(Z)-NCC₆H₄CH=CHC₆H₅, 19466-33-2; 2-HOC₆H₄CHO, 90-02-8; 3-C₆H₅OC₆H₄CHO, 39515-51-0; 3-HOC₆H₄CO(CH₂)₄CH₃, 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(2H)-pyridinyl)benzamides with Hyperglycemic-Hypoglycemic Activity

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A group of N-(3,6-dihydro-1(2H)-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(2H)-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 70, 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(2H)-pyridinyl) amides 1 via the sodium borohydride reduction of N-(carbonylimino)pyridinium ylides,¹ which exhibited significant hypergly-cemic activities.^{2,3} The lead compound **2** elevated blood



R=alkyi, cycloaikyi, arylaikyi, alkyloxy, arylaikyloxy, 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(2H)-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(2H)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 D. 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-



a, R = 2-CH3; b, R = 3-CH3; c, R = 4-CH3; d, R = 3,4-(CH3)2; e, R = 3-F; $f, R = 3-CH_2CH_2CH_2OH; g, R = 4-CH_2CH_2CH_2OH;$ 3-6h, R=3-CH2OCOCH3; 7h, R=3=CH2; 3-6i, R=4-CH2OCOCH3;

71, R= 4-CH2OH; J, R= 3-CH2CH2CO2CH3; k, R= 4-CH2CH2CO2CH3

dienal benzoic acid hydrazones 9, which on heating cyclized to afford the respective N-[(phenylcarbonyl)imino]pyridinium ylides 6g, 1-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-(3,6dihydro-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 reaction⁴ following initial attack by hydride anion at C-2 and/or C-6 (see Scheme III). The 200-MHz ¹H NMR spectrum of 7h (Me₂SO- 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-

⁽¹⁾ Knaus, E. E.; Redda, K. J. Heterocycl. Chem. 1976, 13, 1237. Yeung, J. M.; Corleto, L. A.; Knaus, E. E. J. Med. Chem. 1982, (2)

^{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. Yates, P.; Helferty, P. H.; Mahler, P. Can. J. Chem. 1983, 61, (5)

^{78.}

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



	R	yield, %	procedure			exact mass	
compd				mp, °C	formula	calcd	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	Α	215 - 217	$C_{13}H_{12}N_2O$	212.0950	212.0935
6c	$4-CH_3$	18	Α	oil	$C_{13}H_{12}N_2O$	212.0950	212.0939
6d	$3.4-(CH_3)_2$	59.5	Α	104 - 106	$C_{14}H_{14}N_2O$	226.1106	226.1088
6e	3-F	99.2	В	$179 - 181^{a}$	$C_{12}H_9N_2OF$		ND^{b}
6 f	3-CH ₂ CH ₂ CH ₂ OH	97	В	oil	$C_{15}H_{16}N_2O_2$	256.1212	256.1217
6g	4-CH ₂ CH ₂ CH ₂ OH	33	C	163 - 165	$C_{15}H_{16}N_2O_2$	256.1212	256.1187
6 h	3-CH ₂ OCOCH ₃	97.5	В	oil	$C_{15}H_{14}N_2O_3$	270.1004	270.0992
6i	4-CH ₂ OCOCH ₃	64	В	154 - 155	$C_{15}H_{14}N_2O_3$	270.1004	270.0991
6j	3-CH ₂ CH ₂ CO ₂ CH ₃	87	В	oil	$C_{16}H_{16}N_2O_3$	284.1161	284.1140
6k	4-CH ₂ CH ₂ CO ₂ CH ₃	54	В	136-138	$C_{16}H_{16}N_2O_3$	284.1161	284.1141
61	3-OCH ₃	38.6	С	$136 - 138^{\circ}$	$C_{13}H_{12}N_2O_2$		ND^b
6m	4-OCH ₃	7.6	С	190-191	$C_{13}H_{12}N_2O_2$	228.0898	228.0883
6 n	$3-COCH_3$ (ethylene ketal)	20	С	123 - 125	$C_{16}H_{16}N_2O_3$	284.1161	284.1145
60	4-COCH ₃ (ethylene ketal)	43	С	194 - 195	$C_{16}H_{16}N_2O_3$	284.1161	284.1148

^aLiterature¹⁷ mp 181-182 °C. ^bND = not determined. ^cLiterature¹⁷ mp 137-138 °C.

Scheme II



g.R=4-CH₂CH₂CH₂OH; I,R=3-OCH₃; m,R=4-OCH₃; n,R=3-COCH₃(ethylene ketal); o,R=4-COCH₃(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-(2H)-pyridinyl)benzamide (7i).⁶ The 5- and 4-methoxy-

propyl 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.0** 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(2H)-pyridinyl)benzamides 7 were determined by spectrophotometric measurement of enzymatically produced NADH₂.¹¹

Discussion

A group of N-(3,6-dihydro-1(2H)-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(2H)-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-CH₃ compound 7b (potent hyperglycemic, electron donating), the 5-F analogue 7e (hyperglycemic, electron withdrawing), and the 5-OCH₃ derivative 71 (weak hypo-

(9) Witkop, B.; Patrick, J. B. J. Am. Chem. Soc. 1951, 73, 2196.

(11) Barthelmai, W.; Czok, R. Klin. Wochenschr. 1962, 40, 585.

 ⁽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.

⁽¹⁰⁾ Avasthi, K.; Knaus, E. E. Can. J. Pharm. Sci. 1981, 16, 53.

hypoglycemic-hyperglycemic

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



						act	
						% change in blood glucose	
		yield,				concn post	treatment
compd	R	%	mp, °C	P^a	formula ^b	2 h	4 h
7a	2-CH ₃	45	147-150	5.0	$C_{13}H_{16}N_2O$	$+12 \pm 4.2^{d}$	$+16 \pm 2.4^{d}$
7b	$5-CH_3$	45	156 - 157	23.6	$C_{13}H_{16}N_2O$	$+124 \pm 43^{d}$	$+116 \pm 44^{d}$
7c	$4-CH_3$	61	181 - 182	15.7	$C_{13}H_{16}N_2O$	$+48 \pm 23$	$+43 \pm 23$
7d	$4,5-(CH_3)_2$	24	191 - 192	22.3	$C_{14}H_{18}N_2O$	$+27 \pm 13$	$+20 \pm 6.9$
7e	5-F	100	151 - 153	18.5	$C_{12}H_{13}N_2OF$	$+64 \pm 1.3^{d}$	$+42 \pm 1.0^{d}$
7 f	5-CH ₂ CH ₂ CH ₂ OH	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	$C_{15}H_{20}N_2O_2$	$+4 \pm 0.2$	-6 ± 0.3
7h	$3-\mathrm{CH}_2$	80	157 - 158	23.5	$C_{13}H_{14}N_2O$	$+5 \pm 0.1$	$+4 \pm 0.2$
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	$+6 \pm 0.2$
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
71	$5-OCH_3$	73	162 - 163	41.4	$C_{13}H_{16}N_2O_2$	-7 ± 0.6	-9 ± 0.5
7 m	$4-OCH_3$	93	167 - 168	14.4	$C_{13}H_{16}N_2O_2$	$+5 \pm 0.1$	$+7 \pm 0.3$
7 n	5-COCH ₃	30	179 - 180	0.8	$C_{14}H_{16}N_2O_2$	-5 ± 0.2	-17 ± 0.3^{d}
70	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	$C_{16}H_{22}N_2O_2$	$+1 \pm 0.3$	-9 ± 0.3
7 r	$5-CH_2CH_2CH_2OCOCH_3$	55	163 - 165	31.1	$C_{17}H_{22}N_2O_3$	-8 ± 0.2	$+7 \pm 0.2$
7s	$4-CH_2CH_2CH_2OCOCH_3$	97	140 - 142	33.4	$C_{17}H_{22}N_2O_3$	$+2 \pm 0.6$	$+3 \pm 0.4$
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	$+7 \pm 0.4$
7 v	5-CH(OH)CH ₃	91	181 - 183	2.8	$C_{14}H_{18}N_2O_2$	-8 ± 0.2	-16 ± 0.1^{d}
7 w	$4-CH(OH)CH_3$	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	$C_{12}H_{12}N_2O_2$	$+1 \pm 4.2$	$+4 \pm 0.5$
2						+78	+50
chlorpropamide						-42 ± 12.1^{d}	-38 ± 9.3^{d}

^a Partition coefficient. P = concentration in octanol/concentration in water. ^bAll 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. ^dThe 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 (71,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 70 lowered blood glucose 19% at 4 h. There was no significant difference in hypoglycemic activity between the acetyl analogues 7n,o and the 1hydroxyethyl 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 elévating 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 CDCl₃, unless otherwise stated, with Me₄Si 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 $\pm 0.4\%$ 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 unstable¹⁴ 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 hydrox-ylamine-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.

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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: ¹H NMR (Me₂SO-d₆) δ 2.6 (s, 3 H, CH₃), 7.35–8.32 (m, 8 H, H₃, H₄, H₅ pyridinium hydrogens, phenyl hydrogens), 8.74 (d, J_{5,6} = 7 Hz, 1 H, H₆); IR 1560 (CO) cm⁻¹; exact mass for C₁₃H₁₂N₂O 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)hydroxylamine¹³ (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 $(4 \times 35 \text{ mL})$, decolorization with activated charcoal, drying (Na₂SO₄), 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 $(4 \times 25 \text{ mL})$, 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, 61-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,1-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,1–o. Ylides 6g,1–m were purified by neutral alumina column chromatography with 300 mL of ether/methanol (6g), 300 mL of chloroform-methanol (8:2, v/v) (61), 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) (60, 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 $(4 \times 75 \text{ mL})$, 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 5and 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 71 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 70 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 (70) (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 (Na₂SO₄) 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: ¹H NMR δ 1.25 (d, $J_{CH,CH_3} = 7$ Hz, 3 H, CH₃), 2.02–2.42 (m, 2 H, tetrahydropyridinyl H₃), 3.15–3.58 (m, 1 H, tetrahydropyridinyl H₂), 3.58–3.83 (m, 2 H, tetrahydropyridinyl H₆), 5.51–6.04 (m, 2 H, tetrahydropyridinyl H₄, H₅), 7.03–7.98 (m, 6 H, phenyl hydrogens, NH, exchanges with deuterium oxide); IR 3230 (NH) and 1655 (CO) cm⁻¹. Anal. (C₁₃H₁₆N₂O) C, H, N. 5- and 4-(3-Methoxypropyl)-N-(3,6-dihydro-1(2H)-

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 $(4 \times 50 \text{ mL})$, 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(2H)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(2H)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(2H)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 (Na₂SO₄), and removal of the solvent in vacuo afforded 7v and 7w, respectively.

6-Oxo-N-(3,6-dihydro-1(2H)-pyridinyl)benzamide (7x). N-(3,6-Dihydro-1(2H)-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 $(3 \times$ 40 mL). The combined organic extracts were washed successively with 15% aqueous sodium thiosulfate $(2 \times 30 \text{ mL})$, 10% aqueous sodium carbonate $(2 \times 30 \text{ mL})$, and then brine $(2 \times 30 \text{ mL})$. The methylene chloride extract was dried (Na₂SO₄). 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: ¹H NMR δ 2.32–2.74 (m, 2 H, tetrahydropyridinyl H₃), 3.78 (t, $J_{2,3} = 7$ Hz, 2 H, tetrahydropyridinyl H₂), 5.94 (d, $J_{4,5} = 10$ Hz, 1 H, tetrahydropyridinyl H₅), 6.63 (d of t, $J_{4,5} = 10$ Hz, $J_{3,4} = 7$ Hz, 1 H, tetrahydropyridinyl H₄), 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 (C₆-O) cm⁻¹. Anal. $(C_{12}H_{12}N_2O_2)$ C, H, N.

3-Methyl-N-(hexahydropyridinyl)ben zamide (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 NADH₂ 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 $P = C_{\text{octanol}}/C_{\text{H}_2\text{O}}$, was determined by using the method of Fujita et al.¹⁶ The results are summarized in Table II.

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