performing the tissue culture experiments. This investigation was supported by Grant No. CA 16623 and Career Development Award CA 2525A from the National Cancer Institute, Department of Health, Education and Welfare.

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Aminobenzoic Acid Diuretics. 9.[1] 3,4-Disubstituted 5-Acylaminobenzoic Acids and Related Compounds

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A number of 3,4-disubstituted 5-acylamino-, 5-alkylamino-, and 5-ureidobenzoic acids corresponding to previously described 3,4-disubstituted 5-sulfamoylbenzoic acid diuretics were prepared and screened for their diuretic properties in dogs. The tabulated results reveal that several 3,4-disubstituted 5-formamido and 5-acetamidobenzoic acids possess considerable diuretic potency demonstrating that a 5-sulfamoyl or 5-methylsulfonyl substituent is not a necessity for potent diuretic activity of 3,4-disubstituted benzoic acids. 4-Benzoyl-3-benzyloxy-5-formamidobenzoic acid, one of the most potent compounds of the present series, is approximately one-tenth as potent as bumetanide. The dose response and diuretic pattern indicate high-ceiling diuretic activity and suggest a mode of action similar to that of bumetanide.

In the preceding paper[1] of this series we reported that substitution of the sulfamoyl group by the sterically similar methylsulfonyl group in various 3,4-disubstituted 5-sulfamoylbenzoic acid diuretics resulted in diuretically active compounds. Furthermore, we observed that the 5-methylthio and the 5-methylsulfinyl analogues of the highly active 3-benzylamino-4-phenoxy-5-methylsulfonylbenzoic acid still exhibit significant diuretic activity. In continuation of our investigation dealing with potential substitutes for the sulfamoyl group in benzoic acid diuretics, the present paper deals with the synthesis and diuretic properties of several 3,4-disubstituted benzoic acids carrying an acylamino, a ureido, or an alkylamino substituent in the 5 position.

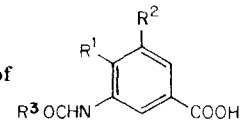
Chemistry. The 3,4-disubstituted 5-acylaminobenzoic acids **26**, **27**, **31–46**, and **48–53** (Table I) were provided by acylation of the corresponding aminobenzoic acids **10–25** (Scheme I). 4-Benzoyl-3-benzyloxy-5-(α-dimethylaminoacetamido)benzoic acid (**47**, Table I) was prepared from the 5-(α-chloroacetamido)benzoic acid **44**. The 5-ureidobenzoic acids **28–30** were obtained from the corresponding aminobenzoic acid **10** by reaction with isocyanic acid or alkyl isocyanate. The latter reaction performed with 5-amino-4-benzoyl-3-benzyloxybenzoic acid (**19**) resulted in the 7-carboxy-2(3*H*)-quinazolinone derivatives **54–57** (Scheme I, Table II) by in situ cyclodehydration of the N′-unsubstituted and N′-alkylated 4-benzoyl-3-benzyloxy-5-ureidobenzoic acids. The starting aminobenzoic acids **10–25** have been described as intermediates in the synthesis of the corresponding 3,4-disubstituted 5-sulfamoylbenzoic acid diuretics[2,3] or have been made available as outlined in Scheme I.

The early finding that **41** possesses potent diuretic activity prompted the preparation of the corresponding 5-*N*-alkylformamido- and 5-monoalkylaminobenzoic acids **60–63** (Table III) as shown in Scheme II. Methylation of the 5-aminobenzoic acid **19** and subsequent saponification resulted in 5-dimethylamino-4-benzoyl-3-benzyloxybenzoic acid (**64**).

Diuretic Effect and Structure–Activity Relationship. The title compounds were screened for their diuretic properties in dogs. For the 3,4-disubstituted 5-acylamino- and 5-ureidobenzoic acids **26–53**, the results are presented in Table I and compared with those of 3-*n*-butylamino-4-phenoxy-5-sulfamoylbenzoic acid (bumetanide) and 4-benzoyl-3-benzyloxy-5-sulfamoylbenzoic acid. The urinary volume and electrolyte excretion reveal that many compounds of this series exhibit considerable diuretic activity and demonstrate that the highest potency is obtained within the 3-substituted 5-formamido- and 5-acetamido-4-benzoylbenzoic acids. For 4-benzoyl-3-benzyloxy-5-formamidobenzoic acid (**41**), one of the most potent compounds, the level of potency after intravenous application is approximately one-tenth that of bumetanide. The onset of diuresis was observed within the first hour after injection and became, except for higher dosage, negligible after 3 h. The dose response and diuretic pattern of **41** indicate high-ceiling diuretic activity and suggest that substitution of the sulfamoyl group by the formamido group in 3,4-disubstituted 5-sulfamoylbenzoic acids may not influence the mode of diuretic action.

With **41**, several variants of the 5-substituent were investigated (**42–47**, Table I; **60–64**, Table III). Except for the 5-acetamidobenzoic acid **42**, exchange of the form-

Table I. Physical Properties and Diuretic and Saluretic Activity of

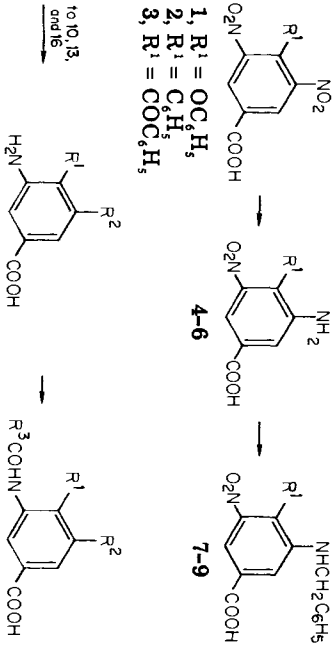


No.	R¹	R²	R³	Method[b]	Mp, °C	Recrystn solvent[c]	Yield,[d] %	Formula[e]	Treatment,[f] mg/kg	Urinary excretion[a] mL/kg of H_2O	mequiv/kg Na^+	mequiv/kg K^+	mequiv/kg Cl^-
26	OC_6H_5	$NHCH_2C_6H_5$	H	E	224–226	EtOH	21	$C_{21}H_{18}N_2O_4$[g]	1	8	1.3	0.26	1.3
									0.25	9	1.1	0.23	1.5
27	OC_6H_5	$NHCH_2C_6H_5$	Me	F	235–236	EtOH	35	$C_{22}H_{20}N_2O_4$[g]	10	27	2.8	0.8	3.8
									1	11	1.4	0.55	2.1
28	OC_6H_5	$NHCH_2C_6H_5$	NH_2	G	213–214	EtOH	31	$C_{21}H_{19}N_3O_4$	1	13	1.3	0.33	1.7
29	OC_6H_5	$NHCH_2C_6H_5$	NHMe	H	220–222	EtOH	44	$C_{22}H_{21}N_3O_4$[g]	1	8	0.7	0.2‡	1.1
30	OC_6H_5	$NHCH_2C_6H_5$	NH-*n*-Pr	H	210–211	Me_2CO–petr ether	11	$C_{24}H_{25}N_3O_4$	10	11	1.1	0.4	1.9
									1	4	0.4	0.12‡	0.3
31	OC_6H_5	$SCH_2C_6H_5$	H	E	194–195	Aq EtOH	42	$C_{21}H_{17}NO_4S$[h]	1	As control			
32	OC_6H_5	$SCH_2CCHCHSCH$	H	E	188–189	Me_2CO–H_2O	32	$C_{19}H_{15}NO_4S_2$[g,h]	1	11	1.3	0.45	1.9
33	C_6H_5	$NHCH_2C_6H_5$	H	E	195–197	Aq EtOH	41	$C_{21}H_{18}N_2O_3$[i]	1	12	1.6	0.43	1.7
34	C_6H_5	$OCH_2C_6H_5$	H	E	200	Aq EtOH	15	$C_{21}H_{17}NO_4$	1	12	1.3	0.39	1.6
35	C_6H_5	$OCH_2C_6H_5$	Me	F	188–189	Aq EtOH	12	$C_{22}H_{19}NO_4 \cdot 0.5H_2O$[i]	1	8	1.0	0.22	1.1
36	C_6H_5	$SCH_2C_6H_5$	H	E	102–104	HCOOH	22	$C_{21}H_{17}NO_3S \cdot 0.25H_2O$[j]	1	As control			
37	COC_6H_5	$NHCH_2C_6H_5$	Me	F	196–198	Aq EtOH	70	$C_{23}H_{20}N_2O_4 \cdot 0.25H_2O$	10	22	1.7	0.58	2.2
									1	6	0.4	0.21‡	0.4
38	COC_6H_5	O-*n*-Pr	H	E	144–145	Aq EtOH	41	$C_{18}H_{17}NO_5$	1	10	2.0	0.52	1.2
39	COC_6H_5	O-*n*-Bu	H	E	180–183	EtOH	49	$C_{19}H_{19}NO_5$[k]	1	17	2.1	0.49	2.6
									0.1 po	6	0.5	0.18‡	0.8
40	COC_6H_5	O-*n*-Bu	Me	F	177–178	Aq EtOH	28	$C_{20}H_{21}NO_5$[k]	1	18	2.1	0.53	2.5
41	COC_6H_5	$OCH_2C_6H_5$	H	E	212–213	EtOH	46	$C_{22}H_{17}NO_5$[k]	5	32[l] ± 11.6	3.7[l] ± 0.94	0.83[l] ± 0.07	4.5[l] ± 1.27
									5 po	21[l] ± 2.1	2.2[l] ± 0.44	0.63[l,‡] ± 0.20	2.9[l] ± 0.78
									5 po[m]	33[l] ± 7.5	3.1[l] ± 0.7	1.09[l] ± 0.16	4.5[l] ± 0.19
									1	22[l] ± 5.9	2.5[l] ± 0.73	0.49[l] ± 0.15	3.1[l] ± 0.83
									1 po	9[l,‡] ± 6.7	1.1[l,‡] ± 0.83	0.23[l,‡] ± 0.10	1.4[l,‡] ± 1.03
									1 po[m]	21[l] ± 1.4	2.5[l] ± 0.41	0.51[l] ± 0.14	3.3[l] ± 0.69
									0.25	18[l] ± 5.5	2.1[l] ± 0.63	0.41[l] ± 0.01	2.6[l] ± 0.78
									0.1	9[l] ± 0.9	1.0[l] ± 0.12	0.24[l,‡] ± 0.05	1.3[l] ± 0.17
42	COC_6H_5	$OCH_2C_6H_5$	Me	F	223–224	EtOH	33	$C_{23}H_{19}NO_5$[k]	1	14	1.3	0.45	3.0
									1 po	14	1.8	0.29	2.2
43	COC_6H_5	$OCH_2C_6H_5$	CF_3	I	231	Aq EtOH	23	$C_{23}H_{16}F_3NO_5$[k]	1	As control			
44	COC_6H_5	$OCH_2C_6H_5$	CH_2Cl	I	214–216	EtOH	32	$C_{23}H_{18}ClNO_5$[k]	1	As control			
45	COC_6H_5	$OCH_2C_6H_5$	Et	I	172–174	EtOH	28	$C_{24}H_{21}NO_5 \cdot C_2H_5OH$[k]	1	7	0.6	0.2‡	0.9
46	COC_6H_5	$OCH_2C_6H_5$	C_6H_5	J	180–182	MeCN	53	$C_{28}H_{21}NO_5 \cdot H_2O$[k]	1	As control			
									1 po				
47	COC_6H_5	$OCH_2C_6H_5$	$CH_2N(Me)_2$	K	264–266	Methyl cellosolve	35	$C_{25}H_{24}N_2O_5 \cdot HCl$[n]	1	As control			
									1 po				
48	COC_6H_5	$OCH_2CCHCHSCH$	H	E	206–208	*o*	24	$C_{20}H_{15}NO_5S$[k]	1	26	3.1	0.64	4.1
									0.25	17	2.2	0.49	2.8
49	COC_6H_5	S-*n*-Pr	H	E	168–170	Aq EtOH	65	$C_{18}H_{17}NO_4S$	1	8	1.0	0.42	1.2
50	COC_6H_5	$SCH_2CH=CH_2$	H	E	182–184	Aq EtOH	58	$C_{18}H_{15}NO_4S$[k]	1	As control			

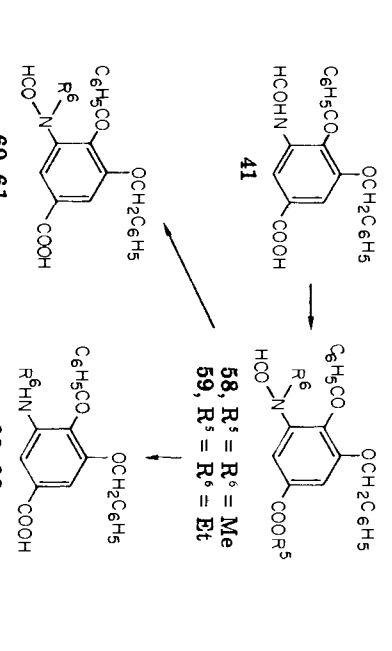
51	COC_6H_5	S-*n*-Bu	H	E	155–156	Aq EtOH	61	$C_{19}H_{19}NO_4S$	1 po	21	2.3	0.65	2.1
									0.25 po	7	0.5	0.28	0.6
52	COC_6H_5	S-*i*-Am	H	E	150–151	Aq EtOH	27	$C_{20}H_{21}NO_4S$[k]	1	15	1.6	0.39	1.9
53	COC_6H_5	$SCH_2C_6H_5$	H	E	168–170	Aq EtOH	65	$C_{22}H_{17}NO_4S$	1 po	26	2.8	0.27	3.5
									0.25 po	10	0.5	0.10[‡]	0.7
4-Benzoyl-3-benzyloxy-5-sulfamoylbenzoic acid[n]									0.25 po	33	3.6	0.89	4.4
									0.1	12	1.0	0.42	2.0
3-*n*-Butylamino-4-phenoxy-5-sulfamoylbenzoic acid (bumetanide)[q]									0.25	39[r] ± 12	4.0[r] ± 1.4	0.84[r] ± 0.38	5.7[r] ± 0.61
									0.1	26[r] ± 8.3	2.4[r] ± 0.4	0.44[r] ± 0.11	3.5[r] ± 0.8
									0.1 po	31[r] ± 7.6	3.3[r] ± 0.9	0.49[r] ± 0.16	4.5[r] ± 1.4
									0.01	10[r] ± 4.8	0.92[r] ± 0.42	0.27[r] ± 0.05	1.4[r] ± 0.5
Control (3 h)										0.93[l] ± 0.35	0.10[l] ± 0.02	0.16[l] ± 0.01	0.08[l] ± 0.02
(6 h)										1.73[l] ± 0.46	0.27[l] ± 0.09	0.24[l] ± 0.03	0.17[l] ± 0.09

[a] For procedure see the Experimental Section; when not otherwise stated, values of a single test are given for a 3-h test period. Values not significantly different from controls (one side 95% confidence limits) are marked with ‡. Where three or more tests were performed, the average ± SD is given. Concrete conclusions should not be drawn from the data presented because most of the data are based on single animal experiments where the urine flow rate and electrolyte excretion rate are not stated for each animal prior to drug administration. [b] The letters relate to the general procedures given in the Experimental Section. [c] Several recrystallizations were usually performed, if necessary, while treating with decolorizing carbon. [d] The yield of analytically pure compounds is given. No attempts were made to optimize the yields. [e] The compounds were analyzed for C, H, N, and, if present, for Cl and S. Analytical results are within 0.4% of the theoretical values unless otherwise stated. [f] When not otherwise stated iv injection in NaOH solution. [g] Dried in vacuo (10–14 mm) at ambient temperature for several hours. [h] Not analyzed for S. [i] Dried in vacuo (10–14 mm) for several hours in the presence of P_2O_5. [j] Dried in vacuo (10–14 mm) for several hours in the presence of KOH. [k] Dried in air. [l] Average of three tests. [m] Values are for a 6-h test period. [n] Cl: calcd, 7.56; found, 7.06. [o] A mixture of EtOH (ten parts) and methyl cellosolve (one part) was used. [p] See ref 3. [q] See ref 4. [r] Average of four tests.

Scheme I

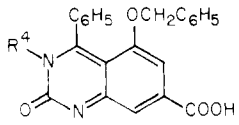


Scheme II



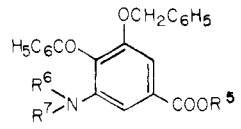
amido group by different acylamino or alkylamino groups abolished or at least drastically decreased the diuretic activity.

Unfortunately, 5-ureidobenzoic acids corresponding to **41** could not be made available due to spontaneous ring closure to the diuretically inactive quinazolinone derivatives **54–57** (Table II). It should, however, be noted that diuretic potency might be retained when the formamido group in 3-benzylamino-5-formamido-4-phenoxybenzoic acid (**26**) is replaced by the unsubstituted ureido group as shown with **28**. The results obtained with **29** and **30** might indicate that N′-alkylation in **28** decreased the potency.

Table II. Physical Properties of 

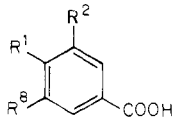
No.	R^4	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
54	H	P	280–282 dec	AcOH	14	$C_{22}H_{16}N_2O_4 \cdot 1.5AcOH$
55	Me	Q	210–212 dec	EtOH	54	$C_{23}H_{18}N_2O_4 \cdot 1.5EtOH$
56	*n*-Pr	Q	207–209 dec	*e*	34	$C_{25}H_{22}N_2O_4 \cdot EtOH$
57	*n*-Bu	Q	206–209 dec	EtOH	26	$C_{26}H_{24}N_2O_4 \cdot EtOH$[f]

[a] See footnoote *b* in Table I. [b] See footnote c in Table I. [c] See footnote *d* in Table I. [d] See footnote *e* in Table I. [e] A mixture of EtOH (ten parts) and methyl cellosolve (one part) was used. [f] C: calcd, 70.87; found, 70.27.

Table III. Physical Properties and Diuretic Activity of 

No.	R^5	R^6	R^7	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]	Diuretic act.[e] (iv, 1 mg/kg)
58	Me	Me	HCO	L	110–112	Aq EtOH	42	$C_{24}H_{21}NO_5$	
59	Et	Et	HCO	L	92–94	EtOH	59	$C_{26}H_{25}NO_5$	
60	H	Me	HCO	M	204–206	Aq EtOH	77	$C_{23}H_{19}NO_5$	Active[f]
61	H	Et	HCO	M	219–221	Aq EtOH	52	$C_{24}H_{21}NO_5$	Inactive
62	H	Me	H	N	183–185	EtOH	43	$C_{22}H_{19}NO_4$[g]	Inactive
63	H	Et	H	N	147–148	EtOH	36	$C_{23}H_{21}NO_4$	Inactive
64	H	Me	Me	O	192–194	EtOH	48	$C_{23}H_{21}NO_4$	Inactive

[a] See footnote *b* in Table I. [b] See footnote c in Table I. [c] See footnote *d* in Table I. [d] See footnote *e* in Table I. [e] For the procedure see footnote *a* in Table I. [f] In the 3-h test period the following parameters per kilogram were obtained: 10 mL of urine, 0.9 mequiv of Na^+, 0.21 mequiv of K^+, and 1.3 mequiv of Cl^-. For controls see Table I. [g] See footnote *i* in Table I.

Table IV. Physical Properties of 

No.	R^1	R^2	R^8	Method[a]	Mp, °C	Recrystn solvent[b]	Yield, %[c]	Formula[d]
4	OC_6H_5	NH_2	NO_2	A	233–235	Aq EtOH	33	$C_{13}H_{10}N_2O_5$[e]
7	OC_6H_5	$NHCH_2C_6H_5$	NO_2	B	193–195	Aq EtOH	41	$C_{20}H_{16}N_2O_5$[e]
8	C_6H_5	$NHCH_2C_6H_5$	NO_2	B	188–189	Aq EtOH	46	$C_{20}H_{16}N_2O_4$[f]
9	COC_6H_5	$NHCH_2C_6H_5$	NO_2	B	197–199	EtOH	47	$C_{21}H_{16}N_2O_5$[g]
10	OC_6H_5	$NHCH_2C_6H_5$	NH_2	C	186–188	Aq MeOH	45	$C_{20}H_{18}N_2O_3$[e]
13	C_6H_5	$NHCH_2C_6H_5$	NH_2	D	179–181	Aq EtOH	48	$C_{20}H_{18}N_2O_2 \cdot 0.25H_2O$[f]
16	COC_6H_5	$NHCH_2C_6H_5$	NH_2	D	192–194	EtOH	47	$C_{21}H_{18}N_2O_3$[g]

[a] See footnote *b* in Table I. [b] See footnote *c* in Table I. [c] See footnote *d* in Table I. [d] See footnote *e* in Table I. [e] Dried in vacuo (10–14 mm) at 80 °C for several hours. [f] See footnote *j* in Table I. [g] See footnote *k* in Table I.

With respect to the influence of the 3- and 4-substituent on potency, the presented data do not permit a precise statement to be made, although there appears to exist some degree of correspondence between the 5-formamido- and the corresponding 5-sulfamoylbenzoic acids previously reported.[2-4]

The present investigation demonstrates clearly that a sulfamoyl or methylsulfonyl group is not a necessity for potent diuretic activity of 3,4-disubstituted benzoic acids.

Experimental Section

For synthetic procedures technical assistance was given by Hanne Hollensen, T. Parbst, and W. Schlichtkrull. Analyses were performed by G. Cornali and W. Egger of these laboratories. Melting points were corrected and taken in open glass capillaries using a Hershberg apparatus. For the typical compounds NMR spectra were taken by N. Rastrup Andersen on a Varian A-60A spectrometer. Spectral features were in accordance with structures.

Diuretic Screening (Tables I and II). Female mongrel dogs weighing from 9 to 30 kg were used. About 16 h before the experiment the dogs were starved but had H_2O available always. The urine was taken by catheter hourly. The Na^+, K^+, and Cl^- were determined by flame photometry and potentiometric titration, respectively. The excretion of H_2O and the electrolytes during 2 h before dosage of the test compound served as control of the conditions.

4-R^1-3-R^2-5-Nitrobenzoic Acids 4 and 7–9 (Table IV). Method A. A stirred solution of 1 (200 g, 0.66 mol) in hot pyridine (300 mL) was diluted with H_2O (2 L). A solution of $Na_2S_2O_4$ (260 g, 1.3 mol, of material iodometricly titrated to contain 87%) in H_2O (2 L) was added dropwise during about 15 min while stirring. After continued stirring for 5 min, the mixture was filtered and the filtrate acidified to pH 2 with 4 N HCl. The mixture was left at ambient temperature for 4 h and at 5 °C for 16–18 h to precipitate crude 4.

Method B. 4, 3-amino-5-nitro-4-phenylbenzoic acid,[3] or 3-amino-4-benzoyl-5-nitrobenzoic acid[5] was benzylated using the process of ref 4, method 3A. The intermediate ethyl benzoates

were saponified with a mixture of 1 N NaOH and EtOH by refluxing for 30–60 min. Cooling and acidification with HCl precipitated crude **7–9**.

4-R[1]-5-Amino-3-benzylaminobenzoic Acids 10, 13, and 16 (Table IV). Method C. To a solution of $Na_2S_2O_4$ (16.1 g, 80 mmol) in H_2O (100 mL) NH_3 (55 mL, 25% in H_2O) was added followed by **7** (9.1 g, 25 mmol) in portions. After heating on a steam bath for 1 h, H_2O (100 mL) followed by 4 N HCl (100 mL) was added and the heating continued for 15 min. Cooling completed the precipitation of crude **10**.

Method D. **8** and **9** were reduced using a previously described procedure (see ref 5, method E), except that the heating following the acidification was omitted.

4-R[1]-3-R[2]-5-NHCOR[3]-Benzoic Acids 26–53 (Table I). Method E. A mixture of **10**, **11** and **12**,[2] **13**, **14** and **15**,[3] or **17–25**[3] and HCOOH (10–15 mL/g of starting amine) was heated on a steam bath for a few minutes followed by stirring at ambient temperature for 2.5–24 h. Cooling and/or dilution with H_2O precipitated the crude reaction product. For **26** the reaction mixture was evaporated in vacuo and crude **26** obtained on trituration with Et_2O.

Method F. A mixture of **10**, **14**,[3] **16**, **18**,[3] or **19**,[3] Ac_2O (1 mL/g of starting amine), and AcOH (5–10 mL/g of starting amine) was heated on a steam bath for 1–5 h. Dilution with H_2O precipitated the crude reaction product. Occasionally a larger amount of Ac_2O (5–10 mL/g of amine) was used, omitting the dilution with AcOH, and usually performing the reaction at ambient temperature.

Method G. A mixture of **10** (3.35 g, 10 mmol), KOCN (1.0 g, 12.3 mmol), and AcOH (50 mL) was stirred at ambient temperature for 5 h. Dilution with H_2O (250 mL) precipitated crude **28**. The purification was performed via the Na salt as described in ref 1, method K.

Method H. To a stirred solution of **10** (1.67 g, 5 mmol) in Me_2CO (25 mL) the appropriate alkyl isocyanate (5 mmol) was added, in case of MeNCO as a 5% solution in Me_2CO. Stirring at ambient temperature for a further 18–60 h and cooling precipitated crude **29** or **30**.

Method I. A mixture of **19**[3] (0.7 g, 2 mmol), the appropriate acyl chloride or anhydride (2.8–3 mmol), pyridine (0.5 mL), and $CHCl_3$ (7 mL) was refluxed for 2–4 h. In the case of **43** the mixture was left at ambient temperature for 60 h. Evaporation in vacuo and trituration with aqueous EtOH yielded crude **43–45**.

Method J. A mixture of **19**[3] (0.7 g, 2 mmol), C_6H_5COCl (0.42 g, 3 mmol), and saturated $NaHCO_3$ (7 mL) was heated on a steam bath for 3 h. After cooling, the precipitated Na salt of **46** was isolated and worked up as described in ref 1, method K.

Method K. A mixture of **44** (0.85 g, 2 mmol) and Me_2NH (10 mL, 20% in H_2O) was left at ambient temperature for 60 h. Evaporation in vacuo and treatment of the residue with concentrated HCl (5 mL) yielded, after cooling, crude **47** as its hydrochloride.

Alkyl 4-Benzoyl-3-benzyloxy-5-*N*-alkylformamidobenzoates 58–59 (Table III). Method L. To a stirred mixture of NaH (0.35 g, 50% in oil) and HMPA (12 mL), **41** (1.0 g, 2.7 mmol) was added in portions followed by the appropriate alkyl iodide (15–16 mmol). The mixture was stirred at ambient temperature for 20 h and crude **58–59** was precipitated on dilution with 0.25 N HCl (50 mL).

4-Benzoyl-3-benzyloxy-5-*N*-alkylformamidobenzoic Acids 60 and 61 (Table III). Method M. To a stirred mixture of **58** or **59** (1 mmol) and EtOH (6 mL), 1 N NaOH (1.1 mL) was added during about 5 min. After stirring for 5–6 h at ambient temperature crude **60** or **61** was precipitated by addition of 1 N HCl (1.5 mL).

4-Benzoyl-3-benzyloxy-5-alkylaminobenzoic Acids 62 and 63 (Table III). Method N. A mixture of **58** or **59** (1.5 mmol), 4 N NaOH (5 mL), and EtOH (5 mL) was refluxed for 3–4 h. Cooling and addition of 4 N HCl (6 mL) precipitated crude **62** or **63**.

4-Benzoyl-3-benzyloxy-5-dimethylaminobenzoic Acid (64) (Table III). Method O. A mixture of **19**[3] (1.73 g, 5 mmol), MeI (2.0 mL), and MeOH (25 mL) was refluxed for 42 h. After 16 and 24 h, additional MeI (each time 2 mL) was added. The resulting solution was evaporated in vacuo. To the residue 2 N NaOH (20 mL) was added and the mixture was heated on a steam bath for 1.5 h. After cooling, the precipitated Na salt of **64** was isolated and worked up as described in ref 1, method K.

5-Benzyloxy-7-carboxy-4-phenyl-2(3*H*)-quinazolinone (54) (Table II). Method P. A mixture of **19**[3] (2.2 g, 6.4 mmol), KOCN (0.75 g, 9.2 mmol), and AcOH (30 mL) was stirred at ambient temperature for 24 h. Cooling completed the precipitation of crude **54**.

3-Alkyl-5-benzyloxy-7-carboxy-4-phenyl-2(3*H*)-quinazolinones 55–57 (Table II). Method Q. A mixture of **19**[3] (0.7 g, 2 mmol), the appropriate alkyl isocyanate (2.7–3.3 mmol), pyridine (0.3 mL), and benzene (7 mL) was left at ambient temperature for **24** h or, in the case of **55**, refluxed for 2 h. Evaporation in vacuo and trituration with 1 N AcOH yielded crude **55–57**.

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References and Notes

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Antileukemic Activity of Derivatives of 1-Phenyl-2,5-dimethyl-3,4-bis(hydroxymethyl)pyrrole Bis(*N*-methylcarbamate)[1]

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Treatment of *N*-aryl-*N*-acetylalanine derivatives, **3**, with acetic anhydride–dimethyl acetylenedicarboxylate gave the dimethyl *N*-aryl-2,5-dimethylpyrrole-3,4-dicarboxylates, **4**. Reduction of **4** and acylation of **5** gave **2a–j** and **6**. All of the title compounds **2a–j** and **6** showed significant reproducible activity in the P388 in vivo antileukemic assay.

During the course of our continuing search for new "lead" structures that possess antineoplastic activity, we prepared some bis(*N*-methylcarbamoyl) derivatives (**1**) of 2,3-dihydro-5-phenyl-6,7-bis(hydroxymethyl)-1*H*-pyrrolizine.[2b] The significant reproducible activity shown by these compounds against P388 lymphocytic leukemic in vivo emphasized the potentially important role the acylated vinylogous carbinolamine moiety plays in determining antineoplastic activity.

The nature of the X substituent in the pyrrolizines, **1**,