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.).

(11) Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175.

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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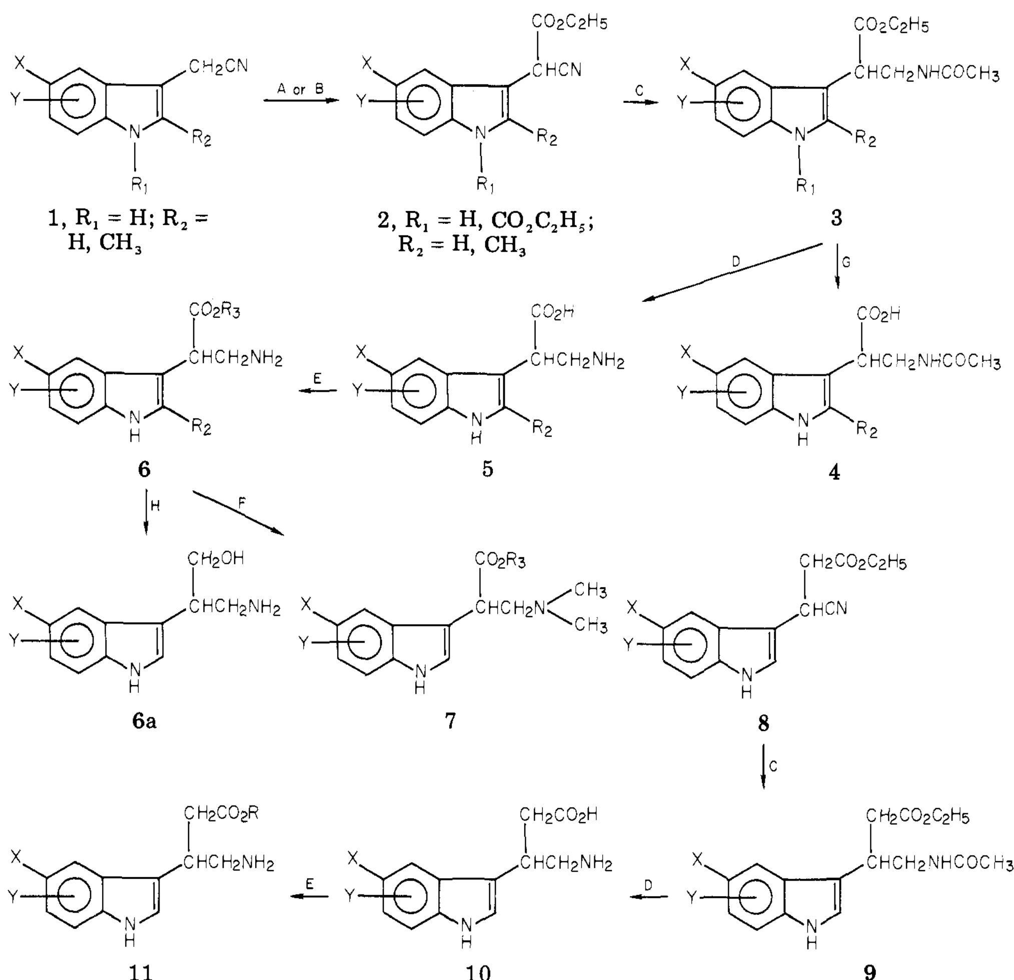
Scheme I

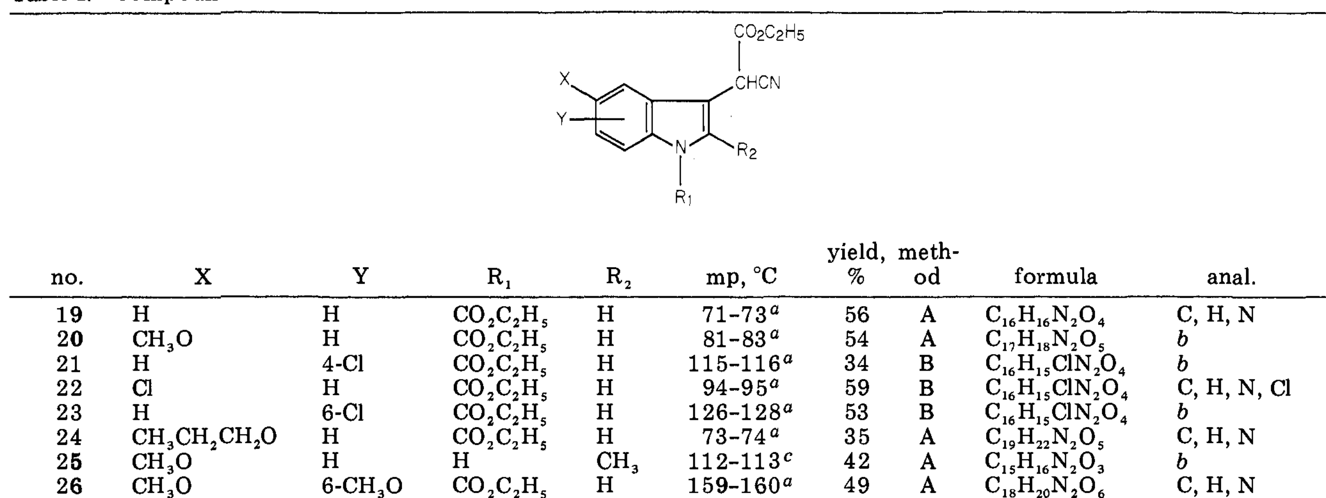


In addition, there is evidence which suggests that tryptophan itself is capable of acting on the central nervous system.[4] Efforts to develop serotonin or tryptophan analogues with relatively specific CNS actions as orally useful therapeutic agents continue. Many structure-activity studies have been concerned with substituent variation on the indole nucleus[5] and with α-alkylation of the side chain.[6] One variation which has not been investigated for its effect on biochemical or pharmacological activity is a shift in the position of the carboxyl group of tryptophan from the α- to the β-carbon atom of the side chain. It seemed to us that such a compound would not follow the usual metabolic route to the 5-hydroxyindolamines because it should not be affected by the ubiquitous L-aromatic amino acid decarboxylase. Additionally, previous pharmacological work led us to believe that the central serotonin receptors which modulate blood pressure are different from other serotonin receptors,[7] allowing the possibility of selective stimulation by an appropriate agonist. The finding that one of the initial group of tryptophan analogues exhibited hypotensive activity in the anesthetized cat prompted an expansion of the series, and the main objective became one of optimizing oral antihypertensive activity. This report describes the synthesis and pharmacological activity of the positional isomer of tryptophan and analogues thereof.

Chemistry. The primary structural type that was desired was **6**, the ester of the positional isomer of tryptophan. The tryptophan isomers were most practically approachable from the 3-indolylacetonitriles,[8] **1** (Scheme I), which were prepared from the corresponding indoles. Cathylation of the 3-indolylacetonitriles with an excess of diethyl carbonate in the presence of 2 equiv of base gave the corresponding N,C-dicathylated product, **2**. When only 1 equiv of base was employed, a complex mixture resulted and a major product could not be isolated from the reaction mixture. Only in one case, **1**, where $R^2 = CH_3$, was the monocathylated product, **22**, isolated as the major product, even in the presence of 2 equiv of base. In the technique employed, the cathylation was conveniently followed by the evolution of EtOH. Metallic Na proved to be the best choice of base in the cathylation, except when interfering substituents, such as halogens, were

(2) D. X. Freedman in "Serotonin and Behavior", J. Barchas and E. Usdin, Eds., Academic Press, New York, 1973, pp 381–383.
(3) D. M. Kuhn, W. A. Wolf, and W. Lovenburg, *Hypertension*, 2, 243 (1980).
(4) (a) E. Hartman, J. Cravens, and S. List, *Arch. Gen. Psychiatry*, **31**, 394 (1974); (b) G. P. Egan and G. Hammad, *Br. Med. J.*, **2**, 701 (1976); (c) A. Coppen, D. Shaw, B. Herzberg, and R. Maggs, *Lancet*, **1**, 1178 (1967); (d) A. J. Prange, I. C. Wilson, C. W. Lynn, L. B. Alltop, and R. A. Strikeleather, *Arch. Gen. Psychiatry*, **30**, 56 (1974); (e) N. S. Kline and B. K. Shah, *Curr. Ther. Res.*, **15**, 484 (1973).
(5) W. T. Comer and A. W. Gomell, in "Medicinal Chemistry", A. Burger, Ed., Wiley-Interscience, New York, 1970, pp 1037–1039.
(6) R. V. Heinzelman and J. Smuszkovicz, *Progr. Drug Res.*, **6**, 75 (1963).
(7) P. Nava-Félix and E. Hong, *J. Cardiovasc. Pharmacol.*, **1**, 46 (1979).
(8) J. Smuszkovics, W. C. Anthony, and R. V. Heinzelman, *J. Org. Chem.*, **25**, 857 (1960).

Table I. Compounds 19-26



no.	X	Y	R_1	R_2	mp, °C	yield, %	method	formula	anal.
19	H	H	$CO_2C_2H_5$	H	71-73[a]	56	A	$C_{16}H_{16}N_2O_4$	C, H, N
20	CH_3O	H	$CO_2C_2H_5$	H	81-83[a]	54	A	$C_{17}H_{18}N_2O_5$	*b*
21	H	4-Cl	$CO_2C_2H_5$	H	115-116[a]	34	B	$C_{16}H_{15}ClN_2O_4$	*b*
22	Cl	H	$CO_2C_2H_5$	H	94-95[a]	59	B	$C_{16}H_{15}ClN_2O_4$	C, H, N, Cl
23	H	6-Cl	$CO_2C_2H_5$	H	126-128[a]	53	B	$C_{16}H_{15}ClN_2O_4$	*b*
24	$CH_3CH_2CH_2O$	H	$CO_2C_2H_5$	H	73-74[a]	35	A	$C_{19}H_{22}N_2O_5$	C, H, N
25	CH_3O	H	H	CH_3	112-113[c]	42	A	$C_{15}H_{16}N_2O_3$	*b*
26	CH_3O	6-CH_3O	$CO_2C_2H_5$	H	159-160[a]	49	A	$C_{18}H_{20}N_2O_6$	C, H, N

[a] From MeOH. [b] Used directly for subsequent reaction. [c] EtOAc-Skellysolve B.

present. In the latter case, NaOEt was used as the base.

Catalytic reduction of the nitriles, **2**, in either neutral or acidic media resulted in very low yields of the corresponding free amine. However, it was found that when reduction of nitriles **2** was carried out in Ac_2O as the solvent, good yields of the N-acetylated amines, **3**, were obtained. Saponification of compounds **3** with 10 N NaOH, followed by acidification of the reaction mixture to the isoelectric region, resulted in concomitant decarboxylation of the resulting carbamic acids, thus yielding the tryptophan isomers **5**.[9] Alternatively, **3** could be saponified using 1 N KOH–MeOH, followed by acidification and concomitant decarboxylation, to give the N-acetylated tryptophan isomers **4**. The esters **6** were obtained from **5** by esterification with MeOH–$SOCl_2$. In many cases, **3** and **5** were not isolated but were subsequently reacted in crude form.

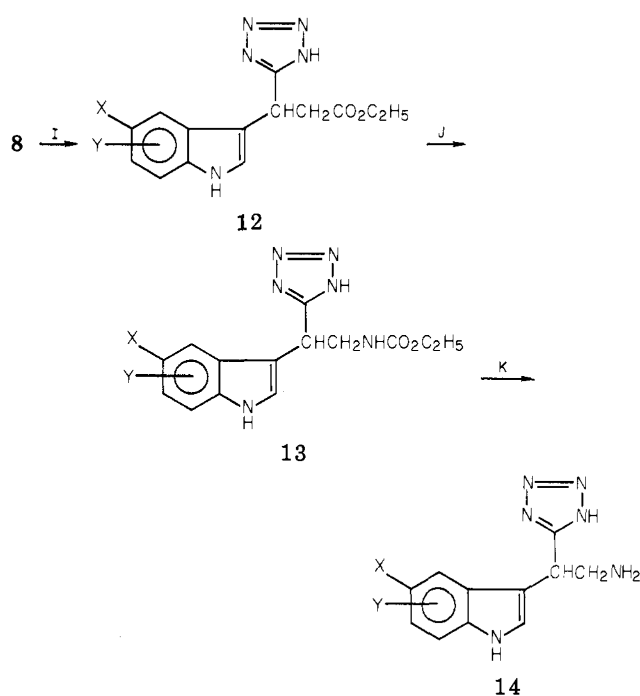
Homologues of **6** were prepared from the nitrile esters **8**, which in turn were prepared from the appropriately substituted indole-3-carboxaldehyde via Knoevenagel condensation and 1,4-addition of cyanide.[10] The scheme subsequently employed for conversion of **8** into the respective homologous esters **11** was identical with that described for conversion of **2** into **6**.

We also wished to study the effect of replacing the carboxyl group of the amino acid with another electron-withdrawing group. For this purpose, the 5-tetrazolyl moiety was chosen and was conveniently introduced by addition of NaN_3 to **8**, giving **12** (Scheme II). Hydrazinolysis of **12**, followed by Curtius rearrangement in the presence of EtOH, gave the urethane **13**, which was subsequently saponified and decarboxylated to give **14**.

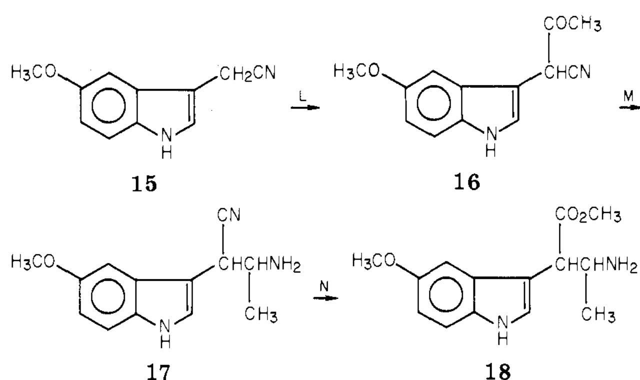
In order to determine the effect of branching on the biological activity, we desired to prepare **18**, which necessitated a different synthetic route (Scheme III). Condensation of EtOAc with **15** gave primarily the C-acylated product **16**. Reductive amination of **16** using $NaCNBH_3$ and NH_4OAc gave the nitrile amine **17**, which was subsequently hydrolyzed to the carboxylic acid and esterified to give **18**.

Reductive alkylation of **6** was accomplished catalytically in the presence of formaldehyde to give the tertiary amine **7**. An additional derivative was prepared from **6** by $LiAlH_4$ reduction to give the alcohol **6a**.

Scheme II



Scheme III



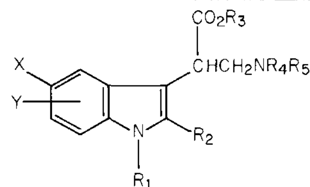
Pharmacological Results and Discussion

Several of the isomeric tryptophan analogues showed hypotensive activity when tested by the intravenous route

(9) At the time that this work was nearing completion, the synthesis of the amino acid **35** by a slightly different technique was disclosed by V. S. Rozhkov, Y. Smushkevich, and N. Suvorov, *Zh. Org. Khim.*, 12, 1076 (1976).

(10) Y. G. Perron and W. F. Minor, *J. Org. Chem.*, 24, 1165 (1959).

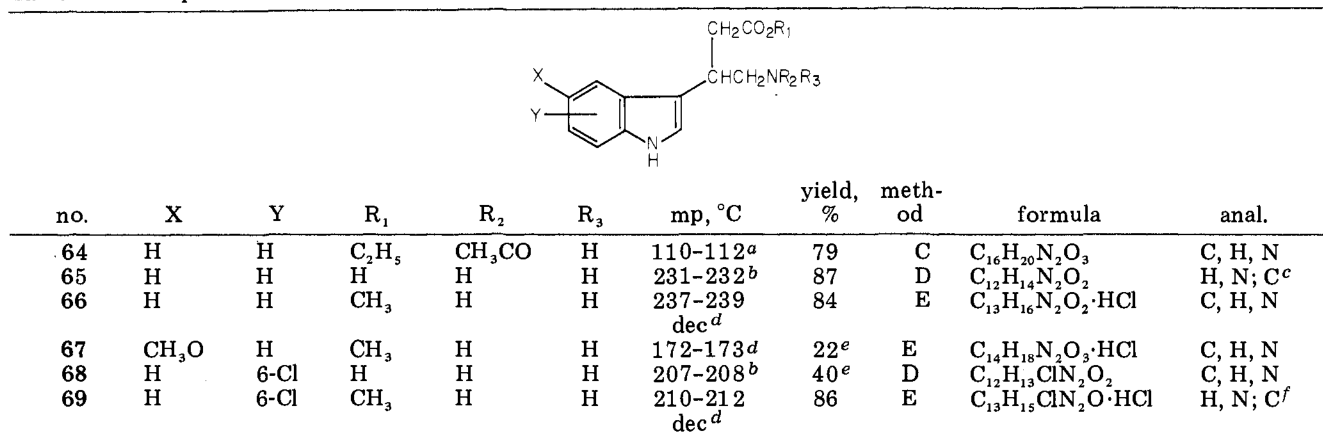
Table II. Compounds 27-63



no.	X	Y	R_1	R_2	R_3	R_4	R_5	mp, °C	yield, %	method	formula	anal.
27	H	H	$CO_2C_2H_5$	H	C_2H_5	CH_3CO	H	115-117[a]	88	C	$C_{18}H_{22}N_2O_5$	C, H, N
28	CH_3O	H	$CO_2C_2H_5$	H	C_2H_5	CH_3CO	H	88-90[a]	56	C	$C_{19}H_{24}N_2O_6$	C, H, N
29	H	4-Cl	$CO_2C_2H_5$	H	C_2H_5	CH_3CO	H	94-95[a]	55	C	$C_{18}H_{21}ClN_2O_5$	C, H, N
30	Cl	H	$CO_2C_2H_5$	H	C_2H_5	CH_3CO	H	114-115[a]	79	C	$C_{18}H_{21}ClN_2O_5$	*b*
31	H	6-Cl	$CO_2C_2H_5$	H	C_2H_5	CH_3CO	H	138-140[a]	72	C	$C_{18}H_{21}ClN_2O_5$	C, H, N
32	$CH_3CH_2CH_2O$	H	$CO_2C_2H_5$	H	C_2H_5	CH_3CO	H	*c*	98	C	$C_{21}H_{28}N_2O_6$	*b*
33	CH_3O	H	H	CH_3	C_2H_5	CH_3CO	H	136-138[a]	70	C	$C_{17}H_{22}N_2O_4$	*b*
34	CH_3O	6-CH_3O	$CO_2C_2H_5$	H	C_2H_5	CH_3CO	H	153-154[a]	92	C	$C_{20}H_{26}N_2O_7$	C, H, N
35	H	H	H	H	H	H	H	246 dec[d]	72	D	$C_{11}H_{12}N_2O_2$	C, H, N
36	CH_3O	H	H	H	H	H	H	205-207 dec[d]	64	D	$C_{12}H_{14}N_2O_3$	H, N; C[e]
37	H	4-Cl	H	H	H	H	H		*f*	D	$C_{11}H_{11}ClN_2O_2$	*b*
38	Cl	H	H	H	H	H	H		71[d,f]	D	$C_{11}H_{11}ClN_2O_2$	*b*
39	H	6-Cl	H	H	H	H	H	245-247 dec[d]	78	D	$C_{11}H_{11}ClN_2O_2$	H, N; C[g]
40	$CH_3CH_2CH_2O$	H	H	H	H	H	H	>270[d]	53	D	$C_{13}H_{18}N_2O_3$	*b*
41	CH_3O	H	H	CH_3	H	H	H	146-147[d]	69	D	$C_{13}H_{16}N_2O_3$	*b*
42	CH_3O	6-CH_3O	H	H	H	H	H		*f*	D	$C_{13}H_{16}N_2O_4$	*b*
43	H	H	H	H	CH_3	H	H	215-216[h]	79	E	$C_{12}H_{14}N_2O_2 \cdot HCl$	C, H; N[i]
44	H	H	H	H	CH_3	CH_3	CH_3	164-165[h]	52	F	$C_{14}H_{18}N_2O_2 \cdot C_2H_2O_4$[j]	C, H, N
45	CH_3O	H	H	H	H	CH_3CO	H	97-99[d]	89	G	$C_{14}H_{16}N_2O_4$	H, N; C[k]
46	CH_3O	H	H	H	CH_3	H	H	212-214[h]	76	E	$C_{13}H_{16}N_2O_3 \cdot HCl$	C, H, N
47	H	4-Cl	H	H	CH_3	H	H	219-221[h]	65	E	$C_{12}H_{13}ClN_2O_2 \cdot HCl$	C, H, N, Cl
48	H	6-Cl	H	H	CH_3	H	H	240-242 dec[h]	98	E	$C_{12}H_{13}ClN_2O_2 \cdot HCl$	C, H, N, Cl
49	CH_3O	H	H	H	CH_3	CH_3	CH_3	164-166[h]	51	F	$C_{15}H_{20}N_2O_3 \cdot C_2H_2O_4$[j]	H, N; C[l]
50	CH_3O	H	H	H	*n*-C_5H_{11}	H	H	163-165[h]	52	E	$C_{17}H_{24}N_2O_3 \cdot HCl$	C, H, N
51	CH_3O	H	H	CH_3	CH_3	H	H	143-144[h]	50	E	$C_{14}H_{18}N_2O_3 \cdot HCl$	H, N; C[m]
52	$CH_3CH_2CH_2O$	H	H	H	CH_3	H	H	226-227[h]	69	E	$C_{15}H_{20}N_2O_3 \cdot HCl$	H, N; C[n]
53	Cl	H	H	H	CH_3	H	H	211-212[h]	72	E	$C_{12}H_{13}ClN_2O_2 \cdot HCl$	C, H, N
54	CH_3O	H	H	H	CH_3CH_2	H	H	187-188[h]	59	E	$C_{14}H_{18}N_2O_3 \cdot HCl$	H, N; C[o]
55	CH_3O	H	H	H	$(CH_3)_2CH$	H	H	177-178[h]	28	E	$C_{15}H_{20}N_2O_3 \cdot HCl$	C, H, N
56	CH_3O	6-CH_3O	H	H	CH_3	H	H	176-177[h]	37	E	$C_{14}H_{18}N_2O_4 \cdot HCl \cdot 0.5H_2O$	C, H, N
57	F	H	H	H	H	H	H	244-245[h]	72	D	$C_{11}H_{11}FN_2O_2$	H, N; C[p]
58	F	H	H	H	CH_3	H	H	186-187[h]	63	E	$C_{12}H_{13}FN_2O_2 \cdot HCl$	C, H, N
59	OH	H	H	H	CH_3	H	H	162-164[h]	80	E	$C_{12}H_{14}N_2O_3 \cdot HCl \cdot 0.5H_2O$	H; C, N[q]
60	CH_3O	H	CH_3	H	CH_3	H	H	209-211[h]	52	E	$C_{14}H_{18}N_2O_3 \cdot HCl$	C, H, N
61	Br	H	H	H	H	H	H	235-236[h]	35	D	$C_{11}H_{11}BrN_2O_2 \cdot H_2O$	C, H, N
62	Br	H	H	H	CH_3	H	H	226-227[h]	69	E	$C_{12}H_{13}BrN_2O_2 \cdot HCl$	C, H, N
63	Br	H	H	H	C_2H_5	H	H	210-212[h]	53	E	$C_{13}H_{15}BrN_2O_2 \cdot HCl$	C, H, N

[a] From EtOAc-Skellysolve B. [b] Used directly for subsequent reaction. [c] Isolated in the form of an oil. [d] From H_2O. [e] C: calcd, 61.52; found, 60.38. [f] Isolated as crude product. [g] C: calcd, 55.35; found, 54.83. [h] From MeOH-EtOAc. [i] N: calcd, 11.00; found, 10.54. [j] Oxalate salt. [k] C: calcd, 60.86; found, 60.33. [l] C: calcd, 55.73; found, 55.00. [m] C: calcd, 56.27; found, 55.32. [n] C: calcd, 57.60; found, 57.18. [o] C: calcd, 56.28; found, 55.75. [p] C: calcd, 59.46; found, 58.67. [q] C, N: calcd, 51.52, 10.02; found, 50.96, 9.63.

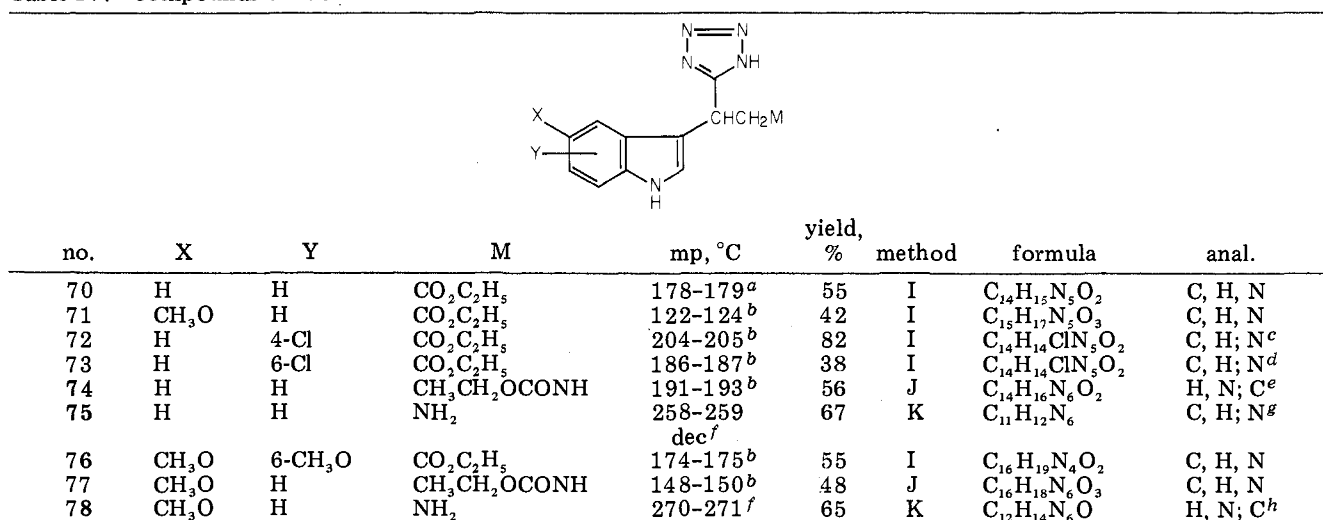
Table III. Compounds 64-69



no.	X	Y	R_1	R_2	R_3	mp, °C	yield, %	method	formula	anal.
64	H	H	C_2H_5	CH_3CO	H	110-112[a]	79	C	$C_{16}H_{20}N_2O_3$	C, H, N
65	H	H	H	H	H	231-232[b]	87	D	$C_{12}H_{14}N_2O_2$	H, N; C[c]
66	H	H	CH_3	H	H	237-239 dec[d]	84	E	$C_{13}H_{16}N_2O_2 \cdot HCl$	C, H, N
67	CH_3O	H	CH_3	H	H	172-173[d]	22[e]	E	$C_{14}H_{18}N_2O_3 \cdot HCl$	C, H, N
68	H	6-Cl	H	H	H	207-208[b]	40[e]	D	$C_{12}H_{13}ClN_2O_2$	C, H, N
69	H	6-Cl	CH_3	H	H	210-212 dec[d]	86	E	$C_{13}H_{15}ClN_2O \cdot HCl$	H, N; C[f]

[a] From EtOAc-Skellysolve B. [b] From H_2O. [c] C: calcd, 66.03; found, 65.23. [d] From MeOH-EtOAc. [e] Overall yield from the nitrile ester **8**. [f] C: calcd, 51.50; found, 51.00.

Table IV. Compounds 70-78



no.	X	Y	M	mp, °C	yield, %	method	formula	anal.
70	H	H	$CO_2C_2H_5$	178-179[a]	55	I	$C_{14}H_{15}N_5O_2$	C, H, N
71	CH_3O	H	$CO_2C_2H_5$	122-124[b]	42	I	$C_{15}H_{17}N_5O_3$	C, H, N
72	H	4-Cl	$CO_2C_2H_5$	204-205[b]	82	I	$C_{14}H_{14}ClN_5O_2$	C, H; N[c]
73	H	6-Cl	$CO_2C_2H_5$	186-187[b]	38	I	$C_{14}H_{14}ClN_5O_2$	C, H; N[d]
74	H	H	CH_3CH_2OCONH	191-193[b]	56	J	$C_{14}H_{16}N_6O_2$	H, N; C[e]
75	H	H	NH_2	258-259 dec[f]	67	K	$C_{11}H_{12}N_6$	C, H; N[g]
76	CH_3O	6-CH_3O	$CO_2C_2H_5$	174-175[b]	55	I	$C_{16}H_{19}N_4O_2$	C, H, N
77	CH_3O	H	CH_3CH_2OCONH	148-150[b]	48	J	$C_{16}H_{18}N_6O_3$	C, H, N
78	CH_3O	H	NH_2	270-271[f]	65	K	$C_{12}H_{14}N_6O$	H, N; C[h]

[a] From EtOAc. [b] From EtOAc-Skellysolve B. [c] N: calcd, 21.92; found, 22.78. [d] N: calcd, 21.92; found, 22.65. [e] C: calcd, 55.99; found, 56.77. [f] From H_2O. [g] N: calcd, 36.82; found, 36.02. [h] C: calcd, 55.80; found, 55.37.

in the anesthetized cat at 10 mg/kg. In the renal hypertensive rat model, however, only a few compounds exhibited significant antihypertensive activity over a 4- to 6-h time period. The most potent compound was the 5-methoxy methyl ester analogue **46**. Even minor variations in the structure of **46** resulted in drastic decreases in activity. For example, methylation at the 1, 2, or α position (**60**, **51**, and **18**, respectively) led to inactive compounds. The 5-hydroxy analogue **59** was quite potent by the iv route in the cat but was inactive orally in the rat, most likely reflecting poor absorption from the gastrointestinal tract. The amino acid analogue **36** was devoid of hypotensive effect even by the iv route, but the amino acid form of the 5-fluoro analogue (**57**) was as effective as the corresponding methyl ester **58**. The isosteric tetrazole derivative **78** failed to retain activity.

The finding that compound **46** was clearly more potent than other members of the series seems to be due to different factors. Thus, polar amino acids like **36** are devoid of activity because of their inability to cross the blood–brain barrier. However, in the case of the ethyl and isopropyl ester analogues (**54** and **55**, respectively), which failed to decrease the blood pressure in the rat by the oral route and in the cat by the intravenous or the intracerebroventricular (icv) routes, such negative results may be attributed to a lack of intrinsic activity and/or affinity for the serotonin receptors that mediate hypotension. Resolution of compound **46** will be carried out in an effort to determine whether there are stereospecificity requirements for the receptor site.

It is evident that the isomeric tryptophan analogue **46** is considerably more potent than its normal tryptophan counterpart **82** or reference tryptophan derivatives, such as 5-hydroxytryptophan (**79**) and 5-hydroxy-α-methyltryptophan ethyl ester (**81**), which have been reported to exhibit antihypertensive activity.[11,12]

The administration of **46** into the left vertebral artery or a lateral brain ventricle of anesthetized cats produced hypotension at doses that were inactive when tested intravenously, indicating that the antihypertensive effect of the compound is due to an effect on the central nervous system.[13] Since the hypotension appeared almost immediately after the administration of **46** into the vertebral artery but was delayed after its icv injection, the site of action of the compound is probably located in the brain stem, which is irrigated by the vertebral artery. The finding that the hypotension caused by **46** was not anta-

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Table V. Antihypertensive Activity of Tryptophan Analogues

		rat BP,[b] mmHg						cat BP,[c] mmHg	
no.	n[a]	c	1 h	2 h	4 h	6 h	8 h	c	Δ
6a	5	182	-13	-15*	-4	-8	0		
18	5	213	-6	-3	-3	+3	+2		
27	10	198	-3	-3	-18*	-22	-18	135	-49
28	10	202	-15*	-12	-21*	-20*	-14	195	-0
29	5	204	-8	-1	+3	0	+2	183	+11
31	10	191	-18	-12	-12	-7	-3	165	-2
35	10	192	-6	-8	-10	-13	-8	153	-10
36	5	211	-1	-10	+2	-6	-2	142	-5
39	5	198	-4	-5	-6	-14	-9	179	-2
43	10	198	-7	-9	-9	-6	-7	156	-53
44	5	197	-2	0	+2	+11	+1	145	-35
45	10	200	-16	-18	-24*	-28*	-8	154	-14
46	10	191	-85*	-71*	-38*	-10	+2	162	-82[d]
47	10	194	-7	-9	-20	-9	-8	131	-10
48	10	193	-14	-23	-17*	-15	-7	140	-7
49	5	184	-9	-2	+1	+14	+13	167	-35
50	5	196	-7	-11	-3	-11	-4	148	+2
51	5	196	+2	-2	-8	-8	-3	164	+1
52	10	197	-6	+6	+8	+9	+5	150	+7[d,e]
53	10	188	-8	-5	0	+2	+5	160	-61
54	5	188	-5	-4	+4	-2	-3	160	-0
55	5	185	+7	-1	+13	+7	+13	181	-48
56	5	204	-15	-2	-4	-7	-2	160	-16
57	10	192	-19*	-26*	-27*	-15	0	180	-25
58	10	187	-28*	-18*	-9	-4	+1	133	-30
59	5	202	+7	+1	+4	0	+7	135	-85
60	5	198	-5	-6	+3	+1	+7	165	+20
61	10	195	-12	-5	0	+5	0	115	-15
62	10	191	-6	-10	+6	+8	+7	125	-35
63	10	191	-3	-7	-2	-3	+1	143	-18
64	5	180	-8	-11	-7	-6	-2	169	-21
65	5	188	-11	-3	-3	-14	+1	152	-11
66	5	207	-1	-11	+2	-7	-1	184	-4
67	10	202	-14	-15	-6	-13	-12	166	-25
68	5	202	+2	+5	-9	-9	-2	160	+5
69	5	199	+2	-4	-3	-11	-6	158	-10
70	10	192	-4	-22*	-27*	-22*	-7	168	+2
71	10	195	-16	-21	-25*	-16	-11	136	-11
72	5	194	-4	-12	-5	-2	+4	135	-35
73	5	202	-5	+2	-4	-17	-11	175	-20
74	10	193	-10	-6	-24*	-17	-15	155	+5
75	5	182	+8	+1	+8	+5	+2	155	-5
76	10	199	-11	-15	-20	-25	-14	164	-6
77	5	207	-2	+2	0	+2	0	160	+5
78	5	202	-2	+5	-2	+3	+13	167	-4
				Reference Compounds[f]					
79	5	184	-9	-5	0	+6	-1	162	-24
80	5	188	-14	0	+2	+2	+1	156	-24
81	5	191	-2	-7	+14	+22*	+6	142	+9
82	5	194	-7	+4	-8	+4	-1	136	-12
83	10	198	-12	-9	-15*	-4	0	165	-22

[a] Number of renal hypertensive rats used in experiment. [b] Changes in mean systolic blood pressure in relation to control (c) values, observed after the oral administration of 10 mg/kg of the compound tested. * = statistically significantly different from control values ($p < 0.05$). [c] Decrease in mean blood pressure of a normotensive anesthetized cat after intravenous administration of 10 mg/kg of the compound tested. [d] Dose administered was 1 mg/kg, iv. [e] The animal died at 10 mg/kg, iv. [f] Reference compounds: 79, 5-hydroxytryptophan; 80, 5-hydroxytryptophan ethyl ester; 81, 5-hydroxy-α-methyltryptophan ethyl ester; 82, 5-methoxytryptophan methyl ester; 83, *dl*-tryptophan.

gonized by methysergide, was partially inhibited by quipazine, and was completely blocked by tolazoline parallels the profile found when icv serotonin was used to induce the hypotension and suggests that **46** is acting by stimulation of serotonin receptors.[14] Classification of serotonin receptors into 5-HT_1 (those that bind only to 5-HT) and 5-HT_2 (those that are located in the brain cortex and bind specifically to serotonin antagonists and to LSD types)[15] led us to postulate that the action of **46** is exerted by stimulation of the 5-HT_1 receptors, since it acts in the brain stem, is not blocked by methysergide, and does not elicit behavioral manifestations of the type induced by 5-hydroxytryptophan, quipazine, or LSD.[16] Compound **46** is being developed as an antihypertensive agent,[17] and further studies to characterize its pharmacological and

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(17) Compound **46** (code designation TR-3369) has been assigned the name, "indorenate" by the USAN.

pharmacokinetic profile are underway.

Experimental Section

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Microanalyses were performed by the analytical group of the Chemistry Department, Miles Laboratories, Inc., and by Midwest Microlabs Ltd., Indianapolis, IN. Where the analyses are indicated only by the elemental symbols, the analytical values were within 0.4% of the theoretical values. All new compounds were submitted for IR and NMR analyses, and the resulting spectra were consistent with the assigned structures. All compounds were judged for homogeneity by TLC on silica gel plates. In the case of amino acids and amino acid esters, the solvent mixture employed for TLC was *n*-BuOH/HOAc/H_2O (4:1:1). Plates were developed by UV light, I_2 vapor, and ninhydrin as applicable.

3-Indolylacetonitriles (1). These compounds were prepared from the corresponding substituted indoles via the standard Mannich route,[18] except for 5-methoxy-2-methyl-3-indolylacetonitrile (1, X = CH_3O; Y = H; R_2 = CH_3) which was prepared from *p*-methoxyphenylhydrazine.[19]

Cathylation of 3-Indolylacetonitriles. Method A. A vigorously stirred solution of the 3-indolylacetonitrile[18] (0.13 mol) in 200 mL of diethyl carbonate was maintained at 110 °C and treated over 30 min with metallic Na (0.26 mol), during which time approximately 2 equiv of EtOH was distilled. The mixture was kept at 110 °C for an additional 60 min, and the bulk of the solvent was removed in vacuo. The mixture was cooled to 5 °C and treated slowly with a solution of 18 mL of HOAc in 100 mL of H_2O. After stirring for 5 min, the mixture was extracted into 200 mL of EtOAc, and the organic layer was washed twice with brine, dried ($MgSO_4$), and evaporated in vacuo to a dark syrup, which was chromatographed on silica gel 60 (EM) eluting with PhH/EtOAc (9:1). The fractions containing the major product were evaporated in vacuo, and the residue was crystallized to give 2.

Ethyl α-cyano-α-(1-carbethoxy-5-methoxy-3-indolyl)-acetate (20): IR ($CHCl_3$) 1775 (C=O), 2250 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15–1.55 (m, 6, $2CO_2CH_2CH_3$), 3.90 (s, 3, OCH_3), 4.05–4.65 (m, 4, $2CO_2CH_2CH_3$), 4.85 (s, 1, α-CH), 6.9–7.1 (m, 2, aromatic H + 2-CH), 7.75 (s, 1, aromatic H), 8.1 (d, 1, aromatic H).

Method B. A solution of NaOEt was prepared from Na (0.05 mol) and 60 mL of EtOH. The solvent was removed in vacuo to dryness. The flask containing the alkoxide cake was cooled to 5 °C and with vigorous stirring was treated rapidly with a solution of the 3-indolylacetonitrile (0.025 mol) in 50 mL of diethyl carbonate, followed by addition of 30 mL of toluene. The mixture was gently heated until distillation commenced at about 80 °C. Toluene was then added dropwise at a rate equal to the rate of distillation. The distillate temperature gradually rose to 110 °C, and distillation was continued for an additional 10 min. The bulk of the solvent was removed in vacuo, and the remaining thick mixture was cooled to 5 °C and treated slowly with a solution of 3 mL of HOAc in 50 mL of H_2O. After stirring for 5 min, the mixture was extracted into 100 mL of Et_2O, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to a syrup, which was crystallized to afford 2.

Reduction of Nitriles. Method C. A solution of 0.04 mol of the nitrile in 150 mL of Ac_2O was hydrogenated at 50 psi in the presence of 1 teaspoon of Raney Ni (W-4) catalyst until 2 equiv of H_2 was taken up (5–16 h). The catalyst was filtered, and the filtrate was evaporated in vacuo to a syrup, which was taken up in 200 mL of EtOAc and shaken repeatedly with 6% K_2CO_3 until the aqueous layer remained basic. The organic layer was dried ($MgSO_4$), evaporated in vacuo, and crystallized to afford 3 or 9.

Ethyl 3-acetamido-2-(1-carbethoxy-5-methoxy-3-indolyl)propionate (28): ^1H NMR ($CDCl_3$) δ 1.05–1.5 (m, 6, $2CO_2CH_2CH_3$), 1.95 (s, 3, $COCH_3$), 3.75 (d, 2, $CHCH_2NH$), 3.85 (s, 3, OCH_3), 3.95–4.55 (m, 5, $2CO_2CH_2CH_3$ + $CHCH_2NH$), 6.05 (br s, 1, NH), 6.8–7.1 (m, 2, aromatic H + 2-CH), 7.45 (s, 1, aromatic H), 7.95 (d, 1, aromatic H).

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Amino Acids. Method D. A mixture of the N-acetylated amino ester (0.01 mol) and 13 mL of 10 N NaOH was refluxed 8 h. The mixture was cooled, diluted with 100 mL of H_2O, treated with Nuchar, and filtered. The filtrate was acidified to pH 5.5 with 6 N HCl, and the resulting mixture was diluted to 200 mL with H_2O, treated with Nuchar, heated to boiling, and filtered while hot. The filtrate was evaporated in vacuo to dryness, and the residue was either crystallized or used directly for subsequent esterification.

Amino Acid Esters. Method E. A stirred suspension of the pure or partially purified amino acid (0.004 mol) in 10 mL of the appropriate alcohol was cooled to -10 °C and treated dropwise with $SOCl_2$ (0.4 mL, 0.0056 mol) over several minutes. The mixture was stirred at ambient temperature for 18 h and the solvent was removed in vacuo. The residue was partitioned between 50 mL of EtOAc and 20 mL of 6% K_2CO_3, and the organic layer was dried ($MgSO_4$) and treated with 1 equiv of either 4 N HCl–dioxane or methanolic oxalic acid. The product was filtered and recrystallized.

Methyl 3-amino-2-(5-methoxy-3-indolyl)propionate hydrochloride (46): IR (KCl) 1730 (C=O) cm^{-1}; NMR (CD_3OD) δ 3.3–3.5 (m, 2, $CHCH_2NH$), 3.73 (s, 3, CO_2CH_3), 3.83 (s, 3, 5-OCH_3), 4.42 (unsym t, 1, $CHCH_2NH$), 6.7–7.4 (m, 4, aromatic ring + 2-CH); MS, *m/e* 248 (M^+ free base).

Reductive Alkylation. Method F. The salt of the amino acid ester 6 (0.0035 mol) was converted to the free base by partitioning between 100 mL of EtOAc and 30 mL of 6% K_2CO_3, drying the organic layer ($MgSO_4$), and evaporating in vacuo. The resulting residue was taken up in 80 mL of MeOH and treated with 37% HCHO (0.6 mL, 0.009 mol), and the solution was hydrogenated at 50 psi in the presence of 0.5 g of 10% Pd/C catalyst for 20 h, during which time 2 equiv of H_2 was taken up. The catalyst was filtered, and the filtrate was evaporated in vacuo to an oil, which was taken up in 100 mL of EtOAc and treated with a methanolic solution of 1 equiv of oxalic acid. The resulting solid was filtered and recrystallized to give 7.

Saponification. Method G. The N-acetylated amino acid ester 3 (0.007 mol) was dissolved in 20 mL of 1 N KOH–MeOH. After standing for 2 h, the solution was evaporated in vacuo, and the residue was stirred with 15 mL of H_2O. The mixture was filtered, and the filtrate was acidified with 1 N H_2SO_4 to pH 3. After standing in the cold for 24 h, the product was collected, washed with ice–water, and recrystallized to give 4.

3-Amino-2-(5-methoxy-3-indolyl)-1-propanol Oxalate Hemihydrate (6a). Method H. The free base of 46 (5 g, 0.02 mol) was prepared as described in method F. The resulting amine was dissolved in 150 mL of dry THF, and this solution was added dropwise to a vigorously stirred suspension of $LiAlH_4$ (2 g) in 50 mL of THF. The temperature of the reaction mixture was maintained at 15–20 °C throughout the addition by periodic cooling. After the addition was complete, the mixture was refluxed for 3 h and allowed to stand at ambient temperature overnight. The mixture was cooled and the excess hydride was destroyed by the addition of 10 mL of H_2O, followed by the addition of 10% NaOH to pH 8. The mixture was treated with 20 mL of H_2O and filtered, and the filtrate was evaporated in vacuo to dryness. The residue was partitioned between 20 mL of H_2O and 400 mL of EtOAc, the organic layer was washed twice more with H_2O (200-mL portions), the combined aqueous extracts were evaporated in vacuo to dryness, and the residue was taken up in 50 mL of MeOH and treated with a solution of anhydrous oxalic acid (1.8 g, 0.02 mol) in 2 mL of MeOH, followed by the addition of anhydrous Et_2O to precipitate the product, which was collected to give 3 g (47%), mp 164–165 °C. Anal. ($C_{14}H_{19}N_2O_{6.5}$) C, H, N.

5-Tetrazolyl Esters 12. Method I. A mixture of the nitrile ester 8 (0.02 mol), NH_4Cl (0.033 mol), and NaN_3 (0.033 mol) in 30 mL of dry DMF was stirred and maintained at 120 °C for 18 h. The solvent was removed in vacuo, and the residue was treated with 35 mL of H_2O and 7 mL of concentrated HCl. The mixture was extracted with EtOAc, the organic layer was washed three times with brine, dried ($MgSO_4$), and evaporated in vacuo, and the residue was crystallized.

5-Tetrazolylurethanes 13. Method J. A. Hydrazinolysis. A solution of the 5-tetrazolyl ester 12 (0.049 mol) and 99–100% hydrazine hydrate (1.1 mol) in 50 mL of MeOH was refluxed for

15 h. The solvent was removed in vacuo, and the residue was treated with 150 mL of H_2O and filtered. The filtrate was acidified to pH 2 with concentrated HCl, and the product was collected, washed with H_2O, and dried.

B. Curtius Rearrangement. A rapidly stirred mixture of the above crude hydrazide hydrochloride (0.0033 mol), 6 mL of 5 N HCl, and 30 mL of Et_2O was cooled to −10 °C and treated over several minutes with a solution of $NaNO_2$ (0.0034 mol) in 2 mL of H_2O. After 10 min, the organic layer was separated and the aqueous portion was washed with another portion of Et_2O. The ethereal extracts were combined and dried ($MgSO_4$) briefly. The solution was treated with 40 mL of absolute EtOH and gently distilled until the temperature of the distillate reached 78 °C, at which point the solution was refluxed for an addition hour and then allowed to stand at ambient temperature for 1 h. The solvent was removed in vacuo, and the residue was crystallized to give 13.

Saponification of Urethanes. Method K. A mixture of the above urethane (0.016 mol) and 26 mL of 3 N NaOH was refluxed 1.5 h. The solution was cooled, slowly acidified to pH 2 with concentrated HCl, and filtered. The filtrate was adjusted to pH 5.0 with NH_4OH, diluted to 300 mL with H_2O, heated to boiling, treated with Nuchar, and filtered while hot. Upon allowing the filtrate to cool slowly, the product crystallized out and was collected and washed with ice–water to give 14.

α-Acetyl-α-(5-methoxy-3-indolyl)acetonitrile (16). Method L. A solution of NaOEt was prepared from Na (6 g, 0.26 mol) and 100 mL of absolute EtOH. After removal of the solvent in vacuo, the alkoxide cake was rapidly treated with vigorous stirring with a solution of 5-methoxy-3-indolylacetonitrile (20.6 g, 0.12 mol) in 120 mL of EtOAc. The mixture was refluxed for 6 h and then allowed to stand at ambient temperature for 18 h, diluted with 200 mL of Et_2O, cooled for 1 h, and filtered. The filter cake was washed with Et_2O and dissolved in 300 mL of H_2O, and the solution was cooled and treated slowly with HOAc to pH 4–5. The mixture was extracted into Et_2O, the organic layer was washed three times with $NaHCO_3$ solution and dried ($MgSO_4$), and the solvent was removed in vacuo to give 15.6 g (61%) of 16 as an oil, which was used directly for the subsequent reaction.

3-Amino-2-(5-methoxy-3-indolyl)butyronitrile (17). Method M. A mixture of 16 (12.5 g, 0.063 mol), NH_4OAc (49 g, 0.63 mol), and $NaBH_3CN$ (4 g, 0.063 mol) in 170 mL of MeOH was stirred at ambient temperature for 5 days. The dark mixture was cooled, slowly treated with concentrated HCl to pH 2, and stirred for 15 min at ambient temperature. The mixture was evaporated in vacuo to dryness, and the residue was partitioned between 300 mL of H_2O and 200 mL of EtOAc. The aqueous layer was washed three times with EtOAc and was then treated slowly with 10 N NaOH to pH 10. The turbid mixture was extracted twice with EtOAc, and the organic extracts were combined, dried ($MgSO_4$), treated with Nuchar, and filtered. The solvent was evaporated in vacuo to give 8.5 g of 17 as an oil, which was pure enough for use in the subsequent reaction.

Methyl 3-Amino-2-(5-methoxy-3-indolyl)butyrate (18). Method N. A mixture of 8.5 g of the above crude amine, 40 mL of 95% EtOH, 10 mL of H_2O, and 10 g of KOH was refluxed for 22 h. After cooling, the mixture was diluted to 250 mL with H_2O and extracted three times with Et_2O. The aqueous layer was adjusted to pH 5.2 with dilute HCl, diluted to 300 mL with H_2O, heated to boiling, treated with Nuchar, and filtered while hot. The filtrate was evaporated in vacuo to dryness and the residue desicated for 2 h. The dried residue was slurried in 50 mL of MeOH, and the mixture was cooled to −10 °C and treated dropwise with $SOCl_2$ (2.3 mL, 0.0325 mol). After the addition, the mixture was stirred for 16 h at ambient temperature, and the solvent was removed in vacuo. The residue was partitioned between 50 mL of EtOAc and 20 mL of 5% K_2CO_3, and the organic layer was dried ($MgSO_4$) and treated with a solution of 2.9 g of anhydrous oxalic acid in 4 mL of MeOH. The solid was collected, affording 0.9 g of 18, mp 145–147 °C dec. Anal. ($C_{16}H_{20}N_2O_7$) H, N; C: calcd, 54.54; found, 55.62.

Pharmacology. Antihypertensive Effects in Rats. Rats were made hypertensive by applying a figure-of-eight ligature to one kidney and removing the other kidney 2 weeks later. At least 4 weeks were allowed to elapse after the second operation before experimental studies were performed. Indirect systolic blood pressure measurements were made with an occluding cuff and pulse sensor system fitted to the rat's tail. Control blood pressure measurements were made before any compounds were administered. Blood pressure measurements were then made 1, 2, 4, 6, and 8 h after the oral administration of the test compounds at the dose level of 10 mg/kg. Statistical significance of the difference between the control and posttreatment value was determined by Wilcoxon's signed rank test.[20]

Hypotensive Effects in Anesthetized Cats. Cats of either sex (2–4 kg) were anesthetized with α-chloralose (80 mg/kg, iv). The trachea, a femoral artery, and a jugular vein were cannulated for adequate ventilation, for drug administration, and to record blood pressure, respectively. Blood pressure was measured with a pressure transducer and was obtained before and 30 min after the administration of an iv dose of 10 mg/kg of compound.

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2- and 6-Methyl-1,4-naphthoquinone Derivatives as Potential Bioreductive Alkylating Agents

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A number of antineoplastic agents possess both the quinone nucleus and an appropriate substituent that permits them to function as bioreductive alkylating agents. To develop new compounds of this type with unique properties, we have synthesized a series of 2- and 6-methyl-1,4-naphthoquinone derivatives and have evaluated them for antineoplastic activity against Sarcoma 180 ascites cells. Several of these quinones showed antitumor activity, causing significant prolongation of the survival time of tumor-bearing mice. Among the most active agents were the mesylates, tosylates, and *N*-(chloroethyl)carbamates of 2- and 6-methyl-1,4-naphthoquinone. That bioreductive activation to a quinone methide might be involved in the mechanism of action of these agents was shown by the finding that compounds with the best leaving groups were the most efficacious as antineoplastic agents.

Solid tumors contain areas of vascular insufficiency that result in the generation of hypoxic tumor cells. These oxygen-deficient cells are an obstacle to the attainment of curative therapy, since hypoxic stem cells are relatively resistant to X-irradiation and are presumed to be relatively resistant to chemotherapy.[1,2] This laboratory has dem-

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