-	- (a)	-	-	214 (4.28), 218sh (4.14), 284 (3.85)
b	CH_3 (b)	CH_3	-	4	57	75	210sh (4.15), 218 (4.27), 223 (4.25), 285 (3.92)
c	CH_3	CH_3	CH_3	120	25	65	202 (4.14), 238 (4.05), 326 (3.65)
d	CH_3 (c)	C_6H_5	-	24	25	60	205 (4.39), 238 (4.15), 328 (3.66)
e	$C_6H_5CH_2$	CH_3	-	15	57	97	204 (4.46), 218sh (4.37), 285 (4.02)
f	$C_6H_5CH_2$	C_6H_5	-	1 (d)	25	77	238 (4.18), 327 (3.75)

(a) This compound was obtained in small yield by acid-catalyzed hydrolysis and cyclization of the quaternary salt obtained by reaction of 2-methylaminopyridine with chloroacetaldoxime. (b) The NMR spectrum showed singlets at 5.68 and 7.00 τ attributed to the methyl protons at positions 1 and 2. (c) The NMR spectrum showed a singlet at 6.60 τ, due to the methyl protons. (d) Warmed for one minute, then allowed to stand.

TABLE II

1-Methylimidazo[1,2-a]pyridinium Salts (X) by Alkylation of Imidazopyridines

					Yield (a)	
	R_2	R_5	R_7	R_8	%	λ max, mμ (log ε)
a	CH_3	CH_3	-	-	9	218 (4.53), 288 (3.97), 298sh (3.91)
b	CH_3	-	CH_3	-	35	219 (4.54), 224sh (4.50), 283 (3.96)
c	C_6H_5	-	CH_3	-	40 (b)	205 (4.58), 210sh (4.56), 221 (4.55), 288 (4.14)
d	CH_3 (c)	-	-	CH_3	68	215sh (4.45), 221 (4.56), 226sh (4.51), 287 (3.99)
e	C_6H_5	-	-	CH_3	80 (d)	212 (4.50), 222 (4.53), 289 (4.14)

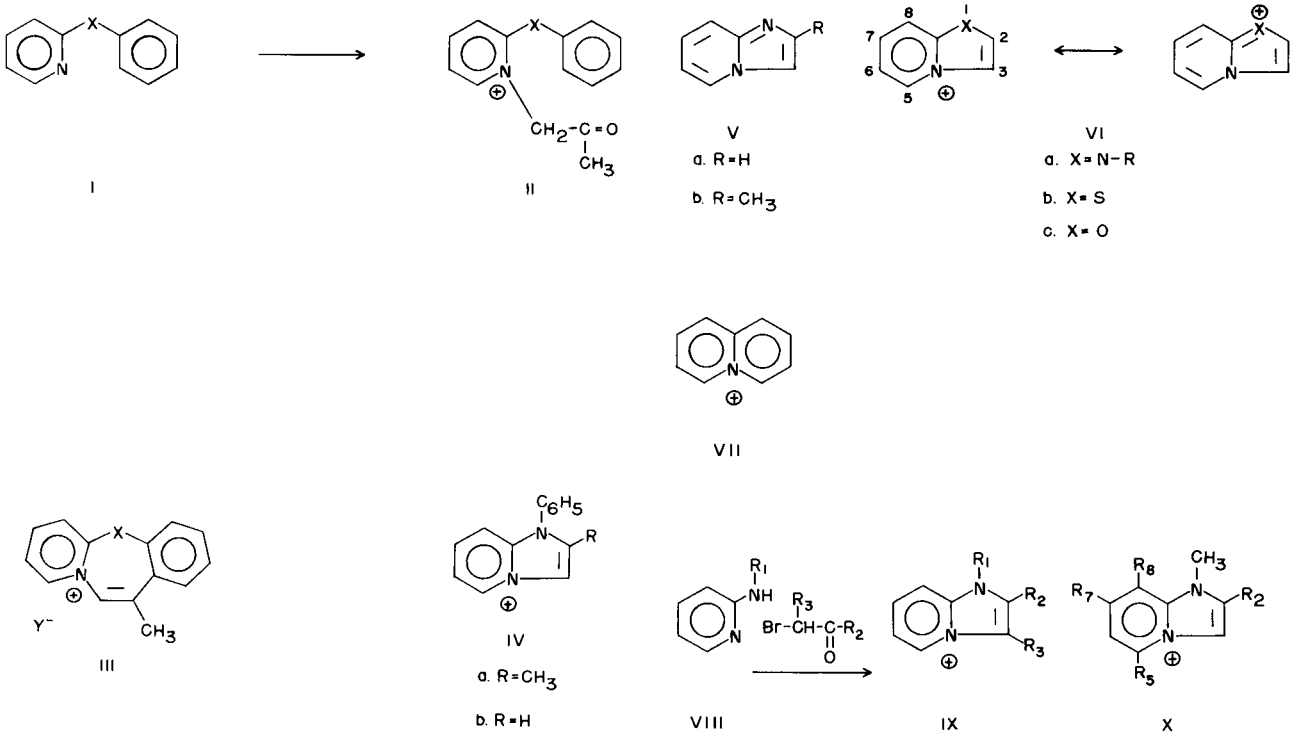
(a) Except as noted, the yields are overall from the 2-amino-x-methylpyridine. (b) 2-Phenyl-7-methylimidazo[1,2-a]pyridine was obtained in 67% yield. Colorless needles from benzene - ligroin, m.p. 164-166°. *Anal.* Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.84; H, 5.83; N, 13.55. (c) The NMR spectrum had three singlets at 7.0, 6.7 and 5.4, attributed to the protons of the three methyl groups. (d) Prepared from crystalline 2-phenyl-8-methylimidazo[1,2-a]pyridine (ref. 13).

TABLE III

Imidazo[1,2-a]pyridinium Salts

IX(a)	Anion	M.P.	Crystalline Form (b)	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	ClO_4	153.5-156	Pris.	$C_8H_9ClN_2O_4$	41.30	41.19	3.90	3.88	12.04	12.13
b	Br	223-225	Powd.	$C_9H_{11}BrN_2\cdot H_2O$ (c)	44.10	43.93	5.34	5.05	11.43	11.35
b	ClO_4	154-156	Rect.	$C_9H_{11}ClN_2O_4$	43.82	44.03	4.50	4.47	11.36	11.50
c	Br	167-170 (d)	Pris.	$C_{10}H_{13}BrN_2\cdot H_2O$	46.34	46.09	5.83	5.62	10.81	11.06
c	ClO_4	178-180	Need.	$C_{10}H_{13}ClN_2O_4$	46.07	46.05	5.03	5.04	10.75	10.92
c	I	220-222	Need.	$C_{10}H_{13}IN_2$	41.68	41.53	4.55	4.52	9.73	9.55
d	Br	198.5-200.5	Rect.	$C_{14}H_{13}BrN_2\cdot H_2O$	54.73	54.77	4.92	5.13	9.12	9.17
d	ClO_4	187-190	Rect.	$C_{14}H_{13}ClN_2O_4$	54.46	54.61	4.24	4.37	9.08	8.88
e	Br	219-220	Aggr.	$C_{15}H_{15}BrN_2$	59.41	59.37	4.99	4.90	9.24	9.50
e	ClO_4	163-164.5	Need.	$C_{15}H_{15}ClN_2O_4$	55.82	55.83	4.68	4.63	8.68	8.50
f	Br	200-202.5	Need.	$C_{20}H_{17}BrN_2\cdot H_2O$	62.67	62.57	5.00	5.03	7.31	7.63
f	ClO_4	132-134	Need.	$C_{20}H_{17}ClN_2O_4$	62.42	62.64	4.45	4.44	7.28	7.56
X										
a	I	210-213 (e)	Powd.	$C_{10}H_{13}IN_2\cdot H_2O$	39.23	39.08	4.94	4.85	9.15	9.34
b	I	242-244	Need.	$C_{10}H_{13}IN_2\cdot H_2O$	39.23	39.32	4.94	5.07	9.15	9.30
c	I	170-172.5	Need.	$C_{15}H_{15}IN_2\cdot {}^1/_2H_2O$	50.15	49.80	4.49	4.32	7.80	7.81
c	ClO_4	118-120 (f)	Need.	$C_{15}H_{15}ClN_2O_4$	55.82	55.80	4.68	4.75	8.68	8.70
d	I	245.5-247	Need.	$C_{10}H_{13}IN_2$	41.68	41.84	4.55	4.57	9.72	9.87
d	ClO_4	187-188.5	Need.	$C_{10}H_{13}ClN_2O_4$	46.07	46.28	5.03	5.00	10.75	10.64
e	I	198-200	Need.	$C_{15}H_{15}IN_2\cdot {}^1/_2H_2O$	50.15	50.60	4.49	4.42	7.80	7.80
e	ClO_4	178-179	Need.	$C_{15}H_{15}ClN_2O_4$	55.82	56.10	4.68	4.69	8.68	8.94

(a) The letters used below IX and X refer to the formulas in Tables I and II respectively. (b) Abbreviations: Irreg. = irregular, pris. = prisms, need. = needles, powd. = microcrystalline powder, rect. = rectangular plates, aggr. = crystal aggregate. (c) Dried at 100°, 48 hours under 2 mm. pressure. (d) The melt resolidified and melted again at 252-254°. (e) Darkens at 180°. (f) Resolidified and remelted at 152-154°.



out by refluxing 20.9 g. for ten hours in 210 ml. of 25% hydrochloric acid. The reaction mixture was neutralized and extracted with ether, and the extract concentrated. Distillation of the residue in a hot air bath by the method of Späth and Dengel (15) afforded 8.2 g. (90%) of a colorless oil. The picrate melted at 195-196° (lit. (14) 190°).

Preparation of 1-alkylimidazo[1,2-a]pyridinium Salts From 2-(Alkylamino)pyridines.

The reaction of 2-(N-methyl) and 2-(N-benzyl)pyridines (16) with α-bromoketones was carried out in acetone as described in Table I. Reactions indicated at 57° were in refluxing acetone, while those indicated at 25° were at room temperature. Analyses are reported in Table III. Perchlorates reported in Table III were prepared by passing a solution of the halide through Dowex-21K exchange resin loaded with perchlorate anion or by addition of perchloric acid to a solution of the halide.

1-(2-Oximinoethyl)-2-methylaminopyridinium Chloride.

To a cold solution of 1 g. of 2-methylaminopyridine in 10 ml. of tetramethylene sulfone, 1.6 g. of chloroacetaldoxime (10) was added and the solution kept in the refrigerator for one week, and then for one week at room temperature. The supernatant liquid was decanted and the solid residue recrystallized yielding 450 mg. (24%) of tan irregular needles, m.p. 176-180°. Recrystallization followed by drying at 65° and 2 mm. pressure overnight, yielded an anhydrous product, m.p. 167.5-169°.

Anal. Calcd. for $C_8H_{12}ClN_3O$: C, 47.64; H, 6.00; N, 20.84. Found: C, 47.44; H, 5.95; N, 20.64.

1-Methylimidazo[1,2-a]pyridinium Perchlorate.

A solution of 200 mg. of 1-(2-oximinoethyl)-2-(methylamino)-pyridinium chloride was dissolved in 48% hydrobromic acid and heated on the steam bath for only 15 minutes. Longer heating destroys the product. The hydrobromic acid was removed under vacuum and the residue dissolved in water. The water solution was passed through Dowex-21K exchange resin loaded with perchlorate anion. The eluate was concentrated under vacuum and the residue crystallized. The melting point of the purest recrystallized material (stout, irregular prisms) was 153.5-156° and the yield was very poor.

Anal. Calcd. for $C_8H_9ClN_2O_4$: C, 41.30; H, 3.90; N, 12.04. Found: C, 41.19; H, 3.88; N, 12.13.

1-Phenylimidazo[1,2-a]pyridinium Perchlorate.

A solution of 1.7 g. of 2-anilinopyridine in 6 ml. of tetramethylene sulfone was allowed to react at room temperature in the dark with 1.18 g. of chloroacetaldoxime over a period of 7 days. The dark oil precipitated by the addition of ethyl acetate could not be crystallized, and was cyclized by heating it on the steam bath in 25 ml. of 48% hydrobromic acid for 4 hours. The acid was removed under vacuum and a small amount of water added to the residue. Addition of perchloric acid to the aqueous solution, followed by cooling overnight yielded dark brown crystals. The crude salt twice recrystallized (charcoal) yielded 0.32 g. (11%) of colorless microcrystals, m.p. 140°; λ max, mμ (log ε) 203 (4.22) and 288 (3.83).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_4$: C, 52.98; H, 3.76; N, 9.51. Found: C, 53.02; H, 3.77; N, 9.26.

1-Methylimidazo[1,2-a]pyridinium Salts (X) by Alkylation of Imidazopyridines.

The appropriate 2-amino(methylpyridine) was allowed to react with an excess of bromoacetone or phenacyl bromide. The reaction time varied from ten days to 1 hour, the longer reactions being allowed to stand in the dark. At the end of the reaction the crude salt of the imidazo[1,2-a]pyridine system was separated, by filtration if a solid, or by decantation of the supernatant if a liquid, and the crude salt washed with ether. The crude salt was added to sodium carbonate solution releasing the free imidazo[1,2-a]pyridine which was usually extracted with ether. To the residue remaining after evaporation of the ether excess of methyl iodide was added and the reaction mixture allowed to stand for several days. The reaction could be hastened considerably by warming the reaction mixture. The 1-methylimidazo-[1,2-a]pyridinium salt (X) was purified by recrystallization. Yields are reported in Table II and analyses in Table III.

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