Synthesis of Imidazo[1,2-*a*]pyridinium Salts from 2-Alkylaminopyridines. A Reexamination

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1-Alkyl-2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyridinium salts (III) have been identified as isolatable intermediates in the synthesis of 1-alkylimidazo[1,2-*a*]pyridinium salts (II) from 2-alkylaminopyridines and α-haloketones. Spectral data suggest that these intermediates exist exclusively as the cyclic ring tautomers III rather than chain tautomers VI.

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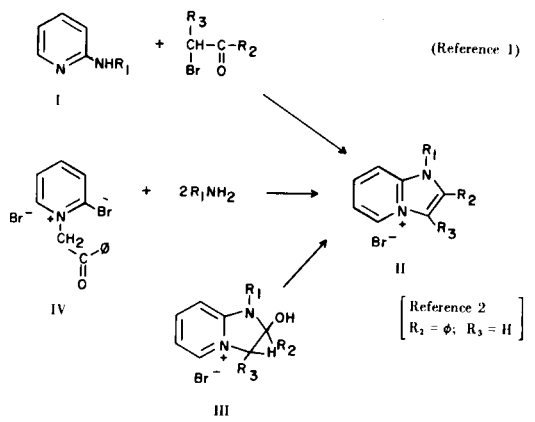
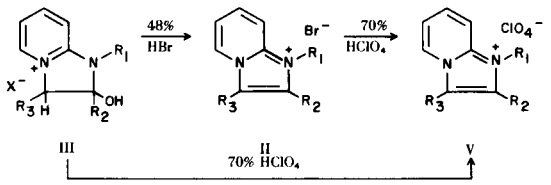
The synthesis of 1-alkylimidazo[1,2-*a*]pyridinium salts (II) *via* (a) reaction of 2-alkylaminopyridines (I) with α-bromoketones and (b) reaction of 2-bromo-1-phenacylpyridinium bromide (IV) with organic amines has been reported by Bradsher and co-workers (1,2) as depicted in Scheme I. The intermediacy of 1-alkyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium bromide (III) was demonstrated in the latter reaction.

Scheme I



We have now found that such cyclic carbinolamine intermediates (III) are also observed in the reaction of 2-alkylaminopyridines with α-bromoketones. In fact, several of the presumed 1-alkylimidazo[1,2-*a*]pyridinium salts reported in the original Bradsher paper (compounds IXc, d, and f from Table I of Reference 1) have now been shown to be the corresponding non-dehydrated 1-alkyl-2-alkyl(aryl)-2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyridinium salts (IIIc, d and f). In our hands the described procedure (1) for the reaction of 2-alkylaminopyridines with α-bromoketones proved to be extremely capricious with mixtures of dehydrated and non-dehydrated salts II and III often being obtained. Although little time was expended in a study of reaction variables, reaction time and/or solvent temperature had no predictive effect on the course of the reaction (3). However, brief heating of the non-dehydrated quaternary carbinolamines, III, (or the mixtures of II and III obtained above) in 48% hydrobromic acid gave the desired imidazo[1,2-*a*]pyridinium bromides (II) in good to excellent yield (4) (Scheme II). In addition,

Scheme II



treatment of III with 70% perchloric acid afforded only the dehydrated imidazo[1,2-*a*]pyridinium perchlorate (V) (Scheme II) (5).

Comparisons of spectral data make these structure assignments unequivocal. The uv spectra of authentic imidazo[1,2-*a*]pyridinium salts (II) [prepared by alkylation of imidazo[1,2-*a*]pyridines] all exhibit a long wavelength maxima in the 285-290 mμ region (see Table II). 1-Alkyl-2-alkyl(aryl)-2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyridinium salts (III), on the other hand lack any absorption in this area and instead display a long wavelength absorption maximum in the 325 mμ region (Table I). The uv spectra of these cyclic carbinolamines (III) are essentially identical to the published (2) spectrum of 1-butyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium bromide (III, R_1 = Bu, R_2 = φ, R_3 = H), the only example of this class of compound reported to date.

Pmr spectroscopy readily distinguishes between II and III. A complete analysis of the pmr spectra of a number of substituted 1-methylimidazo[1,2-*a*]pyridinium iodides has been reported (6) and our data (all ring protons appearing between δ 7.0 ppm and 9.0 ppm; see experimental) on similar derivatives of II are in good agreement with these literature models. The pmr spectra of 1-alkyl-2-alkyl(aryl)-2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyridinium salts (III) are strikingly different from those of the completely aromatic II. Most notable differences occur in the non-aromatic dihydroimidazole portion of the molecule. Proton(s) on the C-3 carbon atom, for example, appear *ca.* 3.5 ppm upfield from the C-3 proton in II (and when R_3 = H, this region integrates for two protons instead of one); an exchangeable hydroxy proton is now present; and aliphatic groups at R_1 and/or R_2 are also shifted upfield by about 1.0 ppm from where they would

appear in the analogous dehydrated, completely aromatic, imidazo[1,2-*a*]pyridinium salt, II.

Cmr spectra, obtained on IIe and IIIe (Table III), were also markedly different. All carbon assignments for 1-benzyl-2-methylimidazo[1,2-*a*]pyridinium bromide (IIe) were in good agreement with the values recently reported (7) by Grant and co-workers for 1-methylimidazo[1,2-*a*]pyridinium iodide. All ring carbon atoms in IIe, for example, are at least 100 ppm downfield from TMS. The cmr spectrum of IIIe, on the other hand, showed the C-3 carbon at 62.4 ppm, a distinctly non-aromatic region. In addition, off-resonance decoupling experiments indicated

Table I

1-Alkyl-2-alkyl(aryl)-2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyridinium Salts (III) from Alkylaminopyridines and α-Haloketones

Compound III				Recrystallization	Yield	M.p.	Uv Spectral Data		
	R_1 =	R_2 =	R_3 =	X =	Solvent			λ max	mμ (log ε)
IIIc	CH_3-	CH_3-	CH_3-	Br-	2-Propanol/ether	57%	152-153°	202 (4.11),	238 (4.04), 326 (3.65)
IIId	CH_3-	φ-	H-	Br-	Acetonitrile	56%	193-197°	205 (4.37),	238 (4.16), 328 (3.61)
IIIe	φ-CH_2-	CH_3-	H-	Cl-	2-Propanol/ether	50%	139-141°	203 (4.07),	239 (4.01), 329 (3.67)
IIIf	φ-CH_2-	φ-	H-	Br-	2-Propanol	72%	202-205°	202 (4.44),	238 (4.18), 327 (3.75)

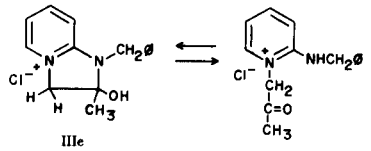
Table II

1-Alkylimidazo[1,2-*a*]pyridinium Salts (II) by Alkylation of Imidazo[1,2-*a*]pyridines (Method A) or by Dehydration of III (Method B)

Compound II				Method (a)	Recrystallization	Yield	M.p.	Uv Spectral Data	
	R_1 =	R_2 =	R_3 =	X =				λ max	mμ (log ε)
IIc	CH_3-	CH_3-	CH_3-	Br-	B	2-Propanol/ether	82%	235-239°	204 (4.21), 229 (4.33), 290 (3.90)
IId	CH_3-	φ-	H-	Br-	B	2-Propanol/ether	93%	199-101°	203 (4.48), 223 (4.31), 288 (4.10)
IIe	φ-CH_2-	CH_3-	H-	Br-	A	2-Propanol/ether	65%	212-214°	204 (4.45), 217sh (4.35), 286 (4.00)
IIf	φ-CH_3-	φ-	H-	Br-	A+B	Acetonitrile/ether	54%	217-219°	207 (4.57), 231sh (4.25), 289 (4.11)

(a) See experimental for explanation.

that two protons were attached to this saturated carbon atom. More importantly the C-2 carbon atom appeared at 90.8 ppm indicative of a saturated carbon atom attached to two heteroatoms. Moreover the cmr spectra of IIIe displayed no absorptions in the carbonyl region, indicating that under these conditions, IIIe, which is the ring tautomer of 1-acetonyl-2-(benzylamino)pyridinium chloride (VIe) exists completely as the cyclic carbinolamine. The in-

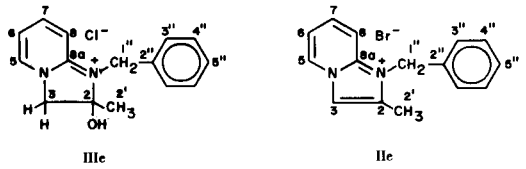


IIIe VIe

frared spectrum of IIIe showed no carbonyl stretching band in the 1660-1800 cm^{-1} region, again indicative of ring rather than chain tautomer (8).

Table III

^{13}C Chemical Shift Assignments for IIIe and IIe



IIIe IIe

Carbon Atom	IIIe	IIe (c)
2	90.8 s	134.0 s
3	62.4 t	112.9 d (d)
5	137.5 d (b)	129.0 d (e)
6	114.9 d (b)	117.6 d
7	145.6 d (b)	133.7 d (e)
8	108.2 d (b)	110.5 d (d)
8a	153.4 s	139.4 s
2′	24.1 q	9.8 q
1″	44.3 t	47.6 t
2″	135.6 s	135.1 s
3″	127.1 d	127.0 d
4″	129.3 d	129.3 d
5″	128.2 d	128.6 d

(a) δ in ppm from TMS with methanol solvent resonance (49.3 ppm) used as an internal standard. (b) Assigned on the basis of coupling patterns in coupled spectra (see F. W. Wehrli and T. Wuthlin, "Interpretation of C-13 NMR Spectra", Heyden, New York, N. Y., 1976, pp. 86-87) and by comparisons to δ values assigned to 1-methylimidazo[1,2-*a*]pyridinium iodide by R. J. Pugmire, J. C. Smith, and D. M. Grant, B. Stanovnik, and M. Tisler, *J. Heterocyclic Chem.*, **13**, 1057 (1976). (c) Assigned from comparisons of δ's from Grant paper (see (b) above). (d,e) Assignments may be reversed.

EXPERIMENTAL

General.

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. Proton nmr spectra were recorded on Varian T-60 and Varian A-60 spectrometers in $DMSO_{d\text{-}6}$ with TMS as the internal standard. The ^{13}C nmr were obtained in the FFT mode on a Varian XL-100-15 (25.2 MHz) spectrometer equipped with a Nicolet Technology 1080 data system. Complete proton decoupling was provided by square wave modulation (9) of the Varian gyrocode heteronuclear decoupler. Methanol solvent resonance (49.3 ppm) was used as an internal standard adjusted relative to TMS to provide chemical shift values. Ir spectra were determined with Perkin-Elmer Model 21 and 237B spectrophotometers (potassium bromide disk). Uv spectra were measured in 95% ethanol using 1 cm matched silica cells on a Cary 11 spectrophotometer. Combustion analyses were performed by the Pfizer Physical Measurements Department.

Preparation of 1-Alkyl-2-alkyl(aryl)-2-hydroxy-2,3-dihydroimidazo-[1,2-*a*]pyridinium Salts (III) from Alkylaminopyridines and α-Haloketones (10).

General Procedure.

2-Hydroxy-1,2,3-trimethyl-2,3-dihydroimidazo[1,2-*a*]pyridinium Bromide (III-c).

2-(Methylamino)pyridine (6.48 g., 0.06 mole) and 3-bromo-2-butanone (9.06 g., 0.06 mole) in acetone (100 ml.) were refluxed overnight. A thick white solid had precipitated from the reaction mixture. After cooling the precipitate was isolated by filtration and washed with cold acetone (20 ml.). Recrystallization from isopropanol/ether (1/1) gave 8.8 g. (0.034 mole, 57%) of product, a white crystalline solid, m.p. 152-153° dec.; pmr: δ 1.60 (s, 3, $-\overset{OH}{\overset{|}{C}}-CH_3$), 1.61 (d, J = 7.0 Hz, 3, $CH_3-\overset{H}{\overset{|}{C}}$), 3.08 (s, 3, N-$CH_3$), 4.73 (q, 1, $CH_3-\overset{H}{\overset{|}{C}}-H$), 6.71 (s, 1, O*H*), 6.90-7.46 (m, 2, $H_6 + H_7$), 8.14 (m, 1, H_8) and 8.60 (d, J = 7.0 Hz, 1, H_5). The uv spectrum is presented in Table I.

Anal. Calcd. for $C_{10}H_{15}BrN_2O$: C, 46.35; H, 5.83; N, 10.81. Found: C, 46.25; H, 5.83; N, 11.08.

The following compounds were prepared by the above procedure. Melting points, recrystallization solvents, yields and uv spectra data are listed in Table I.

2-Hydroxy-1-methyl-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium Bromide (III-d).

This compound was prepared from 2-(methylamino)pyridine and α-bromoacetophenone; pmr: δ 2.83 (s, 3, N-CH_3), 4.90 (s, 2, H_3), 7.05-8.00 (m, 8, H_6, H_7, O*H* and φ), 8.22 (m, 1, H_8), and 8.48 (d, J = 7.0 Hz, 1, H_5).

Anal. Calcd. for $C_{14}H_{15}BrN_2O$: C, 54.74; H, 4.92; N, 9.12. Found: C, 54.97; H, 5.03; N, 8.98.

1-Benzyl-2-hydroxy-2-methyl-2,3-dihydroimidazo[1,2-*a*]pyridinium Chloride (III-e).

This compound was prepared from 2-(benzylamino)pyridine (11) and α-chloroacetone; pmr: δ 1.58 (s, 3, $-\overset{OH}{\overset{|}{C}}-CH_3$), 4.78 (*broad* s, 4, H_3 and -N-CH_2-φ), 6.75-7.57 (m with s at 7.38, 7, φ-, H_6 and H_7), 7.75-8.23 (m, 2, H_8 and O*H*) and 8.50 (d, J = 6.5 Hz, 1, H_5).

Anal. Calcd. for $C_{15}H_{17}ClN_2O \cdot \frac{1}{4}H_2O$: C, 64.06; H, 6.27; N, 9.96. Found: C, 64.13; H, 6.07; N, 10.12.

1-Benzyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium Bromide (IIIf).

This compound was prepared from 2-(benzylamino)pyridine (11) and α-bromoacetophenone; pmr: δ 4.51 (s, 2, $-CH_2-\phi$), 5.10 (s, 2, H_3), 7.25 (s, 5, $-CH_2-\phi$), 6.83-7.30 (m, 2, H_6 and H_7), 7.30-7.92 (m, 5, 2-ϕ), 8.02 (s, 1, O*H*), 7.95-8.40 (m, 1, H_8), and 8.61 (d, J = 6.5 Hz, 1, H_5).

Anal. Calcd. for $C_{20}H_{19}BrN_2O$: C, 62.67; H, 5.00; N, 7.31. Found: C, 62.42; H, 4.94; N, 7.39.

1-Benzylimidazo[1,2-*a*]pyridinium Salts by Alkylaiton of Imidazo-[1,2-*a*]pyridines.

(Method A).

1-Benzyl-2-methylimidazo[1,2-*a*]pyridinium Bromide (IIe).

2-Methylimidazo[1,2-*a*]pyridine (12) (1.48 g., 0.011 mole) and α-bromotoluene (2.22 g., 0.013 mole) in acetonitrile (50 ml.) were refluxed overnight. Cooling and addition of ether (20 ml.) afforded a white precipitate. Recrystallization from isopropanol/ether (1/1) gave 2.19 g. (0.007 mole, 65%) of product, a hard white crystalline solid, m.p. 212-214° [lit. (1) m.p. 219-220°]. Pertinent uv spectral data are listed in Table II; pmr: δ 2.48 (s, 3, $-CH_3$), 5.83 (s, 2, $-CH_2-\phi$), 7.29 (s, 5, $CH_2-\phi$), 7.38-7.72 (m, 1, H_6), 7.82-8.31 (m, 2, H_7 + H_8), 8.41 (s, 1, H_3) and 9.07 (d, J = 6.5 Hz, 1, H_5).

1-Benzyl-2-phenylimidazo[1,2-*a*]pyridinium Bromide (IIf).

2-Phenylimidazo[1,2-*a*]pyridine (13) (500 mg., 0.0026 mole) and α-bromotoluene (514 mg., 0.004 mole) in acetonitrile (30 ml.) were refluxed overnight. Standard workup and recrystallization from acetonitrile/ether (1/1) afforded 505 mg. (0.0013 mole, 54%) of product, a white crystalline solid, m.p. 217-219°. Uv data are presented in Table II; pmr: δ 5.80 (s, 2, $-CH_2\phi$) 6.90-7.85 (m, 11, H_6, $CH_2-\phi$ and 2-ϕ), 7.90-8.50 (m, 2, H_7 + H_8), 8.82 (s, 1, H_3), and 9.14 (d, J = 7.0 Hz, 1, H_5).

Anal. Calcd. for $C_{20}H_{17}BrN_2$: C, 65.76; H, 4.69; N, 7.67. Found: C, 65.75; H, 4.80; N, 7.79.

1-Alkylimidazo[1,2-*a*]pyridinium Salts (II) by Dehydration of 1-Alkyl-2-alkyl(aryl)-2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyridinium Salts (III).

(Method B).

1-Benzyl-2-phenylimidazo[1,2-*a*]pyridinium Bromide (IIf).

1-Benzyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium bromide (IIIf) (250 mg., 0.007 mole) was refluxed in aqueous hydrogen bromide (48%) (20 ml.) for 1 hour. At this point the reaction mixture was concentrated to dryness *in vacuo* to give a brown oil. This material was azeotroped with ethanol and crystallized from acetonitrile/ether (2/1) to yield 100 mg. (0.0003 mole, 42%) of product, a white crystalline solid, m.p. 216-220°. Mixed melting point and spectral data (uv, ir, and pmr) showed this compound to be identical with 1-benzyl-2-phenylimidazo[1,2-*a*]pyridinium bromide, prepared by direct alkylation of 2-phenylimidazo[1,2-*a*]pyridine (*vide supra*).

1,2,3-Trimethylimidazo[1,2-*a*]pyridinium Bromide (IIc).

2-Hydroxy-1,2,3-trimethyl-2,3-dihydroimidazo[1,2-*a*]pyridinium bromide (IIIc) (500 mg., 0.002 mole) in 48% aqueous hydrogen bromide (50 ml.) gave, using the standard procedure, 410 mg. (0.0016 mole, 82%) of product a white crystalline solid, m.p. 235-239° (slow with dec.). Uv spectral data is listed in Table II; pmr: δ 3.37 (s, 6, 2-CH_3-3-CH_3), 4.01 (s, 3, N-CH_3), 7.48-7.80 (m, 1, H_6), 7.95-8.26 (m, 2, H_7 + H_8) and 8.89 (d, J = 7.0 Hz, 1, H_5).

Anal. Calcd. for $C_{10}H_{13}BrN_2 \cdot H_2O$: C, 46.35; H, 5.83; N, 10.81. Found: C, 46.58; H, 5.87; N, 10.76.

1-Methyl-2-phenylimidazo[1,2-*a*]pyridinium Bromide (IId).

2-Hydroxy-1-methyl-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium bromide (IIId) (2.6 g., 0.009 mole) in 48% hydrobromic acid (75 ml.) afforded, using the above generalized procedure, 2.3 g. (0.008 mole, 93%) of product, a white crystalline solid, m.p. 199-203°; uv data, see Table II; pmr: δ 4.00 (s, 3, N-CH_3), 7.51-8.60 (m, 8, ϕ, H_6, H_7 + H_8), 8.83 (s, 1, H_3), and 9.16 (d, J = 7.0 Hz, 1, H_5).

Anal. Calcd. for $C_{14}H_{13}BrN_2$: C, 58.15; H, 4.53; N, 9.69. Found: C, 58.04; H, 4.61; N, 9.51.

1,2,3-Trimethylimidazo[1,2-*a*]pyridinium Perchlorate (IV-c) *via* Dehydration of 2-Hydroxy-1,2,3-trimethyl-2,3-dihydroimidazo-[1,2-*a*]pyridinium Bromide (IIIc) with Perchloric Acid.

2-Hydroxy-1,2,3-trimethyl-2,3-dihydroimidazo[1,2-*a*]pyridinium bromide (IIIc) (2.59 g., 0.010 mole) was dissolved in warm water (50°) (15 ml.) and 10 ml. of perchloric acid (70-72%) was added in one portion. The resulting clear solution was chilled in an ice bath and long white needles slowly precipitated. Filtration gave 1.55 g. (0.006 mole, 59%) of product, a white crystalline solid, m.p. 178-180° (lit. (1) 178-180°) after recrystallization from methanol/ethyl acetate (1/1). The uv spectrum was identical to that of 1,2,3-trimethylimidazo[1,2-*a*]pyridinium bromide (*vide supra*).

Acknowledgement.

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(3) The effect of using α-chloroketones (rather than their α-bromo analogs) was not rigorously examined. However in refluxing acetone 2-(benzylamino)pyridine and α-chloroacetone afforded only IIIe whereas under similar conditions α-bromoacetone gave IIe or a mixture of IIe and IIIe. The replacement of acetone with higher boiling solvents was not examined.

(4) In reference (2) a carbinolamine of type III was converted to an imidazo[1,2-*a*]pyridinium salt (II) using either hot polyphosphoric acid and/or perchloric acid.

(5) This appears to explain the observation in the original Bradsher apper that the misassigned bromide salts (compounds c, d, and f) all analyzed as monohydrates whereas their corresponding perchlorates analyzed as anhydrous materials; *i.e.* a dehydration must have occurred during perchlorate salt formation.

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(10) Sources of all starting materials are indicated in footnotes. No footnote indicates material is commercially available.

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