(*Z*)-$NCC_6H_4CH{=}CHC_6H_5$, 19466-33-2; 2-HOC_6H_4CHO, 90-02-8; 3-$C_6H_5OC_6H_4CHO$, 39515-51-0; 3-$HOC_6H_4CO(CH_2)_4CH_3$, 103119-13-7; 2-picolyl chloride hydrochloride, 6959-47-3; 4-picolyl chloride hydrochloride, 1822-51-1; 3-picolyl chloride hydrochloride, 6959-48-4; 2-(chloromethyl)quinoline hydrochloride, 3747-74-8; 2-bromomethylnaphthalene, 939-26-4; 2-chloroquinoline, 612-62-4; 3-(2-quinolinyloxy)benzaldehyde, 104508-29-4; 5-lipoxygenase, 80619-02-9.

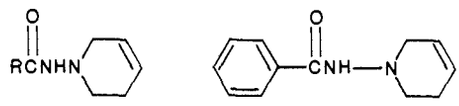
Synthesis of *N*-(3,6-Dihydro-1(2*H*)-pyridinyl)benzamides with Hyperglycemic–Hypoglycemic Activity

Jupita M. Yeung and Edward E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8.
Received April 2, 1986

A group of *N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamides **7** were synthesized to determine the effect that the position and physicochemical properties of substituents attached to the heterocyclic ring have on blood glucose levels. 5-Methyl-*N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamide **7b** was the most active hyperglycemic agent, elevating blood glucose 124% and 116% at 2 and 4 h, respectively, after a 100 mg/kg po dose. The most active hypoglycemic agent was the 4-acetyl analogue **7o**, which was about 50% as active as chlorpropamide, lowering blood glucose 19% at 4 h after a 100 mg/kg po dose. A correlation between blood glucose levels and the partition coefficient *P* was not observed.

In earlier studies we described a facile method for the synthesis of *N*-(3,6-dihydro-1(2*H*)-pyridinyl) amides **1** via the sodium borohydride reduction of *N*-(carbonylimino)-pyridinium ylides,[1] which exhibited significant hyperglycemic activities.[2,3] The lead compound **2** elevated blood



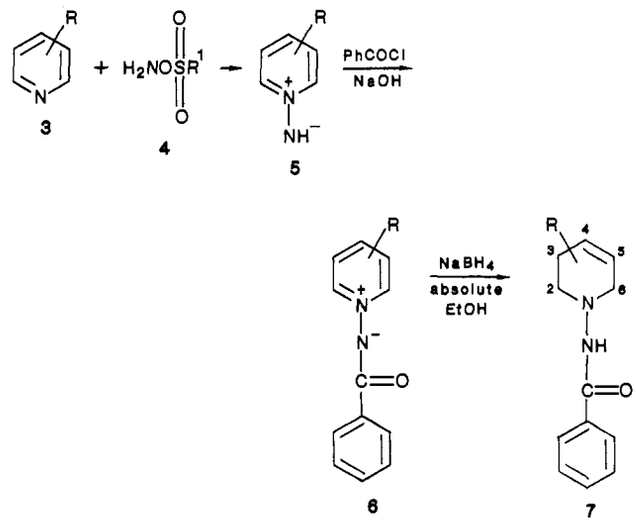
1 **2**

R = alkyl, cycloalkyl, arylalkyl, alkyloxy, arylalkyloxy, aryl, heteroaryl, heteroarylalkyl

glucose 78% and 50% at 2 and 4 h, respectively, after a 100 mg/kg po dose. The nature and position of substituents attached to a phenyl moiety of **1** were determinants of blood glucose concentration. It was therefore of interest to determine the effect of substituents on the 3,6-dihydro-1(2*H*)-pyridinyl ring of **1**, with regard to substituent position and physicochemical properties, upon hyperglycemic activity. Hyperglycemic agents such as **1** may have potential for the treatment of hypoglycemia. We now describe the synthesis and hyperglycemic–hypoglycemic activities of functionalized *N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamides **7**.

Chemistry. *N*-[(Phenylcarbonyl)imino]pyridinium ylides **6** were prepared via two synthetic procedures. Reaction of the nonisolable *N*-iminopyridinium ylides **5a–d**, obtained by amination of pyridines **3a–d** with hydroxylamine-*O*-sulfonic acid (**4**, R^1 = OH), with benzoyl chloride in the presence of 10% aqueous sodium hydroxide afforded ylides **6a–d**. On the other hand, pyridinium ylides **6e–f,h–k** were prepared more efficiently by amination of **3e–f,h–k** with use of the more reactive *O*-(mesitylenesulfonyl)hydroxylamine (**4**, R^1 = 2,4,6-trimethylphenyl) followed by reaction of **5** with benzoyl chloride (Scheme I). Alternatively, reaction of 1-(2,4-dinitrophenyl)-pyridinium chlorides **8g,l–o** with benzoic acid hydrazide yielded the respective 5-(2,4-dinitroanilino)-penta-2,4-dienal benzoic acid hydrazones **9**, which on heating cyclized to afford the respective *N*-[(phenylcarbonyl)imino]-pyridinium ylides **6g,l–o** as illustrated in Scheme II and summarized in Table I. The sodium borohydride reduction of ylides **6a–o** in absolute ethanol at 0 °C for 5 h, unless otherwise noted, afforded the respective *N*-(3,6-dihydro-1(2)-pyridinyl)benzamides **7a–o** as illustrated in Scheme I and summarized in Table II. The formation of the C-3 *exo*-methylene product **7h** from **6h** likely arises via a reductive elimination reaction[4] following initial attack by hydride anion at C-2 and/or C-6 (see Scheme III). The 200-MHz ^{1}H NMR spectrum of **7h** (Me_2SO-d_6) exhibited two 1 H singlets at δ 4.89 and 4.93 assigned to the exocyclic methylene protons.[5] The structure assigned to **7h** was confirmed by unambiguous chemical methods since catalytic hydrogenation of **7h** and **7b** using 10% palladium-

Scheme I



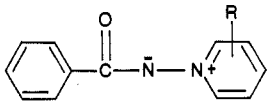
3 **4** **5** **6** **7**

a, R = 2-CH_3; **b**, R = 3-CH_3; **c**, R = 4-CH_3; **d**, R = 3,4-$(CH_3)_2$; **e**, R = 3-F; **f**, R = 3-$CH_2CH_2CH_2OH$; **g**, R = 4-$CH_2CH_2CH_2OH$; **3-6h**, R = 3-CH_2OCOCH_3; **7h**, R = 3 = CH_2; **3-6i**, R = 4-CH_2OCOCH_3; **7i**, R = 4-CH_2OH; **j**, R = 3-$CH_2CH_2CO_2CH_3$; **k**, R = 4-$CH_2CH_2CO_2CH_3$

(1) Knaus, E. E.; Redda, K. *J. Heterocycl. Chem.* **1976**, *13*, 1237.
(2) Yeung, J. M.; Corleto, L. A.; Knaus, E. E. *J. Med. Chem.* **1982**, *25*, 191; **1982**, *25*, 720.
(3) Knaus, E. E.; Redda, K.; Wandelmaier, F. W. U.S. Patent 4088653, May 9, 1978.
(4) Ziegler, F. E.; Sueny, J. G. *J. Org. Chem.* **1967**, *32*, 3216.
(5) Yates, P.; Helferty, P. H.; Mahler, P. *Can. J. Chem.* **1983**, *61*, 78.

0022-2623/87/1830-0104$01.50/0

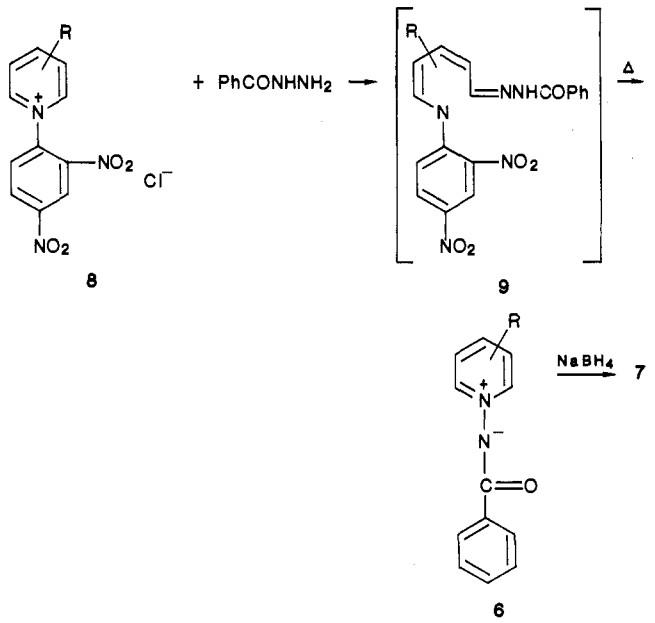
Table I. Some Physical Data of *N*-[(Phenylcarbonyl)imino]pyridinium Ylides **6**



compd	R	yield, %	procedure	mp, °C	formula	exact mass calcd	exact mass found
6a	2-CH_3	37.4	A	118–119	$C_{13}H_{12}N_2O$	212.0950	212.0941
6b	3-CH_3	39	A	215–217	$C_{13}H_{12}N_2O$	212.0950	212.0935
6c	4-CH_3	18	A	oil	$C_{13}H_{12}N_2O$	212.0950	212.0939
6d	3,4-$(CH_3)_2$	59.5	A	104–106	$C_{14}H_{14}N_2O$	226.1106	226.1088
6e	3-F	99.2	B	179–181[a]	$C_{12}H_9N_2OF$		ND[b]
6f	3-$CH_2CH_2CH_2OH$	97	B	oil	$C_{15}H_{16}N_2O_2$	256.1212	256.1217
6g	4-$CH_2CH_2CH_2OH$	33	C	163–165	$C_{15}H_{16}N_2O_2$	256.1212	256.1187
6h	3-CH_2OCOCH_3	97.5	B	oil	$C_{15}H_{14}N_2O_3$	270.1004	270.0992
6i	4-CH_2OCOCH_3	64	B	154–155	$C_{15}H_{14}N_2O_3$	270.1004	270.0991
6j	3-$CH_2CH_2CO_2CH_3$	87	B	oil	$C_{16}H_{16}N_2O_3$	284.1161	284.1140
6k	4-$CH_2CH_2CO_2CH_3$	54	B	136–138	$C_{16}H_{16}N_2O_3$	284.1161	284.1141
6l	3-OCH_3	38.6	C	136–138[c]	$C_{13}H_{12}N_2O_2$		ND[b]
6m	4-OCH_3	7.6	C	190–191	$C_{13}H_{12}N_2O_2$	228.0898	228.0883
6n	3-$COCH_3$ (ethylene ketal)	20	C	123–125	$C_{16}H_{16}N_2O_3$	284.1161	284.1145
6o	4-$COCH_3$ (ethylene ketal)	43	C	194–195	$C_{16}H_{16}N_2O_3$	284.1161	284.1148

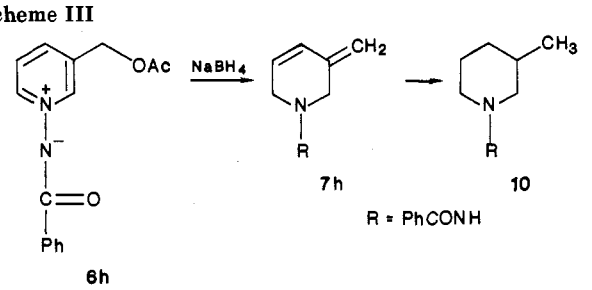
[a] Literature[17] mp 181–182 °C. [b] ND = not determined. [c] Literature[17] mp 137–138 °C.

Scheme II



g, R = 4-$CH_2CH_2CH_2OH$; l, R = 3-OCH_3; m, R = 4-OCH_3; n, R = 3-$COCH_3$(ethylene ketal); o, R = 4-$COCH_3$(ethylene ketal)

Scheme III



on-charcoal and hydrogen gas both afforded 3-methyl-*N*-(hexahydropyridinyl)benzamide (**10**) in 95% yield. The sodium borohydride reduction of the C-4 acetoxymethyl ylide **6i** afforded 4-(hydroxymethyl)-*N*-(3,6-dihydro-1-(2*H*)-pyridinyl)benzamide (**7i**).[6] The 5- and 4-methoxypropyl compounds **7p,q** were prepared by converting the 5- and 4-hydroxypropyl analogues **7f,g** to their respective mesylates and displacement of the mesyl group with use of sodium methoxide. Acetylation of **7f,g** with acetic anhydride afforded the respective 5- and 4-acetoxypropyl analogues **7r,s**. Hydrolysis of the 5- and 4-(methoxycarbonyl)ethyl compounds **7j,k** with methanolic sodium hydroxide yielded the respective 5- and 4-carboxyethyl analogues **7t,u**. Sodium borohydride reduction of the acetyl (ethylene ketal) ylides **6n,o** afforded the respective ethylene ketals of **7n,o**, which were subsequently converted to **7n,o** in the presence of aqueous acetone and pyridinium tosylate.[7] Sodium borohydride reduction of **7n,o** gave the respective 5- and 4-(1-hydroxyethyl) derivatives **7v,w**. The *m*-chloroperbenzoic acid oxidation of **2** afforded the 6-oxo derivative **7x** as the sole product.[8,9] Epoxidation of the olefenic bond was not observed.[10]

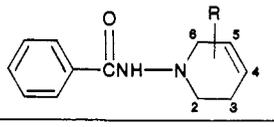
Pharmacology. Blood glucose determinations for the *N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamides **7** were determined by spectrophotometric measurement of enzymatically produced $NADH_2$.[11]

Discussion

A group of *N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamides **7** were investigated to determine the effect that substituent position, substituent chain length, and physicochemical properties of substituents attached to the *N*-3,6-dihydro-1(2*H*)-pyridinyl ring have on blood glucose concentration. These results were compared to that of the lead compound **2**, which elevated blood glucose 78% and 50% at 2 and 4 h, respectively, after a 100 mg/kg po dose (see Table II). The presence and position of a methyl substituent (**7a–d**) were important determinants of hyperglycemic activity where the relative efficacies were 5-CH_3 > 4-CH_3 > 4,5-$(CH_3)_2$ > 2-CH_3. The 5-CH_3 analogue **7b** elevated blood glucose 124% and 116% at 2 and 4 h, respectively, after a 100 mg/kg po dose. A comparison of the activities of the 5-CH_3 compound **7b** (potent hyperglycemic, electron donating), the 5-F analogue **7e** (hyperglycemic, electron withdrawing), and the 5-OCH_3 derivative **7l** (weak hypo-

(6) Nichols, B. W.; Safford, R. *Chem. Phys. Lipids* **1973**, *11*, 222; Chem. Abstr. **1973**, 80, 47412.
(7) Sterzychi, R. *Synthesis* **1979**, 724.
(8) Witkop, B. *Ann. Chim.* **1947**, *558*, 98.
(9) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2196.
(10) Avasthi, K.; Knaus, E. E. *Can. J. Pharm. Sci.* **1981**, *16*, 53.
(11) Barthelmai, W.; Czok, R. *Klin. Wochenschr.* **1962**, *40*, 585.

Table II. Some Physical and Pharmacological Data of *N*-(3,6-Dihydro-1(2*H*)-pyridinyl)benzamides **7**



compd	R	yield, %	mp, °C	P^a	formula[b]	hypoglycemic–hyperglycemic act.:[c] % change in blood glucose concn posttreatment 2 h	4 h
7a	2-CH_3	45	147–150	5.0	$C_{13}H_{16}N_2O$	+12 ± 4.2[d]	+16 ± 2.4[d]
7b	5-CH_3	45	156–157	23.6	$C_{13}H_{16}N_2O$	+124 ± 43[d]	+116 ± 44[d]
7c	4-CH_3	61	181–182	15.7	$C_{13}H_{16}N_2O$	+48 ± 23	+43 ± 23
7d	4,5-$(CH_3)_2$	24	191–192	22.3	$C_{14}H_{18}N_2O$	+27 ± 13	+20 ± 6.9
7e	5-F	100	151–153	18.5	$C_{12}H_{13}N_2OF$	+64 ± 1.3[d]	+42 ± 1.0[d]
7f	5-$CH_2CH_2CH_2OH$	30	167–168	13.2	$C_{15}H_{20}N_2O_2$	−2 ± 1.3	−6 ± 1.4
7g	4-$CH_2CH_2CH_2OH$	47	157–158	16.7	$C_{15}H_{20}N_2O_2$	+4 ± 0.2	−6 ± 0.3
7h	3-CH_2	80	157–158	23.5	$C_{13}H_{14}N_2O$	+5 ± 0.1	+4 ± 0.2
7i	4-CH_2OH	87	173–174	4.4	$C_{13}H_{16}N_2O_2$	−10 ± 0.3	−14 ± 0.2[d]
7j	5-$CH_2CH_2CO_2CH_3$	30	140–142	5.5	$C_{16}H_{20}N_2O_3$	−2 ± 0.3	+6 ± 0.2
7k	4-$CH_2CH_2CO_2CH_3$	73	147–148	8.9	$C_{16}H_{20}N_2O_3$	−9 ± 0.2	−9 ± 0.3
7l	5-OCH_3	73	162–163	41.4	$C_{13}H_{16}N_2O_2$	−7 ± 0.6	−9 ± 0.5
7m	4-OCH_3	93	167–168	14.4	$C_{13}H_{16}N_2O_2$	+5 ± 0.1	+7 ± 0.3
7n	5-$COCH_3$	30	179–180	0.8	$C_{14}H_{16}N_2O_2$	−5 ± 0.2	−17 ± 0.3[d]
7o	4-$COCH_3$	75	203–204	2.4	$C_{14}H_{16}N_2O_2$	−12 ± 0.1	−19 ± 0.4[d]
7p	5-$CH_2CH_2CH_2OCH_3$	83	103–105	8.1	$C_{16}H_{22}N_2O_2$	−10 ± 0.4	−11 ± 0.4
7q	4-$CH_2CH_2CH_2OCH_3$	90	133–134	30.6	$C_{16}H_{22}N_2O_2$	+1 ± 0.3	−9 ± 0.3
7r	5-$CH_2CH_2CH_2OCOCH_3$	55	163–165	31.1	$C_{17}H_{22}N_2O_3$	−8 ± 0.2	+7 ± 0.2
7s	4-$CH_2CH_2CH_2OCOCH_3$	97	140–142	33.4	$C_{17}H_{22}N_2O_3$	+2 ± 0.6	+3 ± 0.4
7t	5-CH_2CH_2COOH	87	193–195	15.3	$C_{15}H_{18}N_2O_3$	−14 ± 0.3[d]	−4 ± 0.3
7u	4-CH_2CH_2COOH	94	160–161	10.0	$C_{15}H_{18}N_2O_3$	−4 ± 0.3	+7 ± 0.4
7v	5-$CH(OH)CH_3$	91	181–183	2.8	$C_{14}H_{18}N_2O_2$	−8 ± 0.2	−16 ± 0.1[d]
7w	4-$CH(OH)CH_3$	92	156–157	1.1	$C_{14}H_{18}N_2O_2$	−10 ± 0.2	−5 ± 0.1
7x	6-O	20	159–160	14.9	$C_{12}H_{12}N_2O_2$	+1 ± 4.2	+4 ± 0.5
2						+78	+50
chlorpropamide						−42 ± 12.1[d]	−38 ± 9.3[d]

[a] Partition coefficient. P = concentration in octanol/concentration in water. [b] All compounds gave analysis for C, H, and N within ±0.4% of theoretical values. [c] The result is the mean value ± SEM of four animals relative to time zero. Hyperglycemic activity is indicated by a plus number and hypoglycemic activity is indicated by a negative number. The dose administered was 100 mg/kg po. [d] The result is statistically significant ($p < 0.05$).

glycemic, electron donating) suggests the nature of the substituent rather than electron effects is relevant to activity. Introduction of substituents other than methyl or fluoro such as hydroxypropyl (**7f,g**), exocyclic methylene (**7h**), hydroxymethyl (**7i**), (methoxycarbonyl)ethyl (**7j,k**), methoxy (**7l,m**), acetyl (**7n,o**), methoxypropyl (**7p,q**), acetoxypropyl (**7r,s**), carboxyethyl (**7t,u**), 1-hydroxyethyl (**7v,w**), or oxo (**7x**) substituents abolished or decreased hyperglycemic activity significantly. The most active hypoglycemic agent **7o** lowered blood glucose 19% at 4 h. There was no significant difference in hypoglycemic activity between the acetyl analogues **7n,o** and the 1-hydroxyethyl derivatives **7v,w**, suggesting electronic effects of substituents are not of major importance. A correlation between the partition coefficient P and blood glucose concentration was not evident from the test results obtained.

In summary, the methyl and fluoro analogues **7a,b,e** are effective orally in elevating blood glucose levels with a duration of action approximating that needed for treating hypoglycemia. The most active hypoglycemic agents **7i,n,o,t**, and **v** exhibited an efficacy between 25% and 50% that of chlorpropamide. It is unlikely that these agents would be of value in controlling blood glucose levels following meals.

Experimental Section

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in $CDCl_3$, unless otherwise stated, with Me_4Si as internal standard on a Varian EM-360A, Bruker WH-200, or Bruker AM-300 spectrometer. Infrared spectra (potassium bromide unless otherwise noted) were taken on a Perkin-Elmer 267 or Nicolet 5DX spectrometer. Mass spectra were measured with an AEI-MS-50 mass spectrometer. All of the products described gave rise to a single spot of TLC with use of three different solvent systems of low, medium, and high polarity. No residue remained after combustion of the products. Microanalyses are within ±0.4% of theoretical values when indicated by symbols of the elements. Preparative TLC was performed on Kieselgel silica gel DF-5 (Camag) plates 0.75 mm in thickness. Fresh hydroxylamine-*O*-sulfonic acid was prepared immediately before use.[12] *O*-(Mesitylenesulfonyl)hydroxylamine (MSH) was prepared according to the procedure of Tamura.[13] MSH is unstable[14] and potentially explosive.[15] Caution in preparing and storing MSH is advisable.

General Synthesis of *N*-[(Phenylcarbonyl)imino]alkylpyridinium Ylides 6a–d. Procedure A. The alkylpyridine **3** (0.4 mmol) was added to a freshly prepared solution of hydroxylamine-*O*-sulfonic acid (0.2 mmol)[12] in cold water (100 mL), and the mixture was heated at 90 °C for 20 min with stirring. The solution was cooled to 25 °C, potassium carbonate (0.2 mmol) was added slowly with stirring, and the water and excess alkylpyridine were removed in vacuo. The residue was triturated with 95% ethanol (200 mL), and the precipitated potassium sulfate was removed by filtration. The filtrate was concentrated at 40 °C,

(12) Rathke, M. W.; Millard, A. A. *Org. Synth.* **1978**, *58*, 32.
(13) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239.
(14) Capino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 3133.
(15) Ning, R. Y. *Chem. Eng. News* **1973**, *51* Dec 17.
(16) Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175.
(17) Fritz, H.; Gleiter, R.; Nastasi, M.; Schuppiser, J. L.; Streith, J. *Helv. Chim. Acta* **1978**, *61*, 2887.

and the residue was dissolved in 10% aqueous sodium hydroxide (20 mL). Benzoyl chloride (40.5 mmol) was added dropwise, and the reaction was allowed to proceed at 25 °C for 12 h. The product that precipitated was recrystallized from methanol to yield the alkylpyridinium ylides **6a–d**. Compound **6a** exhibited the following spectral data: ^{1}H NMR (Me_2SO-d_6) δ 2.6 (s, 3 H, CH_3), 7.35–8.32 (m, 8 H, H_3, H_4, H_5 pyridinium hydrogens, phenyl hydrogens), 8.74 (d, $J_{5,6}$ = 7 Hz, 1 H, H_6); IR 1560 (CO) cm^{-1}; exact mass for $C_{13}H_{12}N_2O$ calcd 212.0950, found (high-resolution MS) 212.0941.

Syntheses of N-[(Phenylcarbonyl)imino]pyridinium Ylides 6e,f,h–k. Procedure B. A solution of *O*-(mesitylenesulfonyl)hydroxylamine[13] (8 mmol) in methylene chloride (2 mL) was added dropwise during 10 min to a solution of the pyridine **3** (8 mmol) in methylene chloride (2 mL) precooled to 0 °C with stirring. The reaction was allowed to proceed for 1 h at 25 °C with stirring. The precipitate was filtered after addition of ether (100 mL) and recrystallized from ethyl acetate–methanol to yield the respective *N*-aminopyridinium mesitylenesulfonate salts **5**. Benzoyl chloride (7.5 mmol) was added dropwise to a solution of the *N*-aminopyridinium mesitylenesulfonate salts **5e–f** (5 mmol) in 10% aqueous sodium hydroxide (25 mL) with stirring, and the reaction was allowed to proceed at 25 °C for 24 h with stirring and then water (30 mL) was added. Extraction with chloroform (4 × 35 mL), decolorization with activated charcoal, drying (Na_2SO_4), and removal of the solvent in vacuo gave impure product, which was purified by elution from a neutral alumina column. The initial 100-mL ether eluate was discarded. Further elution with 300 mL of ether–methanol (9:1, v/v) afforded the respective ylides **6e,f**. The *N*-aminopyridinium mesitylenesulfonate salt **5h,j,k** (7 mmol) was dissolved in benzoyl chloride (2.5 mL), and the mixture was heated at 70 °C for 24 h. The precipitate was filtered and washed with acetone prior to dissolution in saturated aqueous sodium bicarbonate (25 mL). Extraction with chloroform (4 × 25 mL), washing with brine (10 mL), and removal of the solvent in vacuo gave the product, which was purified by neutral alumina column chromatography with ether as eluant to afford the respective ylides **6h** and **6j**. The ylide **6k** was obtained in pure form and did not require purification. The 4-acetoxymethyl ylide **6i** was prepared by a modified procedure. A solution of *O*-(mesitylenesulfonyl)hydroxylamine (1 g, 4.7 mmol) in methylene chloride (5 mL) was added dropwise to an ice-cooled solution of **3i** (0.7 g, 4.7 mmol) in methylene chloride (5 mL). The reaction was allowed to proceed at 25 °C for 1 h to give a viscous oil, which was dissolved in acetonitrile (50 mL). Benzoyl chloride (0.8 mL, 7 mmol) and triethylamine (1.6 mL, 11.6 mmol) were added dropwise in succession to the reaction mixture. The reaction was completed and the product purified as described for the preparation of **6e,f** to yield the 4-acetoxymethyl ylide **6i** (Table II).

General Synthesis of N-[(Phenylcarbonyl)imino]-pyridinium Ylides 6g, 6l–o. Procedure C. A mixture of the pyridine **3g,l–o** (35 mmol) and 1-chloro-2,4-dinitrobenzene (52.6 mmol) in dry acetone (100 mL) was heated at reflux for 15 h. The precipitate was collected after addition of ether (200 mL) and washed with an additional 100 mL of ether to afford the salts **8g,l–o**. Benzoylhydrazine (24 mmol) in methanol (50 mL) was added in five aliquots to an ice-cooled solution of the 2,4-(dinitrophenyl)pyridinium chloride **8g,l–o** (24 mmol) in methanol (50 mL) with stirring. Triethylamine (48 mmol) was added, and the reaction mixture was allowed to stand at room temperature overnight. The solid that precipitated was filtered and washed in succession with 60 mL each of methanol, water, methanol, and ether. The solid obtained was suspended in dioxane–water (4:1, v/v) (200 mL) and heated at reflux for 12 h to afford a clear solution. The solvent was removed in vacuo below 45 °C, water (200 mL) was added to the residue, and the insoluble material was removed by filtration. The filtrate was concentrated in vacuo to give a viscous residue of **6g,l–o**. Ylides **6g,l–m** were purified by neutral alumina column chromatography with 300 mL of ether/methanol (**6g**), 300 mL of chloroform–methanol (8:2, v/v) (**6l**), and 300 mL of chloroform–methanol (9:1, v/v) (**6m**) as eluant. The acetyl (ethylene ketal) ylides **6n,o** were purified by preparative silica gel TLC with chloroform–methanol (9:1, v/v) (**6n**, R_f 0.6) and chloroform–ether (7:3, v/v) (**6o**, R_f 0.2) as development solvents.

General Synthesis of N-(3,6-Dihydro-1(2H)-pyridinyl)-benzamides 7a–o. Procedure D. A solution of the ylide **6a–o** (5 mmol) in 20 mL of absolute ethanol was added dropwise to a solution of sodium borohydride (25 mmol) in absolute ethanol precooled to 0 °C. The reaction was allowed to proceed at 0 °C for 5 h, unless noted otherwise, with stirring. Water (80 mL) was added, and the reaction mixture was allowed to warm to 25 °C. Extraction with chloroform (4 × 75 mL), drying (Na_2SO_4), and removal of the solvent in vacuo afforded the respective products **7a–o**. Those reactions that required a different reaction time and/or products that required purification are outlined below. The 2-methyl compound **7a** was purified by preparative silica gel TLC with chloroform–methanol (9:1, v/v) as development solvent. Extraction of the band having R_f 0.75 yielded an off-white solid, which was sublimed at 125 °C (0.04 mmHg) to yield **7a**. The 5- and 4-methyl derivatives **7b,c** were purified by neutral alumina column chromatography with 300 mL of ether–methanol (4:1, v/v) was eluant. The 4,5-dimethyl analogue **7d** was purified by preparative silica gel TLC using ether–methanol (9:1, v/v) as development solvent, R_f 0.35. The 5-fluoro derivative **7e** was decolorized by using activated charcoal. The 5-(3-hydroxypropyl) analogue **7f** required a reaction time of 6 h and was purified by preparative silica gel TLC with ethyl acetate–acetone (1:3, v/v) as development solvent, R_f 0.5, whereas the 4-(3-hydroxypropyl) derivative **7g** required a reaction time of 8 h and was purified by preparative silica gel TLC with ether–methanol (9:1, v/v) as development solvent, R_f 0.5. A 12-h reaction was used for the preparation of the 3-methylene product **7h**, which was purified by preparative TLC with chloroform–methanol (19:1, v/v) as development solvent, R_f 0.5. The 4-hydroxymethyl analogue **7i** required a reaction time of 8 h and was purified by neutral alumina column chromatography with ether–methanol (9:1, v/v) as eluant. The 2-(methoxycarbonyl)ethyl derivatives **7j** and **7k** were prepared with use of reaction times of 7 and 10 h, respectively, and purification by neutral alumina column chromatography with chloroform as eluant. The 5-methoxy analogue **7l** was prepared with use of a 6-h reaction time with purification by neutral alumina column chromatography with chloroform–methanol (9:1, v/v) as eluant followed by recrystallization from methanol–ether. The 4-methoxy derivative **7m** was subjected to reduction for 30 h, and the product was decolorized with activated charcoal. The ethylene ketal of the 5-acetyl compound **7n** was obtained with use of a 9-h reaction time. This product was purified initially by silica gel column chromatography with ether–methanol (9:1, v/v) as eluant followed by preparative silica gel TLC with ethyl acetate as development solvent, R_f 0.5. The 4-acetyl ethylene ketal **7o** was prepared with use of a 9-h reaction time. The product was decolorized with activated charcoal.

A solution of the ethylene ketal of **7n** (**7o**) (0.84 mmol) in 1 mL of water and 15 mL of acetone containing pyridinium tosylate (0.25 mmol) was heated at reflux for 3 h. Excess solvent was removed in vacuo and chloroform (50 mL) was added. The mixture was washed with saturated sodium bicarbonate (10 mL) and then brine (10 mL). The organic phase was separated and dried (Na_2SO_4) and the solvent removed in vacuo to give a solid product, which was washed with cold ether (10 mL) to yield the respective products **7n** and **7o**.

Compound **7a** exhibited the following spectral data: ^{1}H NMR δ 1.25 (d, J_{CH,CH_3} = 7 Hz, 3 H, CH_3), 2.02–2.42 (m, 2 H, tetrahydropyridinyl H_3), 3.15–3.58 (m, 1 H, tetrahydropyridinyl H_2), 3.58–3.83 (m, 2 H, tetrahydropyridinyl H_6), 5.51–6.04 (m, 2 H, tetrahydropyridinyl H_4, H_5), 7.03–7.98 (m, 6 H, phenyl hydrogens, NH, exchanges with deuterium oxide); IR 3230 (NH) and 1655 (CO) cm^{-1}. Anal. ($C_{13}H_{16}N_2O$) C, H, N.

5- and 4-(3-Methoxypropyl)-N-(3,6-dihydro-1(2H)-pyridinyl)benzamides 7p,q. Methanesulfonyl chloride (3.8 mmol) was added dropwise to a precooled solution of **7f** (**7g**) (0.5 g, 1.9 mmol) and triethylamine (5.8 mmol) in methylene chloride (10 mL) with stirring. The reaction mixture was stirred at 0 °C for 30 min and then sodium methoxide (0.54 g, 10 mmol) in methanol (20 mL) was added in three aliquots.

The reaction was allowed to proceed for 24 h at reflux temperature. Extraction with methylene chloride (4 × 50 mL), washing with brine (20 mL), drying (Na_2SO_4), and removal of the solvent in vacuo afforded pure **7q**. The 5-(3-methoxypropyl) product **7p** was purified by preparative silica gel TLC with

chloroform–methanol (9:1, v/v) as development solvent, R_f 0.4.

5- and 4-(3-Acetoxypropyl)-*N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamides 7r,s. Acetic anhydride (9.6 mmol) was added to a solution of **7f** (**7g**) (0.5 g, 1.9 mmol) in ethyl acetate (20 mL), and the reaction was allowed to proceed at 50 °C for 4 h with stirring. Removal of the solvent in vacuo and purification of the product by neutral alumina column chromatography with ether–methanol (9:1, v/v) as eluant afforded the respective products **7r** and **7s**.

5- and 4-(2-Carboxyethyl)-*N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamides 7t,u. A solution of **7j** (**7k**) (2.8 mmol) in methanol (5 mL) was added to a solution of sodium hydroxide (0.023 g, 5.7 mmol) in methanol (30 mL). The reaction mixture was heated at reflux for 3 h after which the pH was adjusted to 4 by using 0.1 N hydrochloric acid. Removal of the solvent in vacuo gave a solid, which was washed with water (20 mL) and then cold ether (10 mL) to yield the respective products **7t** and **7u**.

5- and 4-(1-Hydroxyethyl)-*N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamides 7v,w. A solution of **7n** (**7o**) in absolute ethanol (20 mL) was added dropwise to a solution of sodium borohydride (25 mmol) in absolute ethanol precooled to 0 °C. The reduction was allowed to proceed for 5 h at 0 °C with stirring. Water (80 mL) was added, and the mixture was allowed to return to 25 °C. Extraction with chloroform (4 × 75 mL), drying (Na_2SO_4), and removal of the solvent in vacuo afforded **7v** and **7w**, respectively.

6-Oxo-*N*-(3,6-dihydro-1(2*H*)-pyridinyl)benzamide (7x). *N*-(3,6-Dihydro-1(2*H*)-pyridinyl)benzamide **2** (0.5 g, 2.48 mmol) was added to a mixture of sodium dihydrogen phosphate monohydrate (0.41 g) and disodium hydrogen phosphate heptahydrate (0.8 g) in water (15 mL) and *m*-chloroperbenzoic acid (0.47 g, 2.72 mmol) in methylene chloride (15 mL). The reaction mixture was stirred at 25 °C for 3 h, additional *m*-chloroperbenzoic acid (0.47 g, 2.72 mmol) was added, and the reaction was allowed to proceed for a further 48 h. The organic layer was separated and the aqueous layer extracted with methylene chloride (3 × 40 mL). The combined organic extracts were washed successively with 15% aqueous sodium thiosulfate (2 × 30 mL), 10% aqueous sodium carbonate (2 × 30 mL), and then brine (2 × 30 mL). The methylene chloride extract was dried (Na_2SO_4). Removal of the solvent in vacuo gave a crude product, which was initially purified by elution from a 2.5 × 20 cm neutral alumina column using ether–methanol (9:1, v/v) (200 mL) as eluant. Removal of the solvent from the eluant and further purification by preparative silica gel TLC with ether–methanol (9:1, v/v) as development solvent afforded **7x** as a white crystalline solid: ^{1}H NMR δ 2.32–2.74 (m, 2 H, tetrahydropyridinyl H_3), 3.78 (t, $J_{2,3}$ = 7 Hz, 2 H, tetrahydropyridinyl H_2), 5.94 (d, $J_{4,5}$ = 10 Hz, 1 H, tetrahydropyridinyl H_5), 6.63 (d of t, $J_{4,5}$ = 10 Hz, $J_{3,4}$ = 7 Hz, 1 H, tetrahydropyridinyl H_4), 7.03–7.9 (m, 5 H, phenyl hydrogens), 10.48 (s, 1 H, NH, exchanges with deuterium oxide); IR 3300 (NH), 1670 (CO), and 1690 (C_6-O) cm^{-1}. Anal. ($C_{12}H_{12}N_2O_2$) C, H, N.

3-Methyl-*N*-(hexahydropyridinyl)benzamide (10). Hydrogenation of **7h** (**7b**) (2.48 mmol) in methanol (20 mL) in the presence of 10% palladium-on-charcoal (50 mg) and hydrogen gas at 40 psi for 4 h, filtration, and removal of the solvent in vacuo afforded a solid, which on recrystallization from ethyl acetate afforded **10** as a white crystalline solid: 95% yield, mp 163–164 °C. Anal. ($C_{13}H_{18}N_2O$) C, H, N.

Blood Glucose Determination. Blood glucose was measured by using the procedure developed by Barthelmai and Czok.[11] Four male Wistar rats weighing 230–260 g were used in each group. The test compound, suspended in 1% tragacanth in distilled water, was administered orally to overnight-fasted rats. Capillary blood samples were obtained from the tail at 0, 2, and 4 h posttreatment. The sera derived from these blood samples were analyzed for glucose by spectrophotometric determination of enzymatically produced $NADH_2$ by using an Abbott ABA-100 analyzer. Table II summarizes the blood glucose concentration results.

Partition Coefficient. The partition coefficient P, which was calculated as $P = C_{octanol}/C_{H_2O}$, was determined by using the method of Fujita et al.[16] The results are summarized in Table II.

Acknowledgment. We are grateful to the Medical Research Council of Canada (Grant MT-4888) for financial support of this work and to the Alberta Heritage Foundation for Medical Research for a Studentship (to J.Y.).

Registry No. **2**, 35990-31-9; **3a**, 109-06-8; **3b**, 108-99-6; **3c**, 108-89-4; **3d**, 583-58-4; **3e**, 372-47-4; **3f**, 2859-67-8; **3g**, 2629-72-3; **3h**, 10072-09-0; **3i**, 1007-48-3; **3j**, 84199-98-4; **3k**, 90610-07-4; **3l**, 7295-76-3; **3m**, 620-08-6; **3n**, 55676-25-0; **3o**, 60553-33-5; **5a**, 51135-75-2; **5b**, 59046-22-9; **5c**, 57156-85-1; **5d**, 104642-44-6; **5e**, 104642-45-7; **5f**, 104642-46-8; **5h**, 104642-47-9; **5j**, 104642-48-0; **5k**, 104642-49-1; **6a**, 17408-47-8; **6b**, 31382-86-2; **6c**, 32363-75-0; **6d**, 104642-55-9; **6e**, 63160-05-4; **6f**, 104642-56-0; **6g**, 104642-57-1; **6h**, 104642-58-2; **6i**, 104642-59-3; **6j**, 104642-60-6; **6k**, 104642-61-7; **6l**, 28460-35-7; **6m**, 104642-62-8; **6n**, 104642-63-9; **6o**, 104642-64-0; **7a**, 104642-65-1; **7b**, 104642-66-2; **7c**, 104642-67-3; **7d**, 104642-68-4; **7e**, 104642-69-5; **7f**, 66611-58-3; **7g**, 104642-70-8; **7h**, 104642-71-9; **7i**, 104642-72-0; **7j**, 104642-73-1; **7k**, 104642-74-2; **7l**, 104642-75-3; **7m**, 104642-76-4; **7n**, 104642-77-5; **7n** (ethylene ketal), 104642-84-4; **7o**, 104642-78-6; **7o** (ethylene ketal), 104642-85-5; **7p**, 104642-79-7; **7q**, 104642-80-0; **7r**, 104642-81-1; **7s**, 104642-82-2; **7t**, 104642-83-3; **7u**, 104642-86-6; **7v**, 104642-87-7; **7w**, 104642-88-8; **7x**, 104642-89-9; **8g**, 104642-50-4; **8l**, 104642-51-5; **8m**, 104642-52-6; **8n**, 104642-53-7; **8o**, 104642-54-8; **10**, 104642-90-2; C_6H_5COCl, 98-88-4; $H_3CCO_2C-OCH_3$, 108-24-7; $HO(CH_2)_2OH$, 107-21-1; $C_6H_5CONHNH_2$, 613-94-5; 1-chloro-2,4-dinitrobenzene, 97-00-7.