by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to give **7b** (0.112 g, 45%), while 0.112 g (45%) of **6** was recovered.

A solution of 0.110 g (0.266 mmol) of **7b** in methanol, saturated with ammonia at 0 °C, was kept overnight at room temperature. The clear solution was evaporated to dryness and **7c** was crystallized from MeOH–EtOAc (0.081 g, 0.245 mmol, 92%): mp 202 °C dec; MS, m/e 329; UV λ_{max} 304 nm and 245 (at pH 1), 292 and 251 (at pH 13), λ_{min} 276 nm (at pH 1), 282 (at pH 13); IR (1700–1200-cm^{-1} region) 1670, 1620, 1480, 1410, 1350, 1320, 1300, 1255, 1205 cm^{-1}; ^1H NMR (CD_3OD) δ 1.54–2.47 (overlapping multiplets, 2 × CH_2 and C*H*CH_2OH), 3.67 (m, C*H*$_2$OH), 4.2 (m, C*H*OH), 5.1 (m, CHN), 6.78 (d, J = 13.04 Hz, vinylic H), 7.00 (d, J = 13.04 Hz, vinylic H), 7.8 (s, H-6); ^{13}C NMR (CD_3OD) 33.9 (C-5′), 40.7 (C-2′), 50.5 (C-5′), 57.7 (C-1′), 64.3 (C-6′), 73.8 (C-3′), 106.4 (C-5), 108.8 (C-α), 129.1 (C-β), 141.7 (C-6) ppm. Anal. ($C_{12}H_{16}N_3O_3Br$) C, H, N.

Biological Evaluation. The methods used for measuring the inhibitory effects of the compounds on virus-induced cytopathogenicity[2] and cell proliferation[33] and for evaluating their efficacy in the treatment of herpes virus infections in animal models, i.e., mice infected intraperitoneally[35] or intracutaneously[36] with HSV-1 (KOS), have all been described previously.

Acknowledgment. This research was supported by the Belgian F.G.W.O. (Fonds voor Geneeskundig Wetenschappelijk Onderzoek) krediet no. 3.0037.83 and 3.0040.83. P.W. is a Senior Research Assistant of the Belgian N.F.W.O. (Nationaal Fonds voor Wetenschappelijk Onderzoek). We thank L. Kerremans, A. Van Lierde, L. Van Berckelaer, F. De Meyer, and W. Zeegers for their excellent technical assistance.

Registry No. **2**, 59967-83-8; **3**, 69975-22-0; **4b**, 95313-01-2; **5a**, 62102-28-7; **5b**, 83967-03-7; **5c**, 95344-18-6; **5d**, 91739-45-6; **5e**, 91661-22-2; **5f**, 91661-25-5; **6**, 95313-02-3; **7b**, 95313-03-4; **7c**, 95313-04-5; methyl acrylate, 96-33-3.

Synthesis and Central Dopaminergic Effects of *N*-(4,6-Dimethyl-2-pyridinyl)benzamides

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N-(4,6-Dimethyl-2-pyridinyl)benzamides **1–24** and the corresponding tertiary derivatives **29–33** were synthesized and studied for possible dopamine-inhibitory properties by testing their effect on motility of naive and reserpinized mice. Unlike the orthopramides, they failed to show any antidopaminergic properties, but some of the secondary derivatives showed instead effects of postsynaptic dopaminergic agonism. The latter compounds were subsequently studied for their effects on apomorphine reversal of reserpine-induced alkinesia and on cerebral HVA levels in rats. Contraversive circling induced by compound **11** in 6-hydroxydopamine-lesioned mice suggests that a direct mechanism was involved.

Benzamide derivatives constitute a class of drugs with diverse pharmacological activities. Some of these molecules now in clinical use have a neuroleptic effect which is somewhat different from that shown by butyrophenones or phenothiazines.[1] In addition to antipsychotic activity, some drugs, such as metoclopramide or sulpiride, have antivomitive[2] and gastric stimulant effects.[3]

It has been shown that some benzamide molecules with a 2-aminopyridine structure exhibit antiinflammatory[4,5] or antiulcerogenic and sedative properties.[6] Our work on the synthesis and antiinflammatory effects of *N*-(4,6-dimethyl-2-pyridinyl)phthalimide derivatives[7] prompted us to synthesize the secondary *N*-(4,6-dimethyl-2-pyridinyl)benzamides **1–24** and the tertiary derivatives **29–33**. Their structural similarity with orthopramides led us to investigate their possible effect on central dopaminergic systems. When these molecules exhibited major effects in tests on the motility of naive or reserpinized mice, additional pharmacological properties were investigated (**1**, **5**, **9**, **11**, and **12**).

Chemistry. The reaction of benzoic acids with amines in the presence of dicyclohexylcarbodiimide constitutes a mild and general procedure for the conversion of 3- and 4-aminopyridines into their benzamides; however, it cannot be used in the case of 2-aminopyridines, even when there is an excess of acid.[8] As acylation of the free amino group in 2-aminopyridine by acid chlorides proceeds readily,[5,6,8] secondary benzamides **1–3** and **9–24** were prepared by this method (Scheme I, method A). No simultaneous hydrogenation of the nitrogen heterocycle was observed when reducing 3- and 4-nitrobenzamides **2** and **3** (method B). Acetylation of the resulting primary amines **4** and **5** with acetyl chloride proceeded without concomitant formation of diamides (method A_1). Salicylamide **8** was obtained by aminolysis of phenyl salicylate (method C).

The normal method of preparing benzamides **29–33** is via N-alkylation of the corresponding secondary benzamides, especially since simultaneous quaternization of heterocyclic nitrogen was a priori excluded in the present case.[9] Nevertheless, methylation trials of benzamide **1**, in the presence of the systems K_2CO_3/acetone, NaH/DMF, CH_3ONa/CH_3OH, and even of KOH/DMSO at 60 °C,[10] were unsuccessful. Although the triflate ion constitutes a more reactive leaving group than the halogen in methyl

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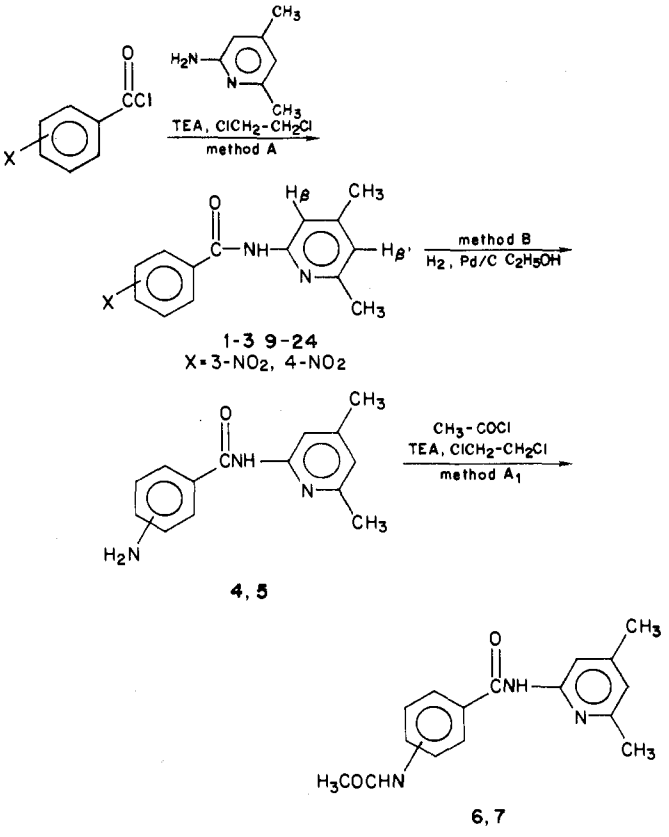
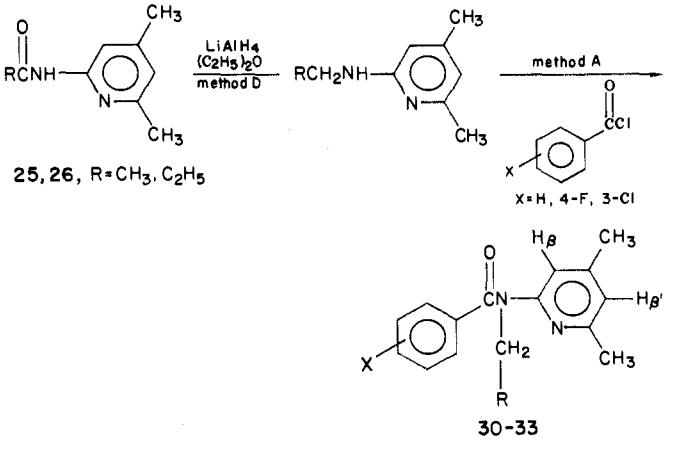
Scheme I



Scheme II



iodide,[11] the reaction with methyl trifluoromethanesulfonate, at 60 °C, was sluggish and the pyridinyl nucleus underwent partial quaternization.

It was possible to carry out methylation of **1** by prolonged heating with methyl iodide in a sealed tube (method E), but the yield was moderate. For tertiary benzamides **30–33**, an alternative synthesis was achieved by benzoylation of the secondary amines **27**, **28**, as outlined in Scheme II (method D). Details of the preparative work are given in the Experimental Section.

In the case of secondary benzamides, observation of a single ^1H NMR signal for NH denoted a single configuration around the amidic C–N bond. When the nitrogen substituent is small, hindered rotation around this bond may result in the existence of two isomers, at normal room temperature.[12] In the present case, the steric constraints imposed by the bulky pyridinyl group permit only one conformation, that in which the NH proton is trans to the carbonyl group. The most striking feature of the NMR spectra was the marked deshielding of β protons as compared with β' protons: about 1.3 ppm throughout the secondary benzamide series. It is likely that this phenomenon was due to the magnetic anisotropy effects of the carbonyl group. In the preferential coplanar conformation of the molecule, the pyridinyl nitrogen is located as far as possible from the carbonyl dipole, and the β proton, contrary to β', comes under paramagnetic effect.

With tertiary benzamides, as soon as there was strong steric crowding (R = CH_3) an upfield shift occurred for β and β' protons ($\Delta\delta$ = 1.40 and 0.40 ppm, respectively) and, to a lesser degree, for γ-CH_3 protons ($\Delta\delta$ = 0.05 ppm). Steric hindrance gave rise to a torsion of the heterocycle resulting in a simultaneous rotation of the pyridinyl substituents, which then located in the zone of diamagnetic anisotropy of the carbonyl group.

Pharmacology. Initially, compounds were tested pharmacologically for effects of spontaneous motility and/or reserpine-induced akinesia in mic . Whenever a significant effect was noted, additional experimental data were obtained in order to improve the accuracy of the results. The presence of antagonism or dopaminergic agonism was further investigated by means of another behavioral test (apomorphine hypermotility of reserpinized mice) and a biochemical test (homovanillic acid HVA levels in the striatum and the limbic system of rats). To determine whether the dopaminergic postsynaptic effect noted in some of the tested compounds was due to direct action, compound **11** was tested in reserpinized mice pretreated with α-methyl-*p*-tyrosine and in unilaterally striatal 6-hydroxydopamine-lesioned mice. Metoclopramide (Mcp) and sultopride (St) were used as reference antidopaminergic benzamides (the methods are described in the Experimental Section).

Results and Discussion

The strongest effect in diminishing spontaneous motility was observed with the nonsubstituted derivative **1** and with two secondary benzamides bearing a 4-amino (**5**) or a 4-fluoro (**9**) substituent on the phenyl ring. Derivatives **1** and **9** also clearly reversed reserpine-induced akinesia as did the 3- and the 4-chloro-substituted secondary benzamides **11** and **12**, though they were less active on spontaneous motility (Tables I and II). The statistical significance of these results, as well as additional experimental data, is shown in Table III.

The decrease in spontaneous motility could not have resulted from dopamine antagonist activity as the above drugs neither reduce apomorphine-induced hypermotility of reserpinized mice[13] nor increase HVA levels[14] in dopamine-rich brain areas.

The slight but significant increase in motility observed after administration of benzamides **1**, **9**, **11**, **12** to reserpine-treated mice strongly suggested activation of postsynaptic dopamine receptors,[15] a finding also supported by biochemical results:[16] significant decreases of HVA levels were observed in the striatum (**1**, **11**) and the limbic system (**11**). Whether this activation was direct or indirect

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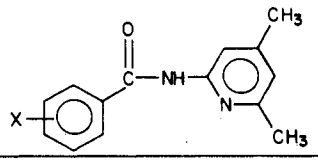
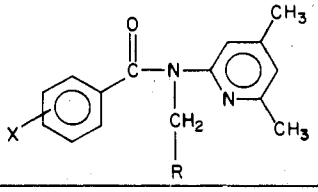
Table I. Physical Properties and Influence of Secondary Benzamides 1–24 on Mice Motility



no.	X	formula	synth method	yield, %	mp, °C	recrystn solv	motility scores[c] naive mice (control value: 815)	motility scores[c] reserpinized mice (control value: 11)
1	H	$C_{14}H_{14}N_2O$	A	81	136	EtOH/H_2O	450	83
2	3-NO_2	$C_{14}H_{13}N_3O_3$	A	75	150	EtOH/H_2O	634	15
3	4-NO_2	$C_{14}H_{13}N_3O_3$	A	88	163[a]	EtOH/H_2O	746	0
4	3-NH_2	$C_{14}H_{15}N_3O$	B	83	117	*i*-Pr_2O	652	4
5	4-NH_2	$C_{14}H_{15}N_3O$	B	79	184[b]	*i*-Pr_2O	337	9
6	3-$NHCOCH_3$	$C_{16}H_{17}N_3O_2$	A_1	81	194	EtOH/H_2O	777	8
7	4-$NHCOCH_3$	$C_{16}H_{17}N_3O_2$	A_1	85	202	EtOH/H_2O	522	12
8	2-OH	$C_{14}H_{14}N_2O_2$	C	83	188	EtOH	747	0
9	4-F	$C_{14}H_{13}FN_2O$	A	78	73	EtOH/H_2O	291	113
10	2-Cl	$C_{14}H_{13}ClN_2O$	A	75	135	EtOH/H_2O	875	4
11	3-Cl	$C_{14}H_{13}ClN_2O$	A	72	100	EtOH/H_2O	617	52
12	4-Cl	$C_{14}H_{13}ClN_2O$	A	85	120	EtOH/H_2O	630	72
13	3-Br	$C_{14}H_{13}BrN_2O$	A	77	93	EtOH/H_2O	826	21
14	4-Br	$C_{14}H_{13}BrN_2O$	A	65	128	EtOH/H_2O	797	0
15	3-CH_3	$C_{15}H_{16}N_2O$	A	75	134	EtOH/H_2O	505	0
16	3-CF_3	$C_{15}H_{13}F_3N_2O$	A	54	82	C_6H_{14}	661	4
17	2-OCH_3	$C_{15}H_{16}N_2O_2$	A	86	88	EtOH/H_2O	646	7
18	3-OCH_3	$C_{15}H_{16}N_2O_2$	A	71	108	EtOH/H_2O	822	0
19	4-OCH_3	$C_{15}H_{16}N_2O_2$	A	84	140	EtOH/H_2O	456	0
20	4-OC_2H_5	$C_{16}H_{18}N_2O_2$	A	86	118	EtOH/H_2O	552	4
21	4-SCH_3	$C_{15}H_{16}N_2OS$	A	89	127	EtOH/H_2O	770	0
22	2-OCH_3, 5-Cl	$C_{15}H_{15}ClN_2O_2$	A	94	138	EtOH/H_2O	748	19
23	2-OCH_3, 5-SO_2CH_3	$C_{16}H_{18}N_2O_4S$	A	78	226	Dioxane	755	2
24	2-OCH_3, 5-$SO_2C_2H_5$	$C_{17}H_{20}N_2O_4S$	A	73	170	EtOH	841	16

[a] Lit.[6] mp 159.5–161 °C. [b] Lit.[6] mp 184–185.5 °C. [c] Number of interrupted beams in 60 min.

Table II. Physical Properties and Influence of Tertiary Benzamides 29–33 on Mice Motility



no.	X	R	formula	synth method	yield, %	mp, °C	recrystn solv	motility scores[b] naive mice (control value: 815)	motility scores[b] reserpinized mice (control value: 11)
29	H	H	$C_{15}H_{16}N_2O$	E	57	160	*i*-Pr_2O	796	toxic
30	H	CH_3	$C_{16}H_{18}N_2O$	A	84	78	C_6H_{14}	914	31
31	H	C_2H_5	$C_{17}H_{20}N_2O$	A	99	*a*		780	8
32	4-F	CH_3	$C_{16}H_{17}FN_2O$	A	62	56	*i*-Pr_2O	965	29
33	3-Cl	CH_3	$C_{16}H_{17}ClN_2O$	A	80	45	C_6H_{14}	941	21

[a] Eb/0.1 mm: 100°, n^{20}_D 1.563. [b] Number of interrupted beams in 60 min.

Table III. Effects of the Selected *N*-Pyridinylbenzamides on Motility of Mice and HVA Levels of Rats

	motility of mice									HVA levels of rats, μg/g			
	naive			reserpine-treated			reserpine- and apomorphine-treated						
compd	score[a]	N[b]	%[c]	score[a]	N[b]	%[c]	score[a]	N[b]	%[c]	corpus striatum[d]	N[b]	limbic system[d]	N[b]
controls	869 ± 61	(25)		11.1 ± 1.8	(34)		435 ± 44	(40)		0.797 ± 0.069	(32)	0.265 ± 0.030	(29)
1	427 ± 72[g]	(13)	−50.9	85.1 ± 30.2[g]	(8)	+667	642 ± 94[f]	(14)	+47.3	0.504 ± 0.127[f]	(12)	0.297 ± 0.051	(12)
5	439 ± 85[g]	(10)	−49.4	0	(4)		385 ± 46	(10)	−11.7	0.308 ± 0.043[f]	(11)	0.268 ± 0.056	(7)
9	299 ± 56[g]	(9)	−65.6	118.2 ± 9.0[g]	(4)	+964	491 ± 77	(9)	+12.8	0.667 ± 0.053	(7)	0.194 ± 0.028	(7)
11	577 ± 70[g]	(15)	−33.6	41.2 ± 11.4[f]	(13)	+271	727 ± 113[g]	(11)	+66.9	0.396 ± 0.079[f]	(18)	0.141 ± 0.033[f]	(17)
12	619 ± 134[f]	(10)	−28.8	73.4 ± 23.3[f]	(9)	+561	577 ± 80[e]	(21)	+32.5	0.644 ± 0.062	(14)	0.355 ± 0.060	(15)
Mcp	126 ± 33[g]	(10)	−85.5				63 ± 18[g]	(12)	−85.4	2.531 ± 0.175[f]	(7)	0.618 ± 0.087[f]	(8)
St	135 ± 34[g]	(10)	−84.5				152 ± 29[g]	(11)	−65.0	1.898 ± 0.183[f]	(7)	0.493 ± 0.091[f]	(6)

[a] Number of interrupted beams in 60 min; means ± SEM. [b] Number of determinations. [c] Variation p.100 referring to controls. [d] Means ± SEM. [e] $p < 0.10$. [f] $p < 0.05$. [g] $p < 0.01$ Student's t test, referring to controls. For details, see Experimental Section.

was investigated for compound 11, which elicited significant contraversive circling in 6-hydroxydopamine-lesioned mice (8.7 ± 2.8 turns recorded for 30 min instead of 2.1 ± 0.6 for controls, $p < 0.05$ with Student's t test), indicating direct apomorphine-like activity. However, as has been reported for drugs such as piribedil[17] or bromocriptine,[18]

which can act directly on dopaminergic receptors, it failed to elicit any behavioral activation after combined treatment with both α-methyl-*p*-tyrosine and reserpine.

Furthermore, although the apomorphine-induced motility of reserpinized mice was increased with derivatives 1, 11, and 12, their moderate dopaminergic agonist activity cannot account for the observed potentiating effect; α_2-adrenergic mechanisms, now under study in our laboratory, should not be ruled out.[19]

Experimental Section

Chemistry. Melting points, recorded on a Kofler apparatus, were not corrected. Elemental analyses of all new compounds were performed on an F and M 185 Hewlett-Packard apparatus; the analytical results obtained were within ±0.4% of theoretical values. Analytical thin-layer chromatography was routinely performed on aluminum plates coated with a 0.2-mm layer of silica gel GF 254 (Merck); the spots were located by UV illumination. IR spectra were run with KBr pellets on a Beckman IR 4230 grating infrared spectrophotometer. The structures of all compounds were confirmed by NMR spectra recorded on Varian EM 360 or XL 100 spectrometers, using $CDCl_3$ or D_3CSOCD_3 as solvent; chemical shifts are reported in parts per million (δ) from internal Me_4Si. The following experimental procedures are representative of the general procedures used to synthesize all of the compounds. Experimental data for **1–24** and **29–33** are provided in Tables I and II, respectively.

***N*-(4,6-Dimethyl-2-pyridinyl)-3-nitrobenzamide (2). Method A.** To a solution of 2-amino-4,6-dimethylpyridine (9.61 g, 78.7 mmol) and triethylamine (15 mL) in dichloroethane (50 mL) was added dropwise a solution of *m*-nitrobenzoyl chloride (14.6 g, 78.7 mmol) in dichloroethane (30 mL) during a period of 0.5 h. After 1 h of stirring, the reaction mixture was evaporated to dryness. The residue was washed with water and neutralized by $NaHCO_3$. Finally the crude benzamide 2 was washed with water and dried. Recrystallization from ethanol-water afforded 16 g (75.4% yield) of the pure compound as white crystals: mp 150 °C; IR (KBr) 3380 (ν_{NH}), 1680 ($\nu_{C=O}$), 1570 (δ_{NH}), 1530 ($\nu_{as}NO_2$), 1350 ($\nu_s NO_2$); ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 6 H, α- and γ-CH_3), 6.90 (d, 1 H, $J_{\beta'\beta}$ = 1.3 Hz, $H_{\beta'}$), 8.13 (d, 1 H, H_b), 7.76, 8.46, 8.90 (m, 4 H, aromatic H). Anal. ($C_{14}H_{13}N_3O_3$) C, H, N.

3-Amino-*N*-(4,6-dimethyl-2-pyridinyl)benzamide (4). Method B. To a solution of *N*-(4,6-dimethyl-2-pyridinyl)-3-nitrobenzamide (2; 15 g, 55.3 mmol) in ethanol (200 mL) was added palladium on charcoal (5%, 1.5 g). The mixture was stirred under an H_2 atmosphere. When consumption of hydrogen ceased, the catalyst was filtered off and the solvent evaporated under reduced pressure. The resulting solid was recrystallized from diisopropyl ether to afford 11.1 g (82.6% yield) of 4 as white crystals: mp 117 °C; IR (KBr) 3420, 3340 (ν_{NH_2}), 3220 (ν_{NH}); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3 H, γ-CH_3), 2.43 (s, 3 H, α-CH_3), 3.93 (s, 2 H, NH_2), 6.81 (d, 1 H, $J_{\beta'\beta}$ = 1.3 Hz, $H_{\beta'}$), 6.93, 7.26 (m, 4 H, aromatic H), 8.13 (d, 1 H, H_β), 8.76 (s, 1 H, NH). Anal. ($C_{14}H_{15}N_3O$) C, H, N.

3-Acetamido-*N*-(4,6-dimethyl-2-pyridinyl)benzamide (6). Method A_1. To a vigorously stirred solution of 3-amino-*N*-(4,6-dimethyl-2-pyridinyl)benzamide (4; 4.5 g, 18.6 mmol) in dichloroethane (50 mL) was added dropwise a solution of freshly distilled acetyl chloride (4 mL) in the same solvent (10 mL). After a 2-h contact, the solvent was distilled off under reduced pressure. The residue was washed with water (100 mL) and neutralized with $NaHCO_3$. After filtration, the crude compound was washed with water, dried, and purified by crystallization from $EtOH/H_2O$ to give 4.28 g (81% yield) of pure product: mp 194 °C; IR (KBr) 3300 (ν acetamido NH), 3220 (ν_{NH}), 1680 ($\nu_{C(O)CH_3}$), 1650 ($\nu_{C(O)NH}$); NMR ($CDCl_3$) δ 2.10 (s, 3 H, $C(O)CH_3$), 2.33 (s, 3 H, γ-CH_3), 2.40 (s, 3 H, α-CH_3), 7.0 (d, 1 H, $H_{\beta'}$), 7.5–8.2 (m, 5 H, aromatic H, acetamido NH), 7.90 (d, 1 H, H_β), 8.60 (s, 1 H, NH). Anal. ($C_{16}H_{17}N_3O_2$) C, H, N.

2-Hydroxy-*N*-(4,6-dimethyl-2-pyridinyl)benzamide (8). Method C. A solution of phenyl salicylate (5.35 g, 25 mmol) and 2-amino-4,6-dimethylpyridine (3.05 g, 25 mmol) in toluene (50 mL) was heated under reflux for 1 h. On standing at room temperature, benzamide 8 crystallized partly in the reaction mixture. The resulting solid was collected by filtration and washed with toluene and diethyl ether. The organic phase was then concentrated in vacuo to afford a second crop. The crude fractions were combined and crystallized from ethanol to yield 4.96 g (82%) of fine white crystals: mp 188–189 °C; IR (KBr) 3320 ($\nu_{NH,OH}$), 1680 ($\nu_{C=O}$); ^{1}H NMR (Me_2SO-d_6) δ 2.56 (s, 3 H, γ-CH_3), 2.66 (s, 3 H, α-CH_3), 7.33 (d, 1 H, $J_{\beta'\beta}$ = 1.33 Hz, $H_{\beta'}$), 8.23 (d, 1 H, H_β), 7.0–8.1 (m, 4 H, aromatic H), 11.8 (s, 1 H, OH), 15.4 (s, 1 H, OH). Anal. ($C_{14}H_{14}N_2O_2$) C, H, N.

***N*-Ethyl-*N*-(4,6-dimethyl-2-pyridinyl)-4-fluorobenzamide (32). Methods D and A.** *N*-(4,6-Dimethyl-2-pyridinyl)acetamide (25) was prepared by heating 2-amino-4,6-dimethylpyridine with acetic anhydride. The crude compound, isolated after adding cold water and aqueous 2 N NaOH, was washed and dried. Crystallization from $EtOH/Et_2O$ afforded a 81% yield of pure **25**, mp 160 °C (lit.[20] mp 157–158 °C). This amide (1.8 g, 11 mmol), solubilized in dry ether (200 mL), was reduced by lithium aluminum hydride (1.9 g, 50 mmol). After 3 h of heating, excess hydride was destroyed by slow addition of ice–water. The two phases were separated. The organic phase was washed with water, dried over Na_2SO_4, and evaporated in vacuo. The resulting oil was distilled in vacuo to give 1.65 g (97%) of 2-(ethylamino)-4,6-dimethylpyridine (**27**), bp 117–120 °C (0.1 mmHg); d^{21}_D 1.542.

Amine **27** (1.5 g, 10 mmol) and triethylamine (2 mL) were dissolved in dichloroethane (50 mL). A solution of 4-fluorobenzoyl chloride (1.58 g, 10 mmol) in dichloroethane (20 mL) was added dropwise, and the reaction mixture was then heated under gentle reflux for 5 h. The solvent was evaporated in vacuo. The solid material was suspended in water and neutralized with $NaHCO_3$. The residue was extracted several times with methylene chloride. The combined organic layers were washed (water), dried (Na_2SO_4), and evaporated to give 2.26 g (83%) of the crude product as an oil. Crystallization from diisopropyl ether afforded 1.69 g (62%) of pure **32**: mp 56 °C; IR (KBr) 1640 ($\nu_{C=O}$); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3 H, CH_3), 2.16 (s, 3 H, γ-CH_3), 2.50 (s, 3 H, α-CH_3), 4.14 (q, 2 H, CH_2), 6.43 (s, 1 H, $H_{\beta'}$), 6.83 (s, 1 H, H_β), 6.95–7.60 (m, 4 H, aromatic). Anal. ($C_{16}H_{17}FN_2O$) C, H, N.

N-(4,6-Dimethyl-2-pyridinyl)propionamide (**26**) was similarly prepared from the primary amine and propionic anhydride: yield 80%, mp 112 (*i*-Pr_2O). Reduction of **26** with lithium aluminum hydride afforded 2-(propylamino)-4,6-dimethylpyridine (**28**) in 96% yield: bp 124–128 °C (0.1 mmHg); n^{21}_D 1.534. Anal. ($C_{10}H_{16}N_2$) C, H, N.

***N*-Methyl-*N*-(4,6-dimethyl-2-pyridinyl)benzamide (29). Method E.** A solution of the secondary benzamide 1 (15.14 g, 67 mmol) and methyl iodide (14.20 g, 100 mmol) in acetonitrile (140 mL) was placed in a sealed tube and heated at 100 °C for 14 h. The solvent was removed under reduced pressure. The residue was neutralized by $NaHCO_3$ and washed with water. The crude compound was purified by column chromatography on silica gel. Elution with dichloromethane afforded 1.3 g of the starting material 1; compound **29** (9.8 g) was isolated with dichloromethane–ethanol (93/7) as eluant. Recrystallization from diisopropyl ether gave 9.2 g (57.2% yield) of pure **29**: mp 160 °C; IR (KBr) 1640 ($\nu_{C=O}$); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3 H, γ-CH_3), 2.50 (s, 3 H, α-CH_3), 3.86 (s, 3 H, NCH_3), 6.35 (s, 1 H, $H_{\beta'}$), 8.15 (s, 1 H, H_β), 7.45 and 8.40 (m, 3 H and 2 H, aromatic H). Anal. ($C_{15}H_{16}N_2O$) C, H, N.

Pharmacology. Drugs. All tested drugs were orally administered with a gastric tube in a 10% acacia gum aqueous suspension at doses of 1 mmol/kg for motility tests, 0.30 mmol/kg for circling behavior, and 1.5 mmol/kg for the biochemical test. The doses of metoclopramide were 0.50 and 0.30 mmol/kg respectively for naive and reserpinized mice and 0.25 mmol/kg for rats. Concentrations of orthopramide hydrochlorides (Labora-

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toires Delagrange, France), apomorphine hydrochloride (Laboratoires Aguettant, France), α-methyl-*p*-tyrosine methyl ester hydrochloride (Sigma U.S.A.), and 6-hydroxydopamine hydrobromide (Sigma, U.S.A.) are expressed for the salts. The reserpine dose indicated (E. Merck, Darmstadt, West Germany) refers to the free base.

All controls were given acacia gum aqueous supension.

Animals. The animals used were male Swiss C.F. mice (25 ± 5 g) and male Wistar C.F. rats (200 ± 20 g), which were kept in a quiet room where the behavioral tests were performed. Room temperature was kept at 21 ± 1 °C, and artificial lighting was used (lights on between 7 a.m. and 7 p.m.). Food and water were given ad libitum.

Motility of Naive Mice. Motility experiments were performed between 9 a.m. and 1 p.m. when locomotor activity was relatively high. Animals were placed in activity cages (Boissier photoactimeter, Apelex, Bagneux, France). Each cage (L = 25.5 cm, W = 20 cm, H = 9 cm) was fitted with two photoelectric units with infrared lights located 1 cm above the floor of the cage in the middle of each side. The activity cages were placed in a closed compartment, which reduced the effects of external stimuli such as light or noise, and connected to a counter. Motility was expressed as the number of interruptions of photocell beams.

Mice were placed for 60 min in the photoactimeter, with one animal in each box. Drugs were administered 1 h before testing. Preliminary experiments were carried out on 6–12 mice and successive ones on 9–25.

Motility of Reserpine-Treated Mice. Tested drugs were administered 20 h after reserpine (10 mg/kg ip) was given to mice and 1 h before the animals (three/box) were placed in the photoactimeter. Motility was recorded for 60 min. Experiments were carried out on at least six mice.

Motility of Reserpine- and α-Methyl-*p*-tyrosine-Treated Mice. Mice were treated in the manner described in the above paragraph, with an additional injection of α-methyl-*p*-tyrosine methyl ester (250 mg/kg ip) 16 h after reserpine.

Motility of Reserpine- and Apomorphine-Treated Mice. Apomorphine (2 mg/kg ip) was injected 20 h after reserpine administration (10 mg/kg ip), as indicated by Elliott et al.,[13] benzamides having been administered 1 h before apomorphine. The motility of each mouse was recorded during 60 min following apomorphine injection.

Circling Behavior. Circling behavior was studied in unilaterally striatal 6-hydroxydopamine-lesioned mice.[21] Six days after lesioning, hypersensitivity to direct dopaminergic agonists was monitored by injection of apomorphine (2 mg/kg ip), which caused contraversive circling. This behavior, recorded for 30 min following acacia gum aqueous suspension or compound 11 administration, is expressed as the number of contraversive turns (m ± SEM). Animals (n = 7) served as their own controls.

HVA Levels in Rat Striatum and Limbic System. The effects of molecules on dopamine turnover in the striatum and limbic system of the rat were studied by determination of HVA concentrations. Brain samples were removed (5 h after drug administration) as described by Bartholini.[22] Extraction from tissue was done according to the method of Murphy et al.,[23] as modified by Pearson and Sharman,[24] and HVA was estimated fluorimetrically.[25]

Acknowledgment. We are grateful to Melle M. R. Le Doare and M. A. Decoodt for expert technical assistance.

Registry No. 1, 94843-50-2; 2, 94843-51-3; 3, 36845-09-7; 4, 94843-52-4; 5, 36845-10-0; 6, 85367-13-1; 7, 94843-53-5; 8, 94843-54-6; 9, 94843-55-7; 10, 94843-56-8; 11, 94843-57-9; 12, 94843-58-0; 13, 94843-59-1; 14, 94843-60-4; 15, 94843-61-5; 16, 94843-62-6; 17, 86439-15-8; 18, 94843-63-7; 19, 86425-35-6; 20, 94843-64-8; 21, 94843-65-9; 22, 94843-66-0; 23, 94843-67-1; 24, 94843-68-2; 25, 5407-88-5; 26, 94843-69-3; 27, 94843-70-6; 28, 94843-71-7; 29, 94843-72-8; 30, 94843-73-9; 31, 94843-74-0; 32, 94843-75-1; 33, 94843-76-2; 2-amino-4,6-dimethylpyridine, 5407-87-4; *m*-nitrobenzoyl chloride, 121-90-4; 4-fluorobenzoyl chloride, 403-43-0.

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Studies on Antianaphylactic Agents. 7.[1] Synthesis of Antiallergic 5-Oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridines[2]

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5-Oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic acids **23** and their tetrazole analogues **24** were synthesized from 4-oxo-4*H*-1-benzopyran-3-carbonitriles **3** or 2-amino-4-oxo-4*H*-1-benzopyran-3-carboxaldehydes **4**. When administered intravenously, they exhibited antiallergic activity in a reaginic PCA test in rats. In the carboxylic acid series, the activity was influenced by the substituents at the 2-position and increased substantially in the following order: Me, OMe < NH_2 < OH, H < NHOMe. On the other hand, in the tetrazole series, 2-unsubstituted derivatives showed the highest activity. Regardless of the kinds of substituents at positions 2 and 3, compounds bearing an alkyl group, especially an isopropyl group at the 7-position, were superior in activity to the corresponding unsubstituted compounds. Among these alkyl derivatives, 3-carboxylic acid derivatives, i.e., **23c** (7-ethyl), **23g** (2-amino-7-isopropyl), **23r** [2-(methoxyamino)-7-isopropyl], and a 3-tetrazole derivative **24c** (7-isopropyl), were 41–184 times as potent as disodium cromoglycate. They also exhibited remarkable activity when administered orally; clinical studies on **23g** (AA-673) are in progress.

The introduction of disodium cromoglycate (DSCG) (**1**) as the first prophylactic agent for treating bronchial asthma[3] prompted many laboratories, including our own, to search for orally active compounds.[4] Recently, we published a report on 3-(1*H*-tetrazol-5-yl)chromones **2**[5] that showed significant oral activity in the rat IgE-mediated

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0022-2623/85/1828-0559$01.50/0