Journal of Medicinal Chemistry, 1971, Vol. 14, No. 10 **963**

Antiulcer Agents. *p*-Aminobenzamido Aromatic Compounds[1]

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

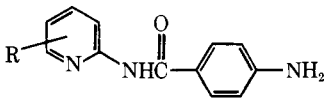
Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001

Received April 26, 1971

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*-Aminobenzanilide 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_2 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[2] 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.[3]



I

6, R = 3-CH_3
2, R = H

The most active was **6**. This is related to the weak antibacterial "carbopyridin"[4] (**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_2 group. However, the structures (**52**, **54**, **57**, **59**, **62**, **64**) are formulated in Table II on the basis of analogy with the literature.[5-9]

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[10]

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 $CHCl_3$ was added 8.7 g (0.0806 mole) of

(1) Presented in part at the Great Lakes Reginal American Chemical Society Meeting, DeKalb, Ill., June 6, 1969.

(2) A. Robert, J. I. Northam, J. E. Nezamis, and J. P. Phillips, *Amer. J. Dig. Dis.*, **15**, 497 (1970).

(3) A. Robert and L. L. Skaletzky, U. S. Patent 3,418,329 (1968); Netherlands Application 6614884; *Chem. Abstr.*, **68**, 59446 (1968).

(4) R. Kuhn, E. F. Möller, G. Wendt, and H. Beinert, *Chem. Ber.*, **75**, 711 (1952).

(5) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, **115**, 217 (1919).

(6) P. N. Craig and J. R. Hoover, U. S. Patent 3,336,191 (1967); *Chem. Abstr.*, **68**, 59585 (1968).

(7) G. Cipens and V. Grinsteins, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 263 (1962); *Chem. Abstr.*, **59**, 12790*f* (1963).

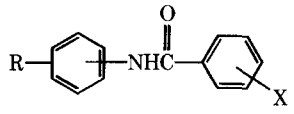
(8) V. P. Schipanov, S. L. Portnova, V. A. Krasnova, Yu. N. Shlivker, and I. Ya. Postoviskii, *Zh. Org. Khim.*, **1**, 2236 (1965); *Chem. Abstr.*, **64**, 11056*d* (1966).

(9) M. W. Bullock, J. J. Hand, and E. L. R. Stokstad, *J. Org. Chem.*, **22**, 568 (1957).

(10) 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 ±0.4% of theor.

TABLE I

BENZAMIDOPYRIDINES



No.	Position of NHCO on pyridine ring	R	X	Method of prepn	Cryst solvent	Yield, %[a]	Mp,[b] °C	Empricial formula	Analyses	LD_{50},[c] mg/kg	CNS depression,[c] mg/kg	Antiulcer activity, ED_{50}, mg/kg[d]
1	2	H	4-NO_2[e]	A	*n*-BuOH	60	239–241	$C_{12}H_9N_3O_3$		>1000	300	
2	2	H	4-NH_2[e]	B	EtOH	80	155–156	$C_{12}H_{11}N_3O$	C, H, N	650	1000	50
3	2	H	4-NH_2·2HCl[e]	C	MeOH	93	>310	$C_{12}H_{13}Cl_2N_3O$		650	—	
4	2	H	4-$NHCOCH_3$	*f*	DMF–H_2O	81	203–204	$C_{14}H_{13}N_3O_2$	C, H, N	>1000	100	
5	2	3-CH_3	4-NO_2	A[f]	AcOH–H_2O	75	196–197	$C_{13}H_{11}N_3O_3$	C, H, N	>1000	—	—
6	2	3-CH_3	4-NH_2	B[f]		48	177–179	$C_{13}H_{13}N_3O$	C, H, N	562	300	35
7	2	3-CH_3	4-NH_2·2HCl	C[f]	MeOH	94	>340 dec	$C_{13}H_{15}Cl_2N_3O$	C, H, Cl, N	562	100	35
8	2	3-CH_3	4-NH_2·maleate	*f*	EtOH	75	134–135.5	$C_{17}H_{17}N_3O_5$	C, H, N			55
9	2	3-CH_3	4-$NHCOCH_3$ ·2H_2O[g]	*f*	EtOH–BuOH–H_2O	65	206	$C_{15}H_{17}N_3O_3$·2H_2O	C, H, N	>1000	—	—
10	2	3-CH_3	4-$N(CH_3)_2$	*f*	*i*-PrOH	77	182–185	$C_{15}H_{17}N_3O$	C, H, N	>1000	300	75
11	2	3-CH_3, (CH_3NCO[h])	4-NO_2	A[i]	EtOH	66	125.5–127	$C_{14}H_{13}N_3O_3$	C, H, N	>1000	100	—
12	2	3-CH_3, (CH_3NCO[h])	4-NH_2	B	EtCOMe	46	170–171.5	$C_{14}H_{15}N_3O$	C, H, N	562	100	—
13	2	3-CH_3	3-NO_2	A[j]	$CHCl_3$–hexane	7.4	166–168	$C_{13}H_{11}N_3O_3$	C, H, N	>1000	—	
14	2	3-CH_3	3-NH_2	B	*i*-PrOH	53	177–179	$C_{13}H_{13}N_3O$	C, H, N			60
15	2	3-CH_3	2-NH_2	*f*	$CHCl_3$–hexane	32	147–149	$C_{13}H_{13}N_3O$	C, H, N	562	100	90
16	2	3-CH_3	H	*f*	PhH–hexane	56	128.5–129.5	$C_{13}H_{12}N_2O$	C, H, N	562	30	50
17	2	3-CH_3	4-CH_3	D	PhH–hexane	71	145.5–146	$C_{14}H_{14}N_2O$	C, H, N	562	300	60
18	2	3-CH_3	4-Cl	D	EtOH–H_2O	76	181–182	$C_{13}H_{11}ClN_2O$	C, H, Cl, N	750	300	—
19	2	3-CH_3	3,4,5-$(OCH_3)_3$	D[f]	*i*-PrOH	92	157.5–159	$C_{16}H_{18}N_2O_4$	C, H, N	562	1000	—
20	2	4-CH_3	4-NO_2	A	AcOH	75	191–192	$C_{13}H_{11}N_3O_3$	C, H, N			—
21	2	4-CH_3	4-NH_2	B[k]	95% EtOH	55	144–145	$C_{13}H_{13}N_3O$	C, H, N	300	300	40 (toxic)
22	2	5-CH_3	4-NO_2	A	EtOH	80	179–180	$C_{13}H_{11}N_3O_3$	C, H, N	>1000	—	
23	2	5-CH_3	4-NH_2	B	$CHCl_3$–hexane	79	167–168	$C_{13}H_{13}N_3O$	C, H, N	562	100	35
24	2	6-CH_3	4-NO_2	A	EtOH	54	133–136	$C_{13}H_{11}N_3O_3$	C, H, N	422	—	
25	2	6-CH_3	4-NH_2	B	DMF–H_2O	80	173–174	$C_{13}H_{13}N_3O$	C, H, N	178	30	75
26	2	4,6-$(CH_3)_2$	4-NO_2	A	EtOAc	62	159.5–161	$C_{14}H_{13}N_3O_3$	C, H, N	>1000	—	—
27	2	4,6-$(CH_3)_2$	4-NH_2	B	95% EtOH	82	184–185.5	$C_{14}H_{15}N_3O$	C, H, N	711	300	50
28	2	5,6-$(CH_3)_2$	4-NO_2	A	95% EtOH	28	161.5–162.5	$C_{14}H_{13}N_3O_3$	C, H, N			—
29	2	5,6-$(CH_3)_2$	4-NH_2	B	EtOH	87	149.5–151	$C_{14}H_{15}N_3O$	C, H, N	750	—	50
30	2	5-Cl	4-NO_2	A	EtCOMe	79	233–234	$C_{12}H_8ClN_3O_3$	C, H, Cl, N	>1000	—	
31	2	5-Cl	4-NH_2	*f*	EtOH	28	191.5–193	$C_{12}H_{10}ClN_3O$	C, H, Cl, N	>1000	1000	50
32	2	3-COOH	4-NO_2	A	AcOH–H_2O	31	275–258	$C_{13}H_9N_3O_5$	C, H, N	562	—	
33	2	3-COOH	4-NH_2	B[l]	H_2O	42	280–281 dec	$C_{13}H_{11}N_3O_3$	C, H, N	56	100	—
34	2	6-$NHCOC_6H_4$-*p*-NO_2	4-NO_2	A[m]	AcOH	81	293–294	$C_{19}H_{13}N_5O_6$	C, H, N			—
35	2	6-$NHCOC_6H_8$-*p*-NH_2	4-NH_2	B[n]	Me_2CO–H_2O	50	250–253	$C_{19}H_{17}N_5O_2$·0.16H_2O[n]	C, H, N	>1000	300	
36	2	OCH_2CH_3	4-NO_2	D	*i*-PrOH	44	139.5–140.5	$C_{14}H_{13}N_3O_4$	C, H, N			—

37	3	H	4-NO_2	A	EtOH–MeOH	88	190.5–192	$C_{12}H_9N_3O_3$	C, H, N	422	—	—
38	3	H	4-NH_2	B	MeOH	86	209.5–211	$C_{12}H_{11}N_3O$	C, H, N			—
39	3	H	4-NH_2·HCl	*f*	H_2O–*i*-PrOH	78	244.5–245.5	$C_{12}H_{12}ClN_3O$	C, H, Cl, N	562	—	100
40	3	2,6-$(CH_3)_2$	4-NO_2	A	MeOH	75	205–206.5	$C_{14}H_{13}N_3O_3$	C, H, N	>1000	—	
41	3	2,6-$(CH_3)_2$	4-NH_2	B	MeOH	88	172.5–173.5	$C_{14}H_{15}N_3O$	C, H, N	562	300	80
42	4	H	4-NO_2	A	MeOH	44	244–245	$C_{12}H_9N_3O_3$	C, H, N	49	—	
43	4	H	4-NH_2	B	MeOH	68	256–257	$C_{12}H_{11}N_3O$	C, H, N			—
44	4	H	4-NH_2·2HCl	C	MeOH	97	>350	$C_{12}H_{13}Cl_2N_3O$	C, H, Cl, N	208	—	60
45	4	H	H[e]	A	H_2O	76	202–205	$C_{12}H_{10}N_2O$	N	12	—	*p*
46	4	H	4-CH_3	A	EtOAc	36	178.5–181	$C_{13}H_{12}N_2O$	C, H, N	18	—	*p*
47	4	H	2,3,5,6-$(CH_3)_4$	*f*	MeOH–H_2O	64	285–312 dec	$C_{16}H_{19}ClH_2O$	C, H, Cl, N	75	—	*p*
48	4	3-Me	4-NO_2	A	Me_2CO	79	166–168	$C_{13}H_{11}N_3O_3$	C, H, N	30	—	
49	4	3-Me	4-NH_2	B	EtOH	85	205–206.5	$C_{13}H_{13}N_3O$	C, H, N	10	—	*p*

[a] Yields are calcd on material melting not less than 2° below highest mp obtained. [b] See ref 10. [c] Lethality and CNS activity were detd ip in mice. For method see R. B. Moffett, A. R. Hanze, and P. H. Seay, *J. Med. Chem.*, **7**, 178 (1964), Table I, footnotes *a* and *b*. The lowest dose showing definite CNS depression is given. A (—) indicates no depression was observed. In some cases mild stimulation was observed. A blank indicates this compd was not tested. [d] The procedure for producing exertion ulcers in rats has been reported.[2] ED_{50} 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. [e] See ref 4. [f] Specific prepn given in Experimental Section. [g] Prepd in these laboratories by Mr. James E. Stafford. [h] Contains a Me group on the amide N. [i] The *p*-nitrobenzoyl chloride soln was added to the 2-(methylamino)-3-picoline in $CHCl_3$ and pyridine below 50° and stirred at room temp for 2 hr. [j] The crude product was chromatogd on SiO_2 and eluted with 5% MeOH in CH_2Cl_2. [k] Hydrogenation in *n*-BuOH. [l] The product of hydrogenation was insol in the reaction mixt. It was concd *in vacuo*, dissolved in 3 l. of H_2O, filtered hot from catalyst, and cooled. [m] Prepd from 2,6-diaminopyridine and an excess of *p*-nitrobenzoyl chloride. [n] Hydrogenation run in glacial AcOH with PtO_2 in place of Pd/C. The crystd and dried product was found by Karl Fischer anal. to contain 0.84% H_2O (equiv to 0.16 H_2O/mol). [o] E. Koenings, G. Kinne, and W. Weiss, *Chem. Ber.*, **57**, 1172 (1924). [p] Too toxic to test.

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_2O, 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/cm² and 25°. After filtn and evapn *in vacuo* at 50°, the product was dissolved in $CHCl_3$, washed (5% $NaHCO_3$, 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^{-1} (amide CO) and numerous arom bands; uv (EtOH) 296 and 218 mμ; and nmr (DMF-d_7) δ 2.27 (s, 3, CH_3), 9.95 (broad s, 1, CONH), 5.7 (broad s, 2, NH_2), 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_2O and 10 ml of AcOH was heated on a steam bath for 15 min, concd *in vacuo*, and dild with aq Na_2CO_3. The product was collected, washed (H_2O), and recrystd from DMF–H_2O, giving 2.9 g (81%) of solid, mp 203–204°.

4'-[(3-Methyl-2-pyridyl)carbamoyl]acetanilide·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 ($C_{15}H_{15}N_3O_2·2H_2O$): H_2O, 11.80; found H_2O, 11.74.

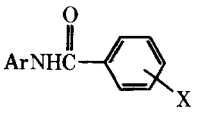
2-[*p*-(Dimethylamino)benzamido]-3-picoline (10).—A soln of 27.2 g (0.1 mole) of 6 in 200 ml of MeOH, 20 ml of AcOH, and 30 ml (0.37 mole) of 37% aq CH_2O was hydrogenated with 2 g of 30% Pd/C at 3.5 kg/cm² and 25°. The theor amt of H_2 was absorbed in 5 hr. After filt, the soln was evapd *in vacuo*, mixed with ice water, and adjusted to pH 8. The solid was collected, washed (aq $NaHCO_3$, H_2O), and dried, giving 23.4 g of nearly white solid, mp 176–182.5°. This was recrystd 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°.

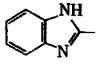
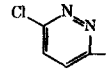
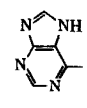
2-(*o*-Aminobenzamido)-3-picoline (15).—A soln of 33 g (0.3 mole) of 2-amino-3-picoline and 16.5 g (0.1 mole) of isatoic anhydride in 100 ml of DMF was heated under reflux for 1 hr, poured into ice water contg 10 g of Na_2CO_3, and extd with Et_2O. The Et_2O soln was extd with dil HCl, and the ext was basified with Na_2CO_3. The resulting oil was extd with Et_2O, washed (satd NaCl), and dried ($MgSO_4$). Evapn left an oil which was chromatogd on SiO_2 and eluted with 5% MeOH in CH_2Cl_2. The product solidified on trituration with Et_2O–hexane and was recrystd from $CHCl_3$–hexane, yielding 7.3 g (32%) of cryst, mp 147–149°.

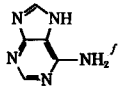
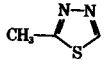
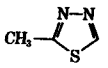
2-Benzamido-3-picoline (16).—A soln of 21.6 g (0.2 mole) of 2-amino-3-picoline and 22.6 g (0.1 mole) of Bz_2O in 500 ml of ether was allowed to stand at room temp for 24 hr and evapd to dryness *in vacuo*. The residue was dissolved in CH_2Cl_2, washed (10% Na_2CO_3, H_2O, satd NaCl), and dried ($MgSO_4$). Evapn left a gum which crystd on trituration with Et_2O–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_2O, aq Na_2CO_3, H_2O), 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^{-1} (C=O) and no NH/OH absorption; nmr ($CDCl_3$) δ 2.33

TABLE II

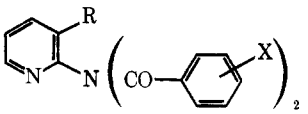


No.	Ar	X	Method of prepn	Crystn solvent	Yield, %[a]	Mp,[b] °C	Empirical formula	Analyses[b]	LD_{50},[c] mg/kg	CNS depression, mg/kg	Antiulcer activity[d] ED_{50}, mg/kg
50		4-NO_2	A	EtOH	55	193–194	$C_{16}H_{15}N_3O_3$	C, H, N	>1000	1000	
51		4-NH_2	B	EtOH–H_2O	61	228–229	$C_{16}H_{17}N_3O$	C, H, N	>1000	300	
52		4-NO_2	A	DMF	44	>360	$C_{10}H_8N_4O_3$	C, H, N	562		
53		4-NH_2	B	MeOEtOH[e]	74	275.5 dec	$C_{10}H_{10}N_4O$	C, H, N	422		60
54		4-NO_2	A	MeOEtOH[e]	44	309–311	$C_{14}H_{10}N_4O_3$	C, H, N	>1000		
55		4-NH_2	B[f]	MeOEtOH[e]–MeOH	10[f]	275–277	$C_{14}H_{12}N_4O$	C, H, N			
56		4-$NH_2 \cdot 2HCl$	*f*	MeOH	60[f]	>360	$C_{14}H_{14}Cl_2N_4O$	C, H, Cl, N	178	300	75
57		4-NO_2[g]	A	DMF	62	338–339	$C_9H_7N_5O_3$	C, H, N	>1000		
58		4-NH_2	B	DMF–MeOH	53	303–306 dec	$C_9H_9N_5O$	C, H, N	750	300	
59		4-NO_2[h]	A	DMF	85	273–273.5	$C_8H_6N_6O_3$	C, H, N	562		
60		4-NH_2	B	DMF–MeOH	82	298.5–299[i]	$C_8H_8N_6O$	C, H, N	178		
61		4-NO_2	A	MeOEtOH[e]	60	255 dec	$C_{11}H_7ClN_4O_3$	C, H, Cl, N	>1000	300	
62		4-NO_2	A	DMF	85	>360	$C_{12}H_8N_6O_3$	C, H, N	750	300	

63		4-NH_2	B[i]	EtOH	89	243–244.5	$C_{12}H_{10}N_6O$	C, H, N	>1000	300	50
64		2,3,5,6-$(CH_3)_4$	*f*	Xylene	52	187–189	$C_{16}H_{17}N_5O$	C, H, N	>1000	1000	
65		2,3,5,6-$(CH_3)_4$		MeOEtOH[e]	6.3	260.5–263.5	$C_{16}H_{17}N_5O$	C, H, N	>1000	100	
66		4-NO_2	A	DMF	57	346–348 dec	$C_{10}H_8N_4O_3S$	C, H, N, S	562		
67		4-NH_2	B[k]	*i*-PrOH	48	255–257	$C_{10}H_{10}N_4OS$	C, H, N, S	750		
68		4-NO_2	A	DMF–EtCOMe	82	294.5–296	$C_{14}H_9N_3O_3S$	C, H, N, S	>1000		
69		4-NH_2	B[k]	EtCOMe	66	199.5–201.5	$C_{11}H_{11}N_3OS$	C, H, N, S	316		
70	Ph	4-NH_2	*l*			238–241[m]	$C_{13}H_{12}N_2O$		422	100	40[n]
71	*o*-$CH_3C_6H_4$	4-NO_2	A[o]	EtOH		161–162[o]	$C_{14}H_{12}N_2O_3$	N	>1000	300	
72	*o*-$CH_3C_6H_4$	4-NO_2	B[p]	$CHCl_3$–hexane		155–156[p]	$C_{14}H_{14}N_2O$	N	104	30	[q]
73	Ph	3-NH_2	*l*			122–124[r]	$C_{13}H_{12}N_2O$		750	100	
74	Ph	2-NH_2	B[s]	Ph	91	116–118[s]	$C_{13}H_{12}N_2O$	C, H, N	1000	300	
81	Atropine sulfate						$C_{17}H_{25}NO_7S$		316	100	1.0
82	Sodium phenobarbital						$C_{12}H_{11}N_2NaO_3$		200	100	50[t]
83	Chlorpromazine·HCl						$C_{16}H_{15}Cl_2N_3O$		150	20	1.5[t]
84	Chlordiazepoxide·HCl						$C_{17}H_{20}Cl_2N_2S$		200	50	20[t]
85	Meprobamate						$C_9H_{18}N_2O_4$		600	200	100

[a] See footnote *a*, Table I. [b] See ref 10. [c] See footnote *c*, Table I. [d] See footnote *d*, Table I. [e] 2-Methoxyethanol. [f] See Experimental Section. [g] Cipens, *et al.*,[7] report mp 337°. [h] Shchipanov, *et al.*,[8] report mp 273–274° dec. [i] Various fractions from DMF–MeOH had dec points from 294 to 299° all had identical ir spectra. [j] Hydrogenated in 2-methoxyethanol; 3.5 days were required to complete reaction. [k] 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. [l] Obtained from K and K Labs. Inc., Plainview, N. Y. [m] G. Lochemann and T. Lobenstein, *Chem. Ber.*, **75,** 1911 (1942), report mp 137–138°. [n] This compd showed good ulcer preventing activity but produced splenomegaly as a side effect. [o] R. Adams and L. M. Werbel, *J. Amer. Chem. Soc.*, **80,** 5799 (1958), report mp 160–161.5°. [p] G. Lockemann and H. Kügler, *Chem. Ber.*, **80,** 479 (1947), report mp 152–153°. [q] Too toxic to test. [r] A. Piutti, *Chem. Ber.*, **16,** 1319 (1883). [s] Prepd by Dr. R. S. Hsi in these laboratories by method B in EtOH with PtO_2 catalyst. The lit. shows a wide discrepancy in reports of mp. See Shah, *J. Indian Inst. Sci.*, **7,** 207 (1920); *Beilstein* II, **14,** 210. [t] Administered sc in this test.

TABLE III



No.	R	X	Crystn solvent	Yield, %[a]	Mp,[b] °C	Empirical formula	Analyses[b]
75	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	27	218–220	$C_{20}H_{14}Cl_2N_2O_2$	C, H, Cl, N
77	CH_3	3,4,5-$(OCH_3)_3$	*i*-PrOH	77[d]	158–160.5	$C_{26}H_{26}N_2O_8$	C, H, N
78	CH_3	4-$N(CH_3)_2$	TMU[e]	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	$C_{21}H_{16}N_4O_7$	C, H, N
80	NO_2	4-NO_2	MeOEtOH[f]	18	213.5–214.5	$C_{19}H_{11}N_5O_8$	C, H, N

[a] See footnote *a*, Table I. All compds in Table III were prepd essentially by method A except as noted. [b] See ref 10. [c] The crude product was dissolved in $CHCl_3$, washed (aq Na_2CO_3, H_2O), and dried ($MgSO_4$). After filtration and evapn the product was crystd from the solvent indicated. [d] Prepn specifically described in the Experimental Section. [e] *p*-Dimethylaminobenzoyl chloride·HCl was made from the corresponding acid and $SOCl_2$ and was used without purification as in method A. The product was extd with CH_2Cl_2, washed (NaOH, H_2O), dried (Na_2SO_4), and evapd. Crystn from 2-methoxyethanol or DMF gave product contg solvent, difficult to remove. Recrystn from tetramethylurea (TMU) gave solvent-free material. [f] The crude product from a 0.36-mole run was refluxed for 2.5 hr with 8 l. of MeOH, 670 ml of H_2O, 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^{-1} etc., no NH/OH peaks; nmr (DMSO-d_6) only aromatic H's between δ 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, calcd 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_2O. 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[11] at 41 kg/cm² and 145°. The product was dissolved in CH_2Cl_2, 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 monohydrochloride, 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 $SOCl_2$ 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_3N 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°.

(11) From Engelhard Industries, Inc., Newark, N. J.

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 $SOCl_2$ 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% $NaHCO_3$. 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_2 developed with 5% MeOH in $CHCl_3$) showed only one spot; ir (Nujol mull) 3360, 3310, 3240, 3150 (NH), 1710, 1685 (CO, C=N), and 1290 cm^{-1} (CN or C=C); nmr ($CDCl_3$) δ 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 2-methoxyethanol giving 1.5 g of **65**: mp 260.5–363.5°; tlc (on SiO_2 developed with 5% MeOH in $CHCl_3$) showed only one spot; ir 3480, 3430, 3300, 3280, 3230, 3140, 3130 (NH), 1750, 1720 (C=O), 1640 cm^{-1} (CO, C=N or C=C); nmr (DMF-d_7) δ 2.11 (d, 6, J = 5 Hz, CH_3), 2.28 (d, 6, J = 2 Hz, CH_3), 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_2O, NH_2). Mass spec mol wt, calcd 295.35; found 295.

Acknowledgments.—The authors wish to thank the following people who contributed to this work: our Department of Physical and Analytical Chemistry for analytical and spectral data; Mr. Wm. Veldkamp for lethality and CNS data; Mr. R. F. Tripp, Mr. J. P. Phillips, and Mr. J. E. Nezamis for technical assistance.