Synthesis of Some *N*-[Pyridyl(phenyl)carbonylamino]-alkyl-1,2,3,6-tetrahydropyridines

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Alkyl substituted 2,4-dinitrophenylpyridinium chlorides **3** are formed by the nucleophilic substitution of 1-chloro-2,4-dinitrobenzene with alkyl pyridines. Reaction of pyridyl acid hydrazides or benzoyl hydrazides **4** with the pyridinium chlorides **3** furnish the isolable 2,4-dinitroanilino derivatives **5** which undergo hydrolysis when refluxed in water:*p*-dioxane mixture (1:4 v/v) to yield the pyridinium ylides **6**. Sodium borohydride reduction of **6** in absolute ethanol at 0° for 4 hours result the formation of the title compounds **7** in moderate to excellent yields.

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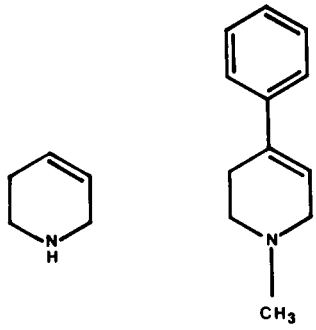
It is well documented in the literature that the structural derivatives of the 1,2,3,6-tetrahydropyridine (THP) ring system **1** are known to exhibit a wide variety of pharmacological activities [1-5]. Their hypotensive, analgesic, anti-inflammatory and antipyretic effects are most prominent. Recently, the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) **2** has attracted a great deal of attention because it was reported to cause parkinsonian-like syndrome through the destruction of the dopaminergic nigrostriatal neurons in primates, including man and several animal species [1,6-10].



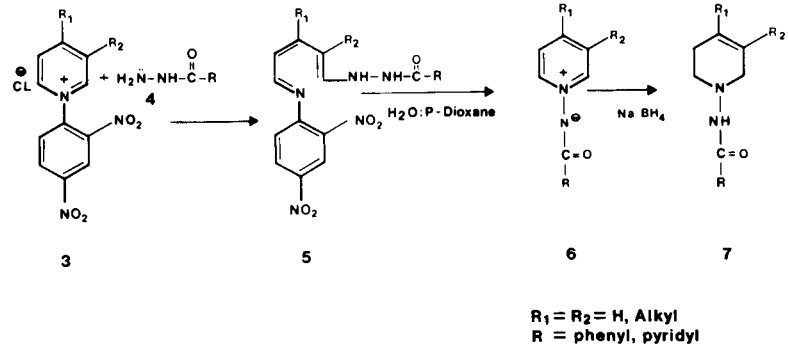
1 **2**

The discovery of the neurotoxic properties of MPTP has lead to the development of a drug inducible model for parkinsonism in monkeys [11-20]. A few years earlier, we have reported [21,22] the synthesis of novel *N*-iminopyridinium ylides employing the method described by Tamura *et. al.*, [23]. Sodium borohydride reduction of the pyridinium ylides in ethanol medium at 0° for 4 hours afforded the *N*-amino-1,2,3,6-tetrahydropyridine derivatives [22,24,25] in good yields. It is interesting to note that the preliminary pharmacological test results of a few of these *N*-amino-1,2,3,6-tetrahydropyridines [26,27] were found to exhibit analgesic, anti-inflammatory and hyperglycemic activities with no observed toxicity even at very high dose levels.

It is of interest now to incorporate alkyl substituents of varying chain lengths on the tetrahydropyridine ring system so as to alter the electronic distribution, steric configuration and lipophilic character of these molecules. These changes in turn are expected to influence the biological activities of the tetrahydropyridine derivatives. In the present study, we describe the synthesis of substituted 1,2,3,6-tetrahydropyridyl derivatives having alkyl groups of 2-4 carbon chain lengths.

Method.

SCHEME 1



The synthetic pathway is outlined in Scheme 1. Appropriate molar amounts of 1-chloro-2,4-dinitrobenzene and alkyl substituted pyridines were refluxed for 12 hours in dry acetone. The resulting *N*-(2,4-dinitrophenyl)pyridinium chlorides **3** were reacted with several pyridyl acid hydrazides or benzoyl hydrazide **4** in methanol containing triethylamine at room temperature for 12 hours to furnish the 2,4-dinitroanilino derivatives **5**. Hydrolysis of **5** with water:*p*-dioxane (1:4 v/v) mixture under reflux for 12 hours furnished the pyridyl(phenyl)carbonyliminopyridinium ylides **6**. Sodium borohydride reduction of **6** in absolute ethanol at 0° for 4 hours afforded the alkyl substituted pyridyl(phenyl)carbonylamino-1,2,3,6-tetrahydropyridines **7**.

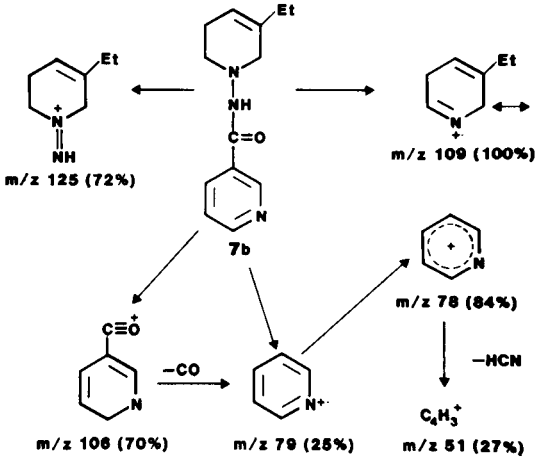
Results and Discussion.

The infra red spectra of the tetrahydropyridines **7** show characteristic amide carbonyl absorptions ranging from 1645 and 1660 cm^{-1} and NH stretching vibrations ranging from 3195 and 3225 cm^{-1}. The ^1H nmr spectra of these tetrahydropyridines display diagnostic patterns. For example, the ^1H nmr spectrum of *N*-(3′-pyridylcarbonylamino)-5-ethyl-1,2,3,6-tetrahydropyridine **7b** recorded in deuteriochloroform shows absorptions at δ of 1.00 (t, J = 7.0 Hz, CH_2CH_3), 1.98 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.30 (m, 2H, C_3-H), 3.15 (t, $J_{2,3}$ = 5.0 Hz, 2H, C_2-H), 3.52 (m, 2H, C_6-H), 5.50 (m, 1H, C_4-H, olefinic), 7.52 (t, $J_{5',4'} = J_{5',6'}$ = 6.0 Hz, 1H, C_5-H), 7.70-8.10 (s, 1H, NH, deuterium oxide exchangeable), 8.40 (d, $J_{4',5'}$ = 6.0 Hz, 1H, C_4-H), 8.72 (d, $J_{6',5'}$ = 6.0 Hz, 1H, C_6-H), 9.22 (s, 1H, C_2-H) consistent with the structure.

The low resolution mass spectrum of **7b** showed the fragment ion m/z 109 as the base peak which could be assigned to the resonance stabilized 5-ethyldihydropyridinium species as shown in Scheme 2. Cleavage of the aminocarbonyl bond results in the fragment ions m/z 125 (72%) and m/z 106 (70%). Carbon monoxide is lost from m/z 106 resulting in the formation of pyridinium ion m/z 79 (25%) which could lead to another fragment ion m/z 78 (84%). Further loss of HCN from m/z 78 produces the widely observed isobutane radical m/z 51 (27%) supporting the structure.

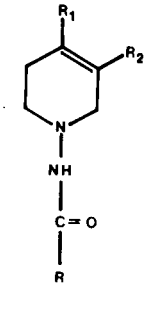
Scheme 2

Mass Spectral fragmentation pattern of 7b

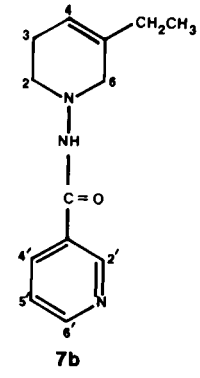


It was observed that the yields of the 3-alkyl substituted pyridinium ylides **6** were consistently higher than the corresponding 4-alkyl substituted analogs. However, yields of the 3 and 4-alkyl-substituted derivatives compared to the non-substituted tetrahydropyridines were found to be lower. This was in agreement with the literature review reported by Sagitullin *et. al* [28].

The Pharmacological evaluation of the tetrahydropyridine derivatives is in progress.



7a – k



7b

EXPERIMENTAL

Infrared spectra were measured on Perkin Elmer 1430 instrument on potassium bromide pellets unless otherwise stated. The ^1H nmr spectra were recorded in deuteriochloroform on a Bruker Hx-270 MHz instrument using chloroform as internal standard unless otherwise stated. Elemental analysis of the compounds were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. The mass spectrum of **7b** was recorded at Florida State University using probe (70-240/40) ms (EI 70 EV 1200V). No residue remained after combustion of the products. 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 Company Inc., Milwaukee, Wisconsin and Fisher Scientific Company, Orlando, Florida.

N-(4′-Pyridylcarbonylimino)-3-ethylpyridinium Ylide (**6a**). General Procedure A.

3-Ethylpyridine (17.46 g, 163 mmoles) was added dropwise to a stirred solution of 1-chloro-2,4-dinitrobenzene (30.00 g, 148 mmoles) in 400 ml of anhydrous acetone. The reaction mixture was refluxed for 12 hours, cooled to 0° for 1 hour and filtered. The residue was washed thoroughly with hexane (2 × 150 ml) and dried *in vacuo* at room temperature to provide a buff colored

solid which was crystallized from absolute ethanol (33.10 g, 66%), mp 191-193°. The obtained *N*-(2',4'-dinitrophenyl)-3-ethylpyridinium chloride (4.00 g, 12.93 mmoles) was reacted with isonicotinic acid hydrazide (1.78 g, 12.93 mmoles) in 125 ml of methanol containing 1.5 ml of triethylamine for 12 hours at room temperature. The brown precipitate was filtered, washed successively with 60 ml each of methanol, water and ether and immediately refluxed in water:*p*-dioxane (1:4 v/v) for 12 hours. The solvent was evaporated *in vacuo* and the residue chromatographed on neutral alumina (Brockmann I, 150 mesh, 58A, Aldrich) (2.5 × 30 cm). The ether:methanol eluent (15:1 v/v, 600 ml) on evaporation furnished **6a** as a brown solid (1.70 g, 58%), mp 154-156°; ^{1}H nmr: δ 1.35 (t, J = 7.5 Hz, 3H, CH_2-C*H*$_3$), 2.82 (q, J = 7.5 H z, 2H, C*H*$_2$CH$_3$), 7.62 (t, $J_{5,4} = J_{5,6}$ = 7.0 Hz, 1H, C_5-H), 7.80 (d, $J_{4,5}$ = 7.5 Hz, 1H, C_4-H), 7.97 (d, $J_{3',2'} = J_{5',6'}$ = 5.0 Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 8.60-8.70 (m, 4H, C_2-H, C_6-H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.48. Found: C, 68.52; H, 5.49; N, 18.26.

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

N-(2',4'-Dinitrophenyl)-3-ethylpyridinium chloride (4.00 g, 12.91 mmoles) was reacted with nicotinic acid hydrazide (1.77 g, 12.90 mmoles) in 125 ml of methanol containing 1.5 ml triethylamine as described under general procedure A. The product **6b** was isolated on a column of neutral alumina (2.5 × 30 cm) using ether:methanol (8:1 v/v, 600 ml) as the eluent and recrystallization from ethyl acetate furnished **6b** as a light yellow solid (2.24 g, 76%), mp 96-98°; ^{1}H nmr: δ 1.32 (t, J = 7.0 Hz, 3H, CH_2C*H*$_3$), 2.80 (q, J = 7.0 Hz, 2H, C*H*$_2$CH$_3$), 7.27-7.35 (m, 1H, $C_{5'}$-H), 7.57 (t, $J_{5,4} = J_{5,6}$ = 6.0 Hz, 1H, C_5-H), 7.70 (d, $J_{4',5'}$ = 6.0 Hz, 1H, $C_{4'}$-H), 8.35-8.42 (m, 1H, C_4-H), 8.58-8.70 (m, 3H, C_2-H, C_6-H, $C_{6'}$-H), 9.32 (s, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.48. Found: C, 68.50; H, 5.57; N, 18.63.

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

N-(2,4-Dinitrophenyl)-3-ethylpyridinium chloride (4.00 g, 12.92 mmoles) was reacted with picolinic acid hydrazide (1.78 g, 12.92 mmoles) in 125 ml of methanol containing 1.5 ml of triethylamine as described under general procedure A. The product **6c** was purified by column chromatography on neutral alumina (2.5 × 30 cm) using ether:methanol (8:1 v/v, 700 ml) as the eluant to give a yellow semi-solid (1.06 g, 36%); ^{1}H nmr: δ 1.23 (t, J = 7.0 Hz, 3H, CH_2C*H*$_3$), 2.71 (q, J = 7.0 Hz, 2H, C*H*$_2$ CH$_3$), 7.26 (m, 1H, $C_{5'}$-H), 7.52 (t, $J_{5,4} = J_{5,6}$ = 7.0 Hz, 1H, C_5-H), 7.66-7.80 (m, 2H, $C_{4'}$-H, C_4-H), 8.13 (d, $J_{3',4'}$ = 8.0 Hz, 1H, $C_{3'}$-H), 8.55-8.72 (m, 3H, C_2-H, C_6-H, $C_{6'}$-H).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.48. Found: C, 68.50; H, 5.41; N, 18.32.

N-(Benzoylimino)-3-ethylpyridinium Ylide (**6d**).

N-(2',4'-Dinitrophenyl)-3-ethylpyridinium chloride (4.00 g, 12.92 mmoles) was reacted with benzoic hydrazide (1.76 g, 12.92 mmoles) in 125 ml of methanol containing 1.5 ml of triethylamine as described under general procedure A. The resulting product which was purified on a column of neutral alumina (2.5 × 30 cm) using the eluent ether:methanol (15:1 v/v, 800 ml) gave **6d** (1.70 g, 58%) as a light yellow solid mp 109-111°; ^{1}H nmr: δ 1.30 (t, J = 7.0 Hz, 3H, CH_2 C*H*$_3$), 2.78 (q, J = 7.0 Hz, 2H, C*H*$_2$ CH$_3$), 7.32-7.42 (m, 3H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H of phenyl), 7.58 (t, $J_{5,4} = J_{5,6}$ = 7.0 Hz, 1H, C_5-H), 7.78 (d, $J_{4,5}$ = 7.5 Hz, 1H, C_4-H), 8.12 (d, $J_{2',6'}$ = 7.0 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H of phenyl), 8.59 (d, 2H, C_2-H, C_6H).

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.23; N, 12.38. Found: C, 74.24; H, 6.10; N, 12.39.

N-(Benzoylimino)-4-ethylpyridinium Ylide (**6e**).

To a stirring solution of 1-chloro-2,4-dinitrobenzene (15.00 g, 70.06 mmoles) in 400 ml of anhydrous acetone, 4-ethylpyridine (8.26 g, 77.08 mmoles) was added dropwise and the reaction mixture was refluxed for 12 hours. The contents were cooled to 0° for 1 hour, filtered and thoroughly washed with hexane (3 × 100 ml) and dried *in vacuo* at room temperature when a black solid was obtained (17.24 g, 72%), mp 133-135°. The *N*-(2',4'-dinitrophenyl)-4-ethylpyridinium chloride (11.50 g, 37.13 mmoles) obtained above was reacted with benzoic hydrazide (6.86 g, 50.38 mmoles) in 80 ml of methanol containing 6.4 ml of triethylamine at room temperature for 8-10 hours. The reaction mixture was cooled to 0-10° for 1 hour and filtered. The residue was washed successively with 100 ml each of ethyl acetate and water and immediately refluxed in water:*p*-dioxane (1:4 v/v, 400 ml) for 12 hours. The reaction medium was evaporated and the residue purified on a column of neutral alumina (5 × 30 cm). The ether-methanol (30:1 v/v, 1 litre) eluent on evaporation gave a solid which was crystallized from benzene:hexane (2:1 v/v) as brown needles of **6e** (0.70 g, 8.3%), mp 124-126°; ^{1}H nmr: δ 1.35 (t, J = 7.0 Hz, 3H, CH_2 C*H*$_3$), 2.89 (q, J = 7.0 Hz, 2H, C*H*$_2$ CH$_3$), 7.37-7.50 (m, 3H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H of phenyl), 7.56 (d, $J_{2',3'}$ = $J_{5',6'}$ = 7.0 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H of phenyl), 8.20 (d, $J_{3,2} = J_{5,6}$ = 7.0 Hz, 2H, C_3-H, C_5-H), 8.70 (d, $J_{2,3} = J_{5,6}$ = 7.0 Hz, 2H, C_2-H, C_6-H).

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.23; N, 12.38. Found: C, 74.54; H, 6.23; N, 12.52.

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

N-(2',4'-Dinitrophenyl)-4-ethylpyridinium chloride (8.00 g, 25.82 mmoles) was reacted with nicotinic acid hydrazide (3.54 g, 25.82 mmoles) in 125 ml of methanol containing 1.5 ml of triethylamine and the reaction mixture worked up as described under the general procedure A. The resulting crude product was purified on neutral alumina column (2.5 × 30 cm) and the ether:methanol (8:1 v/v, 600 ml) eluent gave **6f** as a semi-solid (0.86 g, 15%); ^{1}H nmr: δ 1.35 (t, J = 7.0 Hz, 3H, CH_2 C*H*$_3$), 2.86 (q, J = 7.0 Hz, 2H, C*H*$_2$ CH$_3$), 7.35 (m, 1H, $C_{5'}$-H), 7.51 (d, $J_{3,2}$ = $J_{5,6}$ = 5.0 Hz, 2H, C_3-H, C_5-H), 8.42 (m, 2H, $C_{4'}$-H, $C_{6'}$-H), 8.65 (d, $J_{2,3} = J_{5,6}$ = 7.0 Hz, 2H, C_2-H, C_6-H), 9.35 (s, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.48. Found: C, 68.63; H, 5.79; N, 18.44.

N-(4'-Pyridylcarbonylimino)-4-ethylpyridinium Ylide (**6g**).

N-(2',4'-Dinitrophenyl)-4-ethylpyridinium chloride (4.64 g, 14.97 mmoles) was reacted with isonicotinic acid hydrazide (2.10 g, 14.97 mmoles) in 125 ml of methanol containing 1.5 ml of triethylamine and the reaction mixture was worked up as described under the general procedure A. The resulting product was purified on a column of neutral alumina (2.5 × 25 cm) and the eluent ether:methanol (15:1 v/v, 800 ml) furnished **6g** as brown solid (0.41 g, 12%), mp 154-156°; ^{1}H nmr: δ 1.35 (t, J = 7.0 Hz, 3H, CH_2 C*H*$_3$), 2.85 (q, J = 7.0 Hz, 2H, C*H*$_2$ CH$_3$), 7.50 (d, $J_{3',2'}$ = $J_{5',6'}$ = 6.0 Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 7.95 (d, $J_{3,2} = J_{5,6}$ = 7.0 Hz, 2H, C_3-H, C_5-H), 8.55-8.70 (m, 4H, C_2-H, C_6-H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.48. Found: C, 68.75; H, 5.70; N, 18.45.

N-(4'-Pyridylcarbonylimino)-3-*n*-butylpyridinium Ylide (**6h**).

3-*n*-Butylpyridine was added dropwise to a stirring solution of 1-chloro-2,4-dinitrobenzene (14.98 g, 73.96 mmoles) in anhydrous acetone (250 ml) and refluxed for 12 hours. The solvent was evaporated and the residue azeotroped with methanol (2 × 100 ml) and then dried *in vacuo* at room temperature when *N*-(2',4'-dinitrophenyl)-3-*n*-butylpyridinium chloride was obtained as a dark brown semi-solid (24.00 g, 96%). *N*-(2',4'-Dinitrophenyl)-3-*n*-butylpyridinium chloride (7.90 g, 23.39 mmoles) was reacted with isonicotinic acid hydrazide (3.21 g, 23.39 mmoles) in 125 ml of methanol containing 1.5 ml of triethylamine and the reaction was completed as described under the general procedure A. The resulting product was purified on a column of neutral alumina (2.5 × 30 cm) using ether:methanol (30:1 v/v, 600 ml) as the eluent and **6h** was obtained as a brown semi-solid (2.46 g, 26%); ^{1}H nmr: δ 0.90 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.27-1.42 (sextet, J = 7.5 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.57-1.70 (pentet, J = 7.5 Hz, 2H, $CH_2CH_2CH_2CH_3$), 2.71 (t, J = 7.5 Hz, 2H, $CH_2CH_2CH_2CH_3$), 7.55 (t, $J_{5,4} = J_{5,6}$ = 7.0 Hz, 1H, C_5-H), 7.73 (d, $J_{4,5}$ = 7.5 Hz, 1H, C_4-H), 7.92 (d, $J_{3',2'} = J_{5',6'}$ = 6.0 Hz, 2H, $C_{3'}$-H, $C_{5'}$-H), 8.50-8.70 (m, 4H, C_2-H, C_6-H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.45. Found: C, 70.38; H, 6.50; N, 16.05.

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

N-(2',4'-Dinitrophenyl)-3-*n*-butylpyridinium chloride (6.33 g, 18.75 mmoles) was reacted with nicotinic acid hydrazide (2.57 g, 18.75 mmoles) in 125 ml of methanol containing 1.5 ml of triethylamine and the reaction was completed as described under the general procedure A. The resulting product was purified on a column of neutral alumina (2.5 × 25 cm) using ether:methanol (20:1 v/v, 500 ml) as the eluent and the product **6i** was obtained as a brown semi-solid (2.55 g, 53%); ^{1}H nmr: δ 0.82 (t, J = 7.0 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.20-1.37 (sextet, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.50-1.63 (pentet, J = 7.0 Hz, 2H, CH_2 CH_2 CH_3), 2.63 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CH_3$), 7.22 (m, 1H, C_5-H), 7.50 (t, $J_{5,4} = J_{5,6}$ = 7.0 Hz, 1H, C_5-H), 7.65 (d, $J_{4,5}$ = 8.0 Hz, 1H, C_4-H), 8.30 (dt, $J_{4',5'}$ = 8.0 Hz, $J_{4',6'} = J_{4',2'}$ = 2.0 Hz, 1H, $C_{4'}$-H), 8.52 (m, 3H, C_2-H, C_6-H, $C_{6'}$-H), 9.25 (s, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.45. Found: C, 70.18; H, 6.88; N, 16.51.

N-(2'-Pyridylcarbonylimino)-3-*n*-butylpyridinium Ylide (**6j**).

N-(2',4'-Dinitrophenyl)-3-*n*-butylpyridinium chloride (7.58 g, 22.45 mmoles) was reacted with picolinic acid hydrazide (3.08 g, 22.45 mmoles) in 125 ml of methanol containing 1.5 ml of triethylamine and the reaction was worked up as described under the general procedure A. The resulting product was purified on a neutral alumina column (2.5 × 35 cm) and eluted with ether:methanol (20:1 v/v, 250 ml, 10:1 v/v, 200 ml, 5:1 v/v, 150 ml) when a dark brown semi-solid **6j** (1.04 g, 18%) resulted; ^{1}H nmr: δ 0.91 (t, J = 7.0 Hz, $CH_2CH_2CH_2CH_3$), 1.26-1.45 (sextet, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.55-1.72 (pentet, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CH_3$), 2.72 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CH_3$), 7.32 (m, 1H, C_5-H), 7.56 (t, $J_{5,4} = J_{5,6}$ = 7.5 Hz, 1H, C_5-H), 7.65-7.85 (m, 2H, C_4-H, $C_{4'}$-H), 8.20 (d, $J_{3',4'}$ = 8.0 Hz, 1H, $C_{3'}$-H), 8.55-8.75 (m, 3H, C_2-H, C_6-H, $C_{6'}$-H).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.45. Found: C, 70.40; H, 6.83; N, 16.20.

N-(Benzoylimino)-3-*n*-butylpyridinium Ylide (**6k**).

N-(2',4'-Dinitrophenyl)-3-*n*-butylpyridinium chloride (7.11 g, 27.90 mmoles) was reacted with benzoic hydrazide (3.82 g, 28 mmoles) in 125 ml of methanol containing 1.5 ml triethylamine at room temperature for 12 hours and the reaction was worked up as described under the general procedure A. The resulting brown semi-solid was further purified on a neutral alumina column (2.5 × 35 cm) using ether:methanol (40:1 v/v, 500 ml) as eluent when **6k** was obtained as a yellow semi-solid (2.60 g, 49%); ^{1}H nmr: δ 0.92 (t, J = 7.0 Hz, $CH_2CH_2CH_2CH_3$), 1.30-1.45 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.57-1.70 (m, 2H, CH_2CH_2 CH_2 CH_3), 2.71 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CH_3$), 7.41 (m, 3H, C_3-H, C_4-H, C_5-H of phenyl), 7.52 (t, $J_{5,4} = J_{5,6}$ = 7.0 Hz, 1H, C_5-H), 7.70 (d, $J_{4,5}$ = 8.0 Hz, 1H, C_4-H), 8.14-8.25 (m, 2H, C_2-H, C_6-H of phenyl), 8.57-8.67 (m, 2H, C_2-H, C_6-H).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.69; H, 7.04; N, 11.09.

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

General Procedure B.

N-(4'-Pyridylcarbonylimino)-3-ethylpyridinium ylide **6a** (1.43 g, 6.28 mmoles) was dissolved in 100 ml of absolute alcohol and cooled to 0° under stirring. Sodium borohydride (0.95 g, 25.12 mmoles) was added and stirring continued at 0° for 4 hours when the reduction was completed as monitored by tlc. Excess sodium borohydride was treated with crushed ice (20-25 g) and the reaction mixture allowed to warm up to room temperature. It was then extracted with chloroform (4 × 75 ml) and dried over anhydrous sodium sulfate. Evaporation of the filtered chloroform solution *in vacuo* resulted in a brownish yellow product. Chromatography on neutral alumina column (2.5 × 25 cm) using ether:methanol (20:1 v/v, 600 ml) furnished **7a** as a light yellow solid (1.04 g, 71%), mp 125-127°; ir: ν 3200 (NH), 1648 (C=O) cm^{-1}; ^{1}H nmr: δ 1.00 (t, J = 7.0 Hz, 3H, CH_2 CH_3), 1.95 (q, J = 7.0 Hz, 2H, CH_2 CH_3), 2.25 (m, 2H, C_3-H), 3.05 (t, $J_{2,3}$ = 6.0 Hz, 2H, C_2-H), 3.40 (s, 2H, C_6-H), 5.50 (m, 1H, C_4-H, olefinic), 7.50-7.80 (d, $J_{3',2'} = J_{5',6'}$ = 5.0 Hz, 3H, $C_{3'}$-H, $C_{5'}$-H and NH), 8.70 (d, $J_{2',3'} = J_{6',5'}$ = 5.0 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H).

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.40; N, 18.16. Found: C, 67.62; H, 7.20; N, 18.26.

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

To an ice cold stirring solution of *N*-(3'-pyridylcarbonylimino)-3-ethylpyridinium ylide **6b** (2.24 g, 9.86 mmoles) in 100 ml of ethanol, sodium borohydride (1.50 g, 39.60 mmoles) was added and the reaction was worked up as described under general procedure B. The resulting product was chromatographed on a column of neutral alumina (2.5 × 35 cm) using ether:methanol (20:1 v/v, 400 ml) as eluant and subsequent crystallization in ethyl acetate furnished **7b** as a white solid (0.71 g, 31%), mp 126-128°; ir: ν 3195 (NH), 1660 (C=O) cm^{-1}; ^{1}H nmr: described under results and discussion.

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.40; N, 18.16. Found: C, 67.49; H, 7.43; N, 18.15.

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

To an ice cold stirring solution of *N*-(2'-pyridylcarbonylimino)-3-ethylpyridinium ylide **6c** (1.06 g, 4.67 mmoles) in 100 ml of ab-

solute ethanol, sodium borohydride (0.71 g, 18.66 mmoles) was added and the reaction was worked up as described under the general procedure B. The resulting product was purified on a column of neutral alumina (2.5 × 25 cm) using ether:methanol (20:1 v/v, 500 ml) as eluant and subsequent crystallization in ethyl acetate furnished **7c** as a low melting solid (0.40 g, 36%), mp 88-90°; ir: ν 3210 (NH), 1665 (C=O) cm^{-1}; ^1H nmr: δ 1.00 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.96 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.32 (m, 2H, C_3-H), 3.05 (t, $J_{2,3}$ = 6.0 Hz, 2H, C_2-H), 3.40 (s, 2H, C_6-H), 5.50 (m, 1H, C_4-H, olefinic), 7.42 (m, 1H, C_5-H), 7.82 (td, $J_{4',3'} = J_{4',5'}$ = 8.0 Hz, $J_{4',6'}$ = 1.5 Hz, 1H, C_4-H), 8.20 (dt, $J_{3',4'}$ = 8.0 Hz, $J_{3',5'}$ = 2.0 Hz, $J_{3',6'}$ = 0.5 Hz, 1H, C_3-H), 8.51 (dt, $J_{6',5'}$ = 5.0 Hz, $J_{6',4'}$ = 2.0 Hz, $J_{6',3'}$ = 0.5 Hz, 1H, C_6-H), 8.90 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.40; N, 18.16. Found: C, 67.45; H, 7.44; N, 18.14.

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

Sodium borohydride (1.10 g, 29.00 mmoles) was added to an ice cold stirring solution of *N*-(benzoylimino)-3-ethylpyridinium ylide **6d** (1.55 g, 6.86 mmoles) in 100 ml of absolute ethanol and the reaction mixture was worked up as described under the general procedure B. The resulting product was purified on a neutral alumina column (2.5 × 30 cm) using ether-methanol (20:1 v/v, 400 ml) as the eluant and the product **7d** was obtained as a yellowish white solid on evaporation (0.76 g, 48%), mp 156-159°; ir: ν 3200 (NH), 1650 (C=O) cm^{-1}; ^1H nmr: δ 1.00 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.95 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.70 (s, 2H, C_3-H), 2.95 (t, $J_{2,3}$ = 5.0 Hz, 2H, C_2-H), 3.30 (s, 2H, C_6-H), 5.40 (m, 1H, C_4-H, olefinic), 7.39-7.55 (m, 3H, C_3-H, C_4-H, C_5-H of phenyl), 7.79 (d, $J_{2',6'}$ = 7.0 Hz, 2H, C_2-H, C_6-H of phenyl), 9.47 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.87; N, 12.16. Found: C, 73.17; H, 7.84; N, 12.10.

N-(Benzoylamino)-4-ethyl-1,2,3,6-tetrahydropyridine (**7e**).

Sodium borohydride (0.84 g, 22.20 mmoles) was added to a stirring solution of *N*-(benzoylimino)-4-ethylpyridinium ylide **6e** (0.50 g, 2.21 mmoles) in 80 ml of absolute ethanol at 0°. The reaction was worked up as described under general procedure B. The resulting product was purified on a column of neutral alumina (2.5 × 30 cm) using ether:methanol (40:1 v/v, 800 ml) as eluant. Evaporation and recrystallization of the resulting product from ethyl acetate:hexane (9:1 v/v) furnished **7e** as pale yellow flakes (0.18 g, 35%), mp 182-184°; ir: ν 3200 (NH), 1645 (C=O) cm^{-1}; ^1H nmr: δ 1.02 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.02 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.42 (s, 2H, C_3-H), 3.62 (distorted t, 2H, C_2-H), 4.00 (s, 2H, C_6-H), 5.32 (m, 1H, C_4-H, olefinic), 7.35-7.53 (m, 3H, C_3-H, C_4-H, C_5-H of phenyl), 7.90 (m, 3H, C_2-H, C_6-H of phenyl and NH).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.87; N, 12.16. Found: C, 72.89; H, 7.88; N, 12.14.

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

An ice cold stirring solution of *N*-(3'-pyridylcarbonylimino)-4-ethylpyridinium ylide **6f** (0.86 g, 3.77 mmoles) in 80 ml of absolute ethanol was reduced with sodium borohydride (0.57 g, 15.05 mmoles) as described under the general procedure B. The resulting product was purified on a neutral alumina column (2.5 × 25 cm) while eluting with ether:methanol (20:1 v/v, 600 ml). On evaporation the product **7f** was obtained as a light yellow solid (0.09 g, 10%), mp 145-147°; ir: ν 3220 (NH), 1645 (C=O) cm^{-1}; ^1H nmr: δ 1.02 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.02 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.27 (m, 2H, C_3-H), 3.15 (distorted t, C_2-H), 3.52 (m, 1H, C_6-H), 5.35 (m, 1H, C_5-H, olefinic), 6.70-6.85 (s, 1H, NH, deuterium oxide exchangeable), 7.40 (m, 1H, C_5'-H), 8.20 (d, $J_{5',6'}$ = 5.0 Hz, 1H, C_4'-H), 8.70 (s, 1H, C_6'-H), 9.05 (s, 1H, C_2'-H).

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.40; N, 18.16. Found: C, 67.52; H, 7.43; N, 18.13.

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

An ice cold stirring solution of *N*-(4'-pyridylcarbonylimino)-4-ethylpyridinium ylide **6g** (0.41 g, 1.79 mmoles) in 75 ml of absolute ethanol was reduced with sodium borohydride (0.27 g, 7.15 mmoles) as described under the general procedure B. The resulting product was purified on a column of neutral alumina (2.5 × 25 cm), using ether:methanol (10:1 v/v, 600 ml) as eluent. On evaporation **7g** was obtained as a light brown solid (0.13 g, 29%), mp 150-152°; ir: ν 3200 (NH), 1655 (C=O) cm^{-1}; ^1H nmr: δ 0.98 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.02 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.30 (s, 2H, C_3-H), 3.22 (t, $J_{2,3}$ = 6.0 Hz, 2H, C_2-H), 3.62 (s, 2H, C_6-H), 5.32 (m, 1H, C_5-H, olefinic), 7.92 (d, $J_{3',2'} = J_{5',6'}$ = 6.0 Hz, 2H, C_3'-H, C_5'-H), 8.10-8.40 (s, 1H, NH, deuterium oxide exchangeable), 8.75 (d, $J_{2',3'} = J_{6',5'}$ = 6.0 Hz, 2H, C_2'-H, C_6'-H).

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.40; N, 18.16. Found: C, 67.49; H, 7.43; N, 18.17.

N-(4'-Pyridylcarbonylamino)-5-*n*-butyl-1,2,3,6-tetrahydropyridine (**7h**).

To an ice cold solution of *N*-(4'-pyridylcarbonylimino)-4-*n*-butylpyridinium ylide **6h** (2.46 g, 9.64 mmoles) in 100 ml of absolute ethanol, sodium borohydride (1.46 g, 38.54 mmoles) was added and the reduction was completed as described under the general procedure B. The resulting product was purified on a column of neutral alumina (2.5 × 35 cm) using ether:methanol (40:1 v/v, 600 ml), as eluant. It was then evaporated and crystallized from ethyl acetate when **7h** was obtained as a white solid (0.76 g, 38%), mp 109-112°; ir: ν 3200 (NH), 1655 (C=O) cm^{-1}; ^1H nmr: δ 0.86 (t, J = 7.0 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.15-1.50 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.93 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CH_3$), 2.27 (m, 2H, C_3-H), 3.05 (t, $J_{2,3}$ = 5.5 Hz, 2H, C_2-H), 3.40 (s, 2H, C_6-H), 5.47 (m, 1H, C_4-H, olefinic), 7.52 (s, 1H, NH, deuterium oxide exchangeable), 7.58 (d, $J_{3',2'} = J_{5',6'}$ = 5.0 Hz, 2H, C_3'-H, C_5'-H), 8.70 (d, $J_{2',3'} = J_{5',6'}$ = 5.0 Hz, 2H, C_2'-H, C_6'-H).

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.46; H, 8.16; N, 16.20. Found: C, 69.20; H, 8.20; N, 16.11.

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

To an ice cold stirring solution of *N*-(3'-pyridylcarbonylimino)-3-*n*-butylpyridinium ylide **6i** (2.55 g, 9.97 mmoles) in 100 ml of absolute ethanol, sodium borohydride (1.51 g, 39.87 mmoles) was added and the reduction was completed as described under the general procedure B. The product obtained was purified on a column of neutral alumina (2.5 × 30 cm) using ether:methanol (40:1 v/v, 650 ml) as eluant. Crystallization of the resulting solid from ethyl acetate furnished **7i** as a white solid (1.20 g, 46%), mp 106-108°; ir: ν 3225 (NH), 1645 (C=O) cm^{-1}; ^1H nmr: δ 0.90 (t, 3H, $CH_2CH_2CH_2CH_3$), 1.18-1.45 (m, 4H, $CH_2CH_2CH_2CH_3$),

1.72-2.00 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.30 (m, 2H, C_3-H), 3.08 (t, $J_{2,3}$ = 5.0 Hz, 2H, C_2-H), 3.42 (s, 2H, C_6-H), 5.50 (m, 1H, C_4-H, olefinic), 7.37 (t, 2H, $C_{5'}$-H, and NH), 8.10 (d, $J_{4',5'}$ = 7.0 Hz, 1H, $C_{4'}$-H), 8.71 (distorted d, 1H, $C_{6'}$-H), 8.92 (s, 1H, $C_{2'}$-H).

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.46; H, 8.16; N, 16.20. Found: C, 69.25; H, 8.10; N, 16.51.

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

An ice cold stirring solution of *N*-(2'-pyridylcarbonylimino)-3-*n*-butylpyridinium ylide **6j** (1.04 g, 4.05 mmoles) in 90 ml of absolute ethanol was reduced with sodium borohydride (0.62 g, 16.30 mmoles) as described under the general procedure B. The product obtained was purified on a column of neutral alumina (2.5 × 25 cm) using ether:methanol (40:1 v/v, 350 ml, 20:1 v/v, 200 ml) as the eluant. The product, **7j** was obtained as a brownish yellow semi-solid on evaporation (0.60 g, 57%); ir: ν 3200 (NH), 1650 (C=O) cm^{-1}; ^1H nmr: δ 0.90 (t, J = 7.0 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.23-1.56 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.95 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2CH_3$), 2.31 (m, 2H, C_3-H), 3.05 (t, $J_{2,3}$ = 6.0 Hz, 2H, C_2-H), 3.40 (s, 2H, C_6-CH_2), 5.49 (m, 1H, C_4-CH, olefinic), 7.37-7.50 (m, 1H, $C_{5'}$-H), 7.82 (td, $J_{4',3'}$ = $J_{4',5'}$ = 8.0 Hz, $J_{4',6'}$ = 2.0 Hz, 1H, $C_{4'}$-H), 8.21 (dd, $J_{3',4'}$ = 8.0 Hz, $J_{3',5'}$ = 1.5 Hz, 1H, $C_{3'}$-H), 8.50 (dt, $J_{6',5'}$ = 5.0 Hz, $J_{6',4'}$ = 1.5 Hz, $J_{6',3'}$ = 0.5, 1H, $C_{6'}$-H), 8.90 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.46; H, 8.16; N, 16.20. Found: C, 69.30; H, 8.39; N, 16.15.

N-(Benzoylamino)-5-*n*-butyl-1,2,3,6-tetrahydropyridine (**7k**).

Sodium borohydride (1.54 g, 40.58 mmoles) was added to a stirring ice cold solution of *N*-(benzoylimino)-3-*n*-butylpyridinium ylide **6k** (2.60 g, 10.15 mmoles) in 100 ml of absolute ethanol and the reduction was completed as described under the general procedure B. The resulting product was further chromatographed on a column of neutral alumina (2.5 × 30 cm) using ether (800 ml) as eluant. On evaporation **7k** was obtained as a white solid (0.51 g, 19%), mp 127-129°; ir: ν 3200 (NH), 1645 (C=O) cm^{-1}; ^1H nmr: δ 0.90 (t, J = 7.0 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.22-1.47 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.95 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_2$ CH_3), 2.31 (m, 2H, C_3-H), 3.12 (t, $J_{2,3}$ = 5.0 Hz, 2H, C_2-H), 3.47 (s, 2H, C_6-H), 5.50 (m, 1H, C_4-H, olefinic), 7.40-7.56 (m, 4H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H of phenyl and NH), 7.75 (d, $J_{2',6'}$ = 7.0 Hz, 2H, $C_{2'}$-H, $C_{6'}$-H of phenyl).

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.47; H, 8.68; N, 10.65.

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