Synthesis of Some *N*-[Pyridyl(phenyl)carbonylamino]hydroxyalkyl-(benzyl)-1,2,3,6-tetrahydropyridines as Potential Anti-inflammatory Agents

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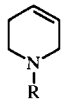
Received May 17, 1994
Revised October 7, 1994

1,2,3,6-Tetrahydropyridines are known to possess analgesic, anti-inflammatory, hyperglycemic and hypoglycemic activities. Substituted 2,4-dinitrophenylpyridinium chlorides **3** were formed by reacting 1-chloro-2,4-dinitrobenzene with hydroxypropyl, hydroxymethyl and benzyl substituted pyridines **2**. Attack of the pyridinium chlorides **3** with pyridylcarbonyl hydrazides or benzoyl hydrazides **4** gave the isolable 2,4-dinitroanilino derivative **5** which underwent hydrolysis when refluxed in water:*p*-dioxane mixture (1:4 v/v) to afford the pyridinium ylides **6**. Sodium borohydride reduction of **6** in absolute ethanol at 0° for 4-6 hours resulted in the isolation of the 1,2,3,6-tetrahydropyridines **7** in good yields.

J. Heterocyclic Chem., **32**, 307 (1995).

Several pharmacological activities of compounds possessing the 1,2,3,6-tetrahydropyridine (THP) ring system **1** were reported in the literature [1-3].



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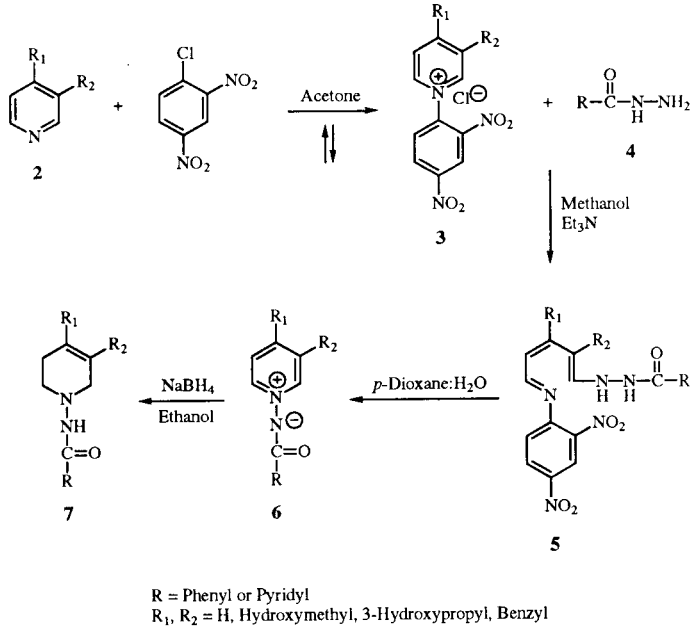
We are interested in the anti-inflammatory, analgesic, and antipyretic activities of the reduced pyridine ring system. It is evident from literature survey that pharmacological activities of these analogs depend on the nature of the substituents on the THP ring system. A well documented case is the neurotoxic activities of *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and related compounds [4,5]. Earlier work by Knaus, Redda and co-workers [6-12] indicated that several *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines showed significant anti-inflammatory, analgesic and hyperglycemic activities on preliminary test results. Subsequently, we extended this work by introducing methyl [13], ethyl [14], *t*-butyl and phenyl [15] groups on the THP ring system in search of an effective, nonacidic, and nonsteroidal anti-inflammatory agent. However, the pharmacological activity results so far obtained in our laboratory showed only moderate to appreciable anti-inflammatory activities but not close to the activity of the reference compound, indomethacin. Our current work deals with the modification of the THP ring system with hydroxypropyl, hydroxymethyl and benzyl substituents to evaluate the anti-inflammatory activities. These substituents are expected to affect the lipophilicity of the derivatives in either direction.

Scheme 1



R = Phenyl or Pyridyl
R_1, R_2 = H, Hydroxymethyl, 3-Hydroxypropyl, Benzyl

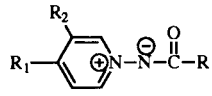
Results and Discussion.

Chemistry.

Appropriately substituted pyridines **2** were reacted with 1-chloro-2,4-dinitrobenzene in acetone under reflux for 12 hours to furnish the *N*-(2,4-dinitrophenyl) pyridinium chlorides **3**. Nucleophilic attack of pyridyl or benzoyl hydrazides **4** on **3** in methanol in the presence of triethylamine results in the formation of 2,4-dinitroanilino derivatives **5**. The targeted *N*-[pyridyl(phenyl)carbonylimino]-alkyl(benzyl)pyridinium ylides **6** result upon hydrolysis with water:*p*-dioxane under reflux [13]. Sodium borohydride reduction [14] of the pyridinium ylides **6** at 0° for 4 hours afforded the *N*-[pyridyl(phenyl)carbonylamino]-hydroxyalkyl or -benzyl-1,2,3,6-tetrahydropyridines **7** as shown in Scheme 1. The results of the synthesis of the

Table 1

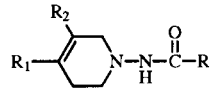
Pyridinium Ylides **6a-6p** Synthetic Data



	R	R_1	R_2	% Yield	mp, °C
6a	4-pyridyl	H	$-CH_2CH_2CH_2OH$	55	120-122
6b	3-pyridyl	H	$-CH_2CH_2CH_2OH$	49	126-128
6c	2-pyridyl	H	$-CH_2CH_2CH_2OH$	33	Semi-solid
6d	Phenyl	H	$-CH_2CH_2CH_2OH$	41	Semi-solid
6e	4-pyridyl	$-CH_2CH_2CH_2OH$	H	79	156-158
6f	3-pyridyl	$-CH_2CH_2CH_2OH$	H	66	164-166
6g	2-pyridyl	$-CH_2CH_2CH_2OH$	H	42	166-168
6h	Phenyl	$-CH_2CH_2CH_2OH$	H	42	153-155
6i	4-pyridyl	H	$-CH_2OH$	84	160-162
6j	3-pyridyl	H	$-CH_2OH$	85	103-105
6k	2-pyridyl	H	$-CH_2OH$	61	160-162
6l	Phenyl	H	$-CH_2OH$	62	123-125
6m	4-pyridyl	H	Benzyl	44	Semi-solid
6n	3-pyridyl	H	Benzyl	50	Semi-solid
6o	2-pyridyl	H	Benzyl	75	Semi-solid
6p	Phenyl	H	Benzyl	68	96-98

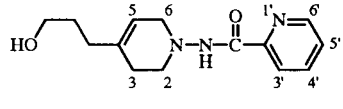
Table 2

1,2,3,6-Tetrahydropyridines **7a-7p** Synthetic Data



	R	R_1	R_2	% Yield	mp, °C
7a	4-pyridyl	H	$-CH_2CH_2CH_2OH$	48	142-144
7b	3-pyridyl	H	$-CH_2CH_2CH_2OH$	48	109-111
7c	2-pyridyl	H	$-CH_2CH_2CH_2OH$	40	Semi-solid
7d	Phenyl	H	$-CH_2CH_2CH_2OH$	59	159-161
7e	4-pyridyl	$-CH_2CH_2CH_2OH$	H	35	165-167
7f	3-pyridyl	$-CH_2CH_2CH_2OH$	H	64	108-110
7g	2-pyridyl	$-CH_2CH_2CH_2OH$	H	69	91-93
7h	Phenyl	$-CH_2CH_2CH_2OH$	H	55	150-152
7i	4-pyridyl	H	$-CH_2OH$	49	124-126
7j	3-pyridyl	H	$-CH_2OH$	22	153-155
7k	2-pyridyl	H	$-CH_2OH$	52	105-107
7l	Phenyl	H	$-CH_2OH$	60	133-135
7m	4-pyridyl	H	Benzyl	56	147-148
7n	3-pyridyl	H	Benzyl	65	138-140
7o	2-pyridyl	H	Benzyl	57	Semi-solid
7p	Phenyl	H	Benzyl	46	153-155

pyridinium ylides **6** and the corresponding 1,2,3,6-tetrahydropyridines **7** are presented in Tables 1 and 2. The spectral data of these compounds display diagnostic absorption patterns. The infrared and ^1H nmr spectra of *N*-(2-pyridylcarbonylamino)-4-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine **7g** are presented here.



7g

The ^1H nmr spectrum recorded in deuteriochloroform shows characteristic absorptions at δ 1.64-1.74 (2H, m, $-CH_2CH_2CH_2OH$), 2.08 (t, J = 7.5 Hz, 2H, $-CH_2CH_2CH_2OH$), 2.26 (s, 2H, C_3-H), 3.08 (t, J = 6 Hz, 2H, C_2-H), 3.45 (s, 2H, C_6-H), 3.65 (t, J = 6.5 Hz, 2H, $-CH_2CH_2CH_2OH$), 5.38 (m, 1H, C_5-H, olefinic), 7.31-7.41 (m, 1H, $C_{5'}$-H), 7.81 (td, $J_{3',4'} = J_{4',5'} = 7.5$ Hz, $J_{4',6'} = 1.5$ Hz, 1H, $C_{4'}$-H), 8.18 (m, 1H, $C_{3'}$-H), 8.49 (m, 1H, $C_{6'}$-H), 8.86 (s, deuterium exchangeable, 1H, NH).

The ir (potassium bromide) spectrum display absorp-

tions at 1675 (C=O), 3200-3400 (NH, -OH) cm^{-1}. The pharmacological evaluation of the tetrahydropyridines is underway.

EXPERIMENTAL

Infrared spectra were measured on a Perkin Elmer 1430 instrument on potassium bromide pellets unless otherwise stated. The ^1H nmr spectra were recorded in deuteriochloroform as an internal standard unless otherwise stated. Elemental analysis of the compounds were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. All the compounds synthesized were found homogeneous on tlc as judged by solvent systems of low, medium and high polarity. Electrothermal R melting point apparatus was used for the determination of melting points and are uncorrected. All the solvents and chemicals used were purchased from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin and Fisher Scientific Company, Orlando, Florida.

N-(4-Pyridylcarbonylimino)-3-(3-hydroxypropyl)pyridinium Ylide (**6a**).

General Procedure A.

N-(2,4-Dinitrophenyl)-3-(3-hydroxypropyl)pyridinium chloride **3a** (6.00 g, 17.66 mmoles) was reacted with isonicotinic acid hydrazide (3.27 g, 23.84 mmoles) in 150 ml of methanol containing 3.00 ml of triethylamine at 0° for 4 hours. The material was filtered and washed with ether (2 x 75 ml) and water (2 x 75 ml). The resulting residue was hydrolysed with 250 ml of *p*-dioxane-water (4:1, v/v) under reflux for 12 hours. The solvents were evaporated *in vacuo* to about 50% of the original volume and the contents were cooled to 0° and 50 ml of distilled water added. The precipitated yellow product, the 2,4-dinitroaniline was filtered, washed with 25 ml of water and rejected. The filtrate and washings were combined and extracted with methylene chloride (3 x 100 ml) to remove more of 2,4-dinitroaniline. The residual aqueous phase was evaporated *in vacuo* at 35°. The product obtained was chromatographed on a column of neutral alumina (Brockmann I, 150 mesh, 58A, Aldrich) (2.5 x 25 cm) using ether:methanol (10:1 v/v, 200 ml, 5:1 v/v, 600 ml) as an eluent and furnished a solid. It was further crystallized from methylene chloride:ethyl acetate (3:1 v/v, 50 ml) as a cream colored solid of **6a** (2.50 g, 55%), mp 120-122°; ^1H-nmr: δ 1.86-2.05 (m, 3H, one H deuterium oxide exchangeable, $-CH_2CH_2CH_2OH$), 2.90 (t, J = 7 Hz, 2H, $-CH_2CH_2CH_2OH$), 3.65 (t, 2H, J = 6 Hz, $-CH_2CH_2CH_2OH$), 7.57-7.65 (m, 1H, C_5-H), 7.81 (d, $J_{4,5}$ = 7.5 Hz, 1H, C_4-H), 7.95 (d, $J_{3',2'} = J_{5',6'}$ = 4.5 Hz, 2H, $C_{3'}$-H, $C_{5'}$-H) 8.56-8.65 (m, 4H, C_2-H, C_6-H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.38; H, 5.99; N, 16.05.

N-(3'-Pyridylcarbonylimino)-3-(3-hydroxypropyl)pyridinium Ylide (**6b**).

A suspension of nicotinic acid hydrazide (4.0 g, 29.16 mmoles), *N*-(2,4-dinitrophenyl)-3-(3-hydroxypropyl)pyridinium chloride **3b** (7.50 g, 22.07 mmoles) and 3.70 ml of triethylamine in 150 ml of anhydrous methanol were stirred at 0-10° for 4 hours and the reaction mixture completed as described in the general procedure A. The product obtained was chromatographed on a column of neutral alumina (2.5 x 25 cm) using ethyl acetate:methanol (9:1 v/v, 400 ml) as the eluent and the resulting solid was recrystallized from methylene chloride:ethyl acetate (3:1 v/v, 150 ml) as a pale yellow solid of **6b** (2.80 g, 49%), mp 126-128°; ^1H-nmr: δ 1.80-2.00 (m, 2H, $-CH_2CH_2CH_2OH$), 2.87 (t, J = 7.5 Hz, 2H, $-CH_2CH_2CH_2OH$), 3.56 (t, J = 6 Hz, 2H, $-CH_2CH_2CH_2OH$), 4.22 (s, deuterium oxide exchangeble, 1H, $-CH_2CH_2CH_2OH$), 7.50 (m, 1H, $C_{5'}$-H), 7.71 (m, 1H, C_5-H), 7.96 (d, $J_{4',5'}$ = 8 Hz, 1H, $C_{4'}$-H), 8.40-8.52 (m, 3H, C_4-H, C_6-H, $C_{6'}$-H), 8.60 (d, $J_{6,5}$ = 5 Hz, 1H, C_2-H), 9.19 (s, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.56; H, 6.15; N, 16.09.

N-(2'-Pyridylcarbonylimino)-3-(3-hydroxypropyl)pyridinium Ylide (**6c**).

Picolinic acid hydrazide (5.48 g, 39.88 mmoles), *N*-(2,4-dinitrophenyl)-3-(3-hydroxypropyl)pyridinium chloride **3c** (10.00 g, 29.43 mmoles) and 5.00 ml of triethylamine were stirred at 0° for 2 hours. The reaction mixture was allowed to stand at 0° for 2 more hours. The resulting solid was filtered and the procedure was completed as described in the general procedure A. The product was chromatographed on a column of neutral alumina (2.5 x 25 cm) employing ether:methanol (10:1 v/v, 200 ml, 5:1 v/v, 600 ml) as eluent and furnished **6c** as a brownish white semi-solid (2.50 g, 33%); ^1H-nmr: δ 1.90 (m, 2H, $-CH_2CH_2CH_2OH$), 2.11 (s, deuterium oxide exchangeable, 1H, $-CH_2CH_2CH_2OH$), 2.87 (t, J = 7 Hz, 2H, $-CH_2CH_2CH_2OH$), 3.62 (t, J = 6 Hz, 2H, $-CH_2CH_2CH_2OH$), 7.33 (m, 1H, $C_{5'}$-H), 7.60 (m, 1H, C_5-H), 7.71-7.85 (m, 2H, C_4-H, $C_{4'}$-H), 8.26 (m, 1H, $C_{3'}$-H), 8.56 (dt, $J_{5',6'}$ = 6 Hz, $J_{4',6'}$ = 1.5 Hz, $J_{3',6'}$ = 1.0 Hz, 1H, $C_{6'}$-H), 8.62-8.72 (complex m, 2H, C_2-H, C_6-H).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.30; H, 5.90; N, 16.29.

N-(Benzoylimino)-3-(3-hydroxypropyl)pyridinium Ylide (**6d**).

N-(2,4-Dinitrophenyl)-3-(3-hydroxypropyl)pyridinium chloride **3d** (6.50 g, 25.36 mmoles) was reacted with benzoic hydrazide (3.52 g, 25.85 mmoles) in 150 ml of methanol containing 3.50 ml of triethylamine at 0-10° for 4 hours. The reaction was completed as described in the general procedure A. The product was chromatographed on a neutral alumina column (2.5 x 20 cm) using ether:methanol (10:1 v/v, 300 ml, 5:1 v/v, 400 ml) as eluent and gave **6d** as a brownish semi-solid (2.02 g, 41%); ^1H-nmr: δ 1.91 (m, 2H, $-CH_2CH_2CH_2OH$), 2.03 (s, deuterium oxide exchangeable, 1H, $-CH_2CH_2CH_2OH$), 2.87 (t, J = 7.5 Hz, 2H, $-CH_2CH_2CH_2OH$) 3.63 (t, J = 6 Hz, 2H, $CH_2CH_2CH_2OH$), 7.35-7.47 (m, 3H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H of phenyl), 7.57 (m, 1H, C_5-H), 7.76 (d, $J_{4,5}$ = 8 Hz, 1H, C_4-H), 8.18-8.20 (m, 2H, $C_{2'}$-H, $C_{6'}$-H of phenyl), 8.53 (d, $J_{6,5}$ = 6.5 Hz, 1H, C_6-H), 8.63 (s, 1H, C_2-H).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.25; H, 6.32; N, 10.87.

N-(4'-Pyridylcarbonylimino)-4-(3-hydroxypropyl)pyridinium Ylide (**6e**).

A suspension of isonicotinic acid hydrazide (4.44 g, 32.38 mmoles), *N*-(2,4-dinitrophenyl)-4-(3-hydroxypropyl)pyridimium chloride **3e** (10.00 g, 29.43 mmoles) and 4.50 ml of triethylamine in 225 ml of methanol was stirred at 0-10° and allowed to react for 4 hours. The reaction was completed as described in the general procedure A. The resulting material was chroma-

tographed on a column of neutral alumina (2.5 x 30 cm) using methylene chloride:methanol (9:1 v/v, 500 ml, 4:1 v/v, 250 ml) as the eluent and **6e** was obtained as a pale brown crystalline solid (6.00 g, 79%). It was further recrystallized from methylene chloride:ethyl acetate:ethanol (2:1:1, v/v/v) as pale brown needles, mp 156-158°; ir: ν 3400-3500 (OH) cm^{-1}; ^{1}H-nmr: δ 1.90 (m, 2H, -$CH_2CH_2CH_2OH$), 2.91 (t, J = 7.5 Hz, 2H, -$CH_2CH_2CH_2OH$), 3.65 (t, J = 6 Hz, 2H, -$CH_2CH_2CH_2OH$), 7.50 (d, $J_{3,2} = J_{5,6}$ = 4.5 Hz, 2H, C_3-H, C_5-H), 7.93 (overlapping ds, $J_{3',2'} = J_{5',6'}$ = 4.5 Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 8.59 (d, $J_{2',3'} = J_{6',5'}$ = 4.5 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H), 8.64 (d, $J_{2,3} = J_{6,5}$ = 4.5 Hz, 2H, C_2-H, C_6-H), O*H* not detected at the concentration used.

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.28; H, 5.95; N, 16.23.

N-(3'-Pyridylcarbonylimino)-4-(3-Hydroxypropyl)pyridinium Ylide (**6f**).

A suspension of nicotinic acid hydrazide (4.44 g, 32.38 mmoles), *N*-(2,4-dinitrophenyl)-4-(3-hydroxypropyl)pyridinium chloride **3f** (10.00 g, 29.43 mmoles), 4.50 ml of triethylamine in 225 ml of methanol were stirred at 0° and the reaction was completed as described in the general procedure A. The crude product obtained was treated with activated carbon and crystallized from methylene chloride:ethyl acetate:ethanol (1.5:1:1, v/v/v) to give **6f** as pale brown needles (5.01 g, 66%); mp 164-166°; ^{1}H-nmr: δ 1.74-1.84 (m, 2H, -$CH_2CH_2CH_2OH$), 2.81 (t, J = 7.8 Hz, 2H, -$CH_2CH_2CH_2OH$), 3.49 (t, J = 6 Hz, 2H, -$CH_2CH_2CH_2OH$), 3.94 (s, deuterium oxide exchangeable, 1H, -$CH_2CH_2CH_2OH$), 7.24-7.29 (m, 1H, $C_{5'}$-H), 7.50 (d, $J_{3,2} = J_{5,6}$ = 5 Hz, 2H, C_3-H, C_5-H), 8.24 (dt, $J_{4',5'}$ = 7.5 Hz, $J_{4',6'} = J_{4',2'}$ = 2 Hz, 1H, $C_{4'}$-H), 8.35 (d, $J_{2,3} = J_{5,6}$ = 5 Hz, 2H, C_2-H, C_6-H), 8.44 (dd, $J_{5',6'}$ = 5 Hz, $J_{4',6'}$ = 2 Hz, 1H, $C_{6'}$-H), 9.07 (m, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.30; H, 5.90; N, 16.21.

N-(2'-Pyridylcarbonylimino)-4-(3-hydroxypropyl)pyridinium Ylide (**6g**).

A suspension of picolinic acid hydrazide (4.44 g, 32.38 mmoles), *N*-(2,4-dinitrophenyl)-4-(3-hydroxypropyl)pyridinium chloride **3g** (10.00 g, 29.43 mmoles) were reacted in 225 ml of methanol containing 4.50 ml of triethylamine at 0° as described in the general procedure A. The resulting product was chromatographed on a column of neutral alumina (2.5 x 30 cm) employing methylene chloride:methanol (9:1 v/v, 500 ml, 4:1 v/v, 400 ml, 3:1 v/v, 200 ml) as an eluent and gave **6g** as a pale yellow product (3.15 g, 42%). Further crystallization from methylene chloride:ethyl acetate:ethanol (1.5:1:0.1, v/v/v) afforded the analytical sample as pale yellow needles, mp 166-168°; ^{1}H-nmr: δ 1.86-1.96 (m, 2H, -$CH_2CH_2CH_2OH$), 2.42 (s, deuterium oxide exchangeable, 1H, -$CH_2CH_2CH_2OH$), 2.90 (t, J = 7.5 Hz, 2H, -$CH_2CH_2CH_2OH$), 3.65 (t, J = 6 Hz, 2H, -$CH_2CH_2CH_2OH$), 7.31-7.36 (m, 1H, $C_{5'}$-H), 7.51 (d, $J_{3,2} = J_{5,6}$ = 7 Hz, 2H, C_3-H, C_5-H), 7.78 (td, $J_{4',5'} = J_{3',4'}$ = 7.5 Hz, $J_{4',6'}$ = 2 Hz, 1H, $C_{4'}$-H), 8.18 (d, $J_{3',4'}$ = 7.5 Hz, 1H, $C_{3'}$-H), 8.62 (d, $J_{2,3} = J_{6,5}$ = 7 Hz, 2H, C_2-H, C_6-H), 8.68 (d, $J_{3',4'}$ = 5 Hz, 1H, $C_{6'}$-H).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.26; H, 5.96; N, 16.25.

N-(Benzoylcarbonylimino)-4-(3-hydroxypropyl)pyridinium Ylide (**6h**).

A suspension of benzoic hydrazide (5.72 g, 42.10 mmoles), *N*-(2,4-dinitrophenyl)-4-(3-hydroxypropyl)pyridinium chloride **3h** (13.00 g, 38.26 mmoles) and 5.90 ml of triethylamine in 150 ml of methanol was stirred at 0° for 30 minutes. The reaction was completed as described in the procedure A. The crude product was treated with activated carbon and then chromatographed on a column of neutral alumina (4.5 x 20 cm) using methylene chloride (250 ml) and methylene chloride:methanol (9:1 v/v, 500 ml, 4:1 v/v, 500 ml) as an eluent and furnished **6h** as a pale yellow solid (4.15 g, 42%). Recrystallization from methylene chloride:ethyl acetate:ethanol (2:1:0.1, v/v/v) furnished the analytical sample as pale brown needles, mp 153-155°; ^{1}H-nmr: δ 1.81-1.91 (m, 2H, -$CH_2CH_2CH_2OH$), 2.60 (s, deuterium oxide exchangeable, 1H, -$CH_2CH_2CH_2OH$), 2.85 (t, J = 7.5 Hz, 2H, -$CH_2CH_2CH_2OH$), 3.60 (t, J = 6 Hz, 2H, -$CH_2CH_2CH_2OH$), 7.34-7.46 (m, 5H, $C_{2'}$-H to $C_{6'}$-H of Phenyl), 8.09-8.13 (m, 2H, C_3-H, C_5-H), 8.55 (d, $J_{2,3} = J_{6,5}$ = 7 Hz, 2H, C_2-H, C_6-H).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.20; H, 6.33; N, 10.85.

N-(4'-Pyridylcarbonylimino)-3-hydroxymethylpyridinium Ylide (**6i**).

N-(2,4-Dinitrophenyl)-3-hydroxymethylpyridinium chloride **3i** (12.00 g, 38.50 mmoles) was reacted with isonicotinic acid hydrazide (5.81 g, 42.36 mmoles) in 150 ml anhydrous methanol containing 5.40 ml of triethylamine and the reaction was completed as described in the general procedure A. The resulting product was treated with activated carbon, filtered through a nylon membrane (MCI) and crystallized from methylene chloride:ethylacetate:methanol (2:1:0.1, v/v) as brownish yellow flakes of **6i** (6.00 g). The mother liquor was chromatographed on a column of neutral alumina (2.5 x 18 cm) using methylene chloride:methanol (9:1 v/v, 400 ml; 4:1 v/v, 250 ml) as an eluent to furnish more of **6i** for a total of (7.25 g, 84%), mp, 160-162°; ^{1}H-nmr: δ 4.76 (d, J = 5.5 Hz, 2H, CH_2OH), 5.70 (t, J = 5.5 Hz, deuterium oxide exchangeable, 1H, CH_2OH), 7.79 (m, 1H, C_5-H), 7.95 (overlapping ds, $J_{2',3'} = J_{5',6'}$ = 4.5 Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 8.05 (d, $J_{4,5}$ = 8 Hz, 1H, C_4-H), 8.62 (overlapping ds, $J_{2',3'} = J_{5',6'}$ = 4.5 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H), 8.70 (d, $J_{6,5}$ = 6 Hz, 1H, C_6-H), 8.77 (s, 1H, C_2-H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.82; H, 4.74; N, 18.33.

N-(3'-Pyridylcarbonylimino)-3-hydroxymethylpyridinium Ylide (**6j**).

To an ice cold suspension of *N*-(2,4-dinitrophenyl)-3-hydroxymethylpyridinium chloride (8.00 g, 25.66 mmoles) in 75 ml of anhydrous methanol were added nicotinic acid hydrazide (3.90 g, 28.44 mmoles) and 3.60 ml of triethylamine. The contents were stirred at 0-10° for 4 hours and the reaction completed as described in the general procedure A. The crude product was treated with activated carbon, filtered, evaporated *in vacuo* and crystallized from methylene chloride:ethyl acetate (2:1, v/v) as pale yellow solid of **6j** (5.00 g). The mother liquor was chromatographed on a column of neutral alumina (2.5 x 18 cm) using methylene chloride (350 ml) and methylene chloride: methanol (9:1 v/v, 250 ml) as an eluent giving more of **6j** for a total weight of (6.00 g, 85%), mp 103-105°; ^{1}H-nmr: δ 4.50 (s, 1H, deuterium oxide exchangeable, -CH_2OH), 4.80 (s, 2H, -CH_2OH), 7.37 (m, 1H, $C_{5'}$-H), 7.64 (m, 1H, C_5-H), 7.91 (d, $J_{4,5}$ = 7.5 Hz, 1H, C_4-H), 8.39 (m, 1H, $C_{4'}$-H), 8.56 (d, $J_{6',5'}$ = 6 Hz, 1H, $C_{6'}$-H), 8.66 (dd, $J_{6,5}$ = 5 Hz, $J_{6,4}$ = 1.5 Hz, 1H, C_6-H),

8.72 (s, 1H, C_2-H), 9.30 (s, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.75; H, 4.76; N, 18.37.

N-(2'-Pyridylcarbonylimino)-3-hydroxymethylpyridinium Ylide (**6k**).

A suspension of *N*-(2,4-dinitrophenyl)-3-hydroxymethylpyridinium chloride **3k** (20.66 g, 66.29 mmoles), picolinic acid hydrazide (10.00 g, 72.92 mmoles) and 9.20 ml of triethylamine in 500 ml of anhydrous methanol were stirred at 0° for 5 hours and the reaction was completed as described in the general procedure A. The resulting product was treated with activated carbon, filtered, evaporated *in vacuo* and crystallized from methylene chloride:methanol:ethyl acetate (9:1:1, v/v) as pale yellow shinning plates of **6k** (7.90 g). The mother liquor was chromatographed on a column of neutral alumina (2.5 x 20 cm) using methylene chloride:methanol (9:1 v/v, 600 ml, 4:1 v/v, 400 ml) as eluents giving additional **6k** for a total of (9.50 g, 61%), mp 160-162°; ^{1}H-nmr: δ 4.76 (s, 2H, -C*H*$_2$OH), 6.60 (s, deuterium oxide exchangeable, 1H, -CH$_2$O*H*), 7.30-7.41 (m, 1H, $C_{5'}$-H), 7.56 (m, 1H, C_5-H), 7.78 (dt, $J_{3',4'} = J_{4',5'} = 7.5$ Hz $J_{4',6'} = 1.5$ Hz, 1H, $C_{4'}$-H), 7.89 (d, $J_{3',4'} = 7.5$ Hz, 1H, $C_{3'}$-H), 8.14 (m, 1H, C_4-H), 8.51 (d, $J_{5,6} = 6.5$ Hz, 1H, C_6-H), 8.66 (m, 2H, C_2-H, $C_{6'}$-H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.88; H, 4.82; N, 18.33.

N-(Benzoylimino)-3-hydroxymethylpyridinium Ylide (**6l**).

A suspension of benzoic hydrazide (8.17 g, 60 mmoles), *N*-(2,4-dinitrophenyl)-3-hydroxymethylpyridinium chloride **3l** (17.00 g, 54.54 mmoles) and 7.60 ml of triethylamine in 250 ml of anhydrous methanol were stirred at 0-10° for 4 hours and the reaction was completed as described in the general procedure A. The resulting product was treated with activated carbon, filtered, evaporated *in vacuo* and crystallized from methylene chloride:ethyl acetate (4:1, v/v) at -10° as brownish yellow leaflets of **6l** (6.80 g). The mother liquor was chromatographed on a neutral alumina column (2.5 x 20 cm) using methylene chloride:methanol (9:1 v/v, 750 ml; 4:1 v/v, 500 ml) as an eluent that yielded additional **6l** for a total of (7.80 g, 62%), mp 123-125°; ^{1}H-nmr: δ 4.67 (m, 3H, -C*H*$_2$OH and O*H* deuterium oxide exchangeable), 7.37-7.47 (complex m, 3H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H, phenyl), 7.53 (m, 1H, C_5-H), 7.80 (d, $J_{4,5} = 8$ Hz, 1H, C_4-H), 8.05-8.17 (m, 2H, $C_{2'}$-H, $C_{6'}$-H, phenyl), 8.45 (d, $J_{6,5} = 6$ Hz, 1H, C_6-H), 8.60 (s, 1H, C_2-H).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.13; H, 5.26; N, 12.25.

N-(4'-Pyridylcarbonylimino)-3-benzylpyridinium Ylide (**6m**).

N-(2,4-Dinitrophenyl)-3-benzylpyridinium chloride **3m** (10.45 g, 28.10 mmoles) was reacted with isonicotinic acid hydrazide (3.85 g, 28.10 mmoles) in 150 ml of methanol in the presence of 1 ml of triethylamine for 12 hours at 25°. The black precipitate formed was filtered, washed successively with 80 ml each of hexane and water and refluxed in water:*p*-dioxane (125 ml, 1:4 v/v) for 12 hours. The solution was evaporated *in vacuo* and the dark brown product chromatographed on a column of neutral alumina (2.5 x 22 cm) using ether:methanol (30:1 v/v, 800 ml, 20:1 v/v, 1000 ml) as an eluent and gave **6m** as an oil that solidified under vacuum (4.00 g, 44%); ^{1}H-nmr: δ 4.10 (s, 2H, C*H*$_2$-phenyl), 7.19-7.40 (m, 5H, phenyl), 7.60 (m, 1H, C_5-H), 7.74 (m, 1H, C_4-H), 7.94 (d, $J_{3',2'} = J_{5',6'} = 4.5$ Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 8.60-8.72 (complex m, 4H, C_2-H, C_6-H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.56; H, 5.26; N, 14.19.

N-(3'-Pyridylcarbonylimino)-3-benzylpyridinium Ylide (**6n**).

Nicotinic acid hydrazide (3.95 g, 28.88 mmoles) and *N*-(2,4-dinitrophenyl)-3-benzylpyridinium chloride **3n** (10.74 g, 28.88 mmoles) were reacted in 125 ml of anhydrous methanol containing 2 ml of triethylamine at 25° for 12 hours and completed as described in the procedure for the synthesis of **6m**. The alumina (2.5 x 22 cm) using ether:methanol (10:1 v/v, 1800 ml) as an eluent and gave **6n** as a yellowish brown semi-solid (2.79 g, 50%); ^{1}H-nmr: δ 4.12 (s, 2H, CH$_2$-phenyl), 7.14-7.47 (complex m, 5H, phenyl), 7.55-7.67 (m, 1H, $C_{5'}$-H), 7.75 (d, $J_{4,5} = J_{5,6} = 7.0$ Hz, 1H, C_5-H), 8.42 (dt, $J_{4,5} = 7.0$ Hz, $J_{2,4} = 1.5$ Hz, 1H, C_4-H), 8.60-8.76 (m, 4H, C_2-H, C_6-H, $C_{4'}$-H, $C_{6'}$-H), 9.35 (s, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.45; H, 5.19; N, 14.57.

N-(2'-Pyridylcarbonylimino)-3-benzylpyridinium Ylide (**6o**).

N-(2,4-Dinitrophenyl)-3-benzylpyridinium chloride **3o** (2.48 g, 6.70 mmoles) was reacted with picolinic acid hydrazide (0.91 g, 6.70 mmoles) in 100 ml of methanol containing 2 ml of triethylamine and completed as described in the procedure for the synthesis of **6m**. The product was chromatographed on a column of neutral alumina (2.5 x 20 cm) using ether:methanol (30:1 v/v, 800 ml) as an eluent and furnished **6o** as a brown semi-solid (1.64 g, 76%); ^{1}H-nmr: δ 4.10 (s, 2H, C*H*$_2$-phenyl), 7.14-7.40 (m, 6H, $C_{5'}$-H, phenyl), 7.60 (dd, $J_{4',5'} = J_{3',4'} = 6.0$ Hz, 1H, $C_{4'}$-H), 7.68-7.85 (m, 2H, C_4-H, C_5-H), 8.10-8.25 (m, 1H, $C_{3'}$-H), 8.60-8.77 (m, 3H, C_2-H, C_6-H, $C_{6'}$-H).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.68; H, 5.24; N, 14.49.

N-(Benzoylimino)-3-benzylpyridinium Ylide (**6p**).

N-(2,4-Dinitrophenyl)-3-benzoylpyridinium chloride **3p** (10.95 g, 29.50 mmoles) was reacted with benzoylhydrazide (3.96 g, 29.50 mmoles) in 200 ml of methanol containing 2 ml of triethylamine as described in the procedure for the synthesis of **6m**. The resulting product was chromatographed on a neutral alumina column (2.5 x 20 cm) using ether:methanol (10:1 v/v, 800 ml) as the eluent to furnish **6p** as a shining solid (6.19 g, 68%), mp 96-98°; ^{1}H-nmr: δ 4.10 (s, 2H, C*H*$_2$-phenyl), 7.17-7.48 (m, 8H, phenyl, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H, benzoyl), 7.58 (dd, $J_{5,6} = J_{4,5} = 7$ Hz, 1H, C_5-H), 7.70 (d, $J_{4,5} = 7$ Hz, 1H, C_4-H), 8.15 (m, 2H, $C_{2'}$-H, $C_{6'}$-H), 8.68 (distorted d, $J_{5,6} = J_{2,4} = 7$ Hz, 2H, C_2-H, C_6-H).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 79.14; H, 5.59; N, 9.72. Found: C, 78.93; H, 5.70; N, 9.68.

N-(4'-Pyridylcarbonylamino)-5-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine (**7a**).

General Procedure B.

N-(4'-Pyridylcarbonylimino)-3-(3-hydroxypropyl)pyridinium ylide **6a** (3.00 g, 11.6 mmoles) was stirred in 150 ml of absolute ethanol at 0° for 30 minutes. Sodium borohydride (3.52 g, 93.05 mmoles) was added and the reduction carried at 0-10° for 5 hours. The reaction mixture was treated with 40 g ice and allowed to warm up to 25°. The product was extracted with methylene chloride (3 x 150 ml) and was washed with 150 ml of brine, filtered through a bed of sodium sulfate and the filtrate

was evaporated *in vacuo*. The solid was chromatographed on a column of neutral alumina (2.5 x 20 cm) using ether:methanol (10:1 v/v, 300 ml, 5:1 v/v, 500 ml) as an eluent and the resulting product was crystallized from ethyl acetate as an off white crystalline solid of **7a** (1.47 g, 48%), mp 142-144°; ir: ν 3220 (NH), 1650 (C=O) cm^{-1}; ^{1}H-nmr: δ 1.69 (m, 2H, -$CH_2CH_2CH_2OH$), 2.07 (t, J = 7.5 Hz, 2H, -$CH_2CH_2CH_2OH$), 2.35 (m, 2H, C_3-H), 3.02 (t, $J_{2,3}$ = 6 Hz, 2H, C_2-H), 3.39 (m, 2H, C_6-H), 4.43 (s, 2H, deuterium oxide exchangeable, -$CH_2CH_2CH_2OH$ and N*H*), 3.60 (J = 6 Hz, 2H, -$CH_2CH_2CH_2OH$), 5.42-5.73 (m, 1H, C_4-H, olefinic), 7.75 (overlapping ds, $J_{2',3'}$ = $J_{5',6'}$ = 4.5 Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 8.67 (d, $J_{2',3'}$ = $J_{6',5'}$ = 4.5 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.25; H, 7.24; N, 16.08.

N-(3'-Pyridylcarbonylamino)-5-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine (**7b**).

A stirred solution of *N*-(3'-pyridylcarbonylimino)-3-(3-hydroxypropyl)pyridinium ylide **6b** (2.00 g, 7.77 mmoles) in 100 ml of absolute ethanol was reduced with sodium borohydride (2.37 g, 62.64 mmoles) at 0° for 5 hours. The reaction was completed as described in the general procedure B. The product was isolated on a column of neutral alumina (2.5 x 25 cm) using ether:methanol (10:1 5:1 v/v 400 ml) as an eluent. Further crystallization from ethyl acetate afforded **7b** as brownish white granules (0.92 g, 45%), mp 109-111°; ir: ν 1645 (C=O), 3215 (NH) cm^{-1}; ^{1}H-nmr: δ 1.70 (m, 2H, -$CH_2CH_2CH_2OH$), 1.81 (s, deuterium oxide exchangeable, 1H, -$CH_2CH_2CH_2OH$), 2.05 (t, J = 7.5 Hz, 2H, -$CH_2CH_2CH_2OH$), 2.32 (s, 2H, C_3-H), 3.10 (t, $J_{2,3}$ = 5.5 Hz, 2H, C_2-H), 3.46 (m, 2H, C_6-H), 3.66 (t, J = 6 Hz, 2H, -$CH_2CH_2CH_2OH$), 5.56 (m, 1H, C_4-H, olefinic), 7.37 (m, 1H, $C_{5'}$-H), 7.46 (s, deuterium oxide exchangeable, 1H, N*H*), 8.11 (dt, $J_{4',5'}$ = 7.5 Hz, $J_{4',6'}$ = $J_{4',2'}$ = 1.5 Hz, 1H, $C_{4'}$-H), 8.70 (d, J = 4.5 Hz, 1H, $C_{6'}$-H), 8.92 (s, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.50; H, 7.12; N, 15.99.

N-(2'-Pyridylcarbonylamino)-5-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine (**7c**).

Sodium borohydride (4.70 g, 124.24 mmoles) was slowly added to an ice cold solution of *N*-(2'-pyridylcarbonylimino)-3-(3-hydroxy-propyl)pyridinium ylide **6c** (4.00 g, 15.54 mmoles) in 200 ml of absolute ethanol. The reaction was completed as described in the general procedure B. The product was chromatographed on a column of neutral alumina (2.5 x 25 cm) using ether:methanol (10:1 v/v, 600 ml) as an eluent and afforded **7c** as a semi-solid (1.64 g, 40%); ir: ν 1675, (C=O), 3240 (NH) cm^{-1}; ^{1}H-nmr: δ 1.68 (m, 2H, -$CH_2CH_2CH_2OH$), 1.96 (s, deuterium oxide exchangeable, 1H, -$CH_2CH_2CH_2OH$), 2.05 (t, J = 7.5 Hz, 2H, -$CH_2CH_2CH_2OH$), 2.32 (m, 2H, C_3-H), 3.05 (t, $J_{2,3}$ = 7.5 Hz, 2H, C_2-H), 3.41 (m, 2H, C_6-H), 3.65 (t, J = 6 Hz, 2H, -$CH_2CH_2CH_2OH$), 5.53 (m, C_4-H, 1H, olefinic), 7.42 (m, 1H, $C_{5'}$-H), 7.83 (td, $J_{3',4'}$ = $J_{4',5'}$ = 7.5 Hz, $J_{4',6'}$ = 1.5 Hz, 1H, $C_{4'}$-H), 8.2 (dd, $J_{3',4'}$ = 7.5 Hz, $J_{3',5'}$ = 1.5 Hz, 1H, $C_{3'}$-H), 8.51 (m, 1H, $C_{6'}$-H), 8.92 (s, deuterium oxide exchangeable, 1H, N*H*).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.25; H, 7.42; N, 16.01.

N-(Benzoylamino)-5-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine (**7d**).

N-(Benzoylimino)-5-(3-hydroxypropyl)pyridinium ylide **6d** (2.50 g, 9.75 mmoles) was reduced with sodium borohydride (2.95 g, 77.98 mmoles) in 100 ml of absolute ethanol as described under the general procedure B. The product was chromatographed on a column of neutral alumina (2.5 x 20 cm) using ether:methanol (10:1 v/v, 500 ml) as an eluent and furnished a semi-solid which was crystallized from methylene chloride:ethyl acetate:hexane (1:3:1 v/v, 400 ml) as cream colored needles of **7d** (1.50 g, 59%), mp 159-161°; ir: ν 1645, (C=O), 3200 (NH) cm^{-1}; ^{1}H-nmr: δ 1.67 (m, 2H, -$CH_2CH_2CH_2OH$), 2.06 (t, J = 7.5 Hz, 2H, -$CH_2CH_2CH_2OH$), 2.32 (m, 2H, C_3-H), 2.97 (t, $J_{2,3}$ = 6 Hz, 2H, -C_2-H), 3.36 (m, 2H, C_6-H), 3.56 (t, J = 6.5 Hz, 2H, -$CH_2CH_2CH_2OH$), 4.69 (s, deuterium oxide exchangeable, 2H, $CH_2CH_2CH_2OH$ and N*H*), 5.51 (m, 1H, C_4-H, olefinic), 7.37-7.57 (complex m, 3H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H, phenyl), 7.77 (m, 2H, $C_{2'}$-H, $C_{6'}$-H, phenyl).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 69.02; H, 7.90; N, 10.61.

N-(4'-Pyridylcarbonylamino)-4-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine (**7e**).

General Procedure C.

A solution of *N*-(4'-pyridylcarbonylimino)-4-(3-hydroxypropyl)pyridinium ylide **6e** (6.65 g, 25.85 mmoles) in methylene chloride:ethanol (1:1 v/v, 100 ml) was added dropwise to a stirred suspension of sodium borohydride (8.05 g, 207.31 mmoles) in 50 ml of absolute ethanol over a period of 2.5 hours at 25° under argon atmosphere and the reaction allowed to proceed for 4 more hours. The reaction mixture was diluted with 500 ml of methylene chloride and 50 ml of water over a period of 35 minutes while stirring. The organic phase was separated, washed with brine, treated with charcoal and filtered through a bed of sodium sulfate. The filtrate was evaporated *in vacuo* and the product chromatographed on a column of neutral alumina (4.5 x 27 cm) using ethyl acetate:methanol (95:5 v/v, 1 litre, 9:1 v/v, 1.5 l) as an eluent. The solid obtained was further crystallized from methylene chloride:ethyl acetate:ethanol (2:1:1, v/v/v) and furnished **7e** as white needles (2.37 g, 35%), mp 165-167°; ir: ν 1650 (C=O), 3245 (NH) cm^{-1}; ^{1}H-nmr: δ 1.44-1.55 (m, 2H, -$CH_2CH_2CH_2OH$), 1.90 (t, J = 7.5 Hz, 2H, -$CH_2CH_2CH_2OH$), 2.11 (s, 2H, C_3-H), 2.87 (t, J = 5.5 Hz, 2H, C_2-H), 3.26 (s, 2H, C_6-H), 3.40 (t, J = 6.5 Hz, -$CH_2CH_2CH_2OH$), 4.03 (s, deuterium oxide exchangeable, 2H, N*H*, -$CH_2CH_2CH_2OH$), 5.20 (m, 1H, C_5-H, olefinic), 7.52 (d, $J_{2',3'}$ = $J_{5',6'}$ = 4.5 Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 8.48 (d, $J_{2',3'}$ = $J_{6',5'}$ = 4.5 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.22; H, 7.40; N, 15.95.

N-(3'-Pyridylcarbonylamino)-4-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine (**7f**).

A solution of *N*-(3'-pyridylcarbonylimino)-4-(3-hydroxypropyl)pyridinium ylide **6f** (6.00 g, 23.32 mmoles) in methylene chloride:ethanol (2:1 v/v, 150 ml) was reduced with a suspension of sodium borohydride (7.26 g, 187.11 mmoles) in 100 ml of absolute ethanol and the reaction completed as described under the general procedure C. The resulting product was chromatographed on a column of neutral alumina (2.5 x 25 cm) using ether:methanol (10:1 v/v, 350 ml, 5:1 v/v, 500 ml, 4:1 v/v, 250 ml) as an eluent. Further crystallization from ethyl acetate:hexane (2:1, v/v) furnished **7f** as white needles (3.90 g, 64%) mp 108-110°; ir: ν 1660 (C=O), 3260 (NH) cm^{-1}; ^{1}H-nmr: δ 1.70 (m, 2H, -$CH_2CH_2CH_2OH$), 1.81 (s, 1H, -$CH_2CH_2CH_2OH$),

2.09 (t, J = 6 Hz, 2H, -CH_2CH$_2$CH$_2$OH), 2.27 (s, 2H, C_3-H) 3.14 (t, J = 5.5 Hz, 2H, C_2-H), 3.50 (s, 2H, C_6-H), 3.66 (t, J = 6 Hz, 2H, -CH$_2$CH$_2$CH_2OH), 5.40 (m, 1H, C_5-H, olefinic), 6.92 (s, deuterium oxide exchangeable, 1H, N*H*), 7.34-7.43 (m, 1H, $C_{5'}$-H), 8.11 (dt, $J_{4',5'}$ = 7.5 Hz, $J_{2',4'}$ = $J_{4',6'}$ = 2 Hz, 1H, $C_{4'}$-H), 8.69 (d, $J_{5',6'}$ = 4.5 Hz, 1H, $C_{6'}$-H), 9.09 (m, 1H, $C_{2'}$H).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.25; H, 7.42; N, 15.93.

N-(2'-Pyridylcarbonylamino)-4-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine (**7g**).

To an ice cold suspension of the *N*-(2'-pyridylcarbonylimino)-4-(3-hydroxypropyl)pyridinium ylide **6g** (1.00 g, 3.89 mmoles) in 50 ml of ethanol sodium borohydride (1.22 g, 31.42 mmoles) was added and stirred at 0-10° for 5 hours and warmed up to room temperature and stirred for 3 more hours. The reaction was completed up as described under the general procedure C. The product was chromatographed on a column of neutral alumina (2.5 x 25 cm) using ethyl ether:methanol (30:1 v/v, 200 ml, 20:1 v/v, 300 ml, 10:1 v/v, 300 ml) and was crystallized from ethyl acetate:hexane (2:1, v/v) to produce **7g** as white rosettes (0.70 g, 69%), mp 91-93°; ir: ν 1675 (C=O), 3300-3500 (NH and OH) cm^{-1}; ^{1}H-nmr: δ 1.64-1.74 (2H, m, -CH$_2$CH_2CH$_2$OH), 2.08 (t, J = 7.5 Hz, 2H, -CH_2CH$_2$CH$_2$OH), 2.26 (s, 2H, C_3-H), 3.08 (t, J = 6 Hz, 2H, C_2-H), 3.45 (s, 2H, C_6-H), 3.65 (t, J = 6.5 Hz, 2H, -CH$_2$CH$_2$CH_2OH), 5.38 (m, 1H, C_5-H, olefinic), 7.31-7.41 (m, 1H, $C_{5'}$-H), 7.81 (td, $J_{3',4'}$ = $J_{4',5'}$ = 7.5 Hz, $J_{4',6'}$ = 1.5 Hz, 1H, $C_{4'}$-H), 8.18 (m, 1H, $C_{3'}$-H), 8.49 (m, 1H, $C_{6'}$-H), 8.86 (s, deuterium exchangeable, 1H, N*H*), O*H* not detected at the concentration used.

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.28; H, 7.38; N, 16.01.

N-(Benzoylcarbonylamino)-4-(3-hydroxypropyl)-1,2,3,6-tetrahydropyridine (**7h**).

To a suspension of the *N*-(benzoylcarbonylimino)-4-(3-hydroxypropyl)pyridinium ylide **6h** (2.50 g, 9.75 mmoles) in 60 ml of absolute ethanol at 0°, sodium borohydride (3.72 g, 9.83 mmoles) was added and the contents stirred at 0-10° for 3 hours and then stirred at room temperature for 3 more hours. The reaction was completed as described under the general procedure C. The product was chromatographed on a column of neutral alumina (2.5 x 26.5 cm) using ethyl acetate:methanol (97:3 v/v, 300 ml, 95:5 v/v, 500 ml, 9:1 v/v, 300 ml) as an eluent and further crystallized from methylene chloride:ethyl acetate:ethanol (1.5:1:0.1, v/v/v) to furnish **7h** as white rosettes (1.40 g, 55%), mp 150-152°; ir: ν 1650 (C=O), 3320 (NH) cm^{-1}; ^{1}H-nmr: δ 1.44-1.54 (m, 2H, -CH$_2$CH_2CH$_2$OH), 1.89 (t, J = 7.5 Hz, 2H, -CH_2CH$_2$CH$_2$OH), 2.10 (s, 2H, C_3-H) 2.86 (t, J = 5.5 Hz, 2H, C_2-H), 3.24 (s, 2H, C_6-H), 3.39 (t, J = 6.5 Hz, 2H, -CH$_2$CH$_2$CH_2OH), 4.05 (s, deuterium oxide exchangeable, 2H, N*H* and -CH$_2$CH$_2$CH$_2$O*H*), 5.20 (m, 1H, C_5-H, olefinic), 7.35-7.20 (3H, complex m, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H, phenyl), 7.55-7.59 (m, 2H, $C_{2'}$-H, $C_{6'}$-H, phenyl).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 69.18; H, 7.78; N, 10.70.

N-(4'-Pyridylcarbonylamino)-5-hydroxymethyl-1,2,3,6-tetrahydropyridine (**7i**).

N-(4'-Pyridylcarbonylimino)-3-hydroxymethylpyridinium ylide **6i** (1.00 g, 4.36 mmoles) was dissolved in methylene chloride:absolute ethanol (1:1 v/v, 50 ml) and added dropwise to a stirred suspension of sodium borohydride (1.33 g, 35 mmoles) in 50 ml of absolute ethanol in an argon atmosphere at 25° for 4.5 hours. The reaction mixture was diluted with 100 ml of methylene chloride and 25 ml of water over a period of 15 minutes while stirring. The organic phase was separated, washed with brine, treated with activated carbon and filtered through a bed of sodium sulfate. The filtrate was evaporated *in vacuo* and chromatographed on preparative tlc on 9 alumina plates (Analtech, alumina GF, 20 x 20 cm, 1000 microns) using ethyl acetate:methanol (96:4, v/v) as the developing solvent. The product with R_f value of 0.23 was scrapped off and extracted with methylene chloride:methanol [9:1 v/v, (3 x 150 ml)] and furnished **7i** as a semi-solid (0.50 g, 49%). It was further crystallized from ethyl acetate to give cream colored rosettes, mp 124-126°; ir: ν 1670 (C=O), 3350 (OH) cm^{-1}; ^{1}H-nmr: δ 2.27 (m, 2H, C_3-H), 3.02 (t, J = 5.5 Hz, 2H, C_2-H), 3.22 (s, deuterium oxide exchangeable, 1H, -CH$_2$O*H*), 3.50 (s, 2H, C_6-H), 4.0 (s, 2H, -CH_2OH), 5.70 (m, 1H, C_4-H, olefinic), 7.60 (d, $J_{2',3'}$ = $J_{5',6'}$ = 5.5 Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 8.09 (s, deuterium oxide exchangeable, 1H, N*H*), 8.65 (d, $J_{2',3'}$ = $J_{5',6'}$ = 5.5 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.25; H, 7.24; N, 16.08.

N-(3'-Pyridylcarbonylamino)-5-hydroxymethyl-1,2,3,6-tetrahydropyridine (**7j**).

A solution of the *N*-(3'-pyridylcarbonylimino)-3-hydroxymethylpyridinium ylide **6j** (5.00 g, 21.81 mmoles) in methylene chloride:absolute ethanol (1:1 v/v, 120 ml) was added dropwise to a stirred suspension of sodium borohydride (6.62 g, 175 mmoles) in 50 ml of absolute ethanol and the reaction was completed as described in the general procedure C. The product was chromatographed on a column of neutral alumina (2.5 x 26 cm) using ethyl acetate:methanol (9:1 v/v, 600 ml, 4:1 v/v, 300 ml, 3:1 v/v, 250 ml) as an eluent and the resulting product was crystallized from methylene chloride to yield **7j** as a crystalline white solid (1.12 g, 22%), mp 153-155°; ir: ν 1650 (C=O), 3400 (OH) cm^{-1}; ^{1}H-nmr (perdeuteriomethanol): δ 2.36 (m, 2H, C_3-H), 3.00 (t, $J_{2,3}$ = 6 Hz, 2H, C_2-H), 3.45 (m, 2H, C_6-H), 3.97 (s, 2H, -CH_2OH), 4.80 (s, deuterium oxide exchangeable, 2H, -CH$_2$O*H* and N*H*), 5.72 (m, 1H, C_4-H, olefinic), 7.52 (m, 1H, $C_{5'}$-H), 8.20 (dt, $J_{4',5'}$ = 8 Hz, $J_{4',6'}$ = $J_{2',4'}$ = 2 Hz, 1H, $C_{4'}$-H), 8.67 (dd, $J_{5',6'}$ = 5 Hz, $J_{4',6'}$ = 2 Hz, 1H, $C_{6'}$-H), 8.93 (m, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.70; H, 7.59; N, 16.08.

N-(2'-Pyridylcarbonylamino)-5-hydroxymethyl-1,2,3,6-tetrahydropyridine (**7k**).

A solution of the *N*-(2'-pyridylcarbonylimino)-3-hydroxymethylpyridinium ylide **6k** (4.00 g, 17.45 mmoles) in methylene chloride:absolute ethanol (1:1 v/v, 140 ml) was added dropwise to a stirred suspension of sodium borohydride (7.00 g, 185 mmoles) in 50 ml of absolute ethanol for 3 hours at 21°. The reaction was completed as described in the general procedure C. The product was first crystallized from ethyl acetate and then from ethyl acetate:methylene chloride (9:1, v/v) and furnished **7k** (2.15 g 52%), mp 105-107°; ir: ν 1670 (C=O), 3250 (NH) cm^{-1}; ^{1}H-nmr: δ 0.91-1.15 (s, deuterium oxide exchangeable, 1H, -CH$_2$O*H*), 1.37 (m, 2H, C_3-H), 3.00 (t, $J_{2,3}$ = 6 Hz, 2H, C_2H), 3.45 (m, 2H, C_6H), 4.06 (s, 2H, -CH_2OH), 5.79 (m, 1H, C_4-H, olefinic), 7.37-7.48 (m, 1H, $C_{5'}$-H), 7.83 (dt, $J_{3',4'}$ = $J_{4',5'}$ = 7.5 Hz, $J_{4',6'}$ = 1.5 Hz, $C_{4'}$-H), 8.21 (m, 1H, $C_{3'}$-H), 8.52 (m, 1H,

$C_{6'}$-H), 8.93 (s, deuterium oxide exchangeable, 1H, N*H*).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.25; H, 7.42; N, 16.01.

N-(Benzoylamino)-5-hydroxymethyl-1,2,3,6-tetrahydropyridine (**7l**).

N-(Benzoylimino)-3-hydroxymethylpyridinium ylide **6l** (4.11 g, 18.00 mmoles) was dissolved in absolute ethanol:methylene chloride (1:1 v/v, 100 ml) and added dropwise to a stirred suspension of sodium borohydride (5.50 g, 145.38 mmoles) in 50 ml of absolute ethanol for 2.5 hours under argon atmosphere at 23° and the reaction was completed as described in the general procedure C. The product was treated with activated carbon and crystallized from methylene chloride:ethyl acetate (3:2, v/v) and gave **7l** as white flakes (1.00 g). The mother liquors were combined and chromatographed on a column of neutral alumina (2.5 x 25 cm) using ethyl acetate:methanol (9:1 v/v, 600 ml, 4:1 v/v, 300 ml, 3:1 v/v, 200 ml) as an eluent and gave additional **7l** for a total weight of (2.50 g, 60%), mp 133-135°; ir: ν 1665 (C=O), 3250 (NH) cm^{-1}; ^{1}H-nmr (perdeuteriomethanol): δ 2.36 (m, 2H, C_3-H), 3.0 (t, $J_{2,3}$ = 6 Hz, 2H, C_2-H), 3.45 (m, 2H, C_6-H), 3.97 (s, 2H, -CH_2OH), 4.80 (s, deuterium oxide exchangeable, 2H, -CH_2OH, NH), 5.72 (m, 1H, C_4-H, olefinic), 7.40-7.60 (complex m, 3H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H, phenyl), 7.73-7.85 (m, 2H, $C_{2'}$-H, $C_{6'}$-H, phenyl).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.88; H, 7.11; N, 12.12.

N-(4'-Pyridylcarbonylamino)-5-benzyl-1,2,3,6-tetrahydropyridine (**7m**).

Sodium borohydride (2.15 g, 56.8 mmoles) was added to a stirred solution of *N*-(4'-pyridylcarbonylimino)-3-benzylpyridinium ylide **6m** (1.85 g, 6.40 mmoles) in 100 ml of absolute ethanol precooled to 0°. The reaction was completed as described in the general procedure C. The product obtained was chromatographed on a column of neutral alumina (2.5 x 20 cm) using ether:methanol (25:1 v/v, 1250 ml) as an eluent and the resulting solid was recrystallized with ethyl acetate to furnish **7m** as a white solid (1.03 g, 56%); ir: ν 1645 (C=O), 3200 (NH) cm^{-1}; ^{1}H-nmr: δ 2.75 (m, 2H, C_3-H), 3.08 (t, $J_{2,3}$ = 6.0 Hz, 2H, C_2-H), 3.28 (m, 2H, CH_2-phenyl), 3.36 (m, 2H, C_6-H), 5.58 (m, 1H, C_4-H), 7.08-7.38 (complex m, 6H, phenyl, NH), 7.45-7.60 (m, 2H, $C_{3'}$-H, $C_{5'}$-H), 8.69 (d, $J_{2',3'}$ = $J_{5',6'}$ = 6.0 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53; N, 14.32. Found: C, 73.60; H, 6.57; N, 14.28.

N-(3'-Pyridylcarbonylamino)-5-benzyl-1,2,3,6-tetrahydropyridine (**7n**).

An ice cold solution of *N*-(3'-pyridylcarbonylimino)-3-benzylpyridinium ylide **6n** (2.00 g, 6.91 mmoles) in 100 ml of absolute ethanol was reduced with sodium borohydride (2.10 g, 55.51 mmoles) for 4 hours. The reaction was completed as described in the general procedure C. The product was chromatographed on a column of neutral alumina (2.5 x 22 cm) using ether:methanol (25:1 v/v, 1500 ml) as an eluent and the resulting solid was recrystallized from ethyl acetate and gave **7n** as a beige colored solid (1.3 g, 65%), mp 138-140°; ir: ν 1640 (C=O), 3218 (NH) cm^{-1}; ^{1}H-nmr: δ 2.38 (m, 2H, C_3-H), 3.12 (t, $J_{2,3}$ = 6.0 Hz, 2H, C_2-H), 3.28 (s, 2H, CH_2-phenyl), 3.40 (m, 2H, C_6-H), 5.60 (d, $J_{3,4}$ = 6.0 Hz, 1H, C_4-H), 7.08-7.30 (m, 5H, phenyl), 7.32-7.59 (m, deuterium oxide exchangeable, 1H, NH), 8.08-8.32 (m, 1H, $C_{5'}$-H), 8.72 (m, 2H, $C_{4'}$-H, $C_{6'}$-H), 9.00 (m, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53; N, 14.32. Found: C, 73.65; H, 6.57; N, 14.20.

N-(2'-Pyridylcarbonylamino)-5-benzyl-1,2,3,6-tetrahydropyridine (**7o**).

An ice cold solution of *N*-(2'-pyridylcarbonylimino)-3-benzylpyridinium ylide **6o** (1.64 g, 5.67 mmoles) in 200 ml of absolute ethanol was reduced with sodium borohydride (2.16 g, 57.10 mmoles) as described under the general procedure C. The product was chromatographed on a neutral alumina column (2.5 x 20 cm) using methylene chloride:methanol (40:1 v/v, 800 ml) as an eluent and furnished **7o** as an oily semi-solid (0.92 g, 57%); ir: ν 1660 (C=O), 3190 (NH) cm^{-1}; ^{1}H-nmr: δ 2.38 (m, 2H, C_3-H), 3.05 (t, $J_{2,3}$ = 6.0 Hz, 2H, C_2-H), 3.28 (s, 2H, CH_2-phenyl), 3.35 (m, 2H, C_6-H), 5.57 (m, 1H, C_4-H), 7.16-7.33 (m, 5H, phenyl), 7.39-7.49 (m, 1H, $C_{5'}$-H), 7.86 (td, $J_{4',5'}$ = $J_{3',4'}$ = 7.5 Hz, $J_{4',6'}$ = 1.5 Hz, 1H, $C_{4'}$-H), 8.19 (m, 1H, $C_{3'}$-H), 8.50 (m, 1H, $C_{6'}$-H), 8.85 (s, deuterium oxide exchangeable, 1H, NH).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53; N, 14.32. Found: C, 73.50; H, 6.38; N, 14.15.

N-(Benzoylamino)-5-benzyl-1,2,3,6-tetrahydropyridine (**7p**).

An ice cold solution of *N*-(benzoylimino)-3-benzylpyridinium ylide **6p** (3.86 g, 13.40 mmoles) in 200 ml of absolute ethanol was reduced with sodium borohydride (3.24 g, 85.65 mmoles) and the reaction completed as described in the general procedure C. The product was recrystallized from methlene chloride:hexane:ethyl-acetate (2:1:1, v/v) and afforded **7p** as a brown solid (1.80 g, 46%); ir: ν 1640 (C=O), 3216 (NH) cm^{-1}; ^{1}H-nmr: δ 2.50 (m, 2H, C_3-H), 3.20 (t, $J_{2,3}$ = 6 Hz, 2H, C_2-H), 3.30 (s, 2H, CH_2Ph), 3.40 (m, 2H, C_6-H), 5.60 (m, 1H, C_4-H), 7.00-7.40 (m, 10H, phenyl), 8.67 (s, deuterium oxide exhangeable, 1H, NH).

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.45; H, 7.18; N, 9.47.

Acknowledgements.

We are grateful to the National Institute of Health, Division of Research Resources, MBRS research funding program, NIH No. GM 08111 and the Research Center at Minority Institutions Grant (RCMI) RR 03020. We are also grateful to the Chemistry Department, NMR Unit, Florida State University, Tallahassee, Florida, for determining all nmr spectra of our compounds.

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