## Antiulcer Agents. p-Aminobenzamido Aromatic Compounds<sup>1</sup>

ROBERT BRUCE MOFFETT,\* ANDRE ROBERT, AND LOUIS L. SKALETZKY

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001

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A series of 2-(p-aminobenzamido)pyridines (I) were found to have a powerful inhibiting effect on experimental gastric ulcers in rats. Attachment of the p-aminobenzamido group at other positions on the pyridine ring, or substitution of other nitrogen heterocycles for pyridine, greatly decreased activity. p-Aminobenzamilde was found to be highly active, but quite toxic. The compds were prepd from p-nitrobenzoyl chloride and the requisite aromatic amine, followed by reduction of the NO<sub>2</sub> group. A number of intermediates and analogs are reported.

Gastrointestinal ulcers are commonly treated by diet, antacids, anticholinergics, or surgery. Anticholinergics reduce the amount of gastric juice and its acidity and also the motility of the stomach and intestine. Although widely used, they are by no means the final answer. Gastric ulcers can be produced in rats by restraint, forced exertion, pylorus ligation, or by administration of certain adrenal cortical hormones. Anticholinergics are active in preventing all these types of ulcers; however, it has been our goal to find an antiulcer agent that does not work by anticholinergic mechanism.

For screening, compds were selected that were thought not to be anticholinergic either on the basis of structure or because they were inactive in the Magnus or other anticholinergic test. Any compd found to prevent exertion ulcers<sup>2</sup> in rats was retested as an anticholinergic. If inactive at doses much higher than the antiulcer dose, it was studied for prevention of all the above kinds of ulcers. Thus, a series of compds (I) was discovered, many of which showed antiulcer activity.<sup>3</sup>



The most active was 6. This is related to the weak antibacterial "carbopyridin"<sup>4</sup> (2) which in turn is related to sulfapyridine. Compd 2 was found to be a much weaker antiulcer agent than 6. Likewise, changing the positions of the various groups on the rings, adding other groups, or changing their nature, reduced or eliminated activity (Table I). The replacement of the pyridine ring by various other heterocyclic rings (Table II) also greatly reduced or eliminated activity. Surprisingly, substitution of a benzene ring in place of the pyridine ring gave a very active anilide (70). However, this was found to be quite toxic.

It is interesting that many of these compds were found to exhibit mild CNS-depressant activity in intact mice. However, there was no close correspondence between antiulcer and CNS-depressant activities, and the better antiulcer agents were active at doses much lower than the depressive doses. Although certain known CNS depressants, for example chlorpromazine, chlordiazepoxide, phenobarbital, meprobamate, etc., were shown to prevent exertion ulcers in rats, the doses required produced overt depression. Tables I and II include a rough indication of CNS-depressant activity in mice of our compd. Several well-known drugs are included for comparison.

The aminobenzamido compounds were made by reduction of the corresponding nitrobenzamides (method B). These were prepared from the appropriate amino heterocycle or aniline and nitrobenzoyl chloride (method A). Representative procedures are given in the Experimental Section. In several cases the reaction of substituted benzoyl chorides with 2-aminopyridines yielded N,N-dibenzoyl compds (Table III). These were inactive as antiulcer agents, but could be easily hydrolyzed to the desired benzamidopyridines (method D). This dibenzoylation could be avoided by the use of the approriate benzoic anhydride (when available) in place of the acid chloride.

In the benzoylation reaction of certain of the aminoheterocyclic compounds, the possibility is recognized that the benzoyl moiety might go on a ring N instead of the NH<sub>2</sub> group. However, the structures (**52**, **54**, **57**, **59**, **62**, **64**) are formulated in Table II on the basis of analogy with the literature.<sup>5-9</sup>

In one case (tetramethylbenzoylation of adenine), two isomers were isolated. Although definitive structure proof is not available, **64** is formulated, on the basis of nmr, as the  $NH_2$ -substituted derivative, and **65** as a ring-substituted compd, possibly a mixture of the 7 and 9 derivatives.

## **Experimental Section**<sup>10</sup>

**2-**(p-Nitrobenzamido)-**3-**picoline (5) (Method A).—To a cold soln of 15 g (0.0806 mole) of *p*-nitrobenzoyl chloride in 20 ml of pyridine and 25 ml of CHCl<sub>3</sub> was added 8.7 g (0.0806 mole) of

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<sup>(10)</sup> Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Ir spectra were obtained on all pure compds and nmr (Varian A-60) on representative examples. These were in accordance with the proposed structures. Where analyses are indicated only by symbols of the elements or functions, anal. results obtained for these elements or functions were within  $\pm 0.4\%$  of theor.

CNS Antindoor	depression, <sup>c</sup> activity,	mg/kg EDso, mg/kgd	300	1000 50		100		300 35	100 35	55			300 75	100	100		60	100 90	30 50	300 60	300	1000		300  40  (toxic)		100 35				30 75	$\frac{1}{30}$ 75 $\frac{1}{50}$ 300 50	30 $75300$ $50$	30 $75300$ $5050$	30 75 300 50 50		30 30 300 50 1000 50	30 300 300 300 50 1000 50 100 100	30 75 300 75 300 50 1000 50 100 10	30 75 300 75 300 50 100 50	30 75 300 75 300 50 1000 50 100 1 300
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	Method	of prepn	A	В	C	f	Ņ	В⁄	Сŕ	م	. <i>S</i>		f	Ą	В	Ϋ́	æ	£	ſ	a	<b>_</b>	D/	A	$\mathbf{B}^{k}$	V	В	V		В	A A	a v a	A A A A	a a a a a	a k a k a k		$\mathbf{H} \mathbf{A}$ $\mathbf{H} \mathbf{A}$ $\mathbf{H} \mathbf{A}$ $\mathbf{H} \mathbf{A}$ $\mathbf{H} \mathbf{A}$	ž > , > B > B > B > B > B	×n × n × n × n × n × n ×	R³ → S → S → B → B → B	B <sub>3</sub> → S → S → B → B → B
		Х	$4-NO_{2}^{e}$	$4-\mathrm{NH}_{2}^{e}$	4-NH <sub>2</sub> ·2HCl <sup>e</sup>	4-NHCOCH <sub>3</sub>	4-NO;	$4-NH_2$	4-NH <sub>2</sub> ·2HCI	$4-\mathrm{NH_2} \cdot \mathrm{maleate}$	4-NHCOCH <sub>3</sub>	$\cdot 2 \Pi_2 O_{\theta}$	$4-N(CH_3)_2$	$4-NO_2$	$4-NH_2$	$3-NO_2$	$3-N11_2$	$2-NH_2$	H	4-CH <sub>3</sub>	4-CI	$3,4,5-(OCH_3)_3$	4-NO <sub>2</sub>	4-N112	$4-NO_2$	4-NH <sub>2</sub>	4-NO,		4-NH <sub>2</sub>	4-NH <sub>3</sub> 4-NO <sub>2</sub>	4-NH <sub>2</sub> 4-NO <sub>2</sub> 4-NH <sub>2</sub>	4-NH <sub>2</sub> 4-NO <sub>2</sub> 4-NH <sub>2</sub> 4-NO <sub>2</sub>	4-NH <sub>2</sub> 4-NO <sub>2</sub> 4-NH <sub>2</sub> 4-NO <sub>2</sub> 4-NH <sub>2</sub>	4-NH, 4-NO, 4-NH, 4-NH, 4-NH, 4-NO,	4-NH, 4-NO, 4-NH, 4-NU, 4-NH, 4-NH, 4-NH,	4-NH, 4-NO, 4-NH, 4-NU, 4-NU, 4-NU, 4-NU, 4-NO,	4-NH 4-NH 4-NU 4-NU 4-NU 4-NH 4-NH 2-NH	4-NH 4-NH 4-NO 4-NH 4-NH 4-NH 4-NH 4-NO 2-NO	4-NH 4-NH 4-NO 4-NH 4-NH 4-NH 4-NH 2-NH 2-NH	4-NH 4-NH 4-NO 4-NO 4-NO 4-NH 4-NH 4-NH 2-NO 4-NH
		ц	Н	Н	Н	Η	3-CH3	3-CH,	3-CH <sub>3</sub>	3-CH,	3-CH <sub>3</sub>		3-CH <sub>3</sub>	$3-CH_3$ , $(CH_3NCO^h)$	$3-CH_3$ , (CH <sub>3</sub> NCO <sup>4</sup> )	3-CH3	3-CH <sub>3</sub>	3-CII <sub>3</sub>	3-CH,	3-CH <sub>3</sub>	3-CH3	3-CH <sub>3</sub>	4-CH <sub>3</sub>	4-CH <sub>3</sub>	5-CH3	5-CH3	6-CH <sub>3</sub>	, ,	6-CH <sub>3</sub>	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub>	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub>	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>2</sub>	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>2</sub>	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>2</sub> 5-Cl	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ), 4,6-(CH <sub>3</sub> ), 5,6-(CH <sub>3</sub> ), 7,6-(CH <sub>3</sub> ), 5-Cl 5-Cl	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ), 4,6-(CH <sub>3</sub> ), 5,6-(CH <sub>3</sub> ), 5,6-(CH <sub>3</sub> ), 5-Cl 5-Cl 3-COH	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>3</sub> 5,6-(CH <sub>3</sub> ) <sub>3</sub> 5-Cl 5-Cl 3-COH 3-COOH	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>3</sub> 5,6-(CH <sub>3</sub> ) <sub>3</sub> 5-Cl 5-Cl 3-COH 3-COOH 3-COOH 6-NHCOC6H <sub>4</sub> -P-NO <sub>2</sub>	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>3</sub> 5,6-(CH <sub>3</sub> ) <sub>3</sub> 5-Cl 5-Cl 3-CO 3-CO 6-NHCOC6H <sub>4</sub> - <i>p</i> -NO <sub>2</sub> 6-NHCOC6H <sub>8</sub> - <i>p</i> -NH <sub>2</sub>	6-CH <sub>3</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 4,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>2</sub> 5,6-(CH <sub>3</sub> ) <sub>2</sub> 5-Cl 5-Cl 3-COH 3-COOH 3-COOH 6-NHCOC6H <sub>4</sub> -p-NO <sub>2</sub> 6-NHCOC6H <sub>8</sub> -p-NH <sub>2</sub>
osition of	ovridine	ring	7	67	2	। २ <b>।</b>	5	5	. 01	1.54	2		67	5	2	¢1	67	2	51	57	57	21	57	51	5	21	57		5	20	ପ୍ର୍ୟୁ	ର୍ଦ୍ୟୁର୍	ରର୍ଷ୍ଣ୍ୟ	ରେବର୍ଷ୍ୟର୍	<b>ରେ ସ ସ ସ ସ ସ</b>	<b>ରର୍ଗ୍ୟର୍ଭ୍ୟ</b> ର ଭ	<b>ਲ਼ਲ਼ਗ਼ਲ਼ਲ਼ਲ਼ਲ਼</b> ਲ਼ਲ਼	<b>ਸ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼</b> ਗ਼	<b>ਸ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼</b> ਗ਼	<b>ਸ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼ ਗ਼</b> ਗ਼
<u> </u>	-	No.		5	. et	: 4	-15	. 9	× 7	• x	6		10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		25	25 26	25 26 27	$25 \\ 28 \\ 28 \\ 28 \\ 28 \\ 28 \\ 28 \\ 28 \\ $	$25 \\ 28 \\ 28 \\ 29 \\ 29 \\ 29 \\ 29 \\ 29 \\ 29$	$   \begin{array}{c}     25 \\     22 \\     23 \\     23 \\     23 \\     23 \\     25 \\      25 \\  $	$ \begin{array}{c} 25\\ 28\\ 28\\ 28\\ 28\\ 31\\ 31\\ 31\\ 31\\ 31\\ 31\\ 31\\ 31\\ 31\\ 31$	$\begin{array}{c} 25\\ 23\\ 32\\ 32\\ 32\\ 32\\ 32\\ 32\\ 32\\ 32\\ 32$	$\begin{array}{c} 25\\ 26\\ 23\\ 22\\ 23\\ 22\\ 23\\ 22\\ 23\\ 22\\ 22\\ 22$	$\frac{3}{2}$ $\frac{3}$	$\begin{array}{c} & & & & & \\ & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & &$	$\begin{array}{c} 25\\ 26\\ 28\\ 32\\ 32\\ 32\\ 32\\ 32\\ 32\\ 32\\ 32\\ 32\\ 32$



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422		562	>1000	562	49		208	12	18	75	30	10	For method
C, H, N	C, H, N	C, H, Cl, N	C, H, N	C, H, N	C, H, N	C, H, N	C, H, Cl, N	Z	C, H, N	C, H, Cl, N	C, H, N	C, H, N	detd in in mice
$C_{12}H_9N_3O_3$	C <sub>12</sub> H <sub>11</sub> N <sub>3</sub> O	C <sub>12</sub> H <sub>12</sub> CIN <sub>3</sub> O	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub>	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O	C <sub>12</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub>	C <sub>12</sub> H <sub>11</sub> N <sub>3</sub> O	C <sub>12</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>3</sub> O	C12H10N2O	$C_{13}H_{12}N_2O$	C <sub>16</sub> H <sub>19</sub> ClH <sub>2</sub> O	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> O <sub>3</sub>	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O	NS activity were
190.5 - 192	209.5 - 211	244.5 - 245.5	205 - 206.5	172.5 - 173.5	244 - 245	256 - 257	>350	202 - 205	178.5 - 181	285–312 dec	166 - 168	205 - 206.5	· Lethality and C
88	86	78	75	88	44	68	67	76	36	64	62	85	oo rof 10
EtOH-MeOH	MeOH	H <sub>2</sub> O- <i>i</i> -PrOH	MeOH	MeOH	MeOH	MeOH	MeOH	$H_2O$	EtOAc	$MeOH-H_2O$	$Me_2CO$	EtOH	on obtained <sup>b</sup> S
V	в	مر	Y	В	Α	в	U	Υ	Υ	£	Α	В	hichest n
$4-NO_2$	$4-NH_2$	4-NH <sub>2</sub> ·HCl	4-NO <sub>2</sub>	$4-NN_2$	$4-NO_2$	$4-\mathrm{NH}_2$	4-NH <sub>2</sub> ·2HCl	H°	4-CH <sub>3</sub>	2,3,5,6-(CH <sub>3</sub> ) <sub>4</sub>	$4-NO_2$	$4-NH_2$	not less than 2° helow
Н	Н	Н	2,6-(CH <sub>3</sub> ) <sub>2</sub>	2,6-(CH <sub>3</sub> ) <sub>2</sub>	Η	Н	Н	Н	Н	Н	3-Me	3-Me	4 on material melting
ŝ	ŝ	3	က	က	4	4	4	4	4	4	4	4	are calor
37	38	39	40	41	42	43	44	45	46	47	48	49	<b>Yields</b>

ot less than  $z^{\circ}$  below highest mp obtained. "See ref 10. "Lethality and CNS activity were detd pp in mice. For method see K. B. Montett, A. K. 178 (1964), Table I, footnotes a and b. The lowest dose showing definite CNS depression is given. A (---) indicates no depression was observed. In A blank indicates this compd was not tested. "The procedure for producing exertion ulcers in rats has been reported.<sup>2</sup> ED<sub>50</sub> is the oral dose necessary to reduce ulcer formation by 50% taking into account both the number as severity of the ulcers. A (---) indicates the compd was substantially inactive. A blank indicates the compd was not tested. \* See ref 4. ' Specific preparimental Section. \* Prepd in these laboratories by Mr. James E. Stafford. \* Contains a Me group on the amide N. ' The *p*-nitrobenzoyl chloride soln was added to the 2-(methylamino)-3-picoline in CHCl<sub>a</sub> and pyridine below 50° and stirred at room temp for 2 hr. *i* The crude product was chromatogd on SiO<sub>2</sub> and eluted with 5% filtered hot from catalyst, and " Prepd from 2,6-diaminopyridine and an excess of *p*-nitrobenzoyl chloride. " Hydrogenation run in glacial AcOH with PtO<sub>2</sub> in place of Pd/C. The crystd and dried product was found Fischer anal. to contain 0.84% H<sub>2</sub>O (equiv to 0.16 H<sub>2</sub>O/mol). " E. Koenings, G. Kinne, and W. Weiss, *Chem. Ber.*, 57, 1172 (1924). " Too toxic to test. MeOH in CH<sub>2</sub>Cl<sub>2</sub>. \* Hydrogenation in n-BuOH. <sup>1</sup> The product of hydrogenation was insol in the reaction mixt. It was coned in vacuo, dissolved in 31. of H<sub>2</sub>O, " rieds are calcd on material metung not less than 2° below highest mp obtained. "See ret 10. " Lethality and CNS activity w Hanze, and P. H. Seay, J. Med. Chem., 7, 178 (1964), Table I, footnotes a and b. The lowest dose showing definite CNS depression some cases mild stimulation was observed. Karl Fischer anal. cooled. by Karl

2-amino-3-picoline, and the soln was stirred on a steam bath overnight. The mixt was dild with 50 ml of EtOH yielding 15.4 g (75%) of yellow cryst, mp 196–198°. A sample was recrystd from AcOH-H<sub>2</sub>O, mp 196–197°.

2-(*p*-Aminobenzamido)-3-picoline (6) (Method B).—A mixt of 13.58 g (0.027 mole) of 5 and 150 ml of 70% aq AcOH was hydrogenated with 1 g of 30% Pd/C at 3.5 kg/cm<sup>2</sup> and 25°. After filtn and evapn *in vacuo* at 50°, the product was dissolved in CHCl<sub>3</sub>, washed (5% NaHCO<sub>3</sub>, water), and again evapd. The amorphous solid crystd slowly from EtOH giving 11 g of light tan cryst contg EtOH, mp 170–174.5° (after sintering at 90°). This was sublimed at 0.002 mm in a bath up to 172° yielding 5.8 g (48.5%) of nearly white solid, mp 177–179°, contg no solvent. Principal spectra bands were: ir (Nujol mull) 3450, 3400, 3320, 3210 (NH); 1640 cm<sup>-1</sup> (amide CO) and numerous arom bands; uv (EtOH) 296 and 218 mµ; and nmr (DMF-d<sub>7</sub>)  $\delta$  2.27 (s, 3, CH<sub>3</sub>), 9.95 (broad s, 1, CONH), 5.7 (broad s, 2, NH<sub>2</sub>), and between 6.6 and 8.4 (m's 7, arom H's).

**Dihydrochloride** (7) (Method C).—A soln of 20.0 g (0.088 mole) of **6** in 200 ml of MeOH was strongly acidified with methanolic HCl. The resulting cryst were collected, washed (*i*-PrOH), and dried, yielding 24.8 g (94%) of white solid, mp some dec at 240–250°, but not all melted at 340°.

Maleate (Salt) (8).—A soln of 20.0 g (0.088 mole) of 6 in 200 ml of MeOH was treated with a soln of 11.6 g (0.1 mole) of maleic acid in 50 ml of MeOH. On diln with 100 ml of *i*-PrOH, 22.6 g (75%) of yellow cryst was obtained, mp 132–134°. Recrystn from 125 ml of EtOH gave 17 g of yellow cryst, mp 134–135.5°.

4'-(2-Pyridylcarbamoyl)acetanilide (4).—A soln of 3.0 g (0.014 mole) of 2 in 10 ml of Ac<sub>2</sub>O and 10 ml of AcOH was heated on a steam bath for 15 min, concd *in vacuo*, and dild with aq Na<sub>2</sub>CO<sub>3</sub>. The product was collected, washed (H<sub>2</sub>O), and recrystd from DMF-H<sub>2</sub>O, giving 2.9 g (81%) of solid, mp 203-204°.

4'-[(3-Methyl-2-pyridyl)carbamoyl]acetanilide  $\cdot 2H_2O$  (9).—A soln of 3 g (0.013 mole) of 6 in 75 ml of AcOH was refluxed for 6 hr, concd *in vacuo*, and dild with water. The product was collected, dried, and recrystd from a mixt of 10 ml of 95% EtOH and 5 ml of BuOH yielding 2.6 g (65%) of solid, mp 206°. This was found by Karl Fischer anal. to be the dihydrate. Calcd (C<sub>15</sub>H<sub>15</sub>-N<sub>3</sub>O<sub>2</sub>·2H<sub>2</sub>O): H<sub>2</sub>O, 11.80; found H<sub>2</sub>O, 11.74.

**2-**[*p*-(**Dimethylamino**)**benzamido**]-**3-picoline** (10).—A soln of 27.2 g (0.1 mole) of 6 in 200 ml of MeOH, 20 ml of AcOH, and 30 ml (0.37 mole) of 37% aq CH<sub>2</sub>O was hydrogenated with 2 g of 30% Pd/C at 3.5 kg/cm<sup>2</sup> and 25°. The theor amt of H<sub>2</sub> was absorbed in 5 hr. After filt, the soln was evapd *in vacuo*, mixed with ice water, and adjusted to pH 8. The solid was collected, washed (aq NaHCO<sub>3</sub>, H<sub>2</sub>O), and dried, giving 23.4 g of nearly white solid, mp 176–182.5°. This was recryst from 300 ml of *i*-PrOH yielding 19.6 g (77%) of light tan cryst, mp 179–184°. A second recrystn from *i*-PrOH gave cryst, mp 182–185°.

**2-(o-Aminobenzamido)-3-picoline** (15).—A soln of 33 g (0.3 mole) of 2-amino-3-picoline and 16.5 g (0.1 mole) of isatoic anhydride in 100 ml of DMF was heated under reflux for 1 hr, poured into ice water contg 10 g of Na<sub>2</sub>CO<sub>3</sub>, and extd with Et<sub>2</sub>O. The Et<sub>2</sub>O soln was extd with dil HCl, and the ext was basified with Na<sub>2</sub>CO<sub>3</sub>. The resulting oil was extd with Et<sub>2</sub>O, washed (satd NaCl), and dried (MgSO<sub>4</sub>). Evapn left an oil which was chromatogd on SiO<sub>2</sub> and eluted with 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>. The product solidified on trituration with Et<sub>2</sub>O-hexane and was recrystd from CHCl<sub>3</sub>-hexane, yielding 7.3 g (32%) of cryst, mp 147-149°.

**2-Benzamido-3-picoline** (16).—A soln of 21.6 g (0.2 mole) of 2-amino-3-picoline and 22.6 g (0.1 mole) of  $Bz_2O$  in 500 ml of ether was allowed to stand at room temp for 24 hr and evapd to dryness *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed (10% Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, satd NaCl), and dried (MgSO<sub>4</sub>). Evapn left a gum which crystd on trituration with Et<sub>2</sub>O-hexane, and was recrystd first from aq EtOH then from PhH-hexane yielding 11.85 g (56%) of white solid, mp 128.5-130°.

**3,3',4,4',5,5'-Hexamethoxy-***N*-(**3-methyl-2-pyridyl**)dibenzamide (77).—To a soln of 46.2 g (0.2 mole) of 3,4,5-trimethoxybenzoyl chloride in 100 ml of dry pyridine was added 10.8 g (0.1 mole) of 2-amino-3-picoline. After stirring on a steam bath for 2 hr, most of the pyridine was distd *in vacuo* and the residue was shaken with ice water. The product was collected, washed (H<sub>2</sub>O, aq Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O), and dried, giving 43.1 g of solid, mp 151-156°. Recystn from 520 ml of *i*-PrOH yielded 38.4 g (77%) of white cryst, mp 158-160.5°. The dibenzoyl structure was confirmed by nmr and mass spec: ir (Nujol mull) 1700, 1685 cm<sup>-1</sup> (C=O) and no NH/OH absorption; nmr (CDCl<sub>3</sub>)  $\delta$  2.33

	Antiulcer activity <sup>d</sup> ED <sub>90</sub> , mg/kg			60			75						
	CNS depression, mg/kg 1000	300					300		300			300	300
	LD <sub>40</sub> , <sup>6</sup> mg/kg >1000	>1000	562	422	>1000		178	>1000	750	562	178	>1000	750
	Analyses <sup>5</sup> C, H, N	С, Н, N	С, Н, N	С, Н, N	С, Н, N	С, Н, N	C, H, Cl, N	С, Н, N	С, Н, N	С, Н, N	С, Н, N	C, H, CI, N	С, Н, N
	Empirical formula C <sub>16</sub> H <sub>15</sub> N <sub>5</sub> O <sub>3</sub>	C <sub>16</sub> H <sub>17</sub> N <sub>8</sub> O	C <sub>10</sub> H <sub>8</sub> N <sub>4</sub> O <sub>3</sub>	$C_{10}H_{10}N_4O$	$C_{14}H_{10}N_4O_3$	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O	СиНиСІ2N4O	C <sub>9</sub> H <sub>7</sub> N <sub>5</sub> O <sub>3</sub>	C <sub>9</sub> H <sub>9</sub> N <sub>5</sub> O	C <sub>8</sub> H <sub>6</sub> N <sub>6</sub> O <sub>3</sub>	C <sub>8</sub> H <sub>8</sub> N <sub>6</sub> O	C <sub>11</sub> H <sub>7</sub> ClN <sub>4</sub> O <sub>3</sub>	C <sub>12</sub> H <sub>8</sub> N <sub>6</sub> O <sub>3</sub>
	Mp <sup>≜</sup> _°C 193-194	228-229	>360	275.5 dec	309-311	275-277	>360	338-339	303306 dec	273-273.5	298.5-299	255 dec	> 360
VBLE II	Yield, % <sup>a</sup> 55	61	44	74	44	10/	607	62	53	85	82	60	85
T ArNHO	Crysta solvent EtOH	Et0H-H2O	DMF	MeOE40H•	MeOEtOH•	MeOEtOH*-MeOH	MeOH	DMF	DMF-MeOH	DMF	DMF-Me0H	MeOEtOH•	DMF
	Method of prepn A	В	V	В	V	B⁄	بر	A	В	¥	В	A	V
	$\frac{X}{4-NO_2}$	$4-\mathrm{NH}_2$	4-NO <sub>2</sub>	$4-NH_2$	$4-NO_2$	4-NH2	4-NH <sub>2</sub> ·2HCl	4-NO <sup>20</sup>	$4-\mathrm{NH}_2$	$4-\mathrm{NO}_2^h$	$4-NH_2$	4-NO <sub>2</sub>	4-NO2
	T T		"HN	N HN				HNN	N	N-N N-N	N-N HN		HN
	No. 50	51	52	53	54	55	<u>56</u>	57	58	59	60	61	62

63		4-NH <sub>2</sub>	Bi	EtOH	68	243-244.5	Çı2H10N6O	С, Н, N	>1000	300	50
64		2,3,ភ,6-(CH <sub>3</sub> ),	مس	Xylene	52	187-189	C <sub>16</sub> H <sub>17</sub> N <sub>5</sub> O	С, Н, N	>1000	1000	
65	HN N	2,3,5,6-(CH <sub>3</sub> ),		MeOFtOH	6.3	260.5-263.5	C <sub>16</sub> H <sub>17</sub> N <sub>5</sub> O	С, Н, N	>1000	100	
99	CH3-CH3-CH3	4-NO2	Υ	DMF	57	346-348 dec	C <sub>10</sub> H <sub>8</sub> N <sub>4</sub> O <sub>3</sub> S	С, Н, N, S	562		
67	CH <sub>3</sub> - <sup>N-N</sup>	4-NH2	$\mathbf{B}^{k}$	i-PrOH	48	255–257	C <sub>10</sub> H <sub>10</sub> N <sub>4</sub> OS	C, H, N, S	750		
68	s €	4-NO <sub>2</sub>	A	DMF-EtCOMe	82	294.5-296	C <sub>14</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub> S	C, H, N, S	>1000		
69	Ê	4-NH <sub>2</sub>	₿¢	EtCOMe	99	199.5-201.5	C <sub>11</sub> H <sub>11</sub> N <sub>5</sub> OS	С, Н, N, S	316		
70	2 2 2	4-NH <sub>2</sub>	1			238-241m	$C_{13}H_{12}N_2O$		422	100	40"
11	0-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-NO <sub>2</sub>	٩	EtOH		161-162°	C <sub>14</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	Z	->1000	300	
72	0-CH <sub>3</sub> C <sub>6</sub> H	4-NO <sub>2</sub>	$\mathbf{B}^{p}$	CHCl <sub>a</sub> -hexane		$155-156^{p}$	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O	N	104	30	đ
73	Ł	3-NH <sub>2</sub>	1			122-124	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O		750	100	
74	Ł	$2-\mathrm{NH}_2$	B,	Ph	16	116-118*	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O	С, Н, N	1000	300	•
81	Atropine sul-						CITH25NO7S		316	100	1.0
82	Sodium phe-						$\mathrm{C}_{12}\mathrm{H}_{11}\mathrm{N}_{2}\mathrm{N}_{3}\mathrm{O}_{3}$		200	100	504
83	Chlorproma-						C <sub>16</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>3</sub> O		150	20	1.5
84	zme·HCl Chlordiazep-						$C_{17}H_{20}Cl_2N_2S$		200	50	20
	oxide·HCl										
85	Meproba- mate						C <sub>9</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>		600	200	100
' See footno v, et al., <sup>8</sup> re	te a, Table I. <sup>b</sup> See ref 10. port mp 273-274° dec. <sup>i</sup> 1	c See footnote $c$ , Various fractions fr	Table I. om DMF	<sup>d</sup> See footnote d, Table I. -MeOH had dec points fro	<sup>•</sup> 2-Metho	xyethanol. / See 299° all had ident	» Experimental Se ical ir spectra.	ction. <sup>a</sup> Cipens, Hydrogenated in	et al., <sup>7</sup> report 2-methoxye	mp 337°. thanol; 3.5	<sup>h</sup> Shchipa- days were

nov, et al.,<sup>8</sup> report mp 273–274° dec. <sup>•</sup> Various fractions from DMF-MeOH had dec points from 294 to 299 and neuronal in spectral of the rest was obtd by neutralization of the required to complete reaction. <sup>\*</sup> Part of the product was insol in the aq AcOH react mixt and after filtn was extd from the catalyst with warm DMF. The rest was obtd by neutralization of the filtrate. <sup>1</sup>Obtained from K and K Labs. Inc., Plainview, N. Y. <sup>m</sup> G. Lochemann and T. Lobenstein, *Chem. Ber.*, **75**, 1911 (1942), report mp 137–138°. <sup>a</sup> This compd showed good ulcer preventing activity but produced splenomegaly as a side effect. <sup>a</sup> R. Adams and L. M. Werbel, *J. Amer. Chem. Soc.*, **80**, 5799 (1958), report mp 160–161.5°. <sup>a</sup> G. Lockemann and H. Kügler, *Chem. Ber.*, **80**, 479 (1947), report mp 152–153°. <sup>a</sup> Too toxic to test. <sup>a</sup> R. Adams and L. M. Werbel, *J. Amer. Chem. Soc.*, **80**, 5799 (1958), report mp 160–161.5°. <sup>a</sup> G. Lockemann and H. Kügler, *Chem. Ber.*, **80**, 479 (1947), report mp 152–153°. <sup>a</sup> Too toxic to test. <sup>a</sup> R. Adams and L. M. Werbel, *J. Amer. Chem. Soc.*, **80**, 5799 (1958), report mp 160–161.5°. <sup>a</sup> G. Lockemann and H. Kügler, *Chem. Ber.*, **76**, 1139°(1883). <sup>a</sup> Prept by Dr. R. S. Hsi in these laboratories by method B in EtOH with PtO<sub>2</sub> catalyst. The lit. shows a wide discrepancy in reports of mp. See Shah, *J. Indian Inst. Sci.*, **7**, 207 (1920); *Beilstein* II, **14**, 210. <sup>a</sup> Administered sc in this test. 8

			Тав	le III			
				0-	$\left( \sum_{i=1}^{N} \right)_{i}$		
No.	R	х	Crystn solvent	Yield, % <sup>a</sup>	$Mp, b \circ C$	Empirical formula	$Analyses^b$
75	$\mathrm{CH}_3$	$4-CH_3$	n-BuOH	$34^{c}$	225 - 227	$C_{22}H_{20}N_2O_2$	C, H, N
76	$CH_3$	4-Cl	n-BuOH	<b>27</b>	218 - 220	$\mathrm{C}_{20}\mathrm{H}_{14}\mathrm{Cl}_2\mathrm{N}_2\mathrm{O}_2$	C, H, Cl, N
77	$CH_3$	$3,4,5-(OCH_3)_3$	<i>i</i> -PrOH	$77^{d}$	158 - 160.5	$C_{20}H_{26}N_2O_8$	C, H, N
78	$CH_3$	$4 - N(CH_3)_2$	TMU <sup>e</sup>	$17^{e}$	213 - 235	$C_{24}H_{26}N_4O_2$	C, H, N
79	$OCH_2CH_3$	$4-NO_2$	i-PrOH	48	172 - 173.5	$\mathrm{C}_{21}\mathrm{H}_{16}\mathrm{N}_4\mathrm{O}_7$	C, H, N
80	$NO_2$	$4-NO_2$	MeOEtOH <sup>4</sup>	18	213.5 - 214.5	$C_{19}H_{11}N_{5}O_{8}$	C, H, N

<sup>a</sup> See footnote *a*, Table I. All compds in Table III were prepd essentially by method A except as noted. <sup>b</sup> See ref 10. <sup>c</sup> The crude product was dissolved in CHCl<sub>3</sub>, washed (aq Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O), and dried (MgSO<sub>4</sub>). After filtration and evapn the product was crystd from the solvent indicated. <sup>d</sup> Prepn specifically described in the Experimental Section. <sup>e</sup> *p*-Dimethylaminobenzoyl chloride ·HCl was made from the corresponding acid and SOCl<sub>2</sub> and was used without purification as in method A. The product was extd with CH<sub>2</sub>Cl<sub>2</sub>, washed (NaOH, H<sub>2</sub>O), dried (Na<sub>2</sub>SO<sub>4</sub>), and evapd. Crystn from 2-methoxyethanol or DMF gave product contg solvent, difficult to remove. Recrystn from tetramethylurea (TMU) gave solvent-free material. <sup>d</sup> The crude product from a 0.36-mole run was refluxed for 2.5 hr with 8 l. of MeOH, 670 ml of H<sub>2</sub>O, and 300 ml of concd HCl. A solid insol in the mixt was recrystd from 2-methoxyethanol giving white solid which was suprisingly found to be the di-*p*-nitrobenzoyl compd: ir (Nujol mull) 1720, 1705 (C==O), 1600, 1525, 1335, 1235, 835 cm<sup>-1</sup> etc., no NH/OH peaks; nmr (DMSO-d<sub>6</sub>) only aromatic H's between  $\delta$  4.3 and 5.6 integrating for 3 on pyridine and 8 on benzene.

(s,  $CH_3$  on pyridine ring) 7.78, 7.87 (two s's, 18,  $OCH_3$ ), and between 7.05 and 8.50 (m's 7, aromatic H); mass spec, mol wt, caled 496.5, found 496.

2-(3,4,5-Trimethoxybenzamido)-3-picoline (19) (Method D).— A soln of 20 g (0.04 mole) of 77 in 500 ml of EtOH, 450 ml of water, and 50 ml of concd HCl was refluxed for 1 hr and evapd *in vacuo* at 50° to a small vol. The residue was dild with ice water, strongly acidified with HCl, and extd twice with Et<sub>2</sub>O. The aq soln was adjusted to pH 8 yielding 11.2 g (92%) of white solid, mp 157–158°. This was recrystd from *i*-PrOH giving 10 g of white cryst, mp 157.5–159°.

**2-**(*p*-Aminobenzamido)-5-chloropyridine (31).—A mixt of 50 g (0.18 mole) of **30** and 300 ml of MeOH was hydrogenated with 5 g of 5% Pt/C and sulfided<sup>11</sup> at 41 kg/cm<sup>2</sup> and 145°. The product was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, filtd from catalyst, and evapd *in vacuo*. The residue was cryst from EtOH yielding 12.3 g (28%) of tan cryst, mp 191.5–193°.

Attempts to carry out this reduction with Pd/C (method B) yielded only the Cl-free product 2.

**3-**(p-Aminobenzamido)pyridine ·HCl (39).--A soln of 24.0 g (0.113 mole) of 37 in 225 ml of 4% aq HCl was dild with 1.8 l. of *i*-PrOH yielding 25.6 g (78%) of fluffy white cryst of mono-hydrochloride, mp 244.5-245.5°.

**2,3,5,6-Tetramethyl-***N***-4-pyridylbenzamide** ·HCl (47).—A soln of 14.3 g (0.08 mole) of 2,3,5,6-tetramethylbenzoic acid and 65 ml of SOCl<sub>2</sub> in 100 ml of PhH was refluxed for 3.5 hr and evapd to dryness *in vacuo*. This crude acid chloride in 50 ml of PhH was added to a soln (9.4 g, 0.1 mole) of 4-aminopyridine and 13.8 ml (0.1 mole) of Et<sub>3</sub>N in 100 ml of THF. After refluxing 1.5 hr and standing overnight, water, PhH, and a little AcOH were added, and the mixt was concd *in vacuo*. The solid was collected, dried, dissolved in 150 ml of MeOH and 75 ml of water at the boiling point, acidified with a few drops of aq HCl, filtd, and concd to 125 ml. On cooling 14.9 g (64%) of white solid was obtained, mp 285–312° dec.

2-(*p*-Aminobenzamido)benzimidazole (55).—This was prepd from 14.2 g (0.05 mole) of 53 by method B, but much of the product sepd as a solid in the reaction mixt. This was filtd and the soln neutralized. The resulting free base was recrystd from 50% methoxyethanol in MeOH giving 1.6 g (10%) of cryst, mp  $275-277^{\circ}$ . **Dihydrochloride** (56).—The solid (55) was extd from the catalyst with DMF and the soln was evapd *in vacuo*. The resulting solid free base in MeOH was converted to the hydrochloride with an excess of ethanolic HCl yielding 9.75 g (60%) of tan solid which did not melt up to 360°. The total yield (base and hydrochloride) was 70%.

N-(2,3,5,6-Tetramethylbenzoyl)adenine (64) and 7- and/or 9-(2,3,5,6-Tetramethylbenzoyl)adenine (65).—A soln of 14.3 g (0.08 mole) of 2,3,5,6-tetramethylbenzoic acid in 50 ml of SOCl<sub>2</sub> and 50 ml of PhH was refluxed for 2 hr and evapd in vacuo. The crude acid chloride was dissolved in 50 ml of PhH and added to a suspension of 10.8 g of adenine in 80 ml of dry pyridine. After stirring on a steam bath for 3 hr, the soln was evapd in vacuo. The residual solid was pulvarized and stirred on a steam bath for 0.5 hr with 200 ml of 5% NaHCO<sub>3</sub>. The crude solid was collected, washed  $(H_2O)$ , dried, and crystd from 600 ml of xylene giving 16.9 g of tan solid. This was boiled with 1 l. of MeOH and filtd from 2.1 g of solid (see below). The MeOH soln was evapd to dryness, and the residue was recrystd from 600 ml of xylene yielding 12.2 g (52%) of 64: mp 187-189°; tlc (on SiO<sub>2</sub> developed with 5% MeOH in CHCl<sub>3</sub>) showed only one spot; ir (Nujol mull) 3360, 3310, 3240, 3150 (NH), 1710, 1685 (CO, C=N), and 1290 cm<sup>-1</sup> (CN or C=C); nmr (CDCl<sub>3</sub>)  $\delta$  2.10 (s, 6,  $CH_3$ ), 2.27 (s, 6,  $CH_3$ ), 6.33 (exchangeable with  $D_2O$ , broad s, 2, NH's), 7.12, 7.91, 8.50 (s's, 1 each, arom H's).

The above solid, insol in MeOH, was recrystd from 40 ml of 2methoxyethanol giving 1.5 g of 65: mp 260.5-363.5°; tlc (on SiO<sub>2</sub> developed with 5% MeOH in CHCl<sub>3</sub>) showed only one spot; ir 3480, 3430, 3300, 3280, 3230, 3140, 3130 (NH), 1750, 1720 (C=O), 1640 cm<sup>-1</sup> (CO, C=N or C=C); nmr (DMF- $d_7$ )  $\delta$ 2.11 (d, 6, J = 5 Hz, CH<sub>3</sub>), 2.28 (d, 6, J = 2 Hz, CH<sub>3</sub>), 7.22, 8.10, and 8.41 (d's, 3 arom H's), 7.47 and 7.70 (broad s's, 2, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>). Mass spec mol wt, calcd 295.35; found 295.

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