(C=C), 1618 (quinone) cm^{-1}; UV–Vis λ_{max} (CH_3OH) 222 nm (ε 21 000), 234 (22 200), 269 (27 800), 503 (15 400), 517 (15 700), 554 (7240). Anal. ($C_{30}H_{26}F_5NO_{11}$) C, H, F, N.

***N*-(Heptafluorobutyryl)-9,10-anhydroadriamycin (17).** A solution of 0.15 mL (0.58 mmol) of heptafluorobutyric anhydride in 3 mL of ether was added dropwise at 0 °C to a stirred solution of 29 mg (0.05 mmol) of adriamycin in 10 mL of dry pyridine. After stirring for 2 h at 10–15 °C, the reaction mixture was worked up in the same manner as before to provide 18 mg (50% yield) of red solid: mp 148–150 °C dec; $[\alpha]_D$ +498° (c 0.009, CH_3OH); IR (KBr) 3410 (broad, OH, NH), 1710 (ketone, amide), 1695 (C=C), 1668 (quinone) cm^{-1}; UV–Vis λ_{max} (CH_3OH) 220 nm (ε 21 700), 233 (24 500), 270 (30 200), 504 (17 000), 516 (16 000), 554 (8000). Anal. ($C_{31}H_{26}F_7NO_{11}\cdot H_2O$) C, H, F, N.

***N*-(Pentafluoropropionyl)-9,10-anhydroadriamycin 14-Valerate (19).** In a like manner, reaction of 300 mg (0.48 mmol) of adriamycin 14-valerate and 1 mL (5 mmol) of pentafluoropropionic anhydride in ethyl acetate–ether afforded 202 mg (54%) of product: mp 215–217 °C dec; $[\alpha]_D$ +270° (c 0.033, CH_3OH); IR (KCl) 3385 (broad, OH, NH), 1720, 1690, 1620 (carbonyls); UV–Vis λ_{max} (CH_3OH) 223 nm (ε 40 400), 241 (29 000), 278 (10 300), 478 (13 100), 495 (12 800), 530 (6150). Anal. ($C_{35}H_{36}F_5NO_{13}$) C, H, N; F: calcd, 12.27; found, 11.82.

***N*-(Heptafluorobutyryl)-9,10-anhydroadriamycin 14-Valerate (20).** As before, 300 mg (0.48 mmol) of adriamycin 14-valerate and 0.9 mL (3.5 mmol) of heptafluorobutyric anhydride in ethyl acetate–ether gave 230 mg (56%) of product: mp 218–220 °C dec; $[\alpha]_D$ +251° (c 0.038, CH_3OH); IR (KCl) 3460, 3420 (OH, NH), 1700, 1618 (carbonyls); UV–Vis λ_{max} (CH_3OH) 223 nm (ε 42 700), 240 (29 500), 277 (9410), 478 (14 000), 494 (13 800), 529 (7320). Anal. ($C_{36}H_{36}F_7NO_{13}\cdot 1.5H_2O$) C, H, F, N.

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Synthesis of *N*-(Carbonylamino)-1,2,3,6-tetrahydropyridines with Analgesic, Antiinflammatory, and Hyperglycemic Activity

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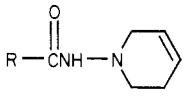
A group of *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines was synthesized to investigate the effects that changes in functionality at the carbonyl group have on analgesic, antiinflammatory, and hyperglycemic activities. One of the most active analgesic compounds was *N*-[(ethoxycarbonyl)amino]-1,2,3,6-tetrahydropyridine (**5o**), which was comparable to that of morphine. Pretreatment with naloxone did not alter the activity of **5o** or **5q**. *N*-[(2-Furanylcarbonyl)amino]-1,2,3,6-tetrahydropyridine (**5q**) was the most potent hyperglycemic agent, elevating blood glucose 181% at 2 and 4 h after a 100 mg/kg po dose.

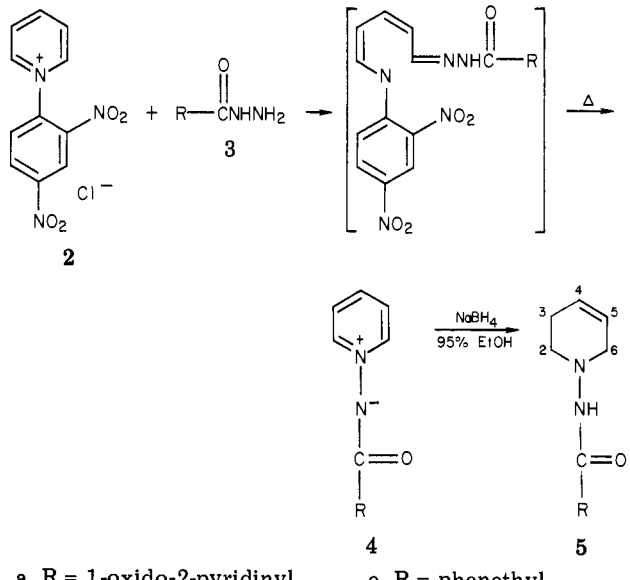
In an earlier study we described a facile method for the synthesis of *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines **1**[1] via the sodium borohydride reduction of *N*-(carbonylimino)pyridinium ylides, which exhibited significant analgesic, antiinflammatory, and hyperglycemic activities.[2] It was therefore of interest to extend this series to determine what effect incorporation of other ring systems and functionality would have on pharmacological activity. We now describe the synthesis and analgesic, antiinflammatory, and hyperglycemic activities of structurally related *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines **5**.



1a, R = phenyl
b, R = 2-pyridyl
1c, R = 3-pyridyl
d, R = 4-pyridyl

Chemistry. *N*-(Carbonylimino)pyridinium ylides **4** were prepared via two synthetic procedures. Reaction of 2,4-dinitrophenylpyridinium chloride (**2**) with carboxylic acid hydrazides **3a–h** yielded the respective 5-(2,4-dinitroanilino)penta-2,4-dienal carboxylic acid hydrazones, which on heating cyclized to *N*-(carbonylimino)pyridinium ylides **4a–h** (Scheme I). Alternatively, reaction of *N*-aminopyridinium iodide (**6**), obtained by amination of pyridine using hydroxylamine-*O*-sulfonic acid, with acid chlorides **7i–t** afforded ylides **4i–t** as illustrated in Scheme II and summarized in Table I. Reduction of ylides **4a–t** using sodium borohydride in ethanol at ice-bath temperature gave the title *N*-(carbonylamino)-1,2,3,6-tetra-

Scheme I

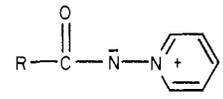


a, R = 1-oxido-2-pyridinyl
b, R = 3-pyridinylmethyl
c, R = 3-indolylmethyl
d, R = 3,4-methylenedioxyphenylmethyl
e, R = phenethyl
f, R = phenoxymethyl
g, R = cyclohexyl
h, R = *n*-hexyl

(1) Knaus, E. E.; Redda, K. *J. Heterocycl. Chem.* **1976**, *13*, 1237.
(2) Knaus, E. E.; Redda, K.; Wandelmaier, F. W. U.S. Patent 4 088 653, May 9, 1978.

0022-2623/82/1825-0191$01.25/0

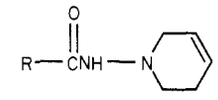
Table I. Some Physical Data of *N*-(Carbonylimino)pyridinium Ylides 4



compd	R	yield, %	procedure	mp, °C	formula	exact mass calcd	exact mass found
4a	1-oxido-2-pyridinyl	21.1	A	201-204	$C_{11}H_9N_3O_2$	215.0695	215.0697
4b	3-pyridinylmethyl	29.2	A	oil	$C_{12}H_{11}N_3O$	213.0906	213.0904
4c	3-indolylmethyl	8	A	oil	$C_{15}H_{13}N_3O$	251.1059	251.1058
4d	3,4-(methylenedioxy)phenylmethyl	47	A	oil	$C_{14}H_{12}N_2O_3$	256.0848	256.0848
4e	phenylethyl	81.5	A	oil	$C_{14}H_{14}N_2O$	226.1106	226.1105
4f	phenoxymethyl	22	A	101-104	$C_{13}H_{12}N_2O_2$	228.0898	228.0898
4g	cyclohexyl	7.4	A	oil	$C_{12}H_{16}N_2O$	204.1263	204.1261
4h	*n*-hexyl	13.6	A	oil	$C_{11}H_{16}N_2O$	192.1262	192.1264
4i	methyl	88	C	167-168[a]	$C_7H_8N_2O$		ND[b]
4j	*tert*-butyl	99.9	C	65-67	$C_{10}H_{14}N_2O$	178.1106	178.1107
4k	cyclopropyl	30	C	151-153	$C_9H_{10}N_2O$	162.0793	162.0792
4l	cyclopentyl	85.6	C	64-66	$C_{11}H_{14}N_2O$	190.1106	190.1107
4m	cycloheptyl	99.5	C	92-93	$C_{13}H_{18}N_2O$	218.1419	218.1421
4n	1-adamantyl	94	E	124-126	$C_{16}H_{21}N_2O$	257.1613	257.1608
4o	ethoxy	82.4	C	106	$C_8H_{10}N_2O_2$	166.0743	166.0741
4p	1-naphthoxymethyl	65.1	E	118-119	$C_{17}H_{14}N_2O_2$	278.1056	278.1056
4q	2-furanyl	86.2	C	227-228	$C_{10}H_8N_2O_2$	188.0585	188.0586
4r	2-thienyl	99.5	C	224-226	$C_{10}H_8N_2OS$	204.0357	204.0359
4s	1-methyl-2-pyrrolyl	86	C	152-154	$C_{11}H_{11}N_3O$	201.0904	201.0902
4t	2-[[1-(1,2,3,6-tetrahydropyridinyl)amino]-carbonyl]-6-pyridinyl[c]						

[a] Literature[10] mp 168 °C. [b] ND = not determined. [c] Not isolated; see procedure F.

Table II. Some Physical Data of *N*-(Carbonylamino)-1,2,3,6-tetrahydropyridines 5



compd	R	yield, %	procedure	mp, °C	partition coefficient (*P*)[a]	formula[b]
5a	1-oxido-2-pyridinyl	82.6	B	91-93	0.48	$C_{11}H_{13}N_3O_2$
5b	3-pyridinylmethyl	51.3	B	133-136	1.11	$C_{12}H_{15}N_3O$
5c	3-indolylmethyl	35.2	B	138-141	ND[c]	$C_{15}H_{17}N_3O$
5d	3,4-(methylenedioxy)phenylmethyl	55	B	oil	4.81	$C_{14}H_{16}N_2O_3$
5e	phenylethyl	24	B	81-84	ND[c]	$C_{14}H_{18}N_2O$
5f	phenoxymethyl	85	B	104-107	0.88	$C_{13}H_{16}N_2O_2$
5g	cyclohexyl	56.2	B	155-158	2.84	$C_{12}H_{20}N_2O$
5h	*n*-hexyl	20.2	B	75-78	ND[c]	$C_{12}H_{22}N_2O$
5i	methyl	100	D	102-103	3.33	$C_7H_{12}N_2O$
5j	*tert*-butyl	99.7	D	133-134	10.6	$C_{10}H_{18}N_2O$
5k	cyclopropyl	88.5	D	124-125	13.3	$C_9H_{14}N_2O$
5l	cyclopentyl	92.3	D	145-146	84	$C_{11}H_{18}N_2O$
5m	cycloheptyl	95.2	D	152-153	31.7	$C_{13}H_{22}N_2O$
5n	1-adamantyl	95	D	194-196	28.3	$C_{16}H_{24}N_2O$
5o	ethoxy	98.2	D	67-68	12.4	$C_8H_{14}N_2O_2$
5p	1-naphthoxymethyl	62.8	D	125-126	91.4	$C_{17}H_{18}N_2O_2$
5q	2-furanyl	100	D	101-102	6.4	$C_{10}H_{12}N_2O_2$
5r	2-thienyl	89.9	D	124-125	76.2	$C_{16}H_{12}N_2OS$
5s	1-methyl-2-pyrrolyl	86.4	D	127-128	20.0	$C_{11}H_{15}N_3O$
5t	2-[[1-(1,2,3,6-tetrahydropyridinyl)amino]-carbonyl]-6-pyridinyl	9	F	225-226	0.3	$C_{17}H_{21}N_5O_2$

[a] *P* = concentration in octanol/concentration in water. [b] All compounds gave analyses for C, H, and N within ±0.4% of theoretical values. [c] ND = not determined.

hydropyridines **5a–t** as illustrated in Schemes I and II and summarized in Table II.

The synthetic procedure illustrated in Scheme II was generally superior to that shown in Scheme I, since this method afforded ylides **4** in higher yield. The reduction of **4** using sodium borohydride gave higher yields of **5** when absolute ethanol was employed as solvent rather than 95% ethanol. Synthesis of the 1-adamantyl and 1-naphthyloxymethyl ylides **4n** and **4p** required the presence of a phase-transfer reagent such as cetyltrimethylammonium bromide. Failure of these reactions in the absence of the phase-transfer reagent is likely due to the low solubility of the acid chlorides **7n** and **7p** in 10% aqueous sodium hydroxide.

Pharmacology. The *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines were tested for analgesic activity using the phenylquinone writhing test[3] and for antiinflammatory

(3) Collier, H. O.; Dinneen, L. C.; Johnson, C. A.; Schneider, C. *Br. J. Pharmacol. Chemother.* **1968**, *32*, 295.

Table III. Some Pharmacological Data of *N*-(Carbonylamino)-1,2,3,6-tetrahydropyridines 5

	analgesic act., inhib act. on phenylquinone writhing[a]		inhib act. on carageenan paw edema[b]			hypoglycemic-hyperglycemic act.[c]		
							% change in blood glucose concns posttreatment	
compd	dose, mg/kg sc	% inhibn	dose, mg/kg sc	% inhibn of 3h	% inhibn of 5h	dose, mg/kg po	2 h	4 h
5a	128	55	128	34	0	128	<-20	<-20
5b	14.5	50	128	50	50	100	0	-6
5c	NT[d]		NT[d]			NT[d]		
5d	60	80	120	0	0	100	+7	+21
5e	120	42	120	83	83	100	+27	+25
5f	25	50	120	83	80	41	+50	
						53		+50
5g	16.5	50	120	50	84	36.5	+50	
						53		+50
5h	NT[d]		NT[d]			NT[d]		
5i	30	99 ± 0.20	NT[d]			100	+35 ± 10.77	+36 ± 7.66
5j	30	100 ± 0.00	NT[d]			100	+70 ± 36.73	+101 ± 73.64
5k	30	100 ± 0.0	NT[d]			100	+66 ± 28.03	+111 ± 35.89
5l	30	98 ± 0.24	NT[d]			100	+54 ± 12.54	+22 ± 2.33
5m	30	98 ± 0.60	NT[d]			100	+100 ± 28.02	+82 ± 36.2
	0.00075	50 ± 0.87	NT[d]			50	+50 ± 17.37	
						60		+50 ± 7.42
5n	30	86 ± 0.93	NT[d]			100	+33 ± 8.20	+22 ± 6.89
5o	30	99 ± 0.20	NT[d]			100	+27 ± 6.92	+91 ± 60.50
	3	85.6 ± 0.68						
	3	86.0 ± 0.32[e]						
	0.00046	50 ± 0.37[f]						
5p	30	76 ± 1.55	NT[d]			100	+9 ± 7.60	+14 ± 6.17
5q	30	99 ± 1.20	NT[d]			100	+181 ± 45.51	+182 ± 71.45
	10	98.4 ± 0.24				17	+50 ± 32.94	
	10	99.2 ± 0.20[g]				30		+50 ± 33.93
	0.0075	50 ± 2.27						
5r	30	77 ± 0.73	NT[d]			100	+116 ± 45.38	+64 ± 17.48
5s	30	90 ± 0.98	NT[d]			100	+35 ± 17.30	+25 ± 12.14
5t	30	60 ± 1.14	NT[d]			100	+8 ± 4.60	+10 ± 5.81
aspirin	50	50						
dextropropoxyphene	56	50						
morphine sulfate	0.038	50 ± 1.61						
indomethacin			12	17	83			

[a] The result is the mean value, or the mean value ± SEM, of five animals. [b] The result is the mean value of six animals. [c] The result is the mean value, or the mean value ± SEM, of four animals. Hyperglycemic activity is indicated by a plus (+) number and hypoglycemic activity as indicated by a negative (-) number. [d] NT = not tested. [e] Naloxone hydrochloride (0.6 mg/kg sc) was administered 15 min prior to injection of 5o. [f] Compound 5o exhibited an ED_{50} of 19.5 mg/kg ± 0.91 (five animals) in the mouse hot-plate test at 55 ± 0.5 °C at 30 min after dosing. Morphine sulfate exhibited an ED_{50} of 3.1 mg/kg sc in the same test (ref 12). [g] Naloxone hydrochloride (2 mg/kg sc) was administered 15 min prior to injection of 5q.

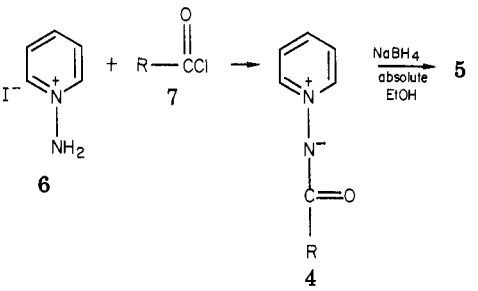
activity using the carrageenan-induced paw edema method.[4] Blood glucose determinations were effected by spectrophotometric measurement of enzymatically produced $NADH_2$[5] (see Experimental Section).

Discussion

The analgesic test results suggest that the *N*-(carbonylamino)-1,2,3,6-tetrahydropyridine moiety is the most important structural feature, since analgesic potency is independent of the steric and physicochemical properties of the R substituent for compounds **5**. For example, compounds having aryl, arylalkyl, aryloxy, alkoxy, alkyl, cycloalkyl, and five-membered heterocyclic ring R substituents all exhibit significant activities relative to aspirin and morphine (See Table III).

The antiinflammatory test results obtained indicate that *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines **5a,b,e–g** exhibit significant activity relative to indomethacin. Incorporation of an ethylene linkage as in **5e** or an oxymethylene group as in **5f** between the phenyl ring and the carbonyl moiety (cf. **1a** which caused a 25 and 50% inhibition after 3 and 5 h for a dose of 64 mg/kg sc)[2] or a methylene spacer between the 3-pyridyl ring and the

Scheme II



i, R = methyl
j, R = *t*-butyl
k, R = cyclohexyl
l, R = cyclopentyl
m, R = cycloheptyl
n, R = 1-adamantyl
o, R = ethoxy
p, R = 1-naphthyloxymethyl
q, R = 2-furanyl
r, R = 2-thienyl
s, R = 1-methyl-2-pyrrolyl
t, R = 2-[[1-(1,2,3,6-tetrahydropyridinyl)amino]carbonyl]-6-pyridinyl

(4) Winter, C. A. "International Symposium on Non-Steroidal Antiinflammatory Drugs", Garattini, S.; Dukes, M. N. Eds.; Excerpta Medica Foundation: Amsterdam, 1965; p 190.
(5) Barthelmai, W.; Czok, R., *Klin. Wochenschr.* **1962**, *40*, 585.

carbonyl group as in **5b** (cf. **1c** which exhibited a 50% inhibition for a dose of 64 mg/kg sc)[2] did not change activity significantly. These results suggest that the distance between the tetrahydropyridine ring nitrogen and the ring system attached to the carbonyl moiety is not crucial for antiinflammatory activity, provided the inactivity of **5d** is attributable to the 3,4-methylenedioxy functionality present. The cyclohexyl derivative **5g** exhibited an activity similar to **1a**, which was reported previously.[2] Oxidation of the pyridyl nitrogen as in **5a** reduced antiinflammatory activity (cf. **1b** which exhibited a 25 and 75% inhibition after 3 and 5 h for a dose of 64 mg/kg sc).[2]

The partition coefficient P does not appear to have a significant influence on analgesic or antiinflammatory activity, since compounds of both high and low polarity are equiactive (See Table II). N-(Carbonylamino)-1,2,3,6-tetrahydropyridines **5** do not act at an opiate receptor, since pretreatment with naloxone hydrochloride did not alter the analgesic activity of **5o** or **5q**. The mechanism by which N-(carbonylamino)-1,2,3,6-tetrahydropyridines exhibit analgesic and antiinflammatory activities has not been determined. It is not known whether these compounds act as prostaglandin synthetase inhibitors.

The influence that the R substituent of N-(carbonylamino)-1,2,3,6-tetrahydropyridines **5** has upon blood glucose concentration was also investigated. Insertion of a spacer, such as the methylene group in **5b** between the 3-pyridyl ring and the carbonyl moiety (cf. **1c** which increased blood glucose **60%** after 2 h for a dose of 200 mg/kg po)[2] or an ethylene linkage as in **5e** (cf. **1a** which elevated blood glucose 78% after 2 h for a dose of 100 mg/kg po),[2] lowered blood glucose significantly. On the other hand, **5f** which has an oxymethylene spacer exhibited a potent hyperglycemic effect similar to **1a**. Oxidation of the pyridyl nitrogen as in **5a** lowers blood glucose concentration significantly, resulting in a mild hypoglycemic activity (cf. **1b** which elevated blood glucose 50% after 2 and 4 h for a dose of 100 mg/kg po).[2] N-(Carbonylamino)-1,2,3,6-tetrahydropyridines **5** do not require an aromatic R substituent, since alkyl (**5i–j**), cycloalkyl (**5g,k–n**), and alkoxy (**5o**) analogues all exhibit hyperglycemic effects. The five-membered ring heterocycles **5q–s** were also prepared in order to examine the effect of ring size and various hetero atoms on hyperglycemic activity. The 2-furanyl derivative **5q** was found to be more potent than the 2-thienyl compound **5r**, which in turn was more potent than the cyclopentyl **5l** and 2-pyrrolyl **5s** analogues. These results (See Table III) suggest that the N-(carbonylamino)-1,2,3,6-tetrahydropyridine moiety likely is the most important structural component, since activity is relatively independent of the nature of the R substituent. A correlation between the partition coefficient P and hyperglycemic activity is not evident from the results obtained. The mechanism by which N-(carbonylamino)-1,2,3,6-tetrahydropyridines elevate blood glucose is under investigation elsewhere.

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 with a Varian EM-360A spectrometer. Infrared spectra (potassium bromide unless otherwise noted) were taken on a Perkin-Elmer 267 spectrometer. Mass spectra were measured with an AEI-MS-50 mass spectrometer. NMR, IR, and mass spectra were in agreement with the assigned structures. All of the products described gave rise to a single spot on TLC using 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. N-Aminopyridinium iodide was prepared according to the procedure of Gösl and Meuwsen[6] by amination of pyridine using freshly prepared hydroxylamine-O-sulfonic acid.[7] 1-Oxido-2-(methoxycarbonyl)-pyridine was prepared according to the literature procedure.[8]

General Method for the Preparation of Carboxylic Acid Hydrazides 3. A solution of hydrazine monohydrate (0.687 g, 13.74 mmol) in 30 mL of methanol was added dropwise to a solution of the appropriate methyl ester or carboxylic acid (13.74 mmol) in methanol (40 mL), and the reaction was allowed to proceed at 60 °C for 1.5 h. Removal of the solvent in vacuo afforded carboxylic acid hydrazides **3a–h**. Using this procedure, we obtained **3a**: yield 2.0 g (95.2%); mp 146–148 °C; IR 3320 (NH), 3180 and 3160 (NH_2), 1660 (CO), 1250 cm^{-1} (N^+O^-); NMR (Me_2SO-d_6) δ 12.12 (s, 1 H, NH, exchanges with deuterium oxide), 8.13–8.7 (m, 2 H, C_3 H, C_6 H), 7.43–7.86 (m, 2 H, C_4 H, C_5 H), 5.0 (s, 2 H, NH_2, exchanges with deuterium oxide). Exact mass for $C_6H_7N_3O_2$: calcd, 153.0538; found (high-resolution MS), 153.0535. Anal. ($C_6H_7N_3O_2$) C, H, N.

Procedure A. General Method for the Preparation of N-(Carbonylamino)pyridinium Ylides 4a–h. A suspension of the carboxylic acid hydrazide **3** (12.95 mmol) in 40 mL of methanol was added to an ice-cooled solution of N-(2,4-dinitrophenyl)pyridinium chloride[9] (**2**; 1.82 g, 6.48 mmol) in 30 mL of methanol with stirring in five aliquots. Triethylamine (0.9 mL) was then added, and the reaction mixture was allowed to stand at room temperature overnight. The solid that precipitated was filtered off and washed in succession with 60 mL each of methanol, water, methanol, and ether. A suspension of the solid obtained above in dioxane–water (4:1, v/v) (200 mL) was heated under reflux for 12 h to afford a clear solution. The solvent was removed in vacuo below 55 °C, water was added to the residue, and the insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure to give a residue, which was purified by elution from a 2.5 × 21 cm neutral alumina column using 250 mL of ether–methanol (1:4, v/v) to give a tan solid. Using this procedure, we obtained **4a**: yield 0.295 g; IR 1250 cm^{-1} (N^+O^-); NMR (Me_2SO-d_6) δ 7.3–7.7 (m, 3 H, 1-oxidopyridinium C_4 H, C_5 H, pyridinium imino C_4 H), 7.85–8.28 (m, 3 H, 1-oxidopyridinium C_3 H, pyridinium imino C_3 H, C_5 H), 8.35 (m, 1 H, 1-oxidopyridinium C_6 H), 8.9 (d, $J_{2,3} = J_{5,6} = 7$ Hz, of d, $J_{2,4} = J_{4,6} = 2$ Hz, 2 H, pyridinium imino C_2 H, C_6 H).

Procedure B. General Method for the Preparation of N-(Carbonylamino)-1,2,3,6-tetrahydropyridines 5a–h. A solution of **4** (0.47 mmol) in 30 mL of 95% ethanol was added dropwise to a solution of sodium borohydride (0.05 g, 1.32 mmol) in 10 mL of 95% ethanol, precooled to 0 °C, during 20 min. After stirring for 4 h at 0 °C, the reaction mixture was poured onto crushed ice (150 mL) and allowed to come to room temperature. Extraction with chloroform (4 × 75 mL), drying (Na_2SO_4), and removal of the solvent in vacuo resulted in **5**. Using this procedure, we prepared **5a**: yield 0.085 g; IR ($CHCl_3$) 3440 (NH), 1680 (CO) and 1260 cm^{-1} (N^+O^-); NMR δ 2.08–2.6 (m, 2 H, tetrahydropyridine C_3 H), 3.19 (t, $J_{2,3} = 6$ Hz, 2 H, tetrahydropyridine C_2 H), 3.35–3.75 (m, 2 H, tetrahydropyridine C_6 H), 5.74 (m, 2 H, tetrahydropyridine C_4 H, C_5 H), 7.2–7.7 (complex m, 2 H, 1-oxidopyridinium C_4 H, C_5 H), 8.08–8.68 (complex m, 2 H, 1-oxidopyridinium C_5 H, C_6 H).

Procedure C. General Method for the Preparation of N-(Carbonylimino)pyridinium Ylides 4. The carboxylic acid chloride **7** (12.45 mmol) was added dropwise with stirring to a solution of **6** (2 g, 8.3 mmol) in 25 mL of 10% aqueous sodium hydroxide. The reaction was allowed to proceed for 24 h at room temperature with stirring, after which water (75 mL) was added. Extraction with chloroform (4 × 75 mL), drying (Na_2SO_4), and removal of the solvent in vacuo gave the crude product, which

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was purified further by dissolution in 150 mL of methanol. Addition of activated charcoal (0.1–0.2 g), stirring for 10 min, filtration, and removal of the solvent in vacuo gave **4**.

Procedure D. General Method for the Preparation of *N*-(Carbonylamino)-1,2,3,6-tetrahydropyridines 5i–s. A solution of **4** (5.62 mmol) in 20 mL of absolute ethanol was added dropwise to a solution of sodium borohydride (1.062 g, 28.09 mmol) in 20 mL of absolute ethanol precooled to 0 °C. The reduction was allowed to proceed for 5 h at 0 °C with stirring. Water (50 mL) was added and the mixture was allowed to return to room temperature. Extraction with chloroform (4 × 75 mL), drying (Na_2SO_4), and removal of the solvent in vacuo gave **5**. Using this procedure, we obtained **5j**: yield 1.019 g; IR 1660 (CO), 3280 cm^{-1} (NH); NMR δ 1.51 (s, 9 H, *t*-Bu), 2.28–2.53 (m, 2 H, C_3 H), 3.1 (t, $J_{2,3}$ = 6 Hz, 2 H, C_2 H), 3.37–3.62 (m, 2 H, C_6 H), 5.76 (m, 2 H, C_4 H, C_5 H), 6.83 (s, 1 H, NH, exchanges with deuterium oxide).

Procedure E. General Method for the Preparation of *N*-(Carbonylimino)pyridinium Ylides 4. Using Phase-Transfer Reaction Conditions. A solution of the carboxylic acid chloride **7** (6.22 mmol) in petroleum ether, bp 90–110 °C (30 mL), was added dropwise to a solution of **6** (1 g, 4.15 mmol) in 10% aqueous sodium hydroxide (10 mL). A catalytic quantity of cetyltrimethylammonium bromide (0.0151 g, 0.04 mmol) was added, and the reaction mixture was heated at 50 °C with vigorous stirring for 48 h. Water (75 mL) was added, and the reaction was completed as described under Procedure C to give **4**.

***N*-[[[2-[[1-(1,2,3,6-Tetrahydropyridinyl)amino]-carbonyl]-6-pyridinyl]carbonyl]amino]-1,2,3,6-tetrahydropyridine (5t). Procedure F.** A solution of 2,6-pyridinedicarboxylic acid chloride **7t** (5 g, 29.94 mmol) in 10 mL of dry dimethylformamide was added dropwise to a solution of **6** (14.43 g, 59.88 mmol) in 50 mL of dry dimethylformamide at 0 °C, with stirring during 30 min. Triethylamine (18.18 g, 179.6 mmol) was added in three aliquots, and the reaction was allowed to proceed for 48 h at 25 °C prior to the addition of water (100 mL). Extraction with chloroform (4 × 150 mL), drying (Na_2SO_4), and removal of the solvent in vacuo afforded a black residue. This residue was dissolved in 15 mL of methanol, and the purple solid that precipitated from solution upon addition of 200 mL of ether was filtered and dried. A solution of the purple solid in 10 mL of absolute ethanol was added dropwise to a solution of sodium borohydride (2.55 g, 67.68 mmol) in 30 mL of absolute ethanol precooled to 0 °C with stirring. The reaction was completed according to procedure D to give a brown solid, which was purified on 20 8 × 8 in. silica gel GFP 254 plates, 0.5 mm in thickness, using chloroform–methanol (9:1, v/v) as the development solvent. Extraction of the band having R_f 0.45 with 300 mL of warm absolute ethanol gave a reddish oil from which **5t** was precipitated as a tan solid upon trituration with 200 mL of ether: yield 0.197 g; IR 1650 (CO), 3165 cm^{-1} (NH); NMR δ 2.19–2.62 (m, 4 H, tetrahydropyridine C_3 H), 3.25 (t, $J_{2,3}$ = 6 Hz, 4 H, tetrahydropyridine C_2 H), 3.66–3.85 (m, 4 H, tetrahydropyridine C_6 H), 5.78 (m, 4 H, tetrahydropyridine C_4 H, C_5 H), 7.92–8.56 (m, 3 H, pyridine C_3 H, C_4 H, C_5 H), 9.09 (s, 2 H, NH, exchange with deuterium oxide).

Pharmacological Methods. Analgesic activity was evaluated by the phenylquinone writhing test.[3] Five male Swiss albino mice weighing 18–22 g were used in each group. The test compound, suspended using ultrasonic mixing in a solution of physiological saline and Tween 80 surfactant, was administered subcutaneously; 30-min later, each mouse received a 0.03% phenyl-*p*-benzoquinone solution in a volume of 0.1 mL/10 g of body weight intraperitoneally. The total number of writhes exhibited by each animal in the test group was recorded and compared to that of a vehicle-treated control group. The percent change is calculated according to the following equation: % change = 100 − (number of writhes in the treated group/number of writhes in the control group) × 100. A compound causing a 30–50% reduction is considered to be slightly active, whereas one causing a greater than 50% reduction in the number of writhes is an active analgesic agent.

Antiinflammatory activity was measured by the method of Winter.[4] Six female Sprague–Dawley rats weighing 120–160 g were used for each group. Carrageenan (0.1 mL, 1%) in physiological saline was injected subcutaneously under the plantar skin of the hind paw following subcutaneous injection of the test compound suspended in physiological saline and Tween 80 surfactant. The volume of the injected paw was measured immediately after and at 3 and 5 h after the injection of the test compound for calculation of percent inhibition. A compound causing a greater than 30% reduction in edema is considered to be an active antiinflammatory agent.

Blood glucose was measured using the procedure developed by Barthelmai and Czok.[5] 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 $NADH_2$ using an Abbott ABA-100 Analyzer. Table I summarizes the pharmacological test results in the above assays.

Partition Coefficient. The partition coefficient *P*, which was calculated as $P = C_{octanol}/C_{H_2O}$, was determined using the method of Fujita.[11]

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