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Syntheses of N-Substituted 2(3,4)-Pyridylcarboxylic Acid Hydrazides with Analgesic and Antiinflammatory Activity

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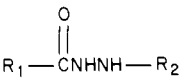
Received March 26, 1979

A group of N-substituted 2(3,4)-pyridylcarboxylic acid hydrazides were synthesized to investigate the effects that changes in functionality on the terminal hydrazide nitrogen have on analgesic and antiinflammatory activities. The most active analgesic–antiinflammatory compound was 1-(2-pyridylcarbonyl)-2-(2-pyridyl)hydrazine (**10a**), which was much more potent than dextropropoxyphene and caused a 100% inhibition of carrageenan-induced paw edema up to 5 h. Pyridylcarbonylhydrazides **5a**, **8**, and **10c** exhibited analgesic activity similar to dextropropoxyphene. Although **10b** was an inactive analgesic agent, it exhibited antiinflammatory activity similar to **10a**.

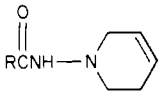
Pyridylcarboxylic acid hydrazide derivatives **1** which



1a, R_1 = 4-pyridyl, R_2 = H
b, R_1 = 4-pyridyl, R_2 = *i*-Pr
c, R_1 = 4-pyridyl, R_2 = $CH_2CH_2CONHCH_2Ph$
d, R_1 = 4-pyridyl, R_2 = CH_2SO_2Na
e, R_1 = 4-pyridyl, R_2 = C_6H_{11}
f, R_1 = 2-pyridyl, R_2 = COMe

exhibit antitubercular (**1a**, isoniazid; **1b**, iproniazid), monoamine oxidase inhibitory (**1b**; **1c**, nialamide), antibacterial (**1d**), CNS depressant (**1e**), and antitumor (**1f**) activities have been reported.[1]

In an earlier study we described a facile method for the synthesis of *N*-[[2(3,4)-pyridylcarbonyl]amino]-1,2,3,6-tetrahydropyridines **2**[2] via the sodium borohydride re-



2, R = 2-, 3-, or 4-pyridyl

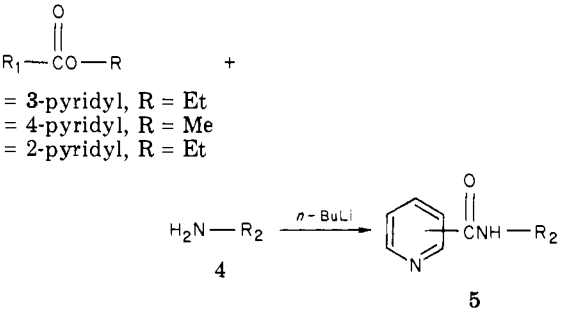
duction of *N*-iminopyridinium ylides, which exhibited significant analgesic and antinflammatory activities.[3] It was therefore of interest to determine what effect replacement of the 1,2,3,6-tetrahydropyridyl ring of **2** by other ring systems and functionality would have on pharmacological activity. We now describe the synthesis and analgesic–antiinflammatory activity of structurally related pyridylcarbonylhydrazides.

Chemistry. Two synthetic procedures were used to prepare pyridylcarbonylhydrazide derivatives in which the terminal hydrazide nitrogen is part of a heterocyclic ring system. For example, reaction of pyridyl esters **3** with the anions of **4**, obtained by addition of *n*-butyllithium, afforded pyridylcarbonylhydrazides **5** (Scheme I).

Treatment of *N*-aminoisoquinoliniuim chloride **6**[4] with 4-pyridylcarbonyl chloride gave rise to the *N*-[(4-pyridylcarbonyl)imino]isoquinolinium ylide **7**, which on subsequent reduction with sodium borohydride in ethanol at 0 °C yielded the 1,2,3,4-tetrahydroisoquinoline derivative **8** (Scheme II).

A group of pyridylcarbonylhydrazides, possessing varied functionality at the terminal hydrazine nitrogen, was

Scheme I



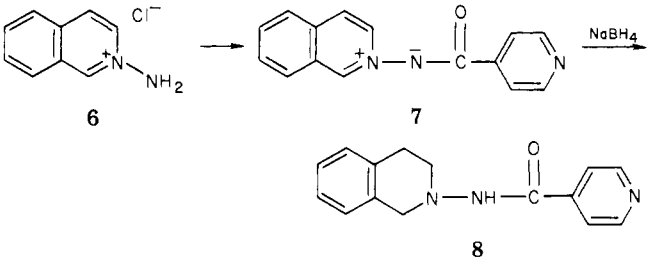
3a, R_1 = 3-pyridyl, R = Et
b, R_1 = 4-pyridyl, R = Me
c, R_1 = 2-pyridyl, R = Et

4

5

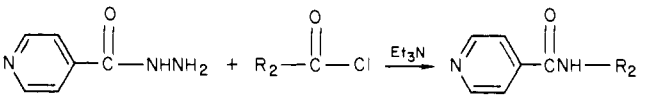
a, R_2 = 1-piperidyl
b, R_2 = 1-morpholinyl
c, R_2 = 1-homopiperidyl
d, R_2 = dimethylamino

Scheme II



6 **7** **8**

Scheme III



1a **9**

a, R_2 = NHCOPh
b, R_2 = $N(COCH_3)_2$

prepared as illustrated by Schemes III and IV and summarized in Table I. Thus, treatment of isonicotinic acid hydrazide **1a** with benzoyl and acetyl chloride using the Schotten–Baumann reaction gave hydrazides **9**. Reaction of pyridyl esters **3b** and **3c** with the anions of 2-pyridyl- and phenylhydrazine **4**, obtained by addition of sodium hydride, afforded pyridylcarbonylhydrazides **10** (Scheme IV).

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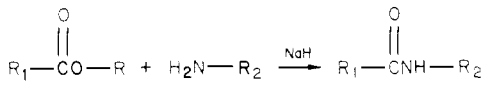
Scheme IV



3 4 10

a, R_1 = 2-pyridyl, R_2 = 2-pyridyl-NH-
b, R_1 = 4-pyridyl, R_2 = 2-pyridyl-NH-
c, R_1 = 4-pyridyl, R_2 = 4-pyridyl-CON(Ph)-

Pharmacology. The compounds synthesized using the methods described in the previous section were tested for analgesic activity using the phenylquinone writhing test[5] and for antiinflammatory activity using the carrageenan-induced paw edema method[6] (see Experimental Section).

Discussion

The analgesic test results indicate that replacement of the 1,2,3,6-tetrahydropyridyl ring of **2a**[3] (81% inhibition at a dose of 128 mg/kg sc) by a piperidyl (**5a**) or 1,2,-3,4-tetrahydroisoquinoline ring (**8**) does not change activity, whereas replacement by a dimethylamino group (**5d**) results in a decrease in activity. On the other hand, the morpholinyl analogue **5b** exhibited very weak activity. The *N*-acyl derivatives **9a** and **9b** exhibit moderate activity relative to the standard compounds aspirin and dextropropoxyphene. Compound **10a** exhibited a very good dose–response with an activity significantly greater than the standard compounds. In contrast, the isomeric **10b** was inactive.

The antiinflammatory test results obtained demonstrate that compounds **5** possessing a piperidyl ring **5a** or dimethylamino substituent **5d** are inactive, whereas **5b** having a morpholinyl ring exhibits significant activity relative to the standard indomethacin. The 1,2,3,4-tetrahydroisoquinoline derivative **8** and **9a** exhibit weak activity, while the *N*-acyl derivatives **9b** and **10c** display moderate activities. On the other hand, the *N*-acyl-2-pyridylhydrazines **10a** and **10b** cause a 100% inhibition of carrageenan-induced paw edema after 5 h.

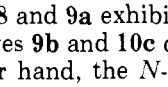
The analgesic and antiinflammatory activities exhibited by **10a** relative to the standards suggest it is worthy of secondary testing. The mechanism by which pyridylcarbonylhydrazides **5** and **8–10** exhibit analgesic and antiinflammatory activities has not been investigated. It is not known whether these compounds act as prostaglandin synthetase inhibitors.

Experimental Section

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in $CDCl_3$ with Me_4Si as internal standard with a Varian EM-360A spectrometer. Infrared spectra (potassium bromide unless otherwise noted) were taken on a Perkin-Elmer 267 spectrometer. Mass spectra were measured with an AEI-MS-50 mass spectrometer, and these exact mass measurements were used in lieu of elemental analysis. 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.

***N*-[(3-Pyridylcarbonyl)amino]piperidine (5a). Procedure A.** A solution of *n*-butyllithium (13.43 mL of a 2.0 M hexane solution, 26.86 mmol) in anhydrous tetrahydrofuran (40 mL), under a nitrogen atmosphere, was precooled to −65 °C. To this a solution of *N*-aminopiperidine (4a; 2.686 g, 26.86 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise, and the reaction was allowed to proceed for 30 min with continuous stirring. A solution of ethyl nicotinate (**3a**; 4.06 g, 26.86 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise, and the reaction was allowed to proceed for 3 h, during which the

Table I. Some Synthetic and Pharmacological Data of *N*-Substituted 2(3,4)-Pyridylcarboxylic Acid Hydrazides



compd	R_1	R_2	yield, %	mp, °C	formula[a]	analgesic act., inhib act. on phenylquinone writhing		inhib act. on carageenan paw edema		
						dose, mg/kg sc	% inhibn	dose, mg/kg sc	% inhibn of **3h**	% inhibn of **5h**
5a	3-C_5H_4N	1-piperidyl	40.3	151–153	$C_{11}H_{15}N_3O$	128	78.4	64	0	0
5b	3-C_5H_4N	1-morpholinyl	6.0	179–181	$C_{10}H_{13}N_3O_2$	128	6.7	128	50.0	17.0
5c	3-C_5H_4N	1-homopiperidyl	42.7	107–110	$C_{12}H_{17}N_3O$	nt[b]		nt[b]		
5d	3-C_5H_4N	NMe_2	34.2	78–80	$C_8H_{11}N_3O$	128	45.0	64	0	0
5e	4-C_5H_4N	NMe_2	6.0	oil	$C_8H_{11}N_3O$	nt[b]		nt[b]		
8	4-C_5H_4N	1,2,3,4-tetrahydroisoquinoline	65.0	192–194	$C_{15}H_{15}N_3O$	128	79.0	128	17.0	17.0
9a	4-C_5H_4N	PhCONH	6.5	215–217	$C_{13}H_{12}N_3O_2$	128	38.3	128	17.0	0
9b	4-C_5H_4N	$(CH_2CO)_2N$	9.3	158–160	$C_{10}H_{11}N_3O_3$	128	32.0	128	50.0	17.0
10a	2-C_5H_4N	2-C_5H_4N-NH	45.3	128–131	$C_{11}H_{10}N_4O$	11.8	50.0	120	100	100
10b	4-C_5H_4N	2-C_5H_4N-NH	7.0	134–136	$C_{11}H_{10}N_4O$	120	0	100	83.0	100
10c	4-C_5H_4N	4-C_5H_4-CON(Ph)	5.4	148–150	$C_{18}H_{14}N_4O$	120	84.0	100	34.0	34.0
aspirin						50	50.0			
dextropropoxyphene						56	50.0			
indomethacin								12	17	83

[a] All new compounds were analyzed for C, H, N, and O using high-resolution mass spectrometry. [b] nt, not tested.

temperature was gradually raised to 25 °C. Distilled water (20 mL) was added slowly. Extraction with chloroform (4 × 100 mL), drying (sodium sulfate), and removal of the solvent in vacuo afforded a yellowish solid, which was recrystallized from acetone to give **5a**: yield 2.22 g (40.3%); mp 151–153 °C; IR 3200 (NH), 1640–1660 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 9.53 (s, 1 H, NH, exchanges with deuterium oxide), 8.93 (d, $J_{2,4}$ = 2 Hz, 1 H, pyridine C_2 H), 8.68 (d, $J_{5,6}$ = 5 Hz, of d, $J_{4,6}$ = 2 Hz, 1 H, pyridine C_6 H), 8.13 (d, $J_{4,5}$ = 8 Hz, of d, $J_{4,6}$ = 2 Hz, 1 H, pyridine C_4 H), 7.48 (d, $J_{4,5}$ = 8 Hz, of d, $J_{5,6}$ = 5 Hz, 1 H, pyridine C_5 H), 2.68–3.06 (m, 4 H, piperidine C_2 and C_6 H), 1.18–1.85 (m, 6 H, piperidine C_3, C_4, and C_5 H). Exact mass for $C_{11}H_{15}N_3O$: calcd, 205.1215; found (high-resolution MS), 205.1220.

***N*-[(3-Pyridylcarbonyl)amino]morpholine (5b).** Reaction of *N*-aminomorpholine (**4b**; 2.314 g, 22.7 mmol) and *n*-butyllithium (22.7 mmol) with ethyl nicotinate (**3a**; 3.428 g, 22.7 mmol) and completion of the reaction as described under procedure A gave a semisolid. Chromatography on a 2.5 × 21 cm neutral alumina column using ether–methanol (10:1, v/v; 375 mL) as eluant gave a solid, which on recrystallization from acetone gave **5b**: yield 0.28 g (6%); mp 179–181 °C; IR ($CHCl_3$) 3340 (NH), 1680 cm^{-1} (CO); NMR δ 7.54 (br s, 1 H, NH, exchanges with deuterium oxide), 3.79 (t, $J_{2,3}$ = $J_{5,6}$ = 4.5 Hz, 4 H, morpholine C_3 and C_5 H), 2.93 (t, $J_{2,3}$ = $J_{5,6}$ = 4.5 Hz, 4 H, morpholine C_2 and C_6 H), Exact mass for $C_{10}H_{13}N_3O_2$: calcd, 207.1008; found (high-resolution MS), 207.1012.

***N*-[(3-Pyridylcarbonyl)amino]homopiperidine (5c).** Reaction of *N*-aminohomopiperidine (**4c**; 1.38 g, 12.1 mmol) and *n*-butyllithium (12.1 mmol) with ethyl nicotinate (**3a**; 1.83 g, 12.1 mmol) as described under procedure A afforded a semisolid product. Purification by elution from a 2.5 × 20 cm neutral alumina column using ether–methanol (10:1, v/v; 300 mL) gave **5c**: yield 1.13 g (42.7%); mp 107–110 °C; IR 3200 (NH), 1665 and 1640 cm^{-1} (CO); NMR δ 2.76–3.43 (m, 4 H, homopiperidine C_2 and C_7 H), 1.33–2.07 (m, 8 H, homopiperidine C_3, C_4, C_5, and C_6 H). Exact mass for $C_{12}H_{17}N_3O$: calcd, 219.1372; found (high-resolution MS), 219.1377.

***N*,*N*-Dimethylnicotinic Acid Hydrazide (5d).** Treatment of *N*,*N*-dimethylhydrazine (**4d**; 1.582 g, 26.37 mmol) and *n*-butyllithium (26.37 mmol) with ethyl nicotinate (**3a**; 3.98 g, 26.37 mmol) and completion of the reaction as described under procedure A gave a semisolid product. The reaction product was purified by elution from a 2.5 × 20 cm neutral alumina column using ether–methanol (1:1, v/v; 500 mL) to give **5d**: yield 1.49 g (34.2%); mp 78–80 °C; IR ($CHCl_3$) 3240 (NH), 1665 cm^{-1} (CO); NMR δ 2.7 (s, 6 H, NMe_2). Exact mass for $C_8H_{11}N_3O$: calcd, 165.0902; found (high-resolution MS), 165.0902.

***N*,*N*-Dimethylisonicotinic Acid Hydrazide (5e).** Methyl isonicotinate (**3b**; 3.612 g, 26.37 mmol) was added to a solution of *N*,*N*-dimethylhydrazine (**4d**; 1.582 g, 26.37 mmol) and *n*-butyllithium (26.37 mmol), and the reaction was completed as described under procedure A to give an oil. Purification by elution from a 2.5 × 22 cm neutral alumina column using 250 mL of ether–methanol (1:3, v/v) gave **5e** as a yellow oil: yield 0.26 g (6.0%); IR ($CHCl_3$) 3340 (NH), 1680 cm^{-1} (CO); NMR δ 2.68 (s, 6 H, NMe_2). Exact mass for $C_8H_{11}N_3O$: calcd, 165.0902; found, (high-resolution MS), 165.0903.

***N*-[(4-Pyridylcarbonyl)imino]isoquinolinium Ylide (7).** Thionyl chloride (66.48 mmol, 4.82 mL) was added to a solution of isonicotinic acid (4.09 g, 33.24 mmol) in dry ether (150 mL) and the mixture was heated under reflux for 4 h. The excess thionyl chloride and ether was distilled off to yield isonicotinic acid chloride, which was dissolved in 50 mL of dry dimethylformamide. To this was added a solution of *N*-aminoisoquinolinium chloride (**6**;[4] 6 g, 33.24 mmol) in 50 mL of dimethylformamide. The solution was stirred for 6 h at 25 °C and then allowed to reflux for 6 h. Removal of the solvent in vacuo gave a crude product, which was subjected to chromatography on a 2.5 × 26 cm neutral alumina column. Elution with ether–methanol (5:1, v/v; 600 mL) gave **7**: yield 1.33 g (16.05%); mp 178–180 °C; NMR (Me_2SO-d_6) δ 10.1 (s, 1 H, isoquinoline C_1 H), 7.8–8.85 (complex m, 10 H, remaining isoquinoline and pyridyl hydrogens). Exact mass for $C_{15}H_{11}N_3O$: calcd, 249.0891; found (high-resolution MS), 249.0892.

***N*-[(4-Pyridylcarbonyl)amino]-1,2,3,4-tetrahydroisoquinoline (8).** A solution of **7** (1.99 g, 7.97 mmol) in 50 mL of 95% ethanol was added dropwise to a solution of sodium borohydride (0.552 g, 14.59 mmol) in 40 mL of 95% ethanol, precooled to 0 °C, during 20 min. After stirring for 4 h at 0 °C, the reaction mixture was poured onto crushed ice (150 mL) and allowed to come to room temperature. Extraction with chloroform (4 × 75 mL), drying (Na_2SO_4), and removal of the solvent in vacuo gave a solid. Elution from a 2.5 × 25 cm neutral alumina column using ether–methanol (9:1, v/v; 300 mL) afforded **8**: yield 1.3 g (65%); mp 192–194 °C; NMR (Me_2SO-d_6) δ 2.9–3.4 (m, 4 H, isoquinoline C_3 and C_4 H), 4.15 (br s, 2 H, isoquinoline C_1 H), 7.2 (m, 4 H, isoquinoline phenyl hydrogens), 7.85 (d, $J_{2,3}$ = $J_{5,6}$ = 5 Hz, of d, $J_{3,5}$ = 1.75 Hz, 2 H, pyridine C_3 and C_5 H), 8.85 (d, $J_{2,3}$ = $J_{5,6}$ = 5 Hz, of d, $J_{3,5}$ = 1.75 Hz, 2 H, pyridine C_2 and C_6 H), 10.1 (s, 1 H, NH, exchanges with deuterium oxide). Exact mass for $C_{15}H_{15}N_3O$: calcd, 253.1205; found (high-resolution MS), 253.1205.

1-Benzoyl-2-(4-pyridylcarbonyl)hydrazine (9a). Procedure B. To an ice-cooled solution of isonicotinic acid hydrazide (**1a**; 0.50 g, 3.65 mmol) and dry triethylamine (1 mL) in dry tetrahydrofuran (60 mL) was added dropwise a solution of benzoyl chloride (0.513 g, 3.65 mmol) in tetrahydrofuran (15 mL). The reaction was allowed to proceed for 6 h at 25 °C with stirring. Extraction with chloroform (4 × 75 mL), drying (sodium sulfate), and removal of the solvent in vacuo afforded a residue, which was purified by elution from a 2.5 × 22 cm neutral alumina column using ether–methanol (1:2, v/v; 300 mL) to give **9a**: yield 0.057 g (6.5%); mp 215–217 °C; IR 3200 (NH), 1670 and 1650 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 10.68 (br s, 2 H, NHNH, exchanges with deuterium oxide), 8.75 (d, $J_{2,3}$ = $J_{5,6}$ = 6 Hz), 2 H, pyridine C_2 and C_6 H), 7.7–8.05 (complex m, 4 H, pyridine C_3 and C_5 H, *o*-phenyl hydrogens), 7.33–7.6 (m, 3 H, *m*- and *p*-phenyl hydrogens). Exact mass for $C_{13}H_{12}N_3O_2$: calcd, 241.0852; found (high-resolution MS), 241.0857.

1,1-Diacetyl-2-(4-pyridylcarbonyl)hydrazine (9b). A solution of acetyl chloride (1.146 g, 14.6 mmol) in dry tetrahydrofuran (30 mL) was added dropwise to an ice-cooled solution of isonicotinic acid hydrazide (**1a**; 1.0 g, 7.3 mmol) and dry triethylamine (30 mL) in tetrahydrofuran (60 mL). The reaction was completed as described under procedure B. The reaction product was recrystallized from absolute ethanol to give **9b**: yield 0.15 g (9.3%); mp 158–160 °C; IR 3250 (NH), 1735, 1705 and 1675 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 11.13 (br s, 1 H, NH, exchanges with deuterium oxide), 2.37 (s, 6 H, $COMe_2$). Exact mass for $C_{10}H_{11}N_3O_3$: calcd, 221.0801; found (high-resolution MS), 221.0802.

1-(2-Pyridylcarbonyl)-2-(2-pyridyl)hydrazine (10a). Procedure C. A solution of 2-pyridylhydrazine (3.23 g, 29.67 mmol) in 50 mL of toluene was added to sodium hydride (1.57 g, 65.34 mmol) suspended in 20 mL of toluene under a nitrogen atmosphere, and the mixture was stirred for 30 min. A solution of ethyl picolinate (**3c**; 29.67 mmol) in 10 mL of toluene was added dropwise, after which the mixture was heated under reflux for 15 h. Addition of water (25 mL), extraction with chloroform (4 × 30 mL), drying (Na_2SO_4), and removal of the solvent in vacuo gave an impure product. Chromatography on a 2.5 × 26 cm neutral alumina column using ether–methanol (9:1, v/v; 600 mL) as eluant afforded **10a**: yield 2.88 g (45.3%); mp 128–131 °C; IR 3220 (NH), 1670 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 3.45 (s, 1 H, NH, exchanges with deuterium oxide), 6.6–6.9 (m, 2 H, pyridylhydrazine C_3 and C_5 H), 7.45–7.9 (complex m, 2 H, pyridylhydrazine C_4 H, pyridylcarbonyl C_5 H), 8.03–8.3 (m, 3 H, pyridylhydrazine C_6 H, pyridylcarbonyl C_3 and C_4 H), 8.7 (m, 2 H, pyridylcarbonyl C_6 H, NH exchanges with deuterium oxide). Exact mass for $C_{11}H_{10}N_4O$: calcd, 214.0854; found (high-resolution MS), 214.0854.

1-(4-Pyridylcarbonyl)-2-(2-pyridyl)hydrazine (10b). Reaction of methyl isonicotinate (**3b**; 33.6 mmol) with a mixture of sodium hydride (1.77 g, 73.9 mmol) and 2-pyridylhydrazine (3.66 g, 33.6 mmol) as described under procedure C gave an impure product which was purified on a 2.5 × 26 cm neutral alumina column. Elution with ether–methanol (9:1, v/v; 300 mL) gave **10b**: yield 0.5 g (7%); mp 134–136 °C; NMR (Me_2SO-d_6) δ 3.4 (s, 1 H, NH, exchanges with deuterium oxide), 7.6–7.95 (m, 2 H, pyridylhydrazine C_3 and C_5 H), 7.4–7.85 (m, 1 H, pyridylhydrazine C_4 H), 7.9 (d, $J_{2,3}$ = $J_{5,6}$ = 5 Hz, of d, $J_{3,5}$ = 1.75 Hz, 2 H, pyridylcarbonyl C_3 and C_5 H), 8.15 (d, $J_{5,6}$ = 6 Hz, of d, $J_{4,6}$ = 2 Hz,

1 H, pyridylhydrazine C_6 H), 8.65 (s, 1 H, NH, exchanges with deuterium oxide), 8.9 (d, $J_{2,3} = J_{5,6} = 6$ Hz, of d, $J_{2,6} = 1.5$ Hz, pyridylcarbonyl C_2 and C_6 H). Exact mass for $C_{11}H_{10}N_4O$: calcd, 214.0842. found (high-resolution MS), 214.0848.

1,2-Bis(4-pyridylcarbonyl)-1-phenylhydrazine (10c). Reaction of methyl isonicotinate (**3b**; 4.16 g, 30.38 mmol) with a mixture of sodium hydride (1.604 g, 66.84 mmol) and phenylhydrazine (30.38 mmol) as described under procedure C gave a product which was purified on a 2.5 × 26 cm neutral alumina column. Elution with ether–methanol (9:1, v/v; 300 mL) gave **10c**: 0.521 g (5.4%); mp 148–150 °C; IR ($CHCl_3$) 1680 and 1710 cm^{-1} (CO); NMR δ 7.1–7.5 (m, 7 H, phenyl, C_3 and C_5 H), 7.65 (d, $J_{2,3} = J_{5,6} = 5$ Hz, of d, $J_{3,5} = 1.75$ Hz, 2 H, C_3 and C_5 H), 8.6 (d, $J_{2,3} = J_{5,6} = 5$ Hz, 2 H, C_2 and C_6 H), 8.72 (d, $J_{2,3} = J_{5,6} = 5$ Hz, 2 H, C_2 and C_6 H), 10.3 (s, 1 H, NH, exchanges with deuterium oxide). Exact mass for $C_{18}H_{14}N_4O_2$: calcd, 318.1106; found (high-resolution MS), 318.1111.

Pharmacological Methods. Analgesic activity was evaluated by the phenylquinone writhing test.[5] Five male Swiss albino mice weighing 18–22 g were used in each group. The test compound, suspended 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 = (no. of writhes in treated group/no. of writhes in control group) × 100 - 100. A compound causing a 30–50% reduction is considered to be slightly active, whereas one causing a greater than 50% reduction in the number of writhes is an active analgesic agent.

Antiinflammatory activity was measured by the method of Winter.[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. Table I summarizes the pharmacological results in the above assays.

Acknowledgment. We are grateful to the Medical Research Council of Canada (Grant MA-4888) for financial support of this work and to the Canadian International Development Agency for a Scholarship (to K.R.).

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Aromatic Hydroxylation of β-Adrenergic Antagonists. Formation of 4′- and 5′-Hydroxy-1-(isopropylamino)-3-[2′-(allyloxy)phenoxy]-2-propanol from Oxprenolol[1]

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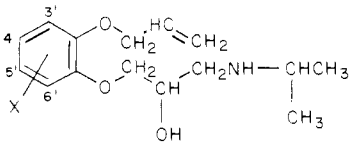
Received February 20, 1979

The metabolic aromatic hydroxylation of oxprenolol [1-(isopropylamino)-3-[2′-(allyloxy)phenoxy]-2-propanol] in rats was examined. Synthesis of the isomeric ring methoxyoxprenolols (**3b–6b**) was accomplished from the isomeric methoxysalicylaldehydes by O-allylation, followed by Baeyer–Villiger oxidation. The propanolamine side chain was elaborated by O-alkylation of the Bayer–Villiger product with epichlorohydrin and subsequent oxirane opening with isopropylamine. Gas chromatography–mass spectra of the trifluoroacetyl derivatives of these standards was compared with urinary metabolites obtained from the rat, after methylation with diazomethane and derivatization with trifluoroacetic anhydride. Both 4′- and 5′-hydroxyoxprenolol (**4a** and **5a**) were present in an approximate 4:1 ratio. No 3′- or 6′-hydroxyoxprenolol (**3a** and **6a**) was detected. The metabolites obtained from a human urine treated in the same manner gave similar results with both **4a** and **5a** present.

β-Adrenergic antagonists have been used in a variety of cardiovascular disorders, including cardiac arrhythmias,[2] angina pectoris, hypertrophic subaortic stenosis, and hypertension, and in other disease states, including psychiatric disorders.[3] In hypertension, they are useful alone or in combination with a variety of other drugs, such as α-adrenergic blocking agents, α-methyldihydroxyphenylalanine, diuretics, vasodilators, etc. Our interests in these agents included their metabolic fate, since in some cases parent drug molecules are converted to compounds which may have pharmacological activity, e.g., metabolites formed from propranolol,[4-7] metoprolol,[8] and alprenolol.[6]

Oxprenolol[9] [1-(isopropylamino)-3-[2-(allyloxy)phenoxy]-2-propanol] (**1**) is an important aryloxypropanolamine β-adrenergic antagonist whose metabolism has been extensively studied.[10-15] Oxprenolol is metabolized by hydroxylation of the aromatic ring, by oxidation of the propanolamine side chain, and by glucuronidation.[10,11,14] A possible glucuronide conjugate of an oxprenolol metabolite has been isolated from rats.[14] A different con-



1, X = H
2, X = OH
3a, X = 3′-OH
b, X = 3′-OMe
4a, X = 4′-OH
b, X = 4′-OMe
5a, X = 5′-OH
b, X = 5′-OMe
6a, X = 6′-OH
b, X = 6′-OMe

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