mixed complex copper histidinate cysteinate has been suggested as having antiinflammatory activity.[18] (viii) Although only a few copper(I) complexes were examined, the results in this study suggest that copper(I) and copper(II) compounds have similar properties when absorbed, both could produce oral and sc activity, and both could produce gastric and local irritation. Since these effects were, in general, dose related for both oxidation states and since Cu(I) and Cu(II) undergo quite different reactions in vitro, a catalytic mechanism of action caused by the exogenous form of the copper is unknown. Copper(I) is a soft Lewis acid and copper(II) is intermediate between hard and soft. Thus, copper(I) would be expected to react with the softer thiols in vivo and copper(II) with the harder N and O donors. It might be expected, therefore, that, initially at least, they would each produce different metabolites. The similarity of their responses in the edema model suggests that both copper(I) and copper(II) are acting by the same mechanism. Thus, probably a series of reactions for both sc and orally administered complexes is involved, leading to the formation of a common metabolite. This could be a different species from that produced following normal absorption of copper through the gut. (ix) The activity of the few active oral compounds could be due to their bypassing of the normal oral copper absorption route. In one orally active compound, Cu_2O, most of the additional copper absorbed is carried in serum on albumin, giving an abnormal copper serum distribution.[19] Another method of absorption would be by topical application. The use of copper bangles in this field has been investigated,[20] and it is claimed that the bangles are effective.

Thus, it is clear that some copper-containing compounds do possess antiinflammatory activity in animal models and the copper would appear to be the active moiety. Species differences, methods of application, and the nature of the copper complex are important variables. Counterirritation caused by injection of potentially irritant compounds may affect the degree of antiinflammatory response, but it would not appear to be the sole mechanism of action of copper. Further work is required, in particular to elucidate the nature of the different copper species present in vivo after sc and oral administration.

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Supplementary Material Available: Table I, containing electronic spectra of some compounds prepared (1 page). Ordering information is given on any current masthead page.

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Synthesis and Antiinflammatory Activity of Some 2-(Substituted-pyridinyl)benzimidazoles[1]

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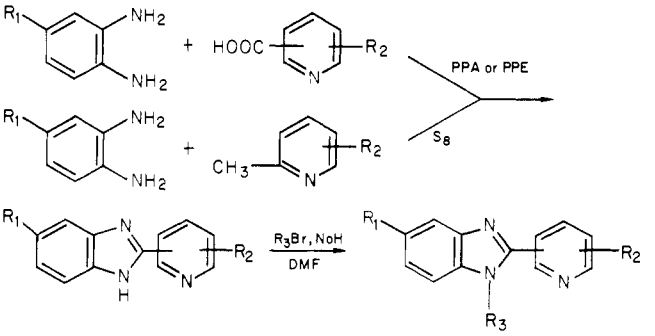
A series of 2-(2-pyridinyl)benzimidazoles was synthesized and evaluated for antiinflammatory activity by the carrageenan-induced rat paw edema assay. Among several active derivatives, 2-(5-ethylpyridin-2-yl)benzimidazole (**6**) was selected for further study. A comparison of compound **6** with phenylbutazone and tiaramide revealed that **6** possesses stronger activity in acute inflammatory models possibly with slightly less gastrointestinal irritation than both phenylbutazone and tiaramide.

Aryl- and heteroarylalkanoic acids have been explored widely as nonsteroidal antiinflammatory agents.[2] Among them, 2-aryl- and 2-heteroaryl-5-benzoxazolealkanoic acids[3] and 2-aryl-5-benzothiazolealkanoic acids[4] were reported to exhibit potential antiinflammatory activities. Acidic antiinflammatory agents tend to accumulate in acidic sites of animal organs, such as inflamed tissue, stomach, and kidney;[5] therefore, gastrointestinal irritation is likely to be produced. Some nonacidic 2-arylbenzazoles, dichlorophenylbenzoxazole[6] and fluorophenylbenzimidazole,[7] have been shown to exhibit antiinflammatory activity and so we thought it pertinent to prepare a group of nonacidic 2-heteroarylbenzazoles in order to derive a new class of antiinflammatory agents with less gastrointestinal irritation.

Scheme I



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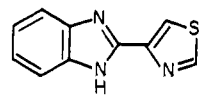
Recently, 2-(4-thiazolyl)benzimidazole (thiabendazole),



thiabendazole

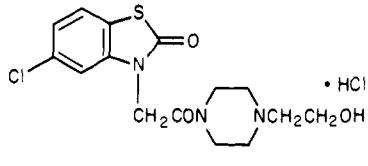
originally developed as an anthelmintic and antifungal agent, was noted to exhibit moderate antiinflammatory and analgesic activities,[8,9] and 2-phenyloxazolopyridines, with a ring system similar to thiabendazole, were also reported to exhibit significant antiinflammatory activity.[10] As one of the modifications of the thiabendazole structure we selected 2-(2-pyridinyl)benzimidazole as a parent compound. This structure was derived using the concept of bioisosterism; i.e., in the ring system, -S- is regarded to be equivalent to -CH=CH- biologically.[11]

The parent compound is known in the literature as a chelating agent;[12] however, no biological activity is recorded for it. Thus, a number of derivatives were synthesized and compared with known antiinflammatory compounds.

Chemistry. The compounds were synthesized by three general methods according to Scheme I. In method A, nuclear-substituted *o*-phenylenediamine was condensed with a pyridinecarboxylic acid derivative in the presence of polyphosphoric acid or polyphosphate ester. In the case where ethoxycarbonyl was the substituent, polyphosphate ester produced superior results. In method B, which was the application of the Willgelodt–Kindler method,[13] *o*-phenylenediamine was allowed to react with a 2-methylpyridine derivative and sulfur. In method C, 1-substituted benzimidazoles were prepared from the corresponding 1*H*-benzimidazoles by the reaction with alkyl halide in the presence of sodium hydride in DMF. Synthetic details are given under Experimental Section.

Results and Discussion

Almost all the compounds were screened for antiinflammatory activity in the carrageenan-induced rat paw edema test and were compared with phenylbutazone and tiaramide hydrochloride. Tiaramide hydrochloride is a



tiaramide hydrochloride

nonacidic antiinflammatory agent which inhibits acute inflammation[14a] and the release of histamine and TXA_2 without affecting the cyclo-oxygenase system.[14b] From the results listed in Tables I and II, the following structure–activity relationships can be deduced.

The parent compound is almost inactive; however, introduction of a lipophilic substituent at the 6 position of the pyridine ring enhances the activity (**5**, **7**, and **12–14**). The electron-donating MeO, Me, and Et groups appear to be more effective. At the 5 position an ethyl group (**6**) is better than other substituents. As for the substituent on the benzimidazole nucleus (R_1), a hydrophilic group generally reduces the activity (**25**, **29**, and **30–32**). Effects of lipophilic groups vary with other substituents on the pyridine ring. A combination of R_1 = OMe with 5- or 6-Et gives the highest activity. Appropriate lipophilicity and electronic properties seem to be required for the molecules to reach the critical site of the activity. All of the 1-substituted 2-(2-pyridinyl)benzimidazoles are inactive. The imidazole NH proton appears to have an important role for activity.

The above results remind us of the hypothesis of Whitehouse,[15] i.e., that lipophilicity and a complex-forming ability with the metal ions may be the chief determinants in conferring antiinflammatory properties on a compound. The preliminary test for the complex-forming ability of the molecules with Fe^{2+} ion reveals the following observations.[16] Several compounds which bear a substituent on the 6 position of the pyridine ring do not form a complex with metal ions, but they exhibit significant antiinflammatory activities. Other compounds which have a substituent at the 1 position of the benzimidazole nucleus are the reverse case. Compound **6** forms a metal complex and also exhibits antiinflammatory activity. Therefore, at least in this series, there is no simple correlation between the complex-forming ability and the antiinflammatory activity.

From the initial screening result in the carrageenan-induced rat paw edema test, compounds **5–7**, **14**, **22–24**, **27**, and **34**, which showed the same degree of activity as phenylbutazone, were selected for further testing in several follow-up assays. The results are given in Table III. The compounds exhibited activity in the contund edema assay with low acute toxicity. Among them, three compounds (**6**, **7**, and **14**) exhibited analgesic activity. Since compounds **7** and **14** showed strong muscle relaxant and CNS-depressant activities as well,[17] compound **6** was selected as an antiinflammatory agent for further study.

Table IV contains all the biological data of significance on compound **6** compared with phenylbutazone and tiaramide. The physically induced edema, such as contund edema and scald edema, which are regarded as the models of acute inflammation, were inhibited strongly by compound **6**. Compound **6** exhibited antipyretic and analgesic activities comparable to phenylbutazone and tiaramide. The UD_{50} values of all three compounds in an acute ulcerogenic assay are also in the same range. The nonacidic compound **6** is slightly less irritating than the acidic phenylbutazone. Nevertheless, since compound **6** is consistently more potent in the three acute inflammatory models than the reference compounds, the therapeutic index of compound **6**, as calculated from its antiinflammatory activities, appears to be two to three times better than that of phenylbutazone and tiaramide.

The prostaglandin synthetase inhibiting activity of compound **6** was one-half that of aspirin and was one-fifth

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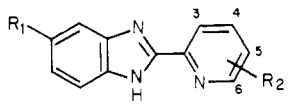
Table I. Antiinflammatory Activity of 2-(2-Pyridinyl)benzimidazoles



no.	R_1	R_2	yield, %	mp, °C	method of prepn	antiinflammatory act.[a] at 100 mg/kg po
1	H	H	74	223.0-224.0	A	22 ± 8[b]
2	H	3-Me	77	159.5-160.0	B	17 ± 10
3	H	4-Me	84	229.0-229.5	B	-4 ± 15
4	H	5-Me	86	229.0-229.5	A	19 ± 7
5	H	6-Me	58	222.5-223.0	B	44 ± 7**
6	H	5-Et	78	172.5-173.0	A	44 ± 5**
7	H	6-Et	74	161.0-161.5	A	41 ± 6**
8	H	5-*n*-Bu	86	138.0-139.0	A	-16 ± 14
9	H	5-CH_2OH	86	203.0-205.0	C[c]	-10 ± 13
10	H	6-CH_2OH	80	193.5-194.5	C	-13 ± 6
11	H	5-COOEt	23	229.0-230.0	C	-16 ± 10
12	H	6-COOEt	24	148.0-149.5	C	31 ± 8*
13	H	6-Cl	70	200.0-200.5	A	30 ± 4*
14	H	6-OMe	76	183.0-184.0	A	47 ± 8**
15	H	6-$CONH_2$	80	268.0-270.0	D[d]	13 ± 13
16	H	6-OH[e]	64	307.0-308.0	C	-7 ± 10
17	Me	H	62	164.0-165.0	A	35 ± 11*
18	OMe	H	71	136.0-137.5	A	34 ± 5*
19	Cl	H	65	141.5-142.5	A	36 ± 11*
20	Me	5-Me	68	166.5-167.0	B	7 ± 7
21	Cl	5-Me	67	170.0-172.0	A	-5 ± 5
22	Me	6-Me	51	208.8-209.5	B	42 ± 7**
23	OMe	6-Me	82	189.0-191.0	B	40 ± 6**
24	Cl	6-Me	72	173.5-174.5	B	39 ± 11*
25	OH	6-Me	67	283.0-284.5	E[f]	6 ± 17
26	Me	5-Et	77	114.0-115.0	A	35 ± 11*
27	OMe	5-Et	68	141.0-142.5	A	58 ± 6**
28	Cl	5-Et	70	169.5-170.5	A	-2 ± 6
29	OH	5-Et	74	247.0-248.0	E	25 ± 15
30	NO_2	5-Et	92	251.0-254.0	C	-5 ± 11
31	NH_2	5-Et	68	184.0-186.0	C	25 ± 14
32	NHAc	5-Et	58	295.0-296.0	C	5 ± 15
33	Me	6-Et	31	169.5-170.5	A	10 ± 5
34	OMe	6-Et	73	147.5-148.5	A	52 ± 4**
35	Cl	6-Et	30	140.5-144.5	A	3 ± 6
36	H	5,6-$(Me)_2$	57	222.0-222.5	A	37 ± 6*
37	Me	5,6-$(Me)_2$	25	202.5-203.5	A	-19 ± 5
38	Me	6-OMe	30	187.5-188.5	A	32 ± 9*
39	Me	6-Cl	50	176.0-177.5	A	36 ± 11*
40	Me	6-OH[e]	53	285.0-286.0	A	-6 ± 3
tiaramide hydrochloride						31 ± 6*
phenylbutazone						43 ± 6**

[a] Carrageenan-induced rat paw edema test. See ref 24. [b] Each value indicates the percent inhibition, mean ± standard error (n = 5), 3 h after carrageenan injection. A single asterisk indicates $p < 0.05$; a double asterisk indicates $p < 0.01$. [c] See Experimental Section. [d] Prepared from 12 by amidation with ammonia-water. [e] Stands for pyridinone form at room temperature. [f] Prepared from the corresponding methoxy compounds (23 and 27) by hydrolysis with 47% HBr.

that of phenylbutazone in our assay. Since the antiinflammatory activity of compound **6** is in the same order as phenylbutazone, its antiinflammatory activity can not be explained in terms of the prostaglandin synthetase inhibitory activity alone. Detailed mechanisms of this compound are now under investigation.

Experimental Section

Melting points were taken on a capillary melting point apparatus (Yamato MR-21). All melting points are uncorrected. The structures of all compounds are supported by their IR (Jasco IRA-1) and ^1H NMR (Hitachi R-24A) spectra. All compounds were analyzed for C, H, and N and were within 0.4% of calculated theoretical values. No attempt was made to maximize yields.

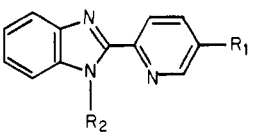
Typical examples of methods A, B, and C are given below. Further detail of the individual compounds are given in Tables I and II.

Method A. 2-(5-Methylpyridin-2-yl)benzimidazole (4). A mixture of 5.9 g (0.055 mol) of *o*-phenylenediamine, 7.1 g (0.052 mol) of 5-methylpicolinic acid, and 40 g of PPA was stirred at 160 °C for 4 h under N_2. After the mixture cooled to 100 °C, it was poured into 400 mL of water. After the PPA was dissolved, the resulting solution was cooled and the pH was adjusted to 7 by the addition of Na_2CO_3. The precipitated solid was filtered off. Recrystallization of the solid from AcOEt yielded **4** as colorless needles: yield 9.3 g (86%); mp 229–230 °C.

Method B. 2-(3-Methylpyridin-2-yl)benzimidazole (2). A mixture of 15.0 g (0.14 mol) of o-phenylenediamine, 15.0 g (0.14 mol) of 2,3-lutidine, and 13.5 g (0.42 mol) of sulfur was stirred at 160 °C for 8 h. After the mixture cooled to room temperature, 200 mL of MeOH was added to the reaction mixture, and the precipitated solid (sulfur) was filtered off. The filtrate was evaporated and the residual red oil was recrystallized from cyclohexane to give **2** as colorless needles: yield 22.6 g (77%); mp 159–160 °C.

Method C. 1-[(Methoxycarbonyl)methyl]-2-(2-pyridinyl)benzimidazole (41). To a solution of 5.9 g (0.03 mol) of 2-(2-pyridinyl)benzimidazole in DMF (80 mL) was added 2.9 g (0.06 mol) of NaH and 6.9 g (0.045 mol) of methyl bromoacetate. After being stirred at 60–80 °C for 2 h, the mixture was filtered and the filtrate was evaporated to give an orange oil. The crude oil was dissolved in $CHCl_3$ (100 mL), washed with water (100 mL × 2), and dried over $MgSO_4$. After evaporation of the solvent,

Table II. Antiinflammatory Activity of 1-Substituted 2-(2-Pyridinyl)benzimidazoles



no.	R_1	R_2	yield, %	mp, °C	antiinflammatory act.[a] at 100 mg/kg po
41	H	CH_2COOCH_3	64	108.0-108.5	−17 ± 12[b]
42	H	CH_2CO-c-$N(CH_2CH_2)_2N$-CH_2CH_2OH	41	169.5-170.5	−4 ± 12
43	Me	CH_2COOCH_3	60	133.0-134.0	NT[c]
44	Me	$CH_2CH_2N(CH_3)_2$	57	84.5-85.5	12 ± 11
45	Me	CH_2CO-c-NC_4H_8	56	248.5-249.0	14 ± 17
46	Me	CH_2CO-c-NC_5H_{10}	40	262.5-263.0	2 ± 5
47	Me	CH_2CO-c-$N(CH_2CH_2)_2N$-CH_3	23	244.0-245.0	11 ± 13
48	Me	CH_2CO-c-$N(CH_2CH_2)_2N$-CH_2CH_2OH	48	212.0-213.0	14 ± 6
49	Et	Me	91	114.0-115.0	5 ± 11
50	Et	Ph	31	104.0-105.0	12 ± 8
51	Et	CH_2Ph	86	94.5-95.5	−18 ± 5
52	Et	CH_2COOCH_3	85	103.5-104.0	9 ± 10
53	Et	CH_2CO-c-NC_4H_8	30	199.0-200.0	−5 ± 5
54	Et	CH_2CO-c-NC_5H_{10}	57	190.0-191.0	NT
55	Et	CH_2CO-c-$N(CH_2CH_2)_2N$-CH_2CH_2OH	52	171.0-172.0	4 ± 8

[a] Carrageenan-induced rat paw edema. See ref 24. [b] Each value indicates the percent inhibition, mean ± standard error (n = 5), 3 h after carrageenan injection. [c] NT = not tested.

Table III. Pharmacological Data of Selected Compounds

no.	inhibn of contund edema[a] at 200 mg/kg po	analgesia[b] at 100 mg/kg po	LD_{50}, mg/kg (mice, ip)
5	59 ± 7***[c]	−[d]	3249
6	81 ± 10***	+	1231
7	85 ± 8***	+	>300
14	NT[e]	+	>300
22	67 ± 9**	−	812
23	39 ± 14	−	3732
24	95 ± 11***	−	1231
27	NT	−	>300
34	87 ± 6***	−	>300

[a] See ref 25. [b] See ref 26. [c] Each value indicates the percent inhibition, mean ± standard error (n = 5), 3 h after contund. A double asterisk indicates $p \leq 0.01$; a triple asterisk indicates $p \leq 0.001$; significantly different from control (Student's t test). [d] + = positive mice ≥ 2; − = positive mice ≤ 1 (n = 3). A mouse which writhes less than half the number of times of the control mouse was named as a positive mouse. [e] NT = not tested.

Table IV. Pharmacological Profiles of Compound 6

	6	phenylbutazone	tiaramide hydrochloride
carrageenan edema[a] (ED_{40},[h] mg/kg po)	70	100	160
contund edema[b] (ED_{40},[h] mg/kg po)	142	200	200
scald edema[c] (ED_{40},[h] mg/kg po)	110	180	200
analgesia[d] (ED_{50},[h] mg/kg po)	140	280	76
antipyrexia[e] (ED_{60},[h] mg/kg po)	68	44	100
PGE synth inhibn[f] (IC_{50},[h] M)	7.6×10^{-5}	1.5×10^{-5}	$>10^{-4}$
ulcerogenicity[g] (UD_{50},[i] mg/kg po)	200	142	163
acute toxicity (LD_{50},[i] mg/kg ip, mice)	1231	616	203

[a] See ref 24. [b] See ref 25. [c] See ref 27 and 28. [d] Acetic acid writhing method. [e] Yeast-induced pyrexia. [f] See ref 30 and 31. [g] See ref 32. [h] Estimated graphically from dose-response curves. [i] Estimated by the Weil's method. See ref 33.

the residue was recrystallized from cyclohexane to give colorless needles of 1-[(methoxycarbonyl)methyl]-2-(2-pyridinyl)benzimidazole (41): yield 5.1 g (64%); mp 108–109 °C.

1-[[[4-(β-Hydroxyethyl)piperazin-1-yl]carbonyl]methyl]-2-(2-pyridinyl)benzimidazole (42). A mixture of 2.7 g (0.01 mol) of 41 and 6.5 g (0.05 mol) of *N*-(β-hydroxyethyl)piperazine was stirred at 100 °C for 4 h. After cooling to room temperature, the reaction mixture was dissolved in $CHCl_3$ (100 mL) and washed with water (50 mL × 2). The organic layer was extracted with 10% HCl (50 mL × 2), and the acid layer was made basic and extracted with $CHCl_3$ (50 mL × 3). The dried extract was evaporated to give a pale yellow powder, which was recrystallized from AcOEt to give 42 as colorless needles: yield 1.5 g (41%); mp 170–171 °C.

2-[5-(Hydroxymethyl)pyridin-2-yl]benzimidazole (9). A mixture of 21.6 g (0.2 mol) of *o*-phenylenediamine, 39.0 g (0.2 mol) of 5-ethyl hydro-2,5-pyridinedicarboxylate, and 300 g of PPE was stirred at 120 °C for 2 h under N_2. The reaction mixture was poured into 1 L of water, and the pH was adjusted to 9 by the addition of Na_2CO_3. The precipitated solid was filtered off. Recrystallization of the solid from EtOH yielded ethyl 5-(benzimidazol-2-yl)nicotinate (11) as colorless needles: yield 12.6 g (23%); mp 229–230 °C.

To a solution of 10.0 g (0.037 mol) of 11 in EtOH (1500 mL) was slowly added 56.0 g (0.48 mol) of $NaBH_4$. After the solution was stirred for 1 h under reflux, 200 mL of acetone was added and evaporated. The residue was washed with 500 mL of water and recrystallized from CH_3CN to give 9 as colorless needles: yield 7.2 g (86%); mp 203–205 °C.

2-(6-Oxopyridin-2-yl)benzimidazole (16). 14, 500 mg (0.0022 mol), was hydrolyzed with 20 mL of 48% HBr at 95 °C for 2 h. After the reaction mixture was neutralized with Na_2CO_3, the precipitated solid was filtered off. The solid was recrystallized from H_2O to give 16 as colorless needles: yield 300 mg (64%); mp 307–308 °C dec; IR (KBr) 3250 (NH), 1680 cm^{-1} (C=O).

2-(5-Ethylpyridin-2-yl)-5(6)-nitrobenzimidazole (30). To a solution of 5.0 g (0.002 mol) of 6 in concentrated H_2SO_4 was slowly added 2 mL of HNO_3 (*d* 1.4) dropwise. The temperature of the reaction mixture was maintained between 0 and 5 °C with an ice bath. After 10 min, the solution was poured into 100 mL of ice–water and neutralized with 1.5 N NaOH. The resulting solid was filtered and recrystallized from AcOEt to give 30 as colorless needles: yield 5.5 g (92%); mp 251–254 °C.

2-(5-Ethylpyridin-2-yl)-5(6)-aminobenzimidazole (31). To a mixture of 1.0 g (0.0037 mol) of 30 and 15 mL of concentrated HCl was added 0.9 g (0.0075 mol) of Sn powder with efficient

stirring. After 10 min, 80 mL of water was added to the mixture, the pH was adjusted to 8 by the addition of 10% Na_2CO_3, and the mixture was extracted with AcOEt (100 mL × 2). The organic layer was dried over $MgSO_4$ and concentrated to 30 mL. The precipitated solid was filtered off to give **31** as yellow prisms: yield 0.6 g (68%); mp 184–186 °C.

2-(5-Ethylpyridin-2-yl)-5(6)-(acetylamino)benzimidazole (32). A mixture of 0.9 g (0.0038 mol) of **31** and 4 mL of Ac_2O was stirred at 100 °C for 20 min. The reaction mixture was concentrated in vacuo, and the resulting solid was recrystallized from MeOH two times to give **32** as colorless prisms: yield 0.61 g (58%); mp 295–296 °C.

Preparation of Pyridinecarboxylic Acid Derivatives. Pyridinecarboxylic acid derivatives were prepared by three general methods. 5-Methylpicolinic acid,[18] 5-ethylpicolinic acid,[19] 6-methylnicotinic acid,[20] and 6-chloropicolinic acid (mp 190 °C) were prepared by the oxidation (SeO_2 or $KMnO_4$) of picoline derivatives. 6-Ethylpicolinic acid,[21] 5,6-dimethylpicolinic acid, and 6-methoxypicolinic acid (identified as the methyl ester, mp 34–35 °C) were prepared by hydrolysis of the corresponding nitriles, which were synthesized the via the *N*-oxides. 5-Ethyl hydro-2,5-pyridinedicarboxylate[22] and 6-ethyl hydro-2,6-pyridinedicarboxylate[23] were prepared by means of partial hydrolysis of the corresponding diester.

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Synthesis and Structure–Activity Relationships among α-Adrenergic Receptor Agonists of the Phenylethanolamine Type

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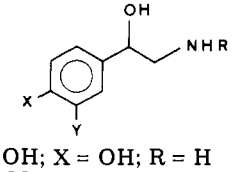
Nineteen arylethanolamine derivatives related to norepinephrine were prepared and tested for α-adrenergic stimulant activity. In one series the analogues possess a *p*-hydroxy function, while the meta position is substituted by methyl, ethyl, isopropyl, cyclohexyl, fluoro, chloro, iodo, carboxy, carbomethoxy, and methylsulfamido groups. The other series is meta hydroxylated with the para position substituted by the same groups. The influence of these groups upon the α-adrenergic activity is discussed, and the compounds are compared to octopamine, normetanephrine, norepinephrine, and norphenylephrine. It has been found that the introduction of an isopropyl, cyclohexyl, and fluoro group in the meta position of octopamine improves its affinity by three, five, and six times, respectively, whereas when these groups are introduced in the para position of norphenylephrine their effects are always detrimental. The most active compound, α-(aminomethyl)(4-fluoro-3-hydroxyphenyl)methanol (**44**), has about one-hundredth the affinity and the same intrinsic activity as norepinephrine.

Norepinephrine (**1a**) is the prototype of α-adrenergic



1a, Y = OH; X = OH; R = H
b, Y = OH; X = OH; R = *i*-Pr
c, Y = $NHSO_2Me$; X = OH; R = *i*-Pr
d, Y = $NHCONH_2$; X = OH; R = *t*-Bu

receptor agonists, and isoproterenol (**1b**) is a potent β-adrenergic agonist. Generally, agonist activity at the α-adrenergic receptor decreases with increasing size of the N-substituent in catecholamine-type molecules, while β activity is often enhanced by the same substitution. Furthermore, a great number of investigations have shown that the catechol moiety of the adrenergic agonists represents the most important part for high activity at adrenergic receptors.[2a,b] In particular, the influence of the *m*-hydroxy group has been emphasized. When one or both of these hydroxy groups in the 3 and 4 positions are absent, without any other aromatic substitution, the overall potency is generally reduced and there is especially a reduction in β activity. Larsen et al.[3] and Brittain et al.[2b]

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