Synthesis of *N*-[[(Substituted-phenyl)carbonyl]amino]-1,2,3,6-tetrahydropyridines with Analgesic and Hyperglycemic Activity

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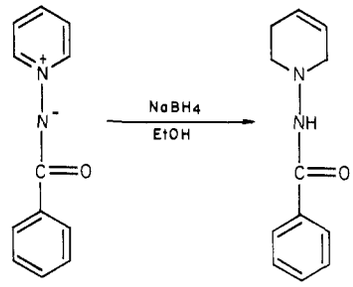
A group of *N*-[(phenylcarbonyl)amino]-1,2,3,6-tetrahydropyridines, **5**, were synthesized to determine the effect that changes in aromatic substitution on the phenyl ring have on analgesic, hyperglycemic, and antiinflammatory activities. All of the *N*-[(phenylcarbonyl)amino]-1,2,3,6-tetrahydropyridines **5** exhibited potent analgesic activity, relative to morphine, irrespective of the position and physicochemical properties of the aromatic substituent. Pretreatment with naloxone did not alter the analgesic activity of the 4-fluorophenyl derivative **5p**. *N*-[[(2-Fluorophenyl)-carbonyl]amino]-1,2,3,6-tetrahydropyridine (**5n**) was one of the most active hyperglycemic agents, elevating blood glucose 213 and 127% at 2 and 4 h after a 100 mg/kg po dose. Incorporation of aromatic substituents into the 3 and 4 positions of 1 abolished antiinflammatory activity.

The sodium borohydride reduction of *N*-(carbonylimino)pyridinium ylides is an attractive method for the synthesis of pharmacologically interesting *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines.[1] A broad-spectrum pharmacological screen indicated that *N*-[(phenylcarbonyl)amino]-1,2,3,6-tetrahydropyridine (1) exhibited



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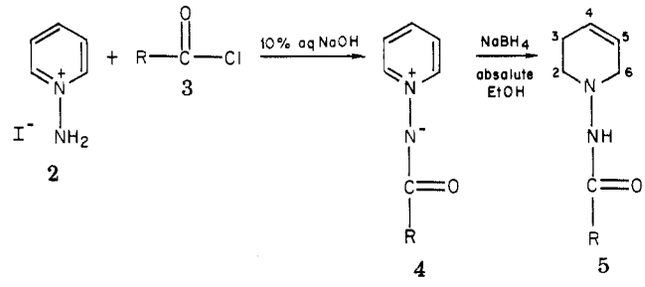
analgesic and antiinflammatory activities comparable to aspirin and indomethacin, respectively.[2] In addition, 1 also exhibited a potent hyperglycemic effect, elevating blood glucose 78% after 2 h for a dose of 100 mg/kg po. It was therefore of interest to determine the effect of aromatic phenyl substituents, with regard to substituent position and physicochemical properties, upon pharmacological activity. We now describe the synthesis and analgesic–hyperglycemic activities of *N*-[[(substituted-phenyl)carbonyl]amino]-1,2,3,6-tetrahydropyridines **5**.

Chemistry. *N*-[(Phenylcarbonyl)imino]pyridinium ylides **4** were synthesized by the reaction of *N*-aminopyridinium iodide **2**, obtained by amination of pyridine using hydroxylamine-*O*-sulfonic acid, with acid chlorides **3** in the presence of 10% aqueous sodium hydroxide (see Table I). Reduction of ylides **4** using sodium borohydride in absolute ethanol at ice-bath temperature gave the title *N*-[(phenylcarbonyl)amino]-1,2,3,6-tetrahydropyridines **5** as illustrated in Scheme I and summarized in Table II.

Pharmacology. The *N*-[[(substituted-phenyl)-carbonyl]amino]-1,2,3,6-tetrahydropyridines were tested for analgesic activity using the phenylquinone writhing[3] and hot-plate[4] tests. Blood glucose determinations were effected by spectrophotometric measurement of enzymatically produced $NADH_2$.[5] Antiinflammatory activity

Scheme I



2 3 4 5

was determined using the carrageenan-induced paw edema method (see Experimental Section).[6]

Discussion

Four complete series of 2-, 3-, and 4-monosubstituted phenyl derivatives, **5**, bearing methoxy, methyl, fluoro, and trifluoromethyl substituents were prepared to investigate the effect of substituent position and physicochemical effects, such as electronic (σ), lipophilic (π), and steric (E_s), upon analgesic and hyperglycemic activity. The analgesic test results indicate that the *N*-[(phenylcarbonyl)-amino]-1,2,3,6-tetrahydropyridine moiety is the important structural feature, since analgesic potency is quite independent of the position and physicochemical properties of the aromatic substituent. For example, there was not a significant difference in activity between compounds having electron-donating substituents, such as methoxyl and methyl, compared to those having electron-attracting substituents, such as fluoro, trifluoromethyl, and nitro. The partition coefficient P does not appear to have a significant influence on analgesic activity (see measured P values in Table II). Compounds having lipophilic substituents, such as methyl, chloro, and trifluoromethyl, exhibit similar activity to those having substituents with low π values, such as methoxyl and nitro. The dose–response relationships for the 3-methyl (**5b**) and 4-fluoro (**5p**) derivatives, which exhibited ED_{50} values of 0.0004 and 0.00036 mg/kg sc, respectively, in the phenylquinone writhing test[3] were quite flat. This prompted us to examine their analgesic activity using an alternate test. The 3-methyl (**5b**) and 4-fluoro (**5p**) compounds exhibited ED_{50} values of 17 and 30 mg/kg sc, respectively, using the hot-plate test, relative to an ED_{50} of 3.09 mg/kg sc for morphine sulfate.[4] *N*-(Carbonylamino)-1,2,3,6-tetrahydropyridines **5** do not act at an opiate receptor, since pretreatment with naloxone hydrochloride did not alter

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(3) Collier, H. O.; Dineen, L. C.; Johnson, C. A.; Schneider, C. *Br. J. Pharmacol. Chemother.* **1968**, *32*, 295.
(4) (a) Eddy, N. B.; Touchberry, C. F.; Lieberman, J. E. *J. Pharmacol. Exp. Ther.* **1950**, *98*, 121. (b) Eddy, N. B.; Leimbach, D. *Ibid.* **1953**, *107*, 385.
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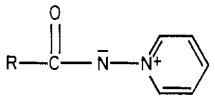
Table I. Some Physical Data of *N*-(Carbonylimino)pyridinium Ylides 4



no.	R	yield, %	mp, °C	formula	exact mass calcd	exact mass found
4a	2-Me-C_6H_4	99.9	111–112	$C_{13}H_{12}N_2O$	212.0950	212.0953
4b	3-Me-C_6H_4	98.2	95–96.5	$C_{13}H_{12}N_2O$	212.0950	212.0944
4c	4-Me-C_6H_4	60	171–173	$C_{13}H_{12}N_2O$	212.0950	212.0942
4d	4-$(Me)_3C$-C_6H_4	97.1	167.5–168.5	$C_{16}H_{18}N_2O$	254.1419	254.1400
4e	3,4-Me_2-C_6H_3	50	154–155	$C_{14}H_{14}N_2O$	226.1106	226.1101
4f	2-MeO-C_6H_4	99.2	103–105	$C_{13}H_{12}N_2O_2$	228.0898	228.0895
4g	3-MeO-C_6H_4	94.6	88–90	$C_{13}H_{12}N_2O_2$	228.0898	228.0882
4h	4-MeO-C_6H_4	34.2	149–151	$C_{13}H_{12}N_2O_2$	228.0898	228.0889
4i	2-Cl-C_6H_4	98.7	119–120	$C_{12}H_9N_2OCl$	232.0403	232.0400
4j	4-Cl-C_6H_4	35.7	184–186	$C_{12}H_9N_2OCl$	232.0403	232.0396
4k	2,4-Cl_2-C_6H_3	94.1	153–154	$C_{12}H_8N_2OCl_2$	267.9984	267.9968
4l	3,5-Cl_2-C_6H_3	68.1	129.5–131	$C_{12}H_8N_2OCl_2$	267.9984	267.9957
4m	3,4-Cl_2-C_6H_3	44	177–179	$C_{12}H_8N_2OCl_2$	267.9984	267.9957
4n	2-F-C_6H_4	97.8	125–126.5	$C_{12}H_9N_2OF$	216.0699	216.0687
4o	3-F-C_6H_4	93	1 9–120	$C_{12}H_9N_2OF$	216.0699	216.0686
4p	4-F-C_6H_4	100	204–204.5	$C_{12}H_9N_2OF$	216.0699	216.0687
4q	2-CF_3-C_6H_4	99	134–135	$C_{13}H_9N_2OF_3$	266.0667	266.0664
4r	3-CF_3-C_6H_4	70	138–139	$C_{13}H_9N_2OF_3$	266.0667	266.0660
4s	4-CF_3-C_6H_4	71.5	183.5–185	$C_{13}H_9N_2OF_3$	266.0667	266.0652
4t	4-O_2N-C_6H_4	NI[a]				

[a] NI = not isolated.

the analgesic activity of **5p**. It is not known whether these compounds act as prostaglandin synthetase inhibitors.

The influence which substituents attached to the phenyl ring of **5** have upon blood glucose concentration was also investigated. These results were compared to that of the unsubstituted parent compound 1, which elevated blood glucose 78 and 50% at 2 and 4 h, respectively, after a 100 mg/kg po dose (see Table II). Examination of the hyperglycemic activities of **5a–c,f–h,n–p,q–s** indicate that the 3-substituted compounds are more potent than the corresponding 4-substituted analogues. All of the 2-substituted compounds were relatively inactive, except for the 2-fluoro (**5n**) compound, which was more potent than the 3-fluoro (**5o**) and 4-fluoro (**5p**) compounds. The low activity of 2-methyl (**5a**), 2-methoxy (**5f**), 2-chloro (**5h**), and 2-trifluoromethyl (**5q**) may be due to an ortho effect. If this is true, one would expect the 2-fluoro (**5n**) compound to exhibit an activity similar to 1, which has a 2-hydrogen atom, since fluorine is most similar in size to hydrogen. The Van der Waals radii of fluorine and hydrogen are 1.35 and 1.2 Å, respectively.[7] 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. The *N*-(carbonylamino)-1,2,3,6-tetrahydropyridines **5** would not alter blood glucose concentration at doses which provide significant analgesic activity, since the dose–response relationship for hyperglycemic activity has a steep slope relative to that observed for analgesic activity. For example, **5b** has no effect on blood glucose concentration at doses below 0.1 mg/kg po.

A previous study indicated that 1 exhibited antiinflammatory activity as indicated by a 25 and 50% inhibition of carrageenan-induced paw edema at 3 and 5 h, respectively, after a 64 mg/kg sc dose.[2] The 4-methyl (**5c**), 4-methoxy (**5h**), 4-chloro (**5j**), and 3,4-dichloro (**5m**) analogues were selected, as described in the manual method for applying the Hansch approach to drug design,[8] to determine the effect of different types of substitution on the phenyl ring of 1 upon antiinflammatory activity. Compounds **5c,h,j,m** were found to be inactive at a dose of 64 mg/kg sc, indicating that substitution at the 3 or 4 position of the phenyl ring abolishes antiinflammatory activity. Indomethacin produces a 17 and 83% inhibition of carrageenan-induced paw edema at 3 and 5 h, respectively, after a 12 mg/kg sc dose.

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 using 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. 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[9] by animation of pyridine using freshly prepared hydroxylamine-*O*-sulfonic acid.[10]

General Synthesis of *N*-(Carbonylimino)pyridinium Ylides 4 (Table I). The acid chloride 3 (12 mmol) was added dropwise to a solution of **2** (8 mmol) in 25 mL of 10% aqueous sodium hydroxide with stirring. The reaction was allowed to proceed for 24 h at 25 °C with stirring and then 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 was purified by elution from a 2.5 × 20 cm neutral alumina oxide column. The initial 100-mL ether eluate was discarded. Further elution with 300 mL of ether–methanol (9:1, v/v) afforded 4. Compound **4a** exhibited the following spectral data: ^1H NMR δ 2.58 (s, 3 H, Me), 7.11–7.38 (m, 3 H, H_3, H_4, and H_5 phenyl hydrogens), 7.38–8.01 (m, 4 H, H_6 phenyl hydrogen, H_3, H_4, and H_5 pyridinium hydrogens), 8.85 (d, $J_{2,3} = J_{5,6} = 6$ Hz,

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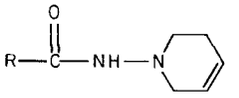
Table II. Some Physical and Pharmacological Data of *N*-(Carbonylamino)-1,2,3,6-tetrahydropyridines 5



						analgesic act., inhib act. on phenylquinone writhing[c]		hypoglycemic–hyperglycemic act.[d]		
									% change in blood glucose concns posttreatment	
no.	R	yield, %	mp, °C	P^a	formula[b]	dose, mg/kg sc	% inhibn	dose, mg/kg po	2 h	4 h
5a	2-Me-C_6H_4	99	162–163	28.8	$C_{13}H_{16}N_2O$	0.004	72.0 ± 2.0	100	−2.8 ± 6.8	−6.3 ± 5.6
5b	3-Me-C_6H_4	72.2	138–139	58.8	$C_{13}H_{16}N_2O$	0.004	56 ± 0.1	100	+117.2 ± 11.0	+108.5 ± 4.9
						0.0004	50 ± 0.80	30	+50 ± 11.6	
						17	50 ± 2.5[e]	34		+50 ± 1.7
5c	4-Me-C_6H_4	98	137–139	33.3	$C_{13}H_{16}N_2O$	0.004	48 ± 0.9	100	+73	+41
5d	4-$(Me)_3C$-C_6H_4	100	147–148	280	$C_{16}H_{22}N_2O$	0.004	48.8 ± 2.2	100	+1.8 ± 7.8	+4.7 ± 6.8
5e	3,4-Me_2-C_6H_3	93	139–140.5	71.3	$C_{14}H_{18}N_2O$	0.004	60.8 ± 2.4	100	+92.3 ± 27.4	+62.8 ± 27.0
5f	2-MeO-C_6H_4	98.5	83.5–84.5	5.5	$C_{13}H_{16}N_2O_2$	0.004	69.6 ± 1.7	100	+5.8 ± 5.9	+6.3 ± 1.2
5g	3-MeO-C_6H_4	97.8	146.5–148	10.5	$C_{13}H_{16}N_2O_2$	0.004	68.8 ± 1.0	100	+113.3 ± 29.1	+72.8 ± 23.3
5h	4-MeO-C_6H_4	79.4	148–150	34.1	$C_{13}H_{16}N_2O_2$	0.004	57.6 ± 2.23	100	+69	+26
5i	2-Cl-C_6H_4	98.5	180–181	34.2	$C_{12}H_{13}N_2OCl$	0.004	52 ± 2.1	100	+16.9 ± 9.0	+21.4 ± 5.8
5j	4-Cl-C_6H_4	95	160–162	19.1	$C_{12}H_{13}N_2OCl$	0.004	61.6 ± 1.3	100	+109	+26
5k	2,4-Cl_2-C_6H_3	97	161–162	30.6	$C_{12}H_{12}N_2OCl_2$	0.004	57.2 ± 3.8	100	-6.5 ± 6.4	+1.3 ± 8.8
5l	3,5-Cl_2-C_6H_3	99.8	181–182	16.4	$C_{12}H_{12}N_2OCl_2$	0.004	69.6 ± 1.8	100	+3.8 ± 8.5	+18.5 ± 13.4
5m	3,4-Cl_2-C_6H_3	93	157–159	26.4	$C_{12}H_{12}N_2OCl_2$	0.004	48.8 ± 1.4	100	+50	+59
5n	2-F-C_6H_4	97.7	132–133	7.5	$C_{12}H_{13}N_2OF$	0.004	64.8 ± 2.1	100	+213 ± 40.1	+127 ± 36.9
								30	+50 ± 10.1	
5o	3-F-C_6H_4	94.6	145–146	44.4	$C_{12}H_{13}N_2OF$	0.004	65.6 ± 1.5	100	+167.3 ± 46.3	+137.8 ± 59.2
5p	4-F-C_6H_4	99.3	153–154	83.9	$C_{12}H_{13}N_2OF$	0.004	55.2 ± 1.0	100	+124 ± 58.5	+154 ± 91.0
						5	69 ± 1.55			
						5	71 ± 1.39[f]			
						0.00036	50 ± 1.07			
						30	50 ± 3.0[e]			
5q	2-CF_3-C_6H_4	100	137–138	5.4	$C_{13}H_{13}N_2OF_3$	0.004	64 ± 2.2	100	+1.2 ± 41.5	+19.6 ± 35.3
5r	3-CF_3-C_6H_4	99.2	169–170.5	26.6	$C_{13}H_{13}N_2OF_3$	0.004	54.4 ± 0.8	100	+114.8 ± 6.2	+102 ± 4.6
5s	4-CF_3-C_6H_4	98.9	173–174	138.3	$C_{13}H_{13}N_2OF_3$	0.004	46.4 ± 1.5	100	+43.3 ± 14.2	+37.3 ± 4.5
5t	4-O_2N-C_6H_4	48.7	202–203	103.3	$C_{12}H_{13}N_3O_3$	0.004	51 ± 1.9	100	+92.6 ± 31.3	+140.6 ± 70.3
1	4-H-C_6H_4				$C_{12}H_{14}N_2O$	0.004	73.6 ± 0.6	100	+78	+50
aspirin						50	50			
dextropropoxyphene						56	50			
morphine sulfate						0.038	50 ± 1.61			
						3.1	50[e]			
chlorpropamide								100	−42 ± 12.1	−38 ± 9.3

[a] Partition coefficient. P = concentration in octanol/concentration in water. [b] All compounds gave analyses for C, H, and N within ±0.4% of theoretical values. [c] The result is the mean value, or the mean value ± SEM, of five animals. [d] 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 is indicated by a negative number. [e] Determined using the hot-plate test 30 min after a subcutaneous dose. [f] Naloxone hydrochloride (1 mg/kg sc) was administered 15 min prior to injection of 5p.

of d, $J_{2,4} = J_{4,6} = 1.5$ Hz, 2 H, H_2, and H_6 pyridinium hydrogens). Exact mass for $C_{13}H_{12}N_2O$: calcd, 212.0950; found (high-resolution MS), 212.0953.

The following modifications to the purification of **4**, which did not require column chromatography, were followed in the specific instances listed below. The 2-methyl derivative **4a** was obtained as a pure product. The 4-*tert*-butyl analogue **4d** was washed with 10 mL of cold ether to obtain a pure sample. Products **4g**, **4i**, and **4q** were purified by decolorization using charcoal. The 2-fluoro compound **4n** was purified by crystallization from methylene chloride, while **4o** was crystallized from ether.

General Synthesis of *N*-(Carbonylamino)-1,2,3,6-tetrahydropyridines 5 (Table II). A solution of the *N*-(carbonylimino)pyridinium ylide **4** (5 mmol) in 20 mL of absolute ethanol was added dropwise to a solution of sodium borohydride (50 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 25 °C. Extraction with chloroform (4 × 75 mL), drying (Na_2SO_4), and removal of the solvent in vacuo gave **5**. In most reactions, the product **5** was isolated pure.

Those products **5** requiring further purification were purified as outlined in the specific instances listed below. The 3-methyl analogue **5b** was purified by elution from a 2.5 × 20 cm neutral alumina column using 300 mL of ether–methanol (9:1, v/v) as eluant. Products **5g** and **5s** were purified by crystallization from ether, while **5i** was recrystallized from chloroform–ether. The 2-fluoro derivative **5n** was decolorized using charcoal. The 4-nitro compound **5t** was purified on 0.5 mm silica gel G plates using $CHCl_3$–MeOH (9:1, v/v) as development solvent. Extraction of the band having R_f 0.5 with hot absolute ethanol afforded **5t**. Alternatively, these compounds can also be purified by elution from a 2.5 × 20 cm neutral alumina column using 300 mL of ether–methanol (9:1, v/v) as eluant. Compound **5a** exhibited the following spectral data: IR 3200 (NH), 1620 (CO) cm^{-1}; ^1H NMR δ 2.08–2.53 (m, 5 H, Me, H_3), 3.11 (t, $J_{2,3} = 7$ Hz, 2 H, H_2), 3.52 (m, 2 H, H_6), 5.73 (m, 2 H, H_4, H_5), 6.87–7.42 (m, 5 H, phenyl hydrogens, NH, exchanges with deuterium oxide). Exact mass for $C_{13}H_{16}N_2O$: calcd, 216.1262; found (high-resolution MS), 216.1254.

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, and 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 − (no. of writhes in treated group/no. of writhes in 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. The hot-plate test using the method of Eddy et al.[4] was also used. Five male Swiss albino mice weighing 18–22 g were used in each group. Mice were put on a hot plate at 55 ± 0.5 °C. The reaction time (jumping) was observed once before and then 30 min after administration of the compound sc.

$$\% \text{ analgesia} = \left(\frac{T_t - T_0}{T_{max} - T_0} \right) \times 100$$

T_0 = control time; T_t = latency time at 30 min; T_{max} = 30 s

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 II summarizes the analgesic and blood glucose concentration results.

Antiinflammatory activity was measured by the method of Winter.[6] 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.

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

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

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Tryptophan Analogues. 1. Synthesis and Antihypertensive Activity of Positional Isomers

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A series of tryptophan analogues having the carboxyl function at the β position was synthesized and tested for antihypertensive activity. The 5-methoxy analogue **46** exhibited antihypertensive activity in the rat via the oral route and was much more potent than the normal tryptophan analogue. The methyl ester was found to be a critical structural feature for activity.

During the past quarter century the physiological function of serotonin in the central nervous system has been the subject of intensive research. Serotonin has been implicated in theories of the etiology of affective disorders,[1] in sleep mechanisms,[2] and in regulation of blood pressure.[3]

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(1) A. Coppen in "Factors in Depression", N. S. Kline, Ed., Raven Press, New York, 1974, pp 33–44.

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