Acridizinium salts. Preparation from 1-(benzylic)-2-formyl and 1-(benzylic)-2-acetyl pyridinium bromides and ring-openings reactions with nucleophilic reagents

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Dedicated to Professor Berhanu Abegaz on his 60th Birthday

Abstract

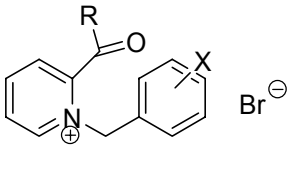
Treatment of pyridine-2-carboxaldehyde or 2-acetyl pyridine with several benzylic bromides led to the corresponding 1-(benzylic)-2-formyl pyridinium bromides or 1-(benzylic)-2-acetyl pyridinium bromides, respectively. The use of MeOH as a solvent in the quaternizations of pyridine-2-carboxaldehyde with benzylic bromides (or in one case benzyl chloride) led to the corresponding pyridinium hemiacetals. These salts were effectively cyclodehydrated to afford the corresponding acridizinium salts. The ring opening reactions of several of the acridizinium salts with hydroxide, oximes, primary amines and a hydrazine have been investigated.

Keywords: Pyridinium salts, acridizinium salts, synthesis, ring opening reactions

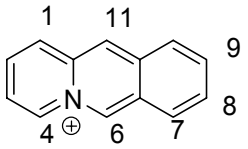
Introduction

A recent review[1] summarizes the status of the synthesis of benzo[b]quinolinium salts (acridizinium salts, Chart 1) and several previous reviews discuss the synthesis and reactions of these salts.[2,3,4] It was reported in 1955[5] that treatment of pyridine 2-carboxaldehyde with benzyl bromide or 4-methyl benzyl bromide for 2-3 weeks at room temperature yielded dark red glassy-like materials containing the corresponding pyridinium bromide salts. These crude glasses on refluxing with 48% aqueous HBr underwent cyclodehydrations to afford 60% and 39% (overall) yields of the corresponding acridizinium bromides (Chart 1). A similar glassy product was reported on treatment of α-bromomethyl naphthalene with pyridine 2-carboxaldehyde which on refluxing with 48% aqueous HBr led to the substituted acridizinium bromide (52% overall).[6] Although it was initially reported that pyridine 2-carboxaldehyde with 3,4-dimethoxybenzyl bromide in DMF led to a crude glassy red product[7], a more recent paper describes the isolation of

an uncharacterized solid which on cyclization with 48% aqueous HBr yielded the substituted acridizinium salt.[8]



R = H or CH_3



benzo[b]quinolinium ion
acridizinium ion

Chart 1

The use of methanol as a solvent for the quaternization of pyridine 2-carboxaldehyde with several methoxy substituted benzylic bromides led to crude uncharacterized products which could be cyclized to their respective acridizinium salts with 48% aqueous HBr.[9] A prior study has reported that treatment of 2-acetylpyridine with benzyl bromide (DMF, 10°C, 23 days) led to a small amount of an oil which on cyclization with liquid HF led to 11-methylacridizinium (isolated as the perchlorate salt).[10]

The quaternizations of 2-(1,3-dioxolan-2-yl)pyridine[11-16] were then reported to be much superior in reactions with benzylic bromides and the respective pyridinium salts could be converted into the acridizinium salts on acidic cyclodehydrations.

Our prior report documented that pyridine-2-carboxaldehyde with α,α'-dibromo-o- or p-xylenes led to the corresponding bis-pyridinium aldehydes which could be cyclized into the corresponding bis-acridizinium salts.[17]

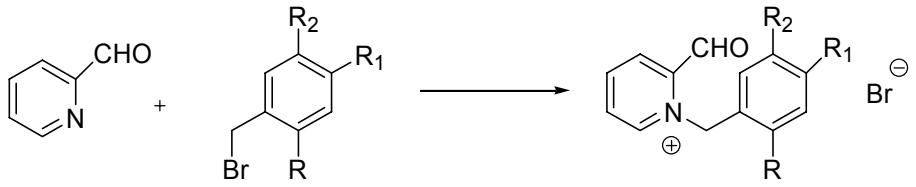
The goal of the present research was to clearly establish the structures of the products formed from the quaternizations of pyridine 2-carboxaldehydes and 2-acetyl pyridine with benzylic halides and the evaluation of the use of methanol as a solvent in these reactions. These substituted pyridinium salts would be converted into the respective acridizinium salts on acidic cyclodehydrations This methodology would obviate the necessity for the use of pyridine acetals or oximes for the preparation of acridizinium salts. In addition, we wish to report on the ring-opening reactions of several of the acridizinium salts with aqueous NaOH solutions, primary amines, oximes and hydrazines.

Results and Discussion

Formation of the pyridinium salts

Treatment of pyridine-2-carboxaldehyde (**1**) with benzyl bromide (**2a**), 4-methyl benzyl bromide (**2b**) or 2,5-dimethoxy benzyl bromide (**2c**) (1:1 molar ratios) in DMF as solvent at 40-45°C for 20-24 h led to the corresponding pyridinium salts **3a, 3b** and **3c**, respectively . These salts

crystallized from the reaction mixture and were readily isolated by filtration in 50-57% yields. Although sensitive to moisture, they could be stored in the freezer for long periods without any perceptible decomposition. The isolation of the free aldehyde (or hydrate) is also dependent on the humidity during the filtration of the solids as under high humidity conditions the hydrates are the predominant product. In Vermont the winter months, when the humidity is low, were clearly the best times to run these reactions.



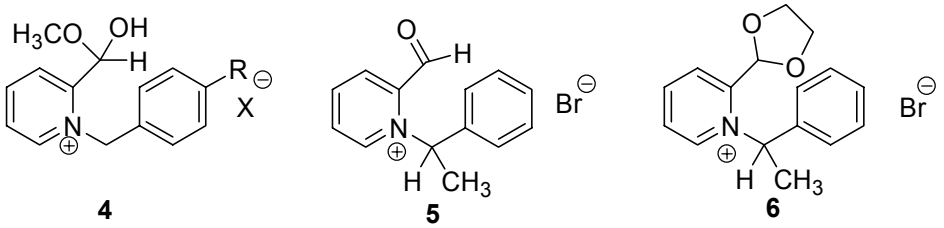
1 **2** **3**

2 and **3**: a, R = R_1 = R_2 = H; b, R = R_2 = H, R_1 = CH_3; c, R = R_2 = OCH_3, R_1 = H

In the ^{1}H NMR spectra (DMSO-d_6 as solvent), the C**H**O proton of the aldehydes are found at δ 10.3 and in the ^{13}C nmr spectra the carbon appears at δ 183. The facile hydrations of the aldehydes are easily detected by a comparison of the ^{1}H and ^{13}C nmr spectra in the absence and presence of D_2O, respectively, which in the former indicates the disappearance of the signal at δ 10.3 and in the latter the disappearance of the signal at δ 183.

The expected reactivity of the aldehyde group is demonstrated by treatment of a suspension of crystalline **3a** in ethyl acetate followed by addition of MeOH to effect solution. On allowing this solution to stand in the freezer for several days, the resultant crystals were collected by filtration to afford the hemiacetal **4a**.

It was then observed that the quaternizations of **1** with **2a** or **2b** in refluxing MeOH as solvent directly led to the hemiacetals salts **4a** (67%) and **4b** (30%)**,** respectively. Treatment of **1** with benzyl chloride in refluxing methanol led to hemiacetal chloride salt **4c** (30%).



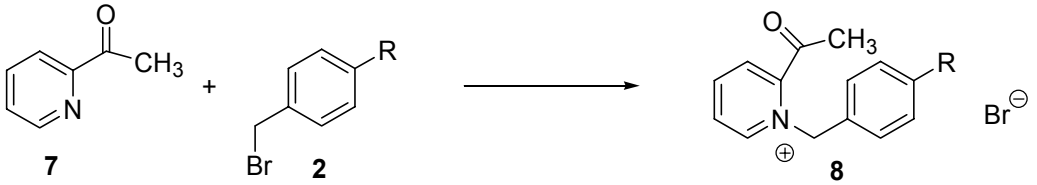
4 **5** **6**

a, X = Br, R = H
b, X = Br, R = CH_3
c, X = Cl, R = H

Attempts to prepare **5** by treatment of pyridine 2-carboxaldehyde (**1**) with α-bromoethylbenzene in DMF were unsuccessful. Styrene is rapidly formed by β-elimination from the α-bromoethylbenzene. The preparation of **6** was accomplished by treatment of the

corresponding acetal of 2-acetyl pyridine with α-bromoethylbenzene following a modified literature procedure.[12]

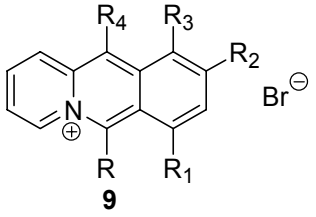
We next turned our attention to the reactions of 2-acetyl pyridine (7) with benzylic bromides. Treatment of 2-acetyl pyridine (7) with an equimolar amount of benzyl bromide (2a) at 60°C in DMF for 48 h led to 1-(benzyl)-2-acetyl pyridinium bromide (8a) in a poor yield (13%). An attempt was made to perform this quaternization in 2-propanol as solvent. After 65 h at room temperature and 45°C for 48 h, the only identifiable material (^{1}H NMR) was the hydrobromide salt of 2-acetyl pyridine. Clearly the rate of reaction of benzyl bromide with 2-propanol (formation of HBr) is competitive with the anticipated quaternization process.



Treatment of 2-acetyl pyridine (**7**) with an equimolar quantity of 4-methyl benzyl bromide (**2b**, DMF, 45-50°C, 216 h) led to 1-(4-methylbenzyl)-2-acetyl pyridinium bromide **8b** (36%).

Acridizinium salts

The cyclodehydrations of the pyridinium salts **3a-c**, **6** and **8a,b** to the corresponding acridizinium salts **9** were accomplished by heating in 48 % aqueous HBr and precipitation of the salts by the addition of THF. The yields and reactions conditions are tabulated in Table 1. Only **8a** cyclized in an extremely poor yield (10%) while **3c** readily underwent cyclization. Hemiacetal **4a** also readily cyclized to afford **9a**. The corresponding tetrafluoroborate salt **9a** (where Br = BF_4) could be isolated on heating **3a** in aqueous tetrafluoroboric acid. Cyclodehydration of **4c** in concentrated HCl led to acridizinium chloride **9a** (where Br = Cl).



a) R = R_1 = R_2 = R_3 = R_4 = H
b) R = R_1 = R_3 = R_4 = H, R_2 = CH_3
c) R = R_2 = R_4 = H, R_1 = R_3 = OCH_3
d) R_1 = R_2 = R_3 = R_4 = H, R = CH_3
e) R = R_1 = R_2 = R_3 = H, R_4 = CH_3
f) R = R_1= R_3 = H, R_2 = R_4 = CH_3

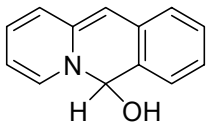
The ^{1}H NMR absorptions for the singlets (DMSO-d_6) at H-6 (except 6) and H-11 (except 9e and f) are also tabulated in Table 1.

Table 1. Reaction conditions, yields and ^{1}H NMR data for the acridizinium salts **9a-f**

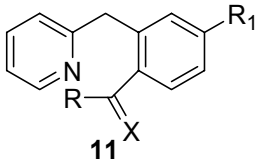
Pyridinium Salt	Acridizinium Salt	Temp, h	% Yield	H-6	H-11
3a	**9a**	90°C, 2 h	87	10.51	9.31
3b	**9b**	90°C, 2h	90	10.39	9.09
3c	**9c**	50°C, 0.5 h	quant	10.41	9.26
6	**9d**	70-90°C, 4h	70	-	9.23
8a	**9e**	95-100°C, 3 h	13	10.40	-
8b	**9f**	120-130°C, 1.5 h	56	10.35	-

Nucleophilic ring openings of the acridizinium salts

It has been previously reported that treatment of acridizinium bromide (**9a**) in water with a 10% aqueous NaOH solution led to an orange precipitate which was tentatively identified as a mixture of the pseudo base **10** and ring-opened aldehyde **11a.**[18,19]



10



11

a, R = R_1 = H, X = O
b, R = H, R_1 = CH_3, X = O
c, R = CH_3, R_1 = H, X = O
d, R = R_1 = H, X = NOH
e, R = H, R_1 = CH_3, X = NOH
f, R = R_1 = H, X = $NOCH_2Ph$
g, R = CH_3, R_1 = H, X =NOH
h, R = H, R_1 = CH_3, X = $N(CH_2)_2CH_3$
i, R = R_1 = H, X = $N(CH_2)_2N(CH_3)_2$
j, R = R_1 = H, X = $NN(CH_3)_2$

We initially evaluated the stability of acridizinium bromide (**9a**) in aqueous solutions of varying pH. The acridizinium bromide was dissolved in 4 aqueous solutions at different pH values: 8 ($NaHCO_3$), 9-10 ($NaHCO_3$/Na_2CO_3), 11 ($NaHCO_3$/Na_2CO_3) and 12 (Na_2CO_3). The salt was stable in $NaHCO_3$ solutions at pH 8, the solution at pH 9-10 formed a orange precipitate after a few minutes while the solutions at pH 11 and 12 formed orange precipitates immediately on addition of the salt.

Attempts to establish the structure of the orange solid via ^{1}H NMR spectroscopy, as prepared via the procedure described by Bradsher,[18] were only partially successful. It was impossible to obtain a pure sample of the pseudo base previously formulated as **10**. The stability of the original solid isolated from the reactions was dependent on the solvent used in the ^{1}H NMR analysis such as $CDCl_3$ or C_6D_6. If the initial crude solid obtained from treatment of acridiziniium bromide (**9a**) was collected and dried for a short period and the ^{1}H NMR recorded in $CDCl_3$, a complex spectra indicated the presence of the ring-opened aldehyde [absorptions at δ 10.29 (C**H**O) and 4.60 (C**H**$_2$)] along with numerous additional absorptions which were difficult to assign. If the same procedure was repeated and the ^{1}H NMR recorded in C_6D_6 [absorptions at δ 10.2 (C**H**O) and 4.4 (C**H**$_2$)] the proportion of ring-opened product was reduced

(approximately10%) but the integrals for the remaining protons amounted to approximately 25-27 protons, indicative of the presence of several species. If the solutions of the $CDCl_3$ and C_6D_6 were allowed to stand for 20 hours, the predominant product was the ring-opened aldehyde **11a**. On allowing the crude orange product to stand in the air for 2 days, the ^{1}H NMR spectrum ($CDCl_3$ or C_6D_6 as solvents) did not show much change in composition.

Treatment of an aqueous solution of acridizinim bromide (**9a**) with 0.1% (pH = 12.5), 2% (pH = 14) or 10% (pH = 14) aqueous NaOH led to an orange solid which was then extracted into $CDCl_3$ in each case. The ^{1}H NMR spectra in each case indicated the presence of the ring-opened aldehyde **11a** with only relative minor absorptions for other species. These solutions on removal of the $CDCl_3$ led to black residues which on dissolving in $CDCl_3$ and ^{1} H NMR still indicated the presence of the aldehyde **11a**. Treatment of the 9-methyl acridizinium bromide (**9b**) with a 0.1% aqueous solution of NaOH followed by extraction into $CDCl_3$ and ^{1}H NMR analysis indicated the presence of the ring-opened aldehyde **11b**. Similarly the 6-methyl acridizinium bromide (**9d**) with 2% aqueous NaOH followed by $CDCl_3$ extraction and 1H NMR analysis indicated the major product as the ring-open ketone **11c**.

The cyclization of the crude orange product, obtained from **9a** on treatment with aqueous NaOH, using 48% aqueous HBr readily led to an excellent yield of **9a.**

Treatment of acridizinium bromide (**9a**) or 9-methyl acridizinium bromide (**9b**) with hydroxylamine (prepared by addition of aqueous $NaHCO_3$ to aqueous hydroxylamine hydrochloride) yielded the oximes **11d** (68%) and **11e** (90%), respectively. The reaction of O-benzylhydroxylamine with acridizinium bromide (**9a**) gave the substituted oxime **11f** (62%). Similarly the addition of hydroxylamine to 6-methyl acridizinium bromide (**9d)** led to the oxime **11g** (68%). In this case the proton NMR indicated the presence of E and Z isomers as shown by the peaks at δ 10.97 and 10.40 (ratio 9:1), 4.18 and 4.00 (ratio 9:1) and 1.99 and 1.91 (9:1). In the ^{1}H NMR spectrum in DMSO-d_6 + D_2O, the disappearance of the δ 10.97 and 10.40 absorptions occurred.

Since the pH of the aqueous hydroxylamine solution remains at 8, this suggests that the oximes arise from an initial attack of the nitrogen electron pair at C-6 of the corresponding acridizinium bromide to yield intermediates which rapidly undergo ring-openings.

The cyclization of oxime **11e** on heating in 48% aqueous HBr led to 9-methyl acridizinium bromide (**9b**).

In order to more fully evaluate the ring-opening reactions, the acridizinium bromides were treated with several primary amines and N,N-dimethylhydrazine. Treatment of 9-methyl acridizinium bromide (**9b**) with 1-aminopropane led to **11h** (78%) while acridizinium bromide (**9a**) on addition of *N,N*-dimethylethylenediamine led to the imine **11i** (quantitative). Both imines were readily identified by ^{1}N NMR and ^{13}C NMR analysis. These imines were unstable on exposure to air for short periods. It might be noted that imine **11h** on heating in 48% aqueous HBr led to 9-methyl acridizinium bromide (**9b**) which was contaminated with the hydrobromide salt of 1-aminopropane (^{1}H NMR analysis). On the other hand treatment of **9a** with the secondary amine pyrrolidine led to an immediate red coloration but which on workup, no

identifiable products could be isolated or characterized by ^{1}H NMR. A similar result has previously been reported on treatment of **9a** with piperidine.[20]

Acridizinium bromide (**9a**) on treatment with N,N-dimethylhydrazine afforded hydrazone **11j** (78%).

In conlusion, we have shown that the use of pyridine 2-carboxaldehyde and 2-acetyl pyridine in reactions with benzylic bromides leads to the direct synthesis of pyridinium salts. The use of methanol as solvent in the reactions of pyridine 2-carboxaldehyde with benzylic halides led to the corresponding pyridinium hemiacetals. These salts undergo cyclizations in 48% aqueous HBr (also HBF_4 and HCl)) to afford the corresponding acridizinium salts. The acridizinium salts undergo facile ring opening reactions with aqueous NaOH, oximes, primary amines and 1,1,-dimethylhydrazine to afford the corresponding ring-opened products. The structure of the intermediate obtained from treatment of acridizinium bromide with aqueous NaOH, could not be firmly established because of facile ring-openings. However, the ring opened products and acidic cyclizations of the crude orange intermediate to the acridizinium salt are quite consistent with the proposed structure **10**.

Experimental Section

General Procedures: The pyridine 2-carboxaldehyde (**1**), 2-acetyl pyridine and benzylic bromides **2a** and **2b** were purchased from Acros. Melting points were taken on a Fisher-Johns or a Mel Temp II apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR data were acquired on a Bruker ARX-500 pulsed spectrometer with TMS or the solvent as an internal standard.

Pyridinium salts

1-Benzyl-2-formyl pyridinium bromide (3a). Pyridine-2-carboxaldehyde (**1**) (1.22 g, 11.1 mmol) and benzyl bromide (**2a**) (1.73 g, 10.0 mmol) were dissolved in DMF (1 mL) and the solution was heated in an oil bath held at 45^{o}C for 24 h during which time a crystalline, yellow solid separated. After cooling, the crystals were collected by filtration and washed thoroughly with ether to afford **3a** as a orange crystalline solid (1.70 g, 61%) which was hygroscopic, mp 179-184 (dec., black liquid). Attempts to recrystallize this product were unsuccessful but the product could be stored in the freezer for long periods, ^{1}H NMR (DMSO-d_6) δ 10.39 (s, 1H), 9.30 (d, J = 5.9 Hz, 1H), 8.91 (t, J = 7.7 Hz, 1H), 8.63 (t, J = 7.8 Hz, 1H), 8.47-8.41 (m, 1H), 7.48-7.36 (m, 5H), 6.37 (s, 2H). ^{1}H NMR (DMSO-d_6 + D_2O) δ 9.01 (d, J = 5.9 Hz, 1H), 8.69 (t, J = 7.8 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.11, (t, J = 7.0 Hz, 1H), 7.43-7.37 (m, 3H), 7.21-7.29 (m, 2H), 6.20 (s, 1H), 6.05 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 183.4, 147.3, 147.2, 133.91, 131.2, 130.0, 129.1, 129.0, 127.99, 127.8, 59.8. ^{13}C NMR (DMSO-d_6 + D_2O) δ 156.8, 147.2, 146.7, 134.2, 123.5, 129.2, 128.0, 127.8, 126.2, 85.2, 53.8. Anal. Calcd. for $C_{13}H_{12}BrNO{\cdot}0.4\ H_2O$: C, 54.67, H, 4.48, N, 4.90. Found: C, 54.96, H, 4.33, N, 4.97.

1-(4-Methylbenzyl)-2-formyl pyridinium bromide (3b). Pyridine-2-carboxaldehyde (**1**) (2.4 g, 20.0 mmol) and 4-methylbenzyl bromide (**2b)** (3.7 g, 20 mmol) were dissolved in DMF (3 mL)

and the solution was heated in an oil bath at 45-50°C for 44 hours during which time the product commenced to separate. After cooling, ether was added and the solid was collected by filtration and washed thoroughly with ether to afford **3b** as pale yellow crystals (4.2 g, 72%), mp 185-197°C. ^{1}H-NMR (DMSO-d_6) δ 10.39 (s, 1H), 9.24 (d, J = 6.0 Hz, 1H), 8.88-8.84 (m, 1H), 8.61-8.58 (m, 1H), 8.43-8.40 (m, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.30 (s, 2H), 2.31 (s, 3H). ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.31 (d, J = 5.9 Hz, 1H), 8.64 (t, J = 7.6 Hz, 1H), 8.34 (d, J = 7.3 Hz, 1H), 8.07 (t, J = 6.8 Hz, 1H), 7.23-7.17 (m, 4H), 6.19 (s, 1H), 5.95 (s, 2H), 2.26 (s, 3H).^{13}C NMR (DMSO-d_6) δ 183.4, 147.2, 147.0, 144.2, 138.7, 131.2, 130.9, 129.8, 129.7, 128.2, 59.6, 20.6.^{13}C NMR (DMSO-d_6 + D_2O) δ 156.8, 147.3, 146.7, 139.2, 131.2, 130.2, 128.4, 128.0, 126.3, 85.4, 59.8, 21.1. Anal. Calcd. for $C_{14}H_{14}BrNO$: C, 57.55, H, 4.83, N, 4.79. Found: C, 57.32, H, 4.60, N, 4.59.

1-(2,5-Dimethoxybenzyl)-2-formylpyridinium bromide (3c). A mixture of pyridine-2-carboxaldehyde (**1**) (0.31 g, 2.5 mmol) and 2,5-dimethoxy benzyl bromide (**2c**) (0.65 g, 2.8 mmol) on DMF (0.05 mL) was placed in an oil bath at 40°C. After 6 hours crystals commenced to separate and the mixture was held at this temperature for a total of 24 hours. The solid was collected by filtration and washed with ether to afford beautiful orange crystals of **3c** (0.48 g, 50%) which on ^{1}H NMR analysis indicated a residual trace of DMF and a small amount of the hydrate. This material was crystallized from acetonitrile to afford yellow-orange crystals, mp 138-140°C. ^{1}H NMR (DMSO-d_6) δ 10.39 (s, 1H), 9.17-9.13 (m, 1H), 8.81 (t, J = 7.8 Hz, 1H), 8.53-8.48 (m, 1H), 8.36-8.29 (m, 1H), 7.15 (d, J = 1.7 Hz, 1H), 7.04-6.99 (m, 2H), 6.23 (s, 2H), 3.80 (s, 3H), 3.62 (s, 3H). ^{1}H NMR (DMSO-d_6 + H_2O) δ 8.78 (d, J = 6.1 Hz, 1H), 8.61 (t, J = 7.8 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 7.03-6.97 (m, 2H), 6.84 (d, J = 2.6 Hz, 1H), 6.31 (s, 1H), 5.86 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 183.4, 153.2; 151.3, 147.1, 146.9, 145.0, 157.1, 153.7, 151.7, 147.1, 146.2, 127.6, 56.0, 55.6, 55.5. ^{13}C NMR (DMSO-d_6 + H_2O) δ 157.1, 153.7, 151.7, 147.1, 146.2, 127.6, 125.8, 122.5, 116.9, 115.9, 113.3, 85.2, 56.5, 56.3, 56.1. Anal. Calcd. for $C_{15}H_{16}BrNO_3$: C, 53.27, H, 4.77, N, 4.14. Found: C, 52.98, H, 4.62, N, 4.07.

Procedure 1. 1-(Benzyl)-2-(1-hydroxy-1-methoxymethyl)pyridinium bromide (4a).

The orange crystalline 1-(benzyl)-2-formyl pyridinium bromide (**3a)** (84 mg, 0.30 mmol) was suspended in ethyl acetate (2 ml) and the mixture heated while MeOH (0.5 mL) was added to effect solution. On standing in the freezer for 4 days, the beautiful yellow crystals were collected by filtration, washed with ethyl acetate and allowed to air dry to afford hemiacetal **4a** (70 mg, 75%), mp 127-128°C. This could be stored in a desiccator for long periods at room temperature. ^{1}H NMR (DMSO-d_6) δ 9.06 (d, J = 5.9 Hz, 1H), 8.73 (t, J = 7.6 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.18 (t, J = 7.6 Hz, 1H), 8.11 (br s, 1H), 7.33-7.46 (m, 3H), 7.33 (d, J = 6.7 Hz, 2H), 6.04 (m, 3H), 3.39 (s, 3H). ^{1}H NMR (DMSO-d_6 + D_2O) δ 9.00 (d, J = 6.1 Hz, 1H), 8.71 (t, J = 7.7 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.16 (t, J = 6.8 Hz, 1H), 7.35-7.45 (m, 3H), 7.30 (d, J = 6.9 Hz, 2H), 6.00 (m, 3H), 3.40 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 154.1, 146.9, 146.8, 134.0, 129.0, 128.8, 127.9, 127.8, 126.3, 91.6, 56.6, 54.2. Anal. Calcd. for C, 54.21, H, 5.20; N, 4.52. Found: C, 53.92, H, 4.98, N, 4.45.

Procedure 2. From pyridine-2- carboxaldehyde and benzyl bromide in MeOH (4a).
The pyridine-2 carboxaldehyde (**1) (**1.07 g, 10 mmol) and benzyl bromide (**2a**, 1.71 g, 10 mmol) were dissolved in methanol (4 mL) and the mixture was refluxed for 2.3 h and allowed to stand overnight. The methanol was removed by rotary evaporation to afford a viscous yellow oil. Tetrahydrofuran (50 mL) was added to yield a yellow solid which was collected by filtration, washed with THF (30 mL) and dried to afford 2.08 g (67%) of crude product. A 1 g portion of this material was treated with ethyl acetate (10 ml) and MeOH (1-2 mL) was added to give a white solid which was collected by filtration and dried (4a, 0.70 g, 70% recovery), mp 122-124^{o} with an identical ^{1}H NMR as the compound prepared in Procedure 1. Attempts to further purify by heating in ethyl acetate followed by addition of methanol led to nice crystals which on ^{1}H NMR analysis indicated the presence of a small amount of pyridinium aldehyde **3a**.
1-(4-Methylbenzyl)-2-(1-hydroxy-1-methoxymethyl)pyridinium bromide (4b). The pyridine-2 carboxaldehyde (**1**) (1.07 g, 10 mmol) and 4-methyl benzyl bromide (**2b**, 1.71 g, 10 mmol) were dissolved in methanol (4 mL) and the mixture was refluxed for 3.75 h. The mixture was placed on the roto-vap to remove the solvent and allowed to stand overnight. The oil was treated with ethyl acetate and methanol was added. Upon cooling in the freezer **4b** (0.90 g, 30%) was obtained. Attempts at crystallization from ethyl acetate-methanol led to crystals which contained some pyridinium aldehyde **3b**, mp 102-104^{o}C. ^{1}H NMR (DMSO-d_6) δ 8.98 (d, J = 6.0 Hz, 1H), 8.71 (t, J = 7.7 Hz, 1H), 8.35 (d, J = 7.5 Hz, 1H), 8.14 (m, 2H), 7.23 (br s, 4H), 6.02 (d, J = 5 Hz, 1H), 5.94 (s, 2H), 3.4 (s, 3H), 2.31 (s, 3H): ^{1}H NMR (DMSO-d_6 + D_2O) the multiplet at 8.14 (2H) merged into a triplet (J = 7.5 Hz, 1H)
1-(Benzyl)-2-(1-hydroxy-1-methoxymethyl)pyridinium chloride (4c). The pyridine-2-carboxaldehyde (**1**) (1.07 g, 10 mmol) and benzyl chloride (1.27 g, 10 mmol) were dissolved in methanol (4 mL) and the mixture refluxed for 5 h. The cooled mixture was placed on the rotary evaporator to remove the methanol which led to a yellow oil. Tetrahydrofuran (40 mL) was added and the mixture was placed in the freezer overnight. The somewhat oily solid was collected by filtration (0.80 g, 30%). The material was placed in ethyl acetate and methanol was added on which a white solid formed. The white solid was collected by filtration (0.30 g, 30%) and washed with THF; mp 131-134^{o}C. The ^{1}H NMR showed trace amounts of the pyridinium aldehyde . Attempts at crystallization from ethyl acetate-methanol led to beautiful crystals which by ^{1}H NMR were shown to contain more pyridinium aldehyde than the original solid. ^{1}H NMR (DMSO-d_6) δ 9.06 (d, J = 6.0 Hz, 1H), 8.72 (t, J = 8.0 Hz, 1H), 8.53 (br s, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.17 (t, J = 6.0 Hz, 1H), 7.43 (m, 3H), 7.35 (m, 2H), 6.03 (m, 3H), 3.41 (s, 3H). ^{1}H NMR (DMSO-d_6 + H_2O) δ disappearance of 8.53 (br s, 1H) indicates O**H** peak.
1-(1-Phenylethyl)2-(1,3-dioxolan-2-yl)pyridinium bromide (6). A solution of 2-(1,3-dioxolan-2-yl)pyridine (1.0 g, 6.6 mmol) and (1-bromoethyl)-benzene (1.3 g, 6.6 mmol) in tetramethylene sulfone (0.5 mL) was allowed to stir at room temperature for 26 days (crystals started to form after 11 days).The product was collected by filtration and washed with ethyl acetate to afford yellow crystals of **6** (1.92 g, 82%). Recrystallization from ethyl acetate-methanol led to beautiful colorless rhombic crystals, mp 139-140^{o}C; lit mp[14] 140-141^{o}C.^{1}H

NMR (DMSO-d_6) δ 8.98 (d, J = 6.2 Hz, 1H), 8.67 (t, J = 7.8 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H),), 8.12 (t, J = 6.4 Hz, 1H), 7.47 (m, 5H), 6.75 (s, 1H), 6.56 (q, J = 6.8 Hz, 1H), 4.20 (m, 4H), 2.04 (d, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 151.6, 146.9, 144.7, 137.5, 129.1, 128.9, 128.8, 127.6, 125.7, 97.3, 65.7, 65.6, 64.6, 20.4.

1-(Benzyl)-2-acetyl pyridinium bromide (8a). The 2-acetyl pyridine (**7**) (1.28 g, 10 mmol) and benzyl bromide (**2a**) 1.81 g, 10 mmol) were dissolved in DMF (0.5 mL). The solution was placed in an oil bath held at 60°C and the mixture was held at this temperature for 48 h. After about 24 h a yellow crystalline solid separated. The dark yellow- brown mixture was then placed in the freezer overnight. The resultant solid was collected by filtration and washed with THF (20 mL) to afford 0.08 g of product **8a**. The filtrate deposited more product which was collected by filtration (0.32 g , total 0.40 g, 13%), mp 105-107°C. This material readily crystallized in nice needles from ethyl acetate-acetonitrile, mp 109-110°C. ^{1} H NMR (DMSO-d_6) δ 9.31 (d, J = 6.1 Hz, 1H), 8.78 (t, J = 7.9 Hz, 1H), 8.66 (d, J = 7.8 Hz, 1H), 8.36 (t, J = 7.5 Hz, 1H), 7.41 (m, 3H), 7.26 (m, 2H), 5.97 (s, 2H), 2.53 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 194.8, 148.3, 148.2, 147.5, 134.0 129.9, 129.8, 128.9, 128.5, 128.2, 61.3, 30.1. Anal. Calcd. for $C_{14}H_{14}BrNO$: C, 57.55, H, 4.82, N, 4.79. Found: C, 57.50, H, 4.58, N, 4.65.

2-Acetyl pyridine hydrobromide. The 2-acetyl pyridine (**7**) (1.21 g, 10 mmol) and benzyl bromide (**2a**) (1.71 g, 10 mmol) were dissolved in 2-propanol (3 mL). The solution was stirred at room temperature for 65 hours during which time a small amount of a white solid started to precipitate. The bath temperature was raised to 45°C for 48 h and the mixture cooled in the refrigerator overnight. The solid was collected by filtration to afford 0.40 g of a hygroscopic solid identified as the hydrobromide salt of 2-acetylpyridine. ^{1}H NMR (DMSO-d_6) δ 8.76 (d, J = 3.0 Hz, 1H), 8.15 (m, 1H), 8.08 (m, 1H), 8.0 (br s, 1H), 7.78 (m, 1H), 2.65 (s, 3H).

(4-Methylbenzyl)-2-acetyl pyridinium bromide (8b). The 2-acetylpyridine (**7**) (2.41 g, 20 mmol) and 4-methyl benzyl bromide (**2b**, 3.90 g, 20 mmol) were dissolved in DMF (2 mL). The solution was placed in an oil bath held at about 45°-50°C for 216 hours. The mixture was cooled to room temperature and the solid was collected by filtration and washed repeatedly with THF to afford a white solid (2.2 g, 36%), mp 134-135°C . The solid readily crystallized from ethyl acetate and methanol to afford beautiful needles of **8b,** mp 135-136°C. ^{1} H NMR (DMSO-d_6) δ 9.25 (d, J = 5.9 Hz, 1H), 8.85 (t, J = 7.7 Hz, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.32 (t, J = 6.9 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 5.89 (s, 2H), 2.58 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 194.9, 148.5, 147.9, 147.4, 138.6, 130.90, 129.8, 129.5, 128.4, 128.3, 61.2, 30.1, 20.6. Anal. Calcd. for $C_{15}H_{16}BrNO$: C, 58.84; H**,** 5.27; N, 4.57. Found: C, 58.78, H, 4.99, N, 4.46.

Acridizinium salts

Procedure 1 (from 3a). Acridizinium bromide (9a). The 1-benzyl-2-formyl pyridinium bromide (**3a) (**325 mg, 1.2 mmol) was dissolved in 48% aqueous HBr (1 mL) and the solution heated in an oil bath held at 90-92°C for 2 hours. The cooled mixture was quenched into THF (50 mL) to afford the product as a bright yellow precipitate. The solid was collected by filtration, washed thoroughly with THF and air dried to yield 0.26 g (87%) of acridizinium

bromide (**9a**) as a lemon-yellow solid; mp 250-252°C, lit.[7] 244-244.5°C. ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H, H-6), 9.31 (d, J = 6.9 Hz, H-4), 9.27 (s, 1H, H-11), 8.58 (d, J = 8.6 Hz, 1H), 8.49 (d, J = 8.6 Hz, 1H), 8.41 (d, J = 8.6 Hz, 1H), 8.13 (t, J = 7.0 Hz, 1H), 8.10 (t, J = 7.0 Hz, 1H), 8.03 (t, J = 7.0 Hz, 1H), 7.96 (t, J = 7.0 Hz, 1H): ^{13}C NMR (DMSO-d_6 + H_2O) δ 139.8, 137.9, 136.0, 135.5, 134.4, 131.9, 131.8, 128.5, 127.6, 127.5, 126.5, 125.4, 123.4.

Procedure 2 (from 4). The hemiacetal pyridinium salt **4a** (43 mg, 0.14 mmol) was placed in 48% aqueous HBr (0.5 mL) and heated in an oil bath held at 90°C for 3 h. The yellow solution was cooled and added to THF (10 mL) and the mixture placed in the freezer overnight. The yellow solid was collected by filtration, washed with THF and dried to yield acridizinium bromide (**9a**, 35 mg, 97%), mp 248-250°C, ^{1}H NMR spectrum identical to salt from Procedure 1.

Procedure 3. Acridizinium chloride from hemiacetal chloride 4c. The hemiacetal chloride salt **4c** (90 mg, 0.34 mmol) was dissolved in concentrated HCl (0.5 mL) in an Ace pressure tube. The mixture was placed in an oil bath at 90°C and held at 110-125°C for 2.5 h. The yellow solution was cooled and addition of THF (20 mL) precipitated a light yellow solid. The solid was collected by filtration, washed with THF and dried to afford acridizinium chloride (**9a,** where Br = Cl) (47 mg, 64%): The salt readily crystallized from ethanol or methanol/ethyl acetate to afford yellow crystals, mp 211-214°C (dec), lit[21] 206-208°C. ^{1}H NMR (DMSO-d_6) δ 10.60 (s, 1H, H-6), 9.37 (d, J = 6.5 Hz, 1H, H-4), 9.28 (s, 1H, H-11), 8.59 (d, J = 8.5 Hz, 1H), 8.50 (d, J = 8.5 Hz, 1H), 8.40 (d, J = 9.0 Hz, 1H), 8.15 (t, J = 7.0 Hz, 1H), 8.09 (t, J = 7.0 Hz, 1H), 8.03 (t, J = 8.0 Hz, 1H), 7.98 (t, J = 7.0 Hz, 1H).

Procedure 4. Acridizinum tetrafluoroborate (from 3a and HBF_4). The 1-benzyl-2-formyl pyridinium bromide (**3a**) (126 mg, 0.45 mmol) was dissolved in 50% aqueous HBF_4 (0.5 mL). The yellow solution was placed in an oil bath at 70°C and kept at this temperature for 16 hours. The mixture was allowed to cool upon which a pale yellow solid separated. Some THF was added and a small amount (23 mg) of a pale yellow solid was collected by filtration. Additional THF was added to the filtrate and the mixture was allowed to stand for 24 hours. The crystals were collected by filtration to afford an additional 70 mg of acridizinium tetrafluoroborate (**9a**, where Br = BF_4) (total of 93 mg, 72% yield), mp 172-175°C, ^{1}H NMR identical to bromide salt **9a.**

Procedure 1. 9-methyl acridizinium bromide (9b) (from 3b). The 1-(4-methylbenzyl)-2-formyl pyridinium bromide (3b) (2.96 g, 0.01 mol) was dissolved in 48% aqueous HBr (12 mL) and the solution was heated in an oil bath held at 90°C for 2 h. The cooled solution was slowly poured into THF (120 mL) and the yellow solid which formed was collected by filtration, washed with THF and air dried to yield the desired product 9b (2.5 g, 90%); Crystallization from ethanol led to beautiful yellow prisms. mp 180-184°C, lit mp[5] 191-193°C. ^{1}H NMR (DMSO-d_6) δ 10.39 (s, 1H, H-6), 9.24 (d, J = 7.0 Hz, 1H, H-4), 9.09 (s, 1H, H-11), 8.53 (d, J = 8.9 Hz, 1H), 8.40 (d, J = 8.7 Hz, 1H), 8.17 (s, 1H, H-10), 8.06-8.00 (m, 1H), 7.93-7.85 (m, 2H), 2.67 (s, 3H, 9-CH_3). ^{13}C NMR (DMSO-d_6 + H_2O) δ 147.3, 138.7, 137.5, 135.7, 134.6, 134.0, 131.6, 127.9, 127.2, 125.3, 124.7, 123.6, 123.0, 23.0.

Procedure 2. From the crude orange solid from treatment of 9-methyl acridizinium bromide (9b) with hydroxide. The crude orange solid (20 mg, 0.09 mmol) was added to 48% aqueous HBr and the solution allowed to stand at room temperature for 48 h. THF (20 mL) was added and the mixture was placed in the freezer. On standing overnight, a yellow-orange oil separated. The THF was decanted and the structure of this oil (10 mg) was identified as 9-methylacridizinim bromide by ^{1}H NMR. The THF on standing in the hood deposited beautiful yellow needles of the salt **9b** (10 mg, 73%).

Procedure 3. (From imine 11h). Imine **11h** (200 mg, 0.73 mmol) was dissolved in 48% aqueous HBr (1 mL) and the solution was placed in an oil bath held at 90^{o}C for 3 h. The mixture was allowed to stand overnight, then partially concentrated under a slow stream of nitrogen and THF (5 mL) was added. The resulting solid was collected by filtration to yield predominantly 9-methyl acridizinium bromide (**9b**) partially contaminated with the hydrobromide salt of 1-propylamine (about 20%) based on the ^{1}H NMR spectral data integral comparisons.

Procedure 4. (from oxime 11e). The oxime **11e** (0.103 g, 0.46 mmol) in 48% aqueous HBr (0.75 mL) was heated in an oil bath held at 80-90^{o}C for 2 h. The cooled solution was poured into THF (15 mL) and the precipitated yellow solid collected by filtration to afford **9b** (0.11 g, 80%).

7,10-Dimethoxyacridizinium bromide (9c). The dimethoxy salt **3c** (39 mg, 0.11 mmol) was treated with 48% aqueous HBr and the mixture was heated in an oil bath held at 50^{o}C for 0.5 h. The cooled orange solution was poured in THF (10 mL) on which an orange solid separated. After allowing the mixture to stand for 1 h, the solid 9c was collected by filtration (35 mg, quantitative). The product readily crystallized from ethyl acetate-methanol or ethanol, mp >235^{o}C (dec).^{1}H NMR (DMSO-d_6) δ 10.41 (s, 1H), 9.49 (d, J = 6.5 Hz, 1H), 9.26 (s, 1H), 8.69 (d, J = 8.5 Hz, 1H), 8.09 (m, 1H), 7.96 (t, J = 7.0 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 4.12 (s, 3H), 4.09 (s, 3H).

^{13}C NMR (DMSO-d_6) δ 148.4, 147.0, 137.4, 135.3, 134.6, 131.5, 128.2, 127.0, 122.4, 119.4, 119.2, 111.5, 107.6, 56.5, 56.4. Anal. Calcd. for $C_{15}H_{14}BrNO_2$: C, 56.27, H, 4,41, N, 4.37. Found: 56.06, H, 4.23, N, 4.19.

6-Methylacridizinium bromide (9d). The pyridinium salt **6** (0.58 g, 1.73 mmol) was treated with 48% aqueous HBr (1.2 mL) and the mixture placed in an oil bath at 70^{o}C. The mixture was held at 90^{o}C temperature for 4 h , cooled and allowed to stand overnight. The orange solution was then quenched into THF (40 mL) on which a bright yellow solid formed. The mixture was allowed to stand overnight and the resultant lemon-yellow solid was collected by filtration and air dried to yield the bromide salt **9d (**0.33 g, 70%) which could be recystallized from ethanol to afford yellow prisms or from ethanol as yellow needles; mp 227-229^{o}C, lit mp[20] 230-231.5^{o}C ^{1}H NMR (DMSO-d_6) 9.35 (d, J = 7.5 Hz, 1H, H-4), 9.23 (s, 1H, H-11), 8.84 (d, J = 8.9 Hz, 1H), 8.60 (d, J = 8.6 Hz, 1H), 8.41 (d, J = 8.5 Hz, 1H), 8.15 (t, J = 6.9 Hz, 1H), 8.09 (t, J = 6.9 HZ, 1H), 8.06 (t, J = 7.6 Hz, 1H), 7.99 (t, J = 6.7 Hz, 1H), 3.50 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 148.4, 137.8, 134.9, 134.3, 131.4, 130.7, 130.2, 128.3, 128.2, 127.4, 125.8, 124.6, 123.1, 17.0.

11-Methyl acridizinium bromide (9e). Pyridizinium salt **8a** (136 mg) was dissolved in 48% aqueous HBr (0.5 mL) and placed in an oil bath heated at 90-100°C for 3 h. The cooled solution was added to THF (10 mL) and the mixture was placed in the freezer. Yellow needles separated which were collected by filtration (13 mg, not pure by ^{1}H NMR). Crystallization from ethanol led to a few yellow crystals, mp 195-197°C, lit mp[11] 199-201°C. ^{1}H NMR (DMSO-d_6 δ 10.40 (s, 1H, H-6), 9.30 (d, J = 7.0 Hz, 1H, H-4), 8.81 (d, J = 9.0 Hz, 1H), 8.65 (d, J = 9.0 Hz, 1H), 8.48 (d, J = 8.5 Hz, 1H), 8.18 (m, 1H), 8.10 (m, 1H), 9.02 (m, 1H), 7.98 (m, 1H), 3.20 (s, 3H).

9,11-Dimethylacridizinium bromide (9f). The 2-acetyl-1-(4-methylbenzyl)pyridinium bromide (**8b)** (270 mg, 0.88 mmol**)** was dissolved in 48% aqueous HBr (1 mL) and the solution was heated in an oil bath the temperature of which was held at 120°-130°C for 1.5 h during which period an oil separated. The mixture was cooled and added to THF (75 mL) which afforded a yellow solid. The mixture was allowed to stand overnight at room temperature and the solid was collected by filtration to afford the salt (**9f**, 0.14 g, 56%). The salt readily crystallized from ethanol, mp > 370°C. ^{1}H NMR (DMSO-d_6) δ 10.35 (s, 1H, H-6), 9.26 (d, J = 7.0 Hz, 1H, H-4), 8.72 (d, J = 9.0 Hz, 1H), 8.38 (s, 1H, H-10), 8.35 (d, J = 8.7 Hz, 1H), 8.04 (t, J = 6.8 Hz, 1H), 7.92 (t, J = 6.8 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 3.12 (s, 3H), 2.70 (s, 3H). ^{13}C NMR ($DMSOd_6$ + H_2O) δ 145.8, 138.2, 136.0, 134.7, 134.3, 133.2, 130.5, 130.2, 128.5, 124.0, 123.9, 122.8, 121.4, 22.4, 13.6. Anal. Calcd. for $C_{15}H_{14}BrN$: C, 62.52, H, 4.90, N, 4.86. Found: C, 62.25, H, 4.64, N, 4.76.

Procedure 1. **2-(2-formylbenzyl)pyridine (11a).** A solution of acridizinium bromide (**9a)** (29 mg, 0.09 mmol) in water (0.6 mL) was treated rapidly with 10% aqueous NaOH (0.2 mL). An orange solid immediately formed and the mixture was stirred for 1 h during which period the color of the solid changed to a lighter orange color. The solid was collected by filtration, washed with water and dried to yield 15 mg (85%) of product as a light pink material. The ^{1}H NMR data were obtained in $CDCl_3$ and C_6H_6. Both indicated the presence of the ring-opened aldehyde **11a** (absorptions at δ 10.3 and 4.6 for $CDCl_3$ and 10.18 and 4.40 for C_6D_6 along with other peaks). ^{1}H NMR ($CDCl_3$) δ 10.29 (s,1H), 8.51 (d, J = 4.8 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.54 (m, 2H), 7.43 (t, J = 7.1 Hz, 1H), 7.38 (d, J = 4.8 Hz, 1H), 7.22 (m, 1H), 4.60 (s, 2H). ^{1}H NMR (C_6D_6) δ 10.18 (s, 1H), 8.33 (J = 4.5 Hz, 1H), 7.60 (J = 7.5 Hz, 1H), 6.95 (m, 2H), 6.93 (m, 2H), 6.81 (d, J = 7.8 Hz, 1H) 6.50 (m, 1H), 4.40 (s, 2H).

Procedure 2. A solution of acridizinium bromide (**9a**) (10 mg) in water (0.3 mL) was treated with 10% aqueous NaOH (8 drops, pH = 14) to yield an orange precipitate. The mixture was stirred for 20 minutes and then $CDCl_3$ (0.6 mL) was added. The $CDCl_3$ layer was separated, dried over Na_2SO_4 and the ^{1}H NMR recorded. The presence of mainly the ring-opened aldehyde **11a** was indicated. Similar results were found using 0.1% (pH = 12.5) or 2% (pH = 14) aqueous NaOH.

Procedure 1. 2-(2-Formyl-5-methylbenzyl)pyridine (11b). A solution of 9-methyl acridizinium bromide (**9b)** (66 mg, 0.24 mmol) in water (1.3 mL) was treated with 10% aqueous NaOH (0.2 mL). An immediate orange precipitate formed and the mixture was allowed to stir for 1 h. The solid was collected by filtration, washed with water and the ^{1}H NMR rapidly

recorded in $CDCl_3$ and also C_6D_6. Both indicated the presence of the ring-opened product but numerous other peaks were also observed. However, if the NMR was recorded again after the NMR solutions stood for 18 h, both solutions now indicated the presence of nearly pure ring-opened aldehyde **11b** (only trace contamination). ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.51 (d, J = 4.3 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.55 (dt, J = 7.7, 1.7 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.16 (s, 1H), 7.08 (m, 2H), 4.56 (s, 2H), 2.38 (s, 3H). ^{1}H NMR (C_6D_6) δ 10.18 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 6.99 (s, 1H), 6.95 (dt, J = 7.7, 1.8 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.50 (m, 1H), 4.46 (s, 2H), 1.92 (s, 3H).

Procedure 2. A solution of 9-methylacridizinium bromide (**9b)** (8 mg) in water (0.3 ml) was treated with a saturated aqueous Na_2CO_3 solution (6 drops, pH = 12.5) to afford an orange precipitate which was extracted into $CDCl_3$. After drying over Na_2SO_4, ^{1}H NMR analysis indicated predominantly the ring-opened aldehyde **11b**.

Procedure 3. A solution of 9-methyl acridizinium bromide (**9b)** (9 mg) in water (0.3 mL) was treated dropwise with aqueous 0.1 % NaOH to afford an orange precipitate. The mixture was stirred for 15 minutes and $CDCl_3$ (0.6 mL) was added. The $CDCl_3$ layer was separated, dried over Na_2SO_4 and analyzed by NMR. The predominant product was the ring opened-aldehyde **11b**.^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1H), 8.51 (d, J = 4.2 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.54 (dt, J = 7.8, 1.6 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.08 (m, 2H), 4.56 (s, 2H), 2.38 (s, 3H).

Procedure 1. 2-(2-Acetylbenzyl)pyridine (11c). Treatment of 6-methylacridizinium bromide (**9d)** (8.5 mg) in water (0.2 mL) with 2% aqueous NaOH (10 drops, pH = 14) and stirring led to an instant color change with the formation of some tan suspended material. After 20 minutes, $CDCl_3$ (0.5 ml) was added and the organic lower orange layer was separated, dried over Na_2SO_4 and analysis by ^{1}H NMR indicated the presence of nearly pure ring-opened product **11c.** Evaporation of the $CDCl_3$ led to a black residue. ^{1}H NMR ($CDCl_3$) δ 8.53 (d, J = 4.3 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.57 (dt, J = 7.7, 1.8 Hz, 1H), 7.45 (m, 1H), 7.34 (m, 2H), 7.16 (d, J = 7.8 Hz, 1H), 7.10 (m, 1H), 4.48 (s, 2H), 2.57 (s, 3H).

Procedure 2. Treatment of 6-methyl acridizinium bromide (**9d**) (11 mg, 0.04 mmol) in water (0.3 mL) with 10% aqueous NaOH (3 drops) led to a dark coloration. After stirring for 1 minute, C_6D_6 was added, the layer was separated and dried over Na_2SO_4. The ^{1}H NMR of the C_6D_6 solution indicated the major component as the ring-opened aldehyde **11c**. ^{1}H NMR (C_6D_6) δ 8.37 (d, J = 4.7 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.05 (J = 7.5 Hz, 1H), 7.02 (m, 3H), 6.90 (t, J = 7.6 Hz, 1H), 6.53 (m, 1H), 4.62 (s, 2H), 2.12 (s, 3H).

2-Pyridin-2-ylmethyl-benzaldehyde oxime (11d). Acrizidinium bromide (**9a)** (250 mg, 0.96 mmol) was dissolved in H_2O (3.7 mL) A solution prepared by dissolving $NH_2OH{\cdot}HCl$ (90 mg, 1.3 mmol) in H_2O (0.6 mL) and neutralized with $NaHCO_3$ (excess) was added rapidly. The suspension was stirred for 45 minutes and then placed in the refrigerator for 30 minutes. The precipitate was collected by filtration to afford **11d** (137 mg, 68%) as a pale yellow powder; mp 167-169^{o}C, lit.[18] 156-157^{o}C. ^{1}H NMR ($CDCl_3$) δ 9.33 (bs, 1H, NOH), 8.51 (d, J = 4.8 Hz, 1H), 8.41 (s, 1H, CH=N), 7.67 (d, J = 7.6 Hz, 1H), 7.56-7.52 (m, 1H), 7.33 (t, J = 7.0 Hz, 1H), 7.29

(m, 2H), 7.11-7.08 (m, 1H), 6.95 (d, J = 7.9 Hz, 1H), 4.39 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 160.4, 149.0, 137.5, 136.8, 131.3, 131.2, 129.7, 127.9, 127.1, 122.9, 121.3, 41.9.

4-Methyl-2-pyridin-2-ylmethyl-benzaldehyde oxime (11e). The 9-methyl acridizinium bromide (**9b)** 0.25 g, 0.9 mmol) was treated with a solution of hydroxylamine hydrochloride (0.14 g, 2 mmol) and saturated $NaHCO_3$ (1 mL). On stirring the mixture for 0.5 h, the precipitated solid was collected by filtration, washed with water and dried to yield the oxime **11e** (0.18 g, 90%), mp 110-112°C. The material readily crystallized from aqueous ethanol to afford white needles, mp 112-113°C. ^1H NMR ($CDCl_3$) δ 8.52 (d, J = 4.7 Hz, 1H), 8.38 (s, 1H), 7.91 (br s, 0.6 H), 7.58 (d, J = 7.8 Hz, 1H), 7.52 (dt, J = 7.7, 1.8 Hz, 1H), 7.07 (m, 3H), 6.95 (d, J = 7.8 Hz, 1H), 4.31 (s, 2H), 2.33 (s, 3H).^1H NMR ($CDCl_3$ + D_2O) δ 8.53 (d, J = 4.8 HZ, 1H), 8.37 (s, 1H), 7.58 (d, 7.8 Hz, 1H), 7.53 (dt, J = 7.7, 1.8 Hz, 1H), 7.09 (m, 3H), 6.95 (d, J = 7.8 Hz, 1H), 4.32 (s, 2H), 2.33 (s, 3H). Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31, H, 6.24, N, 12.38. Found: C, 74.02, H, 6.12, N, 12.19.

2-Pyridin-2-ylmethyl-benzaldehyde *O*-phenyl oxime (11f). Acridizinium bromide (**9a)** (200 mg, 0.77 mmol) was dissolved in an aqueous solution of $NaHCO_3$ (162 mg, 1.93 mmol in 2.5 mL of water). To the stirring solution was added portion wise *O*-benzylhydroxylamine hydrochloride (123 mg, 0.77 mmol). A red oil separated and CH_2Cl_2 (2 mL) was added. The mixture was stirred for 30 minutes, the aqueous layer was discarded, the organic phase was washed with brine, dried over Na_2SO_4 and the solvent removed at diminished pressure. The crude red oil was purified *via* column chromatography (neutral alumina, CH_2Cl_2) to afford **11f (**144 mg, 62%) as an almost colorless oil.^1H NMR (DMSO-d_6): δ 8.62 (s, 1H), 8.4 (d, J = 5.1 Hz, 1H), 7.68-7.64 (m, 2H), 7.36-7.26 (m, 8H), 7.20-7.14 (m, 2H), 5.13 (s, 2H), 4.27 (s, 2H).^{13}C NMR (DMSO-d_6): δ 160.0, 149.0, 148.1, 138.4, 137.6, 136.6, 131.1, 130.2, 129.8, 128.2, 128.0, 127.6, 126.7, 126.6, 122.8, 121.3, 75.2, 40.7. Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79.44, H, 6.00, N, 9.26. Found: C, 79.19, H, 5.98, N, 9.27.

1-(2-Pyridin-2-ylmethylphenyl)ethanone oxime (11g). The 6-methyl acridizinium bromide (**9d**) (100 mg, 0.36 mmol) in water (2 mL) was treated with a solution of hydroxylamine [prepared from hydroxylamine hydrochloride (50 mg, 0.72 mol) and saturated $NaHCO_3$ (2 mL)]. After 20 minutes a solid precipitated and the mixture was allowed to stir for 0.5 h. The crystalline solid was collected by filtration and dried to yield the oxime **11g** (55 mg, 68%). The sample was recrystallized from aqueous ethanol to afford beautiful white needles, mp 152-153°C. ^1H NMR (DMSO-d_6) δ 10.97 (s) 10.40 (s,), 8.44 (d, J = 4.5 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.22 (m 4H), 7.18 (m, 1H), 7.10 (d, J = 7.8 Hz, 1H), 4.18 (s) 4.00 (s), 1.99 (s), 1.91(s), presence of E and Z isomers shown by peaks at δ 10.97 and 10.40 (ratio 9:1); 4.18 and 4.00 (ratio 9:1) and 1.99 and 1.91 (9:1). ^1H NMR (DMSO-d_6 + D_2O) disappearance of the δ 10.97 and 10.40 peaks (NO**H**). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31, H. 6.24, N, 12.28. Found: 74.02, H, 6.25, N, 12.18.

(4-Methyl-2-pyridin-2-ylmethyl-benzylidene)-propylamine (11h). Salt **9b** (200 mg, 0.73 mmol, yellow solid) was treated with 1-aminopropane (0.5 mL) upon which an orange solution immediately formed. Dichloromethane (5 mL) was added and the solution was washed with

water (3 x 4 mL). The dichloromethane extract was dried over Na_2SO_4 and the solvent was removed by rotary evaporation to afford **11h** as an orange oil (0.18 g, quantitative). Attempts to effect further purification were unsuccessful. ^{1}H NMR ($CDCl_3$) δ 8.53 (d, J = 5.0 Hz, 1H), 8.51 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.53-7.49 (m, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.09-7.06 (m, 2H), 6.96 (d, J = 8.0 Hz, 1H), 4.40 (s, 2H, CH_2), 3.47 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.61 (q, J = 7.1 Hz, 2H, CH_2), 0.83 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 160.9, 159.3, 149.2, 140.3, 138.2, 136.4, 132.1, 131.7, 128.1, 127.9, 122.9, 121.0, 63.7, 41.53, 23.9, 21.3, 11.6.

***N,N*-Dimethyl-N'-(2-pyridin-2-ylmethyl-benzylidene)-ethane-1,2-diamine (11i)**. Salt **9a** (250 mg, 0.96 mmol) was suspended in *N,N*-dimethylethylenediamine (1 mL) and the initial suspension slowly became a clear solution. Chloroform was added and the solution was washed 3 times with water. The solvent was dried over $MgSO_4$ and removed at reduced pressure to yield **11i** as a red oil (224 mg ,87%). ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.51 (d, J = 5.02 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.50-47 (m, 1H), 7.35-7.31 (m, 1H), 7.29-7.22 (m, 2H), 7.06-7.04 (m, 1H), 7.94 (d, J = 7.8 Hz), 4.41 (s, 2H, CH_2), 3.64 (t, J = 7.3 Hz, 2H, CH_2N=), 2.51 (t, J = 7.0 Hz, 2H, CH_2N), 2.23 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 160.7, 160.4, 149.2, 138.4, 136.4, 134.6, 131.0, 130.3, 128.1, 127.0, 122.9, 121.1, 60.0, 45.7, 45.5, 41.5.

***N,N*-Dimethyl-*N'*-(2-pyridin-2-ylmethyl-benzylidene)-hydrazine (11j)**. Acrizidinium bromide (**9a)** (180 mg, 0.69 mmol) was dissolved in 1,1-dimethylhydrazine (1 mL). An orange solution formed and the solutions was stirred at room temperature for 30 min. Chloroform (3 mL) was added and the solution was washed with water, the layers separated and the extract dried over Na_2SO_4. After removal of the drying agent by filtration, the solvent was removed at diminished pressure. The crude red oil was purified by column chromatography over neutral alumina (eluent: $CHCl_3$/Et_3N 98:2) to yield **11j** (158 mg, 78%) as an almost colorless oil which quickly darkened on standing in air.^{1}H NMR ($CDCl_3$) δ 8.52 (dd, J= 5.0, 1.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.50 (dt, J = 7.6 Hz, J = 1.8 Hz, 1H), 7.39 (s, 1H), 7.26-7.19 (m, 3 H), 7.08-7.05 (m, 1H), 6.94 (d, J = 7.7 Hz, 1H), 4.33 (s, 2H), 2.85 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 161.2, 149.0, 136.4, 125.7, 135.2, 131.1, 131.0, 127.3, 127.1, 125.5, 123.0, 121.0, 42.7, 42.5.

Acknowledgements

We wish to thank Novuspharma SpA (Bresso, Italy, now merged with CTI, Seattle, WA) for providing financial support for Sergio Cadamuro (Universita di Padova, Padova, Italy) as a visiting graduate student at the University of Vermont and to the Dreyfus foundation for a Senior Scientist Mentor Award used to support Lauren Macnee (undergraduate, University of Michigan) during the summer of 2005.

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