Synthesis and Pharmacological Evaluation of Some *N*-[Pyridyl(phenyl)carbonylamino]methyl-1,2,3,6-tetrahydropyridines

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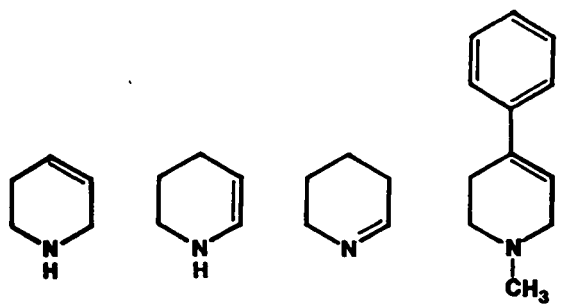
Abstract □ Reaction of some picolines **5** with 1-chloro-2,4-dinitrobenzene (**6**) in acetone furnished methyl-substituted 2,4-dinitrophenylpyridinium chlorides **7**. Further reaction with phenyl(pyridyl)carbonyl hydrazides **8** at room temperature furnished isolable 2,4-dinitroanilino derivatives **9**, which were then refluxed in a water:dioxane mixture (1:4, v/v) to furnish the methyl-substituted phenyl(pyridyl)carbonyl iminopyridinium ylides **10**. Reduction of the ylides with $NaBH_4$ finally gave rise to the desired methyl-substituted phenyl(pyridyl)carbonylamino-1,2,3,6-tetrahydropyridines **11**. The anti-inflammatory activities of **11a–11l** were determined with the carrageenan-soaked sponge model of inflammation in Sprague-Dawley rats, and the analgesic effects of these derivatives were assessed by suppression of acetic acid-induced writhing in male Swiss albino mice. All compounds tested showed moderate to good anti-inflammatory and analgesic effects compared with indomethacin. Compound **11k** was the most active analgesic, and **11h** was the most effective anti-inflammatory agent among the methyl-substituted tetrahydropyridines.

Compounds bearing the pyridine or the piperidine nucleus have been well studied and are known to be biologically active.[1] However, the chemistry and pharmacological activities of tetrahydropyridine derivatives are not well studied.[2–11] There are three possible isomeric tetrahydropyridines: 1,2,3,6-tetrahydropyridines, **1**; 1,2,3,4,-tetrahydropyridines, **2**; and 2,3,4,5,-tetrahydropyridines, **3** (see structures). It was of interest to study the chemistry and biological activities of the 1,2,3,6-tetrahydropyridines[2–16] primarily because of their relatively more stable nature.

The biological activities of some tetrahydropyridines depend greatly on the position and nature of the alkyl and/or aryl groups on the tetrahydropyridine ring. For example, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; **4**) has selective nigrostriatal neurotoxicity and causes persistent parkinsonism in humans,[3,4] monkeys,[5,6] and other animal species.[7–10] Toxicological evaluation of **4** and its analogues by Fries et al.[11] indicated that less or no toxicity was observed when alkyl groups are introduced on the tetrahydropyridine ring. However, studies by Gessner et al.[12] indicated that an increased hydroxylation pattern on the 4-phenyl ring and/or aromatization of the tetrahydropyridine ring could enhance the metabolism of **4**. Further, dihydropteridine reductase could be inhibited by hydroxylated **4** and its hydroxylated analogues. Consequently, definite conclusions on the mechanism of toxicity of **4** and the reasons for the nontoxicity of **4** toward certain animal species remain unclear.

Knaus and co-workers[13–16] reported the synthesis of a series of *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines. Results of preliminary pharmacological tests on these compounds showed that they possess anti-inflammatory, analgesic, and hyperglycemic activities, with no observed toxicities, even at very high doses.[17,18] Our current research is an extension of this work. Accordingly, alkylation of the tetrahydropyridine ring was planned (i.e., introducing methyl groups to increase the bulk, lipophilicity, and electron density of the ring).[19] Target compounds were then examined for anti-inflammatory and analgesic activities. The aim of the research work was to initiate the development of effective nonsteroidal anti-inflammatory agents (NSAIAs). The target molecules, like nonacidic NSAIAs, may be a second-generation class that may produce less gastric mucosal damage as a result of the lack of acidic properties. Toxicological evaluation of the methyl-substituted tetrahydropyridines is needed to correlate their activities with those of **4**.



1 **2** **3** **4**

Results and Discussion

The results of the syntheses of the pyridinium ylides (**10**) and the tetrahydropyridines (**11**) are summarized in Tables I and II, respectively (see structures).

The tetrahydropyridines (**11**) were stable products, and their ^1H NMR patterns were diagnostic. For example, the ^1H NMR data of *N*-(2-pyridylcarbonylamino)-4-methyl-1,2,3,6-tetrahydropyridine (**11g**) recorded in $CDCl_3$ shows absorptions at δ 1.80 (s, 3H, CH_3), 2.25 [s, 2H, C_3-H (tetrahydropyridine)], 3.10 [t ($J_{2,3}$ = 6 Hz), 2H, C_2-H (tetrahydropyridine)], 3.50 [m, 2H, C_6-H (tetrahydropyridine)], 5.35 [m, 1H, C_5-H (olefinic)], 7.40 [m, 1H,

Table I—Results of Synthesis of Compounds 10

Compound[a]	mp, °C[b]	Yield, %
10e	196–198	18
10f	179–181	34
10g	168–170	29
10h	65–67 (oil)	18
10i	185–187	71
10j	141–143	77
10k	Semisolid	48
10l	213–215 (215–217)	88

[a] Formulas: **10e–10g** and **10i–10k**, $C_{12}H_{11}N_3O$; **10h** and **10l**, $C_{13}H_{12}N_2O$. All compounds were analyzed for C, H, and N. [b] Information in parentheses is from ref 20.

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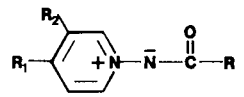
Table II—Synthetic and Pharmacological Data for Compounds 11

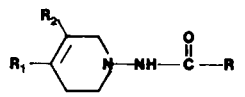
Compound[a]	mp, °C[b]	Yield, %	Anti-inflammatory ID_{50}, mg/kg[c]	Analgesic ID_{50}, mg/kg[d]
11a	142–144 (143)	—[e]	17.9	13.1
11b	119–121 (120)	—	43.6	6.4
11c	82–83 (82)	—	13.8	12.6
11d	137–139 (138)	—	5.0	20.0
11e	156–158	58	32.1	25.6
11f	150–152	30	49.1	20.9
11g	75–77	28	29.5	22.8
11h	182–183 (182)	45	9.6	40.4
11i	143–145	39	57.2	8.7
11j	143–145	40	18.5	10.8
11k	92–94	42	39.1	7.8
11l	154–156 (156)	46	20.9	9.9
Indomethacin	—	—	3.0	5.3

[a] Formulas: **11e–11g**, $C_{12}H_{15}N_3O$; **11h** and **11l**, $C_{13}H_{16}N_2O$. Compounds **11e–11l** were analyzed for C, H, and N. [b] Values in parentheses are from ref 13 (**11a–11d**) and ref 20 (**11h** and **11l**). [c] Inhibition of leukocyte migration by 50% in the rat carrageenan-soaked sponge model of inflammation. [d] Inhibition of acetic acid-induced writhing by 50%. [e] —, Not determined.



Compound	R	R_1	R_2
10e	4-Pyridyl	CH_3	H
10f	3-Pyridyl	CH_3	H
10g	2-Pyridyl	CH_3	H
10h	Phenyl	CH_3	H
10i	4-Pyridyl	H	CH_3
10j	3-Pyridyl	H	CH_3
10k	2-Pyridyl	H	CH_3
10l	Phenyl	H	CH_3

N-[Pyridyl(phenyl)carbonylimino]methylpyridinium ylides, **10**



Compound	R	R_1	R_2
11a	4-Pyridyl	H	H
11b	3-Pyridyl	H	H
11c	2-Pyridyl	H	H
11d	Phenyl	H	H
11e	4-Pyridyl	CH_3	H
11f	3-Pyridyl	CH_3	H
11g	2-Pyridyl	CH_3	H
11h	Phenyl	CH_3	H
11i	4-Pyridyl	H	CH_3
11j	3-Pyridyl	H	CH_3
11k	2-Pyridyl	H	CH_3
11l	Phenyl	H	CH_3

N-[Pyridyl(phenylcarbonylamino]methyl-1,2,3,6-tetrahydropyridines, **11**

C_5-H (pyridine)], 7.80 [td ($J_{4,3} = J_{4,5} = 8$ Hz, $J_{4,6} = 2$ Hz), 1H, C_4-H (pyridine)], 8.20 [d ($J_{3,4} = 8$ Hz), 1H, C_3-H (pyridine)], 8.50 [dt ($J_{6,5} = 5$ Hz, $J_{6,4} = 1.5$ Hz, $J_{6,3} = 1$ Hz), 1H, C_6-H (pyridine)], and 8.85 [s, 1H, NH (exchanges with deuterium oxide)]. These data are in agreement with the structure.

The ID_{50} (the dose needed to inhibit the response by 50%) values for the anti-inflammatory activity of the derivatives **11a–11l** in the carrageenan-soaked sponge model of inflammation in the rat[21] are given in Table II. The reference compound in these experiments was indomethacin (ID_{50}, ~3 mg/kg in this model). The present investigations show that none of the new compounds tested were as potent as indomethacin in inhibiting the migration of leukocytes to the site of inflammation. All the compounds tested, **11a–11l**, inhibited leukocyte migration in a dose-dependent manner. Compared with the unsubstituted compounds (**11a–11d**), **11i**, **11k**, and **11l** were less active (Table II). Treatment with **11e**, **11g**, or **11h** resulted in intermediate activity when compared with the corresponding unsubstituted compounds. In contrast, **11j** showed a 2.5-fold increase in activity compared with the unsubstituted 3-pyridyl compound. Taken together, these results indicate that only for **11j** did substitution increase anti-inflammatory activity. For all the other cases of new compounds, substitution did not improve activity compared with the corresponding unsubstituted compounds.

Also in Table II are results of analgesic activity assessed as the ID_{50} values in the acetic acid-induced writhing model in mice. In this model, the reference compound, indomethacin, has an ID_{50} of ~5.3 mg/kg. Table II shows that none of the compounds were more potent than the reference compound, indomethacin. All compounds tested inhibited acetic acid-induced writhing in a dose-dependent manner. Treatment with **11k**, **11i**, or **11l** resulted in increased analgesic activity when compared with the corresponding unsubstituted compounds. By contrast, **11e–11h** were less active than the 3-methyl-substituted derivatives (**11i–11l**) and their corresponding unsubstituted compounds (**11a–11d**). Taken together, these results indicate that, except for substitution with a 3-methyl group, substitution results in increased analgesic activity, compared with the unsubstituted compounds.

Experimental Section

Materials—Chemicals and solvents used in the work were purchased from Aldrich Chemical Company Inc., Milwaukee, WI, and Fisher Scientific Company, Orlando, FL. The neutral alumina used for chromatography was Brockman I, 150 mesh, 58 A. Melting points were determined on an electrothermal melting-point apparatus and are uncorrected. A Perkin-Elmer 1430 IR instrument was used for IR spectral measurements on KBr pellets, unless otherwise noted. The ^1H

NMR spectra were recorded in $CDCl_3$ (unless otherwise stated), with chloroform as the internal standard, on a Bruker HX 270-MHz instrument. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN. All the products were found homogeneous when analyzed by TLC with solvent systems of low, medium, and high polarity. No residue remained after combustion of the products.

Pharmacology—Anti-inflammatory activity was assessed by the carrageenan-soaked sponge model of inflammation[21] in Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) weighing 140–180 g. Polyester sponges (Fisher) were sterilized and then injected with 0.3 mL of sterile 1% carrageenan in saline. Lightly anesthetized animals (five animals per group) were treated with the indicated concentrations of drugs dissolved in 10% ethanol in water or 5% dimethyl sulfoxide in propylene glycol by intraperitoneal injection. Two sterile sponges were then implanted subcutaneously, one in each axilla, and the incision was closed with 9-mm autoclips. After 5 h, animals were sacrificed, sponges were immediately removed and placed in the barrel of a 10-mL syringe, and the leukocytes were washed out with 1 mL of phosphate-buffered saline containing heparin at 10 units/mL. Exudate volumes were measured by weighing on a Mettler balance, and aliquots of cells were diluted and quantitated in Neubauer chambers.

Analgesic effect was assessed by suppression of acetic acid-induced writhing[22] in 21–24-g male Swiss albino mice (Harlan Sprague-Dawley). Drugs to be tested for suppression of abdominal constriction responses were dissolved in 10% ethanol or 5% dimethyl sulfoxide in propylene glycol and administered subcutaneously to groups of 6–10 animals. After 30 min, animals were injected intraperitoneally with 0.25 mL of 6% acetic acid in water. After 5 min, the number of writhes was counted for a period of 15 min.

The ID_{50} values were calculated from best fit linear regression lines relating dose to response, in which response was expressed as percent inhibition compared with untreated controls.

Chemistry—Appropriate molar amounts of methyl-substituted pyridines (5) and 1-chloro-2,4-dinitrobenzene (6) were refluxed in dry acetone, with stirring, for 12 h to furnish *N*-(2,4-dinitrophenyl)pyridinium chlorides (7). Pyridyl or phenyl acid hydrazides (8) were then reacted with 7 in methanol in the presence of triethylamine at room temperature for 12 h to afford the ring-opened product 9, which, upon hydrolysis with a water:*p*-dioxane mixture (1:4, v/v), furnished the pyridyl- or phenylcarbonyliminopyridinium ylides (10) and 2,4-dinitroaniline. Sodium borohydride reduction of the pyridinium ylides (10) at 0 °C in absolute ethanol for 4 h yielded the targeted methyl-substituted pyridyl- or phenylcarbonylamino-1,2,3,6-tetrahydropyridines (11; Scheme I).

Procedure A—*N-(4-Pyridylcarbonylimino)-4-methylpyridinium Ylide (10e)*—4-Picoline (6.6 g, 70.87 mmol) was added in a dropwise manner to a stirring solution of 1-chloro-2,4-dinitrobenzene (13.07 g, 64.52 mmol) in 150 mL of anhydrous acetone, and the contents were refluxed for 12 h. The reaction mixture was cooled to 10 °C for 1 h, filtered, washed thoroughly with hexane and ether, and dried at room temperature to give a dark brown solid. The solid was crystallized from absolute ethanol to furnish *N*-(2,4-dinitrophenyl)-4-methylpyridinium chloride (7a) as a black solid (14.6 g, 76%; mp, 142–145 °C). Compound 7a (5.6 g, 18.94 mmol) was reacted with isonicotinic acid hydrazide (2.6 g, 18.95 mmol) in 100 mL of methanol containing 1.5 mL of triethylamine for 12 h at room temperature. The dark brown precipitate formed was filtered and washed successively with 60 mL each of methanol, water, methanol, and ether. The resulting residue was immediately refluxed in water:*p*-dioxane (1:4, v/v, 200 mL) for 12 h. The solvent was evaporated under reduced pressure, and semisolid residue resulted. The product was chromatographed on a neutral alumina column (2.5 × 25 cm) with 900 mL of ether:methanol (8:1, v/v) as eluant and subsequently crystallized from ethyl acetate to furnish 10e as reddish-brown feathery crystals (0.74 g, 18%); ^1H NMR:δ 2.60 (s, 3H, CH_3), 7.52 [d ($J_{2,3} = J_{5,6}$ = 5 Hz), 2H, C_3-H, C_5-H (pyridinium)], 8.03 [d ($J_{3,2} = J_{5,6}$ = 5 Hz), 2H, C_3-H, C_5-H (pyridine)], 8.63 [d ($J_{2,3} = J_{6,5}$ = 5 Hz), 2H, C_2-H, C_6-H (pyridine)], 8.71 [d ($J_{2,3} = J_{6,5}$ = 5 Hz), 2H, C_2-H, C_6-H (pyridinium)]. Anal. ($C_{12}H_{11}N_3O$) C,H,N.

Compounds 10f–10h were similarly prepared. Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds. (Experimental details and complete analytical data are available from the authors.)

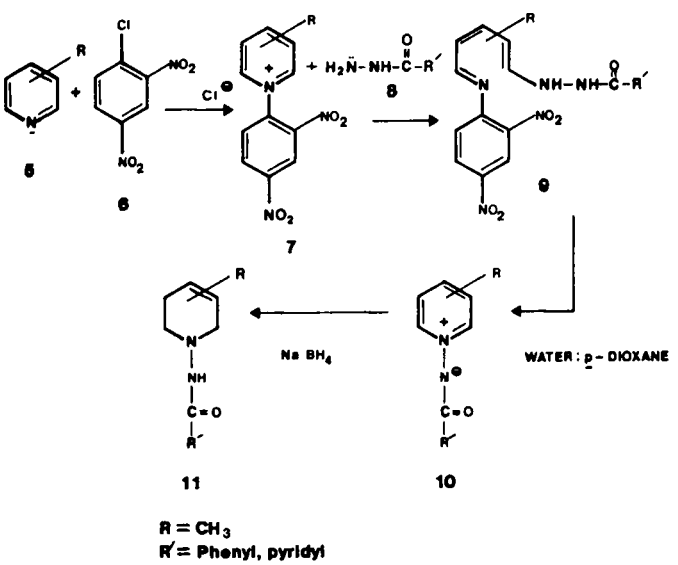
N-(4-Pyridylcarbonylimino)-3-methylpyridinium Ylide (10i)—3-Picoline (10 g, 107.37 mmol) was slowly added in a dropwise manner to a stirring solution of 1-chloro-2,4-dinitrobenzene (19.77 g, 97.61 mmol) in anhydrous acetone (200 mL), and the reaction mixture was refluxed for 12 h. The contents were cooled to 10 °C for 1 h, filtered, and washed with hexane (100 mL). The product was crystallized from absolute ethanol as a gray solid [*N*-(2,4-dinitrophenyl)-3-methylpyridinium chloride (7e), 25.38 g, 88%]. Compound 7e (3.02 g, 10.21 mmol) and isonicotinic acid hydrazide (1.41 g, 10.28 mmol) were reacted in 100 mL of methanol containing 1.5 mL of triethylamine at room temperature for 12 h. The synthesis reaction was continued as described for 10e until a dark brown solid was obtained. Chromatography on a neutral alumina column (2.5 × 25 cm) and elution with 600 mL of ether:methanol (8:1, v/v) furnished a brown solid. This solid was crystallized from ethyl acetate to afford 10i as light brown flakes (1.55 g, 71%); ^1H NMR:δ 2.52 (s, 3H, CH_3), 7.60 [t ($J_{5,4} = J_{5,6}$ = 7.0 Hz), 1H, C_5-H (pyridinium)], 7.78 [d ($J_{4,5}$ = 7.5 Hz), 1H, C_4-H (pyridinium)], 7.98 [d ($J_{3,2} = J_{5,6}$ = 6 Hz), 2H, C_3-H, C_5-H (pyridine)], 8.60–8.70 [m, 4H, C_2-H, C_6-H (pyridinium), and C_2-H, C_6-H (pyridine)]. Anal. ($C_{12}H_{11}N_3O$) C,H,N.

Compounds 10j–10l were similarly prepared. Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds. (Experimental details and complete analytical data are available from the authors.)

N-(4-Pyridylcarbonylamino)-4-methyl-1,2,3,6-tetrahydropyridine (11e)—A solution of the ylide 10e (0.74 g, 3.47 mmol) in 75 mL of absolute ethanol was cooled to 0 °C while being stirred. Excess sodium borohydride (0.53 g, 14 mmol) was added, and the stirring was continued for 4 h at 0 °C. The reaction was arrested by adding crushed ice (25 g), and the solution was allowed to warm up to room temperature. The product was then extracted with chloroform (4 × 75 mL), and the extract was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield a light yellow solid. This solid was chromatographed on a neutral alumina column (2.5 × 25 cm) with 600 mL of ether:methanol (15:1, v/v) as the eluant. Further crystallization from ethyl acetate gave the light yellow solid 11e (0.44 g, 58%); IR:3190 (NH), 1645 (C=O) cm^{-1}; ^1H NMR:δ 1.70 (s, 3H, CH_3), 2.25 [s, 2H, C_3-H (tetrahydropyridine)], 3.20 [t ($J_{2,3}$ = 6 Hz), 2H, C_2-H (tetrahydropyridine)], 3.55 [s, 2H, C_6-H (tetrahydropyridine)], 5.35 [m, 1H, C_5-H (olefinic)], 7.85 [d ($J_{2,3} = J_{5,6}$ = 6 Hz), 2H, C_3-H, C_5-H (pyridine)], 8.05–8.20 [br s, 1H, NH (exchanges with deuterium oxide)], 8.75 [s, 2H, C_2-H, C_6-H (pyridine)]. Anal. ($C_{12}H_{15}N_3O$) C,H,N.

Compound 11f was similarly prepared. Satisfactory analytical data (±0.4% for C, H, and N) were reported. (Experimental details and complete analytical data are available from the authors.)

N-(2-Pyridylcarbonylamino)-4-methyl-1,2,3,6-tetrahydropyridine (11g)—Sodium borohydride (2.22 g, 58.68 mmol) was added to a stirring solution of 10g (1.25 g, 5.86 mmol) in 100 mL of absolute ethanol at 0 °C, and the reaction was continued as for 11e. The resulting product was chromatographed on a neutral alumina column (2.5 × 30 cm) with 500 mL of ethyl acetate:hexane (1:1, v/v) as the eluant. The resulting low-melting solid was crystallized from ethyl



Scheme I

acetate:hexane (1:3, v/v) to afford **11e** as light brown needles (0.35 g, 28%); IR:3200 (NH), 1645 (C=O) cm^{-1}; ^1H NMR: described in *Results and Discussion*. Anal. ($C_{12}H_{15}N_3O$) C,H,N.

Compound **11h** was similarly prepared. Satisfactory analytical data (±0.4% for C, H, and N) were reported. (Experimental details and complete analytical data are available from the authors.)

N-(4-Pyridylcarbonylamino)-5-methyl-1,2,3,6-tetrahydropyridine (11i)—To a stirring solution of **10i** (1.55 g, 7.26 mmol) in 100 mL of absolute ethanol (precooled to 0 °C), sodium borohydride (1.11 g, 29.34 mmol) was added, and the reaction was continued as described for **11e**. The resulting product was chromatographed on a column of neutral alumina (2.5 × 20 cm) with 400 mL of ether:methanol (15:1 v/v) as the eluant. Further crystallization from ethyl acetate gave **11i** as cream white needles (0.62 g, 39%); IR:3220 (NH), 1645 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6):δ 1.72 (s, 3H, CH_3) 2.15 [s, 2H, C_3-H (tetrahydropyridine)], 2.92 [t ($J_{2,3}$ = 5 Hz), 2H, C_2-H (tetrahydropyridine)], 3.25 [s, 2H, C_6-H (tetrahydropyridine)], 5.40 [m, 1H, C_4-H (olefinic)], 7.70 [d ($J_{3,2} = J_{5,6}$ = 5 Hz), 2H, C_3-H, C_5-H (pyridine)], 8.70 [d ($J_{2,3} = J_{6,5}$ = 5 Hz), 2H, C_2-H, C_6-H (pyridine)], 9.80 (s, 1H, NH (exchanges with deuterium oxide)]. Anal. ($C_{13}H_{16}N_3O$) C,H,N.

N-(3-Pyridylcarbonylamino)-5-methyl-1,2,3,6-tetrahydropyridine (11j)—Sodium borohydride (1.22 g, 32.25 mmol) was added to a stirring solution of **10j** (1.68 g, 7.87 mmol) in 100 mL of absolute ethanol at 0 °C and the reaction was continued as described for **11e**. The resulting product was chromatographed on a column of neutral alumina (2.5 × 25 cm) with 400 mL of ether:methanol (15:1, v/v) as the eluant. Further crystallization from ethyl acetate furnished **11j** as cream white feathery crystals (0.68 g, 40%); IR:3200 (NH), 1650 (C=O) cm^{-1}; ^1H NMR:δ 1.65 (s, 3H, CH_3), 2.35 [m, 2H, C_3-H (tetrahydropyridine)], 3.25 [t ($J_{2,3}$ = 6 Hz), 2H, C_2-H (tetrahydropyridine)], 3.55 [s, 2H, C_6-H (tetrahydropyridine)], 5.50 [m, 1H, C_4-H (olefinic)], 7.65 [t ($J_{5,4} = J_{5,6}$ = 6 Hz), 1H, C_5-H (pyridine)], 8.25–8.50 [br s, 1H, NH (exchanges with deuterium oxide)], 8.60 [d ($J_{4,5}$ = 6 Hz), 1H, C_4-H (pyridine)], 8.75 [d ($J_{6,5}$ = 5 Hz), 1H, C_6-H (pyridine)], 9.45 [s, 1H, C_2-H (pyridine)]. Anal. ($C_{12}H_{15}N_3O$) C,H,N.

Compounds **11k** and **11l** were similarly prepared. Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds. (Experimental details and complete analytical data are available from the authors.)

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