spraying with saturated $(NH_4)_2SO_4$. Compounds containing amino groups were also detected with ninhydrin spray. All analytical samples were essentially TLC homogeneous. Melting points were determined with a Mel-Temp apparatus and are not corrected. The UV absorption spectra were determined in 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH with a Cary 17 spectrophotometer. The ^1H NMR spectra were determined with a Varian XL-100-15 spectrometer in Me_2SO-d_6 with tetramethylsilane as an internal reference: chemical shifts quoted in the case of multiplets are measured from the approximate center. The high-pressure liquid chromatographic analysis was carried out with a Waters Associates ALC-242 chromatography with an M-6000 pump and equipped with a μPorasil column (0.25 in. × 30 cm) using $CHCl_3$ (1% EtOH) as the solvent. The stop–flow UV spectra were determined with a Beckman 25 UV spectrophotometer interfaced to the chromatograph. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

4-Amino-1-β-D-arabinofuranosylimidazo[4,5-*c*]pyridine (3). A solution of 4-amino-6-chloro-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazo[4,5-*c*]pyridine (29.8 g, 52.2 mmol) in 1.3 L of EtOH containing 1 equiv of HCl and 5 g of 30% Pd/C catalyst was hydrogenated at 40–50 psi for about 48 h. The catalyst was removed by filtration and extracted with boiling water, which was cooled, neutralized, and evaporated to dryness. The residue was recrystallized from water with charcoal treatment: yield 6.6 g (46.8%); mp 286–288 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) at pH 1 and 7, 262 nm (10.5); at pH 13, 264 nm (10.9); NMR (Me_2SO-d_6) δ 3.5 (broad, H_2O), 3.7 (m, $H_{4'}$, and 2 $H_{5'}$), 4.15 (m, $H_{2'}$ and $H_{3'}$), 5.6 (broad, OH), 6.13 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$ and NH_2), 6.85 (d, H_7), 7.65 (d, H_6), 8.2 (s, H_2). Anal. ($C_{11}H_{14}N_4O_4 \cdot 0.33H_2O$) C, H, N.

4,6-Dichloro-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazo[4,5-*c*]pyridine (β-5). To a suspension of 54 mg (0.287 mmol) of 4,6-dichloroimidazo[4,5-*c*]pyridine (4) and 0.5 g of 4Å molecular sieves in 10 mL of dry 1,2-dichloroethane was added a solution of 2,3,5-tri-*O*-benzylarabinofuranosyl chloride (0.288 mmol from 164 mg of 1-*p*-nitrobenzoyl-2,3,5-tri-*O*-benzylarabinofuranose) in 15 mL of dry 1,2-dichloroethane and an additional 0.5 g of molecular sieve. The mixture was refluxed overnight with stirring. The solid removed by filtration was washed with chloroform, and the combined organic solvents were washed with saturated sodium bicarbonate followed by water. The solution was dried over $MgSO_4$, filtered, and evaporated to dryness: yield 181.3 mg. This material (127.7 mg) was shown by HPLC with stop–flow UV scans to be a mixture of two 1-substituted (5) and two 3-substituted (6) imidazo[4,5-*c*]pyridines and was resolved by chromatography on silica gel plates (Brinkmann) developed three times with cyclohexane–ethyl acetate (3:1). Elution of the major band with ethyl acetate gave the 1-β isomer (β-5) as a glass (63 mg, 37%): UV (95% EtOH) λ_{max} ($\epsilon \times 10^{-3}$) 208 (54.6), 252 (sh), 258 (7.03), 273 (5.67), 281 nm (sh); NMR ($CDCl_3$) δ 3.65 (m, 2 $H_{5'}$), 4.25 (m, $H_{2'}$, $H_{3'}$, $H_{4'}$, $O_{2'}$-CH_2), 4.6 (m, $O_{3'}$-CH_2, $O_{5'}$-CH_2), 5.98 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$), 7.0 and 7.3 (2 m, Ph and H_7), 8.25 (s, H_2).

Repetition of the reaction using 37.4 g (0.199 mol) of 4 and 113.3 g (0.2 mol) of 1-*p*-nitrobenzoyl-2,3,5-tri-*O*-benzylarabinofuranose followed by chromatography on a silica gel column (Mallinkrodt 7, 2.25 × 41 in.) with cyclohexane–ethyl acetate (3:1) twice gave 39.4 g (33.5%) of material that was used directly in the next step.

4-Amino-6-chloro-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazo[4,5-*c*]pyridine (7). A solution of 5 g (8.5 mmol) of 4,6-dichloro-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazo[4,5-*c*]pyridine in 50 mL of ethanol saturated with anhydrous ammonia (0 °C) was heated in a stainless-steel bomb at 140 °C for 4 days. The residue from evaporation of the reaction mixture was dissolved in hot ethanol, and the solution was treated with charcoal and filtered through Celite. The solid that crystallized from the chilled solution was removed by filtration, washed with EtOH, and dried in vacuo: yield 2.6 g (54%); mp 115–116 °C. Recrystallization from EtOH gave 2.3 g (48%): mp 116–117 °C; NMR ($CDCl_3$) δ 3.7 (m, 2 $H_{5'}$), 4.2 (m, $H_{2'}$, $H_{3'}$, $H_{4'}$ and $O_{2'}$-CH_2), 4.57 (2 s, $O_{3'}$-CH_2 and $O_{5'}$-CH_2), 5.45 (br s, NH_2), 5.98 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$), 6.65 (s, H_7), 6.9 and 7.3 (2 m, phenyl), 8.4 (s, H_2). Anal. ($C_{32}H_{31}ClN_4O_4 \cdot 0.5C_2H_5OH$) C, H, N.

Acknowledgment. The authors are indebted to Dr. W. C. Coburn, Jr., Mrs. M. C. Thorpe, Mrs. C. Richards, and Mrs. S. A. Campbell for the microanalytical, spectral, and HPLC data reported and to W. M. Shannon and G. Arnett for the antiviral data reported.

Syntheses and Diuretic Activity of 1,2-Dihydro-2-(3-pyridyl)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one and Related Compounds

Harlie A. Parish, Jr.,* Richard D. Gilliom,

Department of Chemistry, Southwestern at Memphis, Memphis, Tennessee 38112

William P. Purcell,

Department of Medicinal Chemistry, College of Pharmacy, The University of Tennessee Center for the Health Sciences, Memphis, Tennessee 38163

Ronald K. Browne, Roy F. Spirk, and Harold D. White

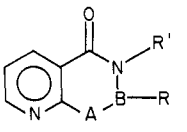
Biological Development, Marion Laboratories, Kansas City, Missouri 64137. *Received July 27, 1981*

The title compound, **5**, was prepared and found to be a potent diuretic in the rat. At 27 mg/kg, urine output was 250% of the saline control, and the excretion of electrolytes was similar to the hydrochlorothiazide control. At 80 mg/kg, the potassium excretion was the same as the saline control, and the sodium and chloride excretions more than doubled. Several analogues were prepared and tested. Some show diuretic activity.

This paper reports our efforts to synthesize a potassium-sparing diuretic using a pyrido[2,3-*d*]pyrimidine as the lead compound. Some potassium-sparing diuretics, such as triamterene, are derivatives of nitrogen-containing heterocyclic compounds. They usually are not of sufficient natriuretic potency when used alone and frequently must be delivered in conjunction with other diuretic agents in order to augment natriuresis and reduce potassium loss.[1]

0022-2623/82/1825-0098$01.25/0

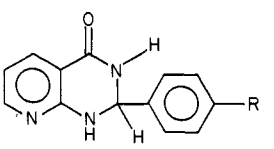
Table I. Chemical and Diuretic Data on Pyrido Derivatives[a]



compd	formula	A-B	R'	R	mp, °C	% yield	synthetic method	dosage, mg/kg	% urine output of control
saline									100
furosemide								20	444
								40	517
2	$C_{11}H_7N_3O_2$	N=C	H	1-furyl	234-235	24	A	25	167
								100	212
								400	36[b]
3	$C_{11}H_9N_3O_2$	NH-CH	H	1-furyl	241-243	37	B	25	121
								100	194
								400	193
4	$C_{11}H_6N_3O_2Br$	NH-CH	H	4-bromo-1-furyl	242-243	57	B	25	101
								100	94
								400	110
5	$C_{12}H_{10}N_4O$	NH-CH	H	3-pyridyl	251-252	46	B	25	221
								100	220
								400	185
6	$C_{12}H_{11}N_3O_2$	NH-CH	CH_3	1-furyl	178-179	31	C	25	209
								100	233
								400	95[c]

[a] Testing Procedure 1. See Experimental Section. [b] Five of eight rats died. [c] Four of eight rats died.

Table II. Chemical and Diuretic Data on 2-Pyrido[2,3-*d*]pyrimidin-4-one Derivatives[a]



compd	formula	R	mp, °C	% yield	synthetic method	dosage, mg/kg	% urine output of control	Na^{+b}	Cl^{-b}	K^{+b}
saline							100	1.2	1.3	0.4
HCTZ[c]						25	201	2.5	2.8	0.7
7	$C_{13}H_{11}N_3O$	H	263-265	76	D	25	114	1.3	1.4	0.5
						75	146	1.8	1.8	0.6
8	$C_{16}H_{17}N_3O$	isopropyl	256-257	53	D	25	137	1.5	1.6	0.6
						75	114	1.3	1.4	0.6
9	$C_{14}H_{10}F_3N_3O$	trifluoro-methyl	308-310	34	E	25	106	1.3	1.4	0.4
						75	98	1.2	1.3	0.4
10	$C_{13}H_{10}N_4O_3$	nitro	295-296	74	E	25	110	1.2	1.3	0.4
						75	115	1.5	1.7	0.6

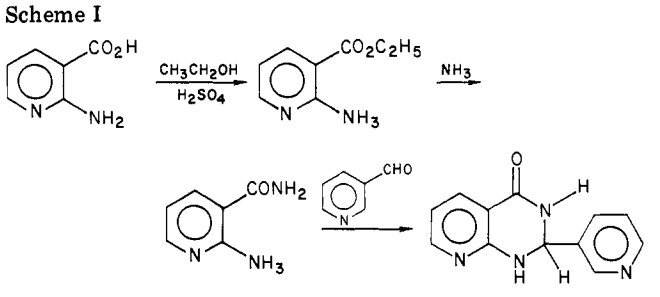
[a] Testing procedure 2. See Experimental Section. [b] Total milliequivalents excreted. [c] Hydrochlorothiazide.

Osselaere and Lepiere,[2,3] found that 2-(3-pyridyl)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (1) had high diuretic activity, but the potassium-sparing properties were not reported. We designed compounds to include derivatives of different fused heterocyclic rings and measured the effect these molecular modifications have on the electrolyte content of urine.

Chemistry. The synthetic methods were essentially modifications of Osselaere and Lapiere.[2,3] Compound **2** was prepared by condensing furoyl chloride with 2-aminonicotinamide.

Compounds **3–5**, **7–10**, **14**, and **15** were synthesized by condensing 2-aminonicotinamide with the appropriate aldehyde. Compounds **6** and **16** were prepared by using 2-amino-*N*-methylnicotinamide as a reagent. 2-Amino-*N*-methylnicotinamide was prepared by reacting methylamine with ethyl 2-aminonicotinate.

Scheme I

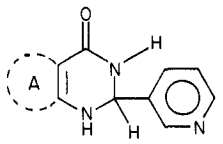


5

Compound **11** was made by condensing 4-amino-5-imidazolecarboxamide with 3-pyridinecarboxaldehyde. Compound **13** was prepared by reacting benzyl 3-amino-

(1) G. H. Mudge in Goodman and Gilman's "The Pharmacological Basis of Therapeutics", 6th ed., A. G. Gilman, L. S. Goodman, and A. Gilman, Eds., Macmillan, New York, 1980, pp 908–909.
(2) J. P. Osselaere and C. L. Lapiere, *Eur. J. Med. Chem.*, **9**, 305 (1974).
(3) J. P. Osselaere, *Eur. J. Med. Chem.*, **9**, 310 (1974).

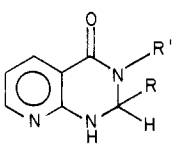
Table III. Chemical and Diuretic Data on 3-(3-Pyridyl)pyrimidin-4-one Derivatives[a]



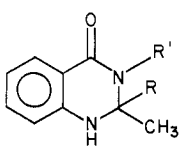
compd	formula	A	mp, °C	% yield	synthetic method	dosage, mg/kg	% urine output of control	Na^{+b}	Cl^{-b}	K^{+b}
saline							100	1.1	1.2	0.3
HCTZ[c]						25	194	2.2	2.5	0.6
11	$C_{10}H_9N_5O$	1*H*-imidazo[4,5]	248-249	25	F	25	138	1.4	1.3	0.6
12	$C_{13}H_{11}N_3O$	benzo	219-221	43	B[d]	25	96	1.0	1.1	0.4
13	$C_{11}H_9N_5O$	pyrazino[2,3]	238-239	8	H	75	97	1.2	1.2	0.4

[a] Testing procedure 2. See Experimental Section. [b] Total milliequivalents excreted. [c] Hydrochlorothiazide. [d] Synthetic method B was used with 2-aminobenzamide substituted for 2-aminonicotinamide.

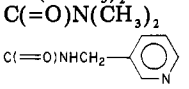
Table IV. Chemical and Diuretic Data on Pyrido and Benzo Derivatives[a]



14-16



17-19

compd	formula	R	R′	mp, °C	% yield	synthetic method	dosage, mg/kg	% urine output of control	Na^{+b}	Cl^{-b}	K^{+b}
saline								100	1.1	1.2	0.3
HCTZ[c]							25	194	2.2	2.5	0.6
14	$C_{13}H_{12}N_4O$	4-aminophenyl	H	249-250	23	I	50	128	1.5	1.5	0.5
15	$C_{12}H_{12}N_4O$	*N*-methyl-2-pyrrole	H	228-229	15	B	25	124	1.5	1.4	0.3
							50	113	1.0	1.0	0.2
16	$C_{13}H_{12}N_2O$	3-pyridyl	CH_3	157-158	71	C	75	149	1.7	1.7	0.5
17	$C_{12}H_{16}N_2O_3$	$CH(OCH_3)_2$	H	168-170	51	J	25	118	1.2	1.2	0.4
18	$C_{12}H_{15}N_3O_2$	$C(=O)N(CH_3)_2$	H	188-192	29	K	150	100	1.1	1.4	0.4
19	$C_{16}H_{16}N_4O_2$		H	236-237	53	K	150	120	1.4	1.5	0.5

[a] Testing procedure 2. See Experimental Section. [b] Total milliequivalents excreted. [c] Hydrochlorothiazide.

Table V. Diuretic Effects of 1,2-Dihydro-2-(3-pyridyl)-3*H*-pyrido[2,3-*d*]pyrimidine-4-one (5), 1,2-Dihydro-2-(2-furyl)-3-methylpyrido[2,3-*d*]pyrimidin-4-one (6), and Hydrochlorothiazide[a]

compd	oral dose, mg/kg	mL excreted		total mequiv excreted		
		2 h	5 h	Na^+	Cl^-	K^+
saline		2.4 ± 0.1	6.0 ± 0.95	0.9 ± 0.1	1.1 ± 0.1	0.4 ± 0.1
HCTZ[b]	12	7.9 ± 0.6	16.0 ± 0.6	2.5 ± 0.1	2.8 ± 0.1	0.6 ± 0.03
5	25	8.0 ± 1.3	21.0 ± 1.0	2.5 ± 0.1	2.8 ± 0.03	0.6 ± 0.1
6	25	4.6 ± 0.6	12.2 ± 1.3	1.8 ± 0.2	1.8 ± 0.2	0.8 ± 0.1
saline		2.5 ± 0.3	7.9 ± 0.4	1.1 ± 0.1	1.2 ± 0.1	0.4 ± 0.1
5	3	4.4 ± 0.8	8.1 ± 0.5	1.4 ± 0.2	1.6 ± 0.2	0.4 ± 0.1
5	9	3.0 ± 0.7	7.6 ± 0.4	1.1 ± 0.03	1.3 ± 0.1	0.4 ± 0.04
5	27	10.4 ± 1.7	20.1 ± 1.9	2.2 ± 0.2	2.6 ± 0.2	0.6 ± 0.1
5	81	6.0 ± 1.5	19.6 ± 0.8	2.6 ± 0.1	2.6 ± 0.1	0.4 ± 0.1
HCTZ	1	7.8 ± 0.9	13.9 ± 1.4	2.0 ± 0.2	2.5 ± 0.2	0.6 ± 0.1
HCTZ	3	8.1 ± 0.5	15.8 ± 0.9	2.4 ± 0.1	2.7 ± 0.1	0.6 ± 0.1
HCTZ	9	7.5 ± 1.3	14.6 ± 1.0	2.2 ± 0.1	2.7 ± 0.1	0.6 ± 0.1
HCTZ	27	8.4 ± 1.1	15.1 ± 1.0	2.5 ± 0.3	3.0 ± 0.4	0.8 ± 0.3

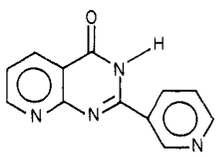
[a] Animals received 25 mL/kg of saline in the absence or presence of drug. Mean values plus or minus SEM of two rats per cage ($N = 8$). Testing procedure 2. See Experimental Section. [b] Hydrochlorothiazide.

pyrazine-2-carboxylate with ammonia to give 3-amino-2-carboxyamidopyrazine, which was then condensed with 3-pyridinecarboxaldehyde.

Compound 17 was prepared from anthranilamide and pyruvaldehyde dimethyl acetal. Compounds 18 and 19 were prepared by reacting the product of the reaction of anthranilamide and ethyl pyruvate with dimethylamine for 18 and with 3-(aminomethyl)pyridine for 19.

Diuretic Activity. In our attempt to design a potassium-sparing diuretic, we have taken Osselaere and Lapiere's most potent compound, 1, and broken it down into several molecular regions for systematic examination. The compounds that we synthesized and evaluated are given in Tables I–IV.

The contribution of the heterocyclic ring, R′, was studied first. Although 1 is not similar to the potent diuretic



1

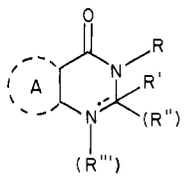


Chart used for structural study

furosemide, which contains a furyl group, it was thought that incorporating a furyl group in our lead might be advantageous. At low dosages the furyl derivative **2** was active, but at high dosages, 400 mg/kg, the compound was toxic; during the 24 h of observation after the test, five of the eight rats died.

The reduction of a double bond in the nucleus of a molecule can increase activity dramatically. For example, the reduction of the 3,4 double bond in chlorothiazide give the potent diuretic hydrochlorothiazide. Diuretic activity decreased, however, after the 3,4 double bond in **2** was reduced. No toxicity was observed in the 24 h of observation during the test.

Since **1** contains the 3-pyridyl group, it appeared logical to make the saturated analogue **5**. Indeed, this was the most potent compound in our study.

In the study of this molecular region, four parent ring systems were evaluated: 2-furyl, **3**; 3-pyridyl, **5**; phenyl, **7**; and the *N*-methyl-2-pyrryl, **15**. The 3-pyridyl derivative **5** was the most potent.

Many diuretics contain halogen. In furosemide and hydrochlorothiazide the halogen is in a polar region in the molecule. It was thought that the polarity of **3** could be increased by placing a halogen on the furyl ring. The 4-bromo-2-furyl derivative **4** was chosen to test the hypothesis. It, however, was inactive.

Osselaere examined the effect of a hydroxyl and a hydrogen at position 3 in **1**.[3] The hydroxyl compound was less active, which might indicate that a more hydrophobic group at this position would increase activity. Compound **6** with a methyl group at position 3 was synthesized to test this possibility. At low concentrations **6** is potent, but at 400 mg/kg it is toxic: four of eight rats died in the test.

The position occupied by the fused pyridine ring, A, was the next region examined. A series based on a fused imidazole, benzene, pyridine, and pyrazine was synthesized. The benzo compound, **12**, and the pyrazino[2,3] compound, **13**, were inactive. The 1*H*-imidazo[4,5] compound, **11**, showed marginal activity, and the pyrido compound, **5**, was the most potent compound in the study.

These preliminary data seem to suggest a correlation between the basicity of the parent ring in the A region and activity. The pyrido derivative, **5**, is the most potent and the pyridine ring is the most basic of the four rings tested.[4] Pyrazine and benzene are the least basic, and the pyrazino[2,3] derivative, **13**, and the benzo derivative, **12**, were both inactive.

Compounds **5** and **6** at 25 and 100 mg/kg are the most potent compounds in this study. Compound **6** has a methyl group at position 3, and **5** is unsubstituted. Compound **16** was synthesized to evaluate the effects of a methyl group at position 3 on compound **5**. The resulting derivative shows marginal activity.

Compounds **7**–**10** and **14** were synthesized for a limited QSAR study.[5] A series was designed with substitutional variation at the para position of the phenyl ring in the R′ region. The series included a hydrogen for the base line and isopropyl, methyl, nitro, and amino groups to spread the physicochemical parameters.[6]

The compounds substituted with the nitro group, **10**, and with the trifluoromethyl group, **9**, showed no activity. The unsubstituted compound, **7**, the isopropyl derivative, **8**, and the amino derivative, **14**, showed marginal activity. There was not sufficient quantitative information in the pharmacological data to provide meaningful QSAR analyses.

In the remaining series we varied R′ with a methyl group at R″. Compounds **17**–**19** were inactive.

The most potent compounds, **5** and **6**, were studied in greater detail. Compound **5** was the more potent, so the dose–response was determined with hydrochlorothiazide as a control. The minimum effective dose that increased urine output was 27 mg/kg for **5** and 1 mg/kg for hydrochlorothiazide.

The most important finding of this study was that the urine output of **5** at 27 mg/kg was 250% of the saline control and that at 81 mg/kg the potassium excretion was the same as the saline control and the sodium and chloride excretion more than doubled.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken on a Varian EM360A, and infrared spectra were taken on a Perkin-Elmer 521; all spectra were consistent with the expected structure. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, and by Wyeth Laboratories, Philadelphia, PA. All samples were analyzed for carbon, hydrogen, and nitrogen. The analytical results were within ±0.4% of the theoretical values.

2-Aminonicotinamide. Ethyl 2-aminonicotinate[2] (6.0 g, 0.036 mol) and 150 mL of methanol which had been saturated with anhydrous ammonia were heated in an autoclave at 75–80 °C for 5 days. After the solution was concentrated, a solid separated. Recrystallizing from ethanol gave 3.9 g (80% yield) of 2-aminonicotinamide, mp 194–197 °C.

Method A. 2-(2-Furyl)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (2). Ethyl 2-aminonicotinate (1.5 g, 0.0090 mol), furoyl chloride (2.6 g, 0.020 mol), and 8 mL of pyridine were refluxed for 15 min. After the mixture was chilled, a solid was collected and recrystallized from ethanol: yield 1.7 g; mp 149–152 °C. This solid was placed in an autoclave with 35 mL of methanol which had been saturated with ammonia. After 6 h at 110–120 °C, the sample was concentrated and a solid separated. After recrystallization from ethanol, 0.5 g (24% yield) of product was obtained: mp 234–235 °C; ^{1}H NMR (Me_2SO-d_6) δ 6.8 (1 H, m), 7.3 (2 H, m), 7.95 (1 H, m), 8.4 (1 H, m), 8.8 (1 H, m).

Method B. 1,2-Dihydro-2-(2-furyl)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (3). 2-Aminonicotinamide (2.95 g, 0.022 mol) and 22 mL of furfural were heated to reflux, and then the heating mantle was removed. When the solution cooled, a solid separated, which was recrystallized from isopropyl alcohol with carbon to give 2.6 g (46% yield) of **3**: mp 241–243 °C; ^{1}H NMR (Me_2SO-d_6, D_2O–D_2SO_4) δ 5.85 (1 H, s), 6.35 (2 H, m), 6.8 (1 H, m), 7.6 (1 H, m), 8.2 (2 H, m).

Method C. 1,2-Dihydro-2-(2-furyl)-3-methylpyrido[2,3-*d*]pyrimidin-4-one (6). Ethyl 2-aminonicotinate (3.0 g, 0.018 mol) and 60 mL of 40% aqueous methylamine were heated in an autoclave for 4 h at 90 °C. The solvent was removed under vacuum. A solid separated, which was recrystallized from methanol. Furfural (20 mL) was added to the solid; the solution was heated to reflux, and then the heating mantle was removed.

(4) A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

(5) W. P. Purcell, G. E. Bass, and J. M. Clayton, "Strategy of Drug Design, A Molecular Guide to Biological Activity", Wiley, New York, 1973.

(6) W. P. Purcell, *Eur. J. Med. Chem.*, 10, 335 (1975).

After the solution cooled, 50 mL of diethyl ether was added and a dark solid separated, which was recrystallized from isopropyl alcohol with carbon to give 1.5 g (31% yield) of **6**, mp 178–179 °C.

Method D. 1,2-Dihydro-2-(4-isopropylphenyl)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (8). A mixture of 2-aminonicotinamide (2.1 g, 0.0153 mol), 20 mL of *p*-isopropylbenzaldehyde, and 0.2 g of $ZnCl_2$ was heated to reflux with stirring. After 12 min the reaction mixture solidified. The solid mass was triturated in methanol to give 2.8 g (70% yield). This solid was recrystallized from ethanol to give 2.2 g (53% yield) of **8**, mp 256–257 °C.

Method E. 1,2-Dihydro-2-[4-(trifluoromethyl)phenyl]-3*H*-pyrido[2,3-*d*]pyrimidin-4-one (9). A solution of 2-aminonicotinamide (2.0 g, 0.0148 mol), 4-(trifluoromethyl)benzaldehyde (Fairchild Chemical Co.; 4.55 g, 0.026 mol), 0.2 g of zinc chloride, and 20 mL of diglyme was heated to reflux for 2.5 h. After the solution cooled, a solid separated, which was triturated in methanol to give 1.5 g (34% yield) of **9**, mp 308–310 °C.

Method F. 2,3-Dihydro-6-hydroxy-2-(3-pyridyl)purine (11). A solution of 4-amino-5-imidazolecarboxyamide hydrochloride (5.0 g, 0.031 mol), 3-pyridinecarboxaldehyde (6.2 g, 0.058 mol), sodium acetate (4.15 g), and 100 mL of ethanol was refluxed for 5 min. The product was isolated by filtration and recrystallized from 300 mL of isopropyl alcohol with 45 mL of water to give 1.7 g (25% yield) of **11**, mp 248–249 °C.

Method H. 1,2-Dihydro-2-(3-pyridyl)-3*H*-pyrazino[2,3-*d*]pyrimidin-4-one (13). Into an autoclave was added 160 mL of methanol saturated with ammonia and benzyl 3-aminopyrazine-2-carboxylate (Aldrich Chemical Co.; 9.8 g, 0.0043 mol). The reaction was heated at 90 °C for 3 h. After this time a solid had separated, which was collected. The product, 3-aminopyrazine-2-carboxamide, 5.8 g, mp 232–235 °C, was used without purification for the next step. 3-Aminopyrazine-2-carboxamide was added to 5 mL of 3-pyridinecarboxaldehyde and refluxed for 3 min. After the mixture was left standing overnight, a solid separated, which was recrystallized from ethanol and carbon and then from isopropyl alcohol to give 0.8 g (8% yield) of **13**, mp 238–239 °C.

Method I. 1,2-Dihydro-2-(4-aminophenyl)-3*H*-pyrido-[2,3-*d*]pyrimidin-4-one (14). 1,2-Dihydro-2-(4-nitrophenyl)-3*H*-pyrido[2,3-*d*]pyrimidine-4-one (**10**; 1.5 g, 0.0055 mol), 0.1 g of platinum oxide, and 125 mL of absolute ethanol were added to hydrogenation bomb on a Parr shaker. The reaction was shaken with 19 psi of hydrogen for 20 h at 25 °C. After it was removed from the hydrogenation apparatus, the solution was heated to dissolve the solid organic material, and the catalyst was removed by filtration. The yellow solution was placed in the freezer overnight. A solid was collected, which was recrystallized from 75 mL of ethanol with decolorizing carbon to give 0.3 g (23% yield) of **14**, mp 249–250 °C.

Method J. 1,3-Dihydro-2-methyl-2-(diethoxymethyl)-3*H*-benzo[*d*]pyrimidin-4-one (17). A mixture of anthranilamide (20 g, 0.15 mol), pyruvaldehyde dimethyl acetal (25 mL, 0.21 mol), 250 mL of toluene, and 0.2 g of *p*-toluenesulfonic acid was refluxed with the aid of a Dean–Stark trap. After the mixture was refluxed for 10 min, 3 mL of water was collected in the trap. The reaction mixture was cooled and a solid separated. After recrystallization from ethanol, 18 g (51% yield) of product was obtained, mp 168–170 °C.

Method K. 1,3-Dihydro-2-methyl-2-(*N*,*N*-dimethylcarbamyl)-3*H*-benzo[*d*]pyrimidin-4-one (18). A mixture of anthranilamide (5 g, 0.037 mol), methyl pyruvate (10 mL), and diglyme (25 mL) was refluxed for 45 min. After the mixture was left standing overnight, a solid separated, which was collected by filtration to give 4.0 g of solid, mp 223–226 °C. A 3.5-g sample of the above compound was added to 10 mL of dimethylamine (40% solution in water) and 25 mL of methanol. The solution was refluxed for 4 h and then concentrated to an oil on the rotary evaporator. Acetone was added and the product separated. After recrystallization from ethanol, 2.5 g (29% yield) of solid was obtained, mp 188–192 dec.

Pharmacology. Diuretic Testing. Procedure 1. The diuretic activity was measured on groups of eight male rats of Sprague–Dawley descent. The diuretic test is a modification of the method of Lipschitz.[7] The drug vehicle (5% acacia–isotonic saline) was tested as the control, and furosemide was tested for comparison with the test compounds.

All animals were fasted for 18 h prior to administration of the test compound but received water ad libitum. All dosages were administered with the aid of an oral dosing needle.

Immediately after dosing, the animals were placed in metabolism cages designed to separate the urine and feces. The urine was then collected in plastic bottles for 5 h after dosing. During this 5-h interval, no feed or water was available for the test animals. At the end of the 5-h period, the animals were removed from the metabolism cages. At this time an effort to force the animals to expel any urine remaining in their bladders was accomplished by pulling at the base of their tails.

Diuretic Testing. Procedure 2. Studies were performed using male Sprague–Dawley rats (195–225 g) which were fasted and deprived of water for 18 h prior to dosing. Compounds were orally administered, dissolved in 25 mL/kg of saline on the morning of the test. Control animals received 25 mL/kg of saline alone. Groups of eight rats were used, and immediately after dosing, pairs of rats were placed in a metabolism cage. The volume of urine collected at 5-h after dosing was measured.

Acknowledgment. The authors thank Drs. P. B. Russell and S. C. Bell for having our compounds evaluated for urine electrolyte and elemental analyses at Wyeth Laboratories, Inc.

(7) W. L. Lipschitz, Z. Hadidian, and A. Kerpcsar, *J. Pharmacol. Exp. Ther.*, 79, 97 (1943).