Synthesis of 3-Substituted *N*-Aminopyridinium Salts (1)

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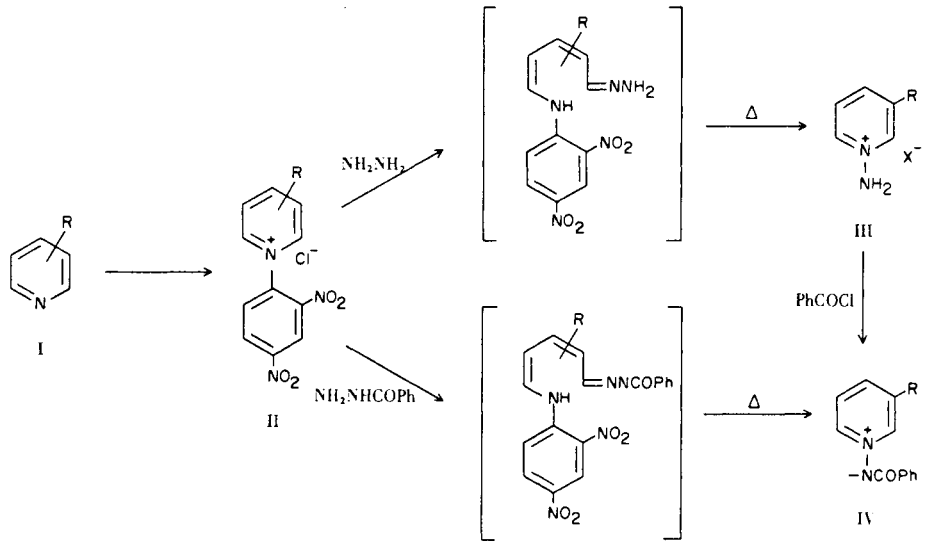
Ring opening of *N*-(2,4-dinitrophenyl)pyridinium chlorides with hydrazine followed by recyclization resulted in the formation of *N*-aminopyridinium salts. The scope of this reaction sequence was determined and several new 3-substituted *N*-aminopyridinium salts were prepared.

Recently we described a new method for the preparation of *N*-amine salts of pyridine, 3- and 4-picolines, 3,5-lutidine and isoquinoline (2). This route involves ring opening of *N*-(2,4-dinitrophenyl)pyridinium chloride with hydrazine followed by recyclization to yield *N*-aminopyridinium chloride in moderate yield. It appeared to be worthwhile to examine the generality of this method for preparing *N*-aminopyridinium salts, because of increasing interests in the chemistry of heteroaromatic *N*-imines (3,4) and the limited scope of the other known methods (3,5). In the present paper the scope of this method and the preparation of several new 3-substituted *N*-aminopyridinium salts which are the precursors of the corresponding *N*-imines are reported.

In order to make use of the method *N*-(2,4-dinitrophenyl)pyridinium chlorides (II) were required. Fortunately, the preparation of these salts has already been studied in detail by Vompe, *et al.* (6) and others (3,7). Their results are summarized as follows: (i) when R = 3-Me, OH, OMe, NHAc, NMe_2, I, $CONEt_2$, $CONH_2$ and 4-NHAc, NHPh, OMe in I, the corresponding salts (II) can be readily obtained; (ii) when R = 3-Br, COOEt and 4-COOEt, the reaction occurs only under forcing conditions of high temperature; (iii) when R = 3-Cl, F, CN, NO_2, COOH, and 4-Cl, Br, CN, NO_2, no reaction takes place; (iv) 2-substituted pyridines do not give the salts.

On the basis of these data we chose pyridine derivatives (I) bearing the following substituents for the present study; 3-Et, I, $CONH_2$, $CONEt_2$, NHAc, NH_2, COOH, CH_2OH, OH, and 4-NHAc, OMe.

Following the procedure described earlier (2), the pyridinium salt (II) was dissolved in water and treated with hydrazine hydrate. Dioxane was added and the suspension was heated under reflux for 10-15 hours to give the corresponding *N*-aminopyridinium salt (III). The structures of III were confirmed by elemental analysis



a, R = 3-Et; b, R = 3-I; c, R = 3-$CONH_2$; d, R = 3-$CONEt_2$;
e, R = 3-NHAc; f, R = 3-NH_2; g, R = 3-COOH; h, R = 3-CH_2OH

TABLE I

3-Substituted *N*-Aminopyridinium Salts

Compd.	R	X	Recryst'd from	M.p. °C	Yield from II, %	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
IIIa	Et	picrate	EtOH	118-119	(a)	$C_{13}H_{13}N_5O_7$	44.45	3.73	19.94	44.28	3.82	19.61
IIIb	I	picrate	MeOH	163-164	43	$C_{11}H_8IN_5O$	29.42	1.79	15.59	29.22	1.61	15.48
IIIc	$CONH_2$	Cl	MeOH	227-228	46	$C_6H_8ClN_3O$	41.51	4.65	24.20	41.46	4.76	23.84
IIId	$CONEt_2$	Cl	iso-PrOH	172-173	31	$C_{10}H_{16}ClN_3O$	52.29	7.02	18.29	52.16	7.00	17.94
IIIe	NHAc	Cl	MeOH	233-235	27	$C_7H_{10}ClN_3O$	44.81	5.32	22.40	44.75	5.08	22.09
IIIf	NH_2	I	EtOH	141-142 (b)	(c)							
IIIg	COOH	Cl	MeOH	218-219	(d)	$C_6H_7ClN_2O_2$	41.28	4.04	16.04	41.76	4.09	15.61

(a) Prepared by hydrolysis of IVa. (b) Lit. (9) m.p. 140-141°. (c) Prepared by hydrolysis of IIIe. (d) Prepared by hydrolysis of IIIc.

TABLE II

3-Substituted *N*-Benzoyliminopyridinium Betaines

Compd.	R	Recryst'd from	M.p. °C	Yield from II, %	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
IVa	Et	C_6H_6-ligroin	123-124	68	$C_{14}H_{14}N_2O$	74.31	6.24	12.38	74.37	6.23	12.37
IVc	$CONH_2$	MeOH	270-271	44	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42	64.66	4.67	17.32
IVd	$CONEt_2$ (a)	C_6H_6-ligroin	96-97	49	$C_{17}H_{19}N_3O_2$	68.66	6.44	14.13	68.93	6.29	14.10
IVe	NHAc (b)	MeOH	228-229	46	$C_{14}H_{13}N_3O_2$	65.87	5.13	16.46	65.99	5.09	16.33
IVf	NH_2 (c)	Me_2CO	200-201	(d)	$C_{12}H_{11}N_3O$	67.59	5.20	19.71	68.05	5.34	19.35
IVh	CH_2OH	Me_2CO	123-124	24	$C_{13}H_{12}N_2O_2$	68.41	5.30	12.27	68.40	5.55	12.20

(a) The picrate: m.p. 205-206.5° C (from ethanol); *Anal.* Calcd. for $C_{23}H_{22}N_6O_9$: C, 52.47; H, 4.21; N, 15.97. Found: C, 52.25; H, 4.26; N, 15.83. (b) The chloride: m.p. 215-216° C (from methanol); *Anal.* Calcd. for $C_{14}H_{14}ClN_3O_2$: C, 57.64; H, 4.84; N, 14.40. Found: C, 57.53; H, 4.82; N, 14.18. (c) The chloride: m.p. 225-227° C (from methanol); *Anal.* Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.84; N, 16.82. Found: C, 57.73; H, 4.91; N, 16.89. (d) Prepared by hydrolysis of IVe.

TABLE III

Spectral Data of 3-Substituted *N*-Benzoyliminopyridinium Betaines (IV)

Compd.	IR (KCl), cm^{-1}				UV (dioxane), $m\mu$	
IVa		1600	1555	1350	239	353
IVc	1700	1590	1550	1340	244	360
IVd	1640	1590	1550	1330	244	360
IVe	1700	1600	1560	1350	253	348
IVf		1590	1540	1350	250	344
IVh		1590	1550	1340	241	353

and ultraviolet spectra which showed strong absorption bands between 330 to 340 $m\mu$ after alkali treatment (4). Furthermore, the *N*-amino derivatives (IIIc,e) were converted into the corresponding *N*-benzoylimines (IVc,e) by a Schotten-Baumann reaction and were found to be identical to those synthesized as described below. As shown in Table I, this method was found to be effective for the preparation of IIIb-e. However, ethyl and hydroxymethyl derivatives (IIa and IIb) gave a mixture of the hydrochlorides of the corresponding III and I. Attempts to prepare *N*-amino-3-hydroxy-, 4-acetamido-, and 4-methoxypyridinium salts were unsuccessful. For the preparation of the *N*-amino derivatives of 3-amino- and 3-carboxypyridines (IIIf and IIIg), this method could not be applied due to difficulty in obtaining the corresponding salts (II). However, these two compounds (IIIf and IIIg) were readily obtained by acid hydrolysis of IIIe and IIIc in 80 and 91% yields, respectively.

For a comparison of yields, the corresponding *N*-benboylimino derivatives (IV) were also prepared by the application of this method with minor modification (see Experimental part). The 3-amino derivative (IVf) was prepared by acid hydrolysis of IVe. The results are summarized in Table II.

The ir and uv spectral data for the *N*-benzoylimines are shown in Table III. Three characteristic absorption bands at 1590-1600, 1540-1560 and 1330-1350 cm^{-1} in the ir spectrum (in potassium chloride) and ultraviolet maximum at 340-360 $m\mu$ in dioxane were diagnostically important in that they were in agreement with the earlier reports of these properties (2,8).

In summary the method can be applied successfully to the synthesis of *N*-aminopyridinium salts bearing 3-substituents such as alkyl, NHAc, I, $CONH_2$, and $CONEt_2$. Further studies of the chemistry of these ylides are in progress.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Hitachi-EPI G 2 spectrophotometer and uv spectra on a Hitachi EPS-3T spectrophotometer.

N-(2,4-Dinitrophenyl)-3-ethylpyridinium Chloride (IIa).

According to the procedure of Vompe, *et al.* (6), a solution of 3-ethylpyridine (Ia) (12.8 g.) and 2,4-dinitrochlorobenzene (24.4 g.) in dry acetone (30 ml.) was heated under reflux for 3 hours. The precipitated solid was collected and recrystallized from 2-propanol, m.p. 202-203°, yield, 23.4 g. (73%).

Anal. Calcd. for $C_{13}H_{12}ClN_3O_4$: C, 50.41; H, 3.90; N, 13.56. Found: C, 50.29; H, 3.97; N, 13.41.

N-(2,4-Dinitrophenyl)-3-hydroxymethylpyridinium Chloride (IIh).

A solution of 3-hydroxymethylpyridine (Ih) (5.5 g.) and 2,4-dinitrochlorobenzene (10.1 g.) in dry acetone (20 ml.) was warmed at 50° for 6 hours to give a black resinous oil, which solidified after washing with acetone. The solid was treated with charcoal and recrystallized from ethanol, m.p. 113-114°, yield, 11.8 g. (71.5%).

Anal. Calcd. for $C_{12}H_{10}ClN_3O_5 \cdot H_2O$: C, 43.72; H, 3.67; N, 12.75. Found: C, 44.05; H, 3.86; N, 12.86.

N-Amino-3-acetamidopyridinium Chloride (IIIe).

The general procedure used is illustrated by this example. *N*-(2,4-Dinitrophenyl)-3-acetamidopyridinium chloride (IIe) (3.4 g.) was dissolved in hot water (14 ml.) and cooled to 0°. To the ice-cooled solution was added dropwise hydrazine-hydrate (0.5 ml.) and the reaction mixture was allowed to stand overnight. Dioxane (56 ml.) was added and the suspension was heated under reflux for 13 hours. The solvent was removed under reduced pressure and water was added to the residue. The insoluble material was removed by filtration. The filtrate was treated with charcoal and concentrated to give colorless crystals of IIIe, which was recrystallized from methanol, m.p. 233-235°, yield, 0.51 g. (27%).

In a similar manner, IIIb-d were synthesized. However, similar treatment of IIa resulted in the formation of a mixture of IIIa (X = Cl) and 3-ethylpyridine (Ia). An authentic sample of IIIa was prepared by hydrolysis of IVa with 10% hydrochloric acid and characterized as its picrate. The results are summarized in Table I.

N-Amino-3-aminopyridinium Iodide (IIIf).

A solution of IIIe (100 mg.) in 10% hydrochloric acid was heated on a water bath for 6 hours. The solvent was removed to give white crystals of the chloride which were recrystallized from ethanol: m.p. 180-181°; yield, 62 mg. (80%): the iodide; m.p. 141-142° (lit. (9) 140-141°).

N-Amino-3-carboxypyridinium Chloride (IIIg).

Using a similar treatment described above, IIIc (203 mg.) provided IIIg: m.p. 218-219°; yield, 185 mg. (71%). For the elemental analysis see Table I.

Benzoylation of *N*-Amino-3-acetamidopyridinium Chloride (IIIe).

A mixture of IIIe (188 mg.) and benzoyl chloride (141 mg.) in 10% sodium hydroxide was stirred at room temperature overnight. The precipitated crystals of IVe were collected and recrystallized from methanol, m.p. 228-229°, yield, 162 mg. (62%).

Similarly, IIIc was converted to IVc.

N-Benzoylimino-3-ethylpyridinium Betaine (IVa).

The general procedure is described by this example. To an ice-cooled solution of IIa (3.6 g.) in methanol (10 ml.) was added dropwise benzoylhydrazine (3.1 g.) in methanol (20 ml.) and then triethylamine (1.3 g.). The reaction mixture was allowed to stand at room temperature overnight. The precipitated solid was collected and washed with methanol, water, methanol and ether in this order. A suspension of the solid obtained above in dioxane-water (4:1) (75 ml.) was heated under reflux for 12 hours until a clear solution was obtained. The solvent was removed under reduced pressure below 45°. Water was added to the residue and the insoluble material was removed by filtration. The filtrate was concentrated to give white crystals of IVa, m.p. 123-124°, yield, 1.55 g. (68%). In a similar manner, IId and IIh gave IVd and IVh, respectively.

In the cases of IVc and IVe which were insoluble in water, the work-up procedure was slightly modified as follows: the reaction mixture was acidified with 10% hydrochloric acid and the insoluble material was removed. The filtrates were concentrated below 45° to give the hydrochlorides, which, upon treatment with 10% sodium hydroxide, yielded the *N*-benzoylimines, IVc and IVe.

N-Benzoylimino-3-aminopyridinium Betaine (IVf).

This compound was prepared by hydrolysis of IVe in a similar manner described for the preparation of IIIf in 20% yield, m.p. 200-201°.

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