2,3-Disubstituted 1,8-Naphthyridines as Potential Diuretic Agents[1]

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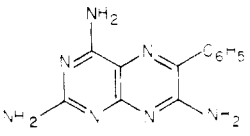
A large number of 2,3-disubstituted 1,8-naphthyridines were prepared either directly by the Friedlander reaction or by subsequent reaction of the bicyclic products. Ten compounds, with potassium-sparing properties, were active in a saline-loaded rat diuretic screen at 15 mg/kg (ip). Seven displayed activity comparable to triamterene, 2-amino- and 2-amino-*N*-amidino-1,8-naphthyridine-3-carboxamide being more potent. The saluretic data for the former are reported.

Triamterene (**1**), a triaminopteridine, possesses potent potassium-sparing diuretic activity. In a previous report,[1] we have shown that simplified molecules with less electron-withdrawing aza atoms and electron-donating substituents than triamterene may possess diuretic activity. Many 2,3-disubstituted 1,6-naphthyridines (**2**) displayed diuretic activity in a saline-loaded rat screen, but subsequent study indicated lack of an antikaliuretic effect. Early work showed that 2-amino-1,8-naphthyridine-3-carboxamide (**3**) and the hydrochloride monohydrate (**3a**) were more potent than **1**, while retaining antikaliuretic activity. We have now prepared a series of 2,3-disubstituted derivatives of **3** in order to evaluate substituent effects and also aza atom requirements by comparing the data to that previously reported for **2**.[1]



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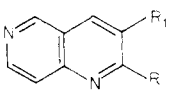

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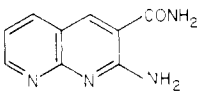


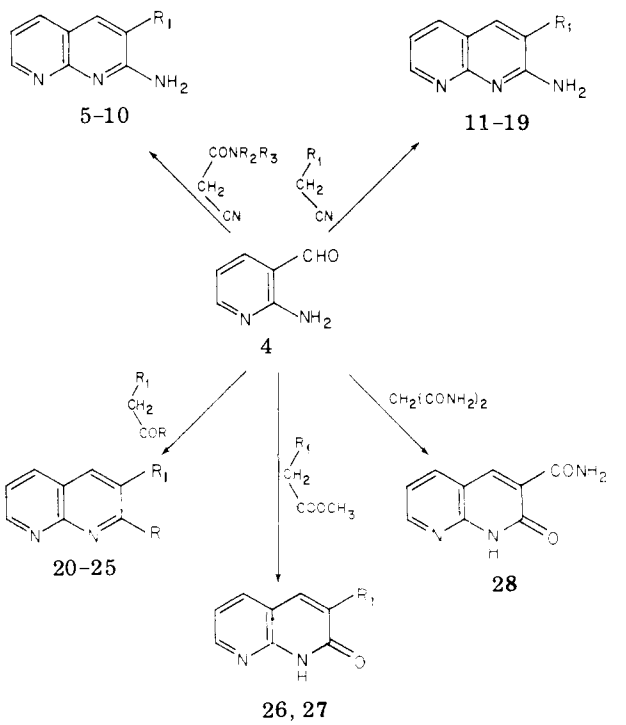
3

Chemistry. The most direct method for the preparation of the majority of the required 1,8-naphthyridines reported in Table I appeared to be the Friedlander reaction. Indeed a few of these, namely, **3**, **13**, **15**, **35**, and **51**, have been previously reported using this method with piperidine as catalyst.[2,3] In many cases extension of these classical conditions by condensation of the intermediate 2-aminonicotinaldehyde (**4**)[4] with methylene compounds, using either piperidine or sodium hydroxide as catalysts, realized the required compounds (**3**, **5–28**, **35**, and **51**) (Scheme I). Thus, the discovery of the potent diuretic activity of **3** prompted the direct synthesis of a number of related compounds with only slight structural modifications. The piperidine-catalyzed condensation of **4** with N-substituted cyanoacetamides afforded the secondary amides **5–9**. Similar reaction with the less activated *N*,*N*-dimethylcyanoacetamide gave the unexpected **26**; however, with sodium hydroxide the desired *N*,*N*-dimethyl derivative **10** was obtained in good yield.

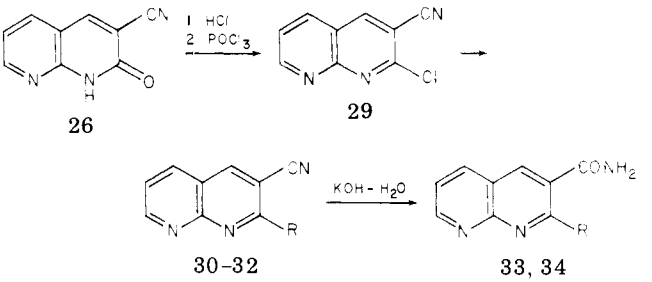
Direct substitution of aryl and heteroaryl groups in position 3 of the 1,8-naphthyridine nucleus was accomplished by treating **4** with various cyanomethylene derivatives. The more strongly activated methylene derivatives readily gave **11–14** with piperidine as catalyst, while sodium hydroxide was required for the compounds **15–18**. The fact that **19** required sodium hydroxide as catalyst can be rationalized by steric factors.

Further, compounds **20–25** were obtained when **4** was treated with the respective ketones and piperidine as catalyst for the highly activated methylene and sodium hydroxide for the weakly acidic starting materials. Compound **24** was previously prepared via the decarboxylation of the corresponding 3-carboxy derivative.[3]

Scheme I



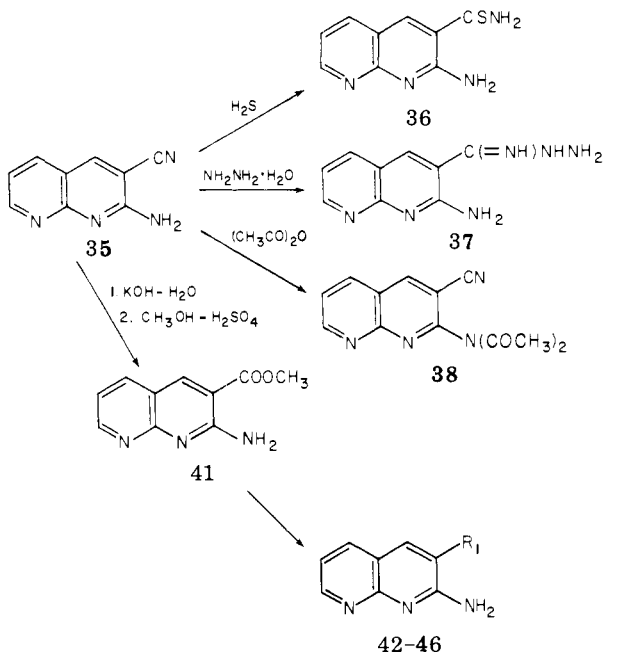
Scheme II



Also, reaction of **4** with methyl cyanoacetate and piperidine gave the naphthyridin-2-one, **26**, resulting from cyclization at the ester group rather than the nitrile, presumably due to greater electrophilicity of the former. Similar reaction of **4** with dimethyl malonate afforded the anticipated ester **27**, while malonamide, upon elimination of ammonia and water, gave **28**.

The remaining naphthyridines were synthesized by subsequent reaction of the bicyclic products mentioned above. Thus, modifications of the 2-amino moiety of **3** were realized via nucleophilic displacement of the precursor 2-chloro-3-cyano compound, **29**, with subsequent

Scheme III



hydrolysis. This versatile intermediate was prepared by treatment of the hydrochloride salt of **26** with boiling phosphorus oxychloride (Scheme II). The strong electron-withdrawing influence of the neighboring ring nitrogen and 3-cyano group of **29** greatly facilitated nucleophilic displacement of the halogen. Thus, reaction with sodium methoxide and gaseous alkylamines readily afforded the corresponding nitriles **30–32**. The latter two were subsequently converted to the amides **33** and **34** by simple potassium hydroxide hydrolysis. The amides **48** and **52** were similarly prepared.

The previously reported 2-amino-3-cyano-1,8-naphthyridine[3] (**35**) was a useful intermediate for the synthesis of most of the remainder of the compounds inaccessible via the direct method (Scheme III). Treatment of **35** with H_2S gas in the presence of triethylamine and pyridine afforded nearly a quantitative yield of the thioamide **36**. When **35** was treated with refluxing hydrazine hydrate, the corresponding hydrazone **37** was readily formed. In addition, treatment with acetic anhydride for a short reflux time gave the unexpected diacetyl derivative **38**. The monoacetyl product was isolated using an even shorter reaction time. An application of the conventional Fischer–Speier esterification of the previously reported base hydrolysis product of **35**,[3] with a mixture of methanol and concentrated sulfuric acid, readily gave the methyl ester **41**. Subsequent treatment of this ester with various amines gave the corresponding hydrazides **42** and **43** and the guanidines **44** and **45**, as well as the triazine **46**. Similar treatment of **27** with hydrazine hydrate gave the hydrazide **49**. Since attempts to prepare the 3-phenylsulfonyl-2-one (**47**) directly from **4** were unsuccessful, due in part to the bulkiness of the methylene compound, this naphthyridine was prepared by nitrous acid treatment of **19**.

Biological Activity Data. The biological activities were measured by modification of the classical method of Lipschitz[6] using saline-loaded rats, as previously described.[1] All of the compounds reported in Table I were screened at 2 and 15 mg/kg and the active compounds are shown in Table II. These ten active compounds were further tested in nonloaded rats at 15 mg/kg for ionic effects as described in the Experimental Section. All displayed diuretic and natriuretic but not kaliuretic activity. This screen was extended to investigate the most potent compound, 2-amino-1,8-naphthyridine-3-carboxamide, and its hydrochloride salt (**3** and **3a**) as shown in Table III.

Some compounds are close analogues of other diuretics. Thus, **15**, the analogue of triamterene,[7] was inactive at 15 mg/kg in the saline-loaded screen. However, both **15** and the related compound **13**, when screened at 30 mg/kg, gave responses of 49 and 44% above control, respectively. The 2,3-dimethyl compound **23** and the morpholinoethylcarboxamide **9**, both analogues of active pteridines,[7,8] were also inactive at 15 mg/kg. A number of 2-aryl-3-substituted compounds, related to a series of 2-arylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones,[9] were found to be inactive, apart from **51**. The *N*-amidino-3-aminopyrazine-2-carboxamides[10] are potent potassium-sparing diuretics, and of the two guanidine compounds screened, **44** was more potent than triamterene while **45** was inactive.

A large number of 2-amino-3-carboxamides were screened in view of their structural relationship to the pteridine diuretic SK&F 6874[7,11] and the potent response of **3** and **3a**. Derivatization such as 2-acetylation (**50**), 2-N-methylation (**33**), and 3-N-methylation (**5**) gave inactive compounds. In the 3-N-alkylation homologous series, methyl to butyl (**5–8**), the methyl (**5**) and ethyl (**6**) were inactive, while the propyl (**7**) and butyl (**8**) were as inactive as triamterene at the high dose level.

Only three active compounds did not contain the 2-amino-3-carbamoyl moiety, namely, the 3-cyano compounds **35** and **51** and a 2-phenyl (**51**) and a 2-one (**28**) compound. However, the other seven 3-cyano, six 2-aryl, and four 2-ones were inactive. Possibly these compounds exhibited a different mechanism of action, as is the case with the pteridine diuretics,[11] and indeed a characteristic delayed diuretic response was only noted with the 2-amino-3-carbamoyl compounds. Of the 49 1,8-naphthyridines screened, only ten were active; yet, of the 14 containing the 2-amino-3-carbamoyl moiety, seven were active. This suggests greater structural and electronic selectivity for drug–receptor interaction than the 1,6-naphthyridine series.[1] However, the far greater diuretic potency of **3**, with retention of antikaliuretic activity, as compared to triamterene indicates that in the latter, most probably only N-1 is essential for drug–receptor interaction but that the electronic contribution of other moieties such as N-8 and the *o*-amino group enhances this interaction.

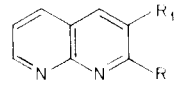
Experimental Section

Diuretic Screening. The saline-loaded rat screen, used to comparatively investigate the diuretic properties of all the compounds in Table I, has been previously reported.[1] The two different control values which can be noted in Table II are a result of screening the compounds in two batches. Further screening of the active compounds was for ionic effects without saline loading, as is subsequently described.

Adult male albino rats of the Wistar strain weighing between 225 and 275 g were fasted overnight (18 h) with H_2O allowed ad libitum. Groups of eight were injected intraperitoneally with the compounds at a dose of 15 mg/5 ml/kg as solutions or suspensions in distilled water, with a further group injected with distilled water as a control. The rats were then placed in clean metabolism cages and urine was collected and recorded for a 6-h period. The cumulative sample was then estimated, using a Radiometer FLM2 photometer, for sodium and potassium expressed as milliequivalents excreted and Na^+/K^+. The data reported in Table III which were carried out by the Wellcome Foundation utilize a greater range of dose levels and Ca^{2+} quantitation but follow similar methodology.

Synthesis. Melting points were determined with a Gallenkamp block and are uncorrected. Where analyses (Dr. Strauss, Oxford,

Table I. Chemical Properties of 2,3-Disubstituted 1,8-Naphthyridines



No.	R	R_1	Formula	Method[a-d]	Recrystn solvent	Mp, °C	Yield, % [c,d]	Analyses[c,d]
3	NH_2	$CONH_2$	$C_9H_8N_4O$	*d*	Et cellosolve	287–288 dec	*d*	*d*
3a	NH_2·HCl	$CONH_2$	$C_9H_8N_4O$·HCl·H_2O		MeOH	289–290 dec	90	C, H, Cl, N
5	NH_2	$CONHCH_3$	$C_{10}H_{10}N_4O$·H_2O	A (2)	H_2O	222–223	59	C, H, N
6	NH_2	$CONHC_2H_5$	$C_{11}H_{12}N_4O$	A (2)	Dioxane	218–220 dec	70	C, H, N
7	NH_2	CONH-*n*-C_3H_7	$C_{12}H_{14}N_4O$	A (24)	C_6H_6	165–166	80	C, H, N
8	NH_2	CONH-*n*-C_4H_9	$C_{13}H_{16}N_4O$	A (24)	C_6H_6	173–174	66	C, H, N
9	NH_2	$CONH(CH_2)_2$-*c*-$N(CH_2CH_2)_2O$	$C_{15}H_{19}N_5O_2$	A (24)	Abs EtOH	223–225	72	C, H, N
10	NH_2	$CON(CH_3)_2$	$C_{11}H_{12}N_4O$	B (3)	Abs EtOH	228–230	56	C, H, N
11	NH_2	*p*-C_6H_4-F	$C_{14}H_{10}FN_3$	A (2)	*n*-BuOH	239–241	91	C, H, F, N
12	NH_2	*p*-C_6H_4-NO_2	$C_{13}H_{10}N_4O_2$	A (6)	C_6H_6	>300	88	C, H, N
13	NH_2	2-Pyridyl	$C_{13}H_{10}N_4$	*c*	Et cellosolve	215–216	*c*	*c*
14	NH_2	3-Pyridyl	$C_{13}H_{10}N_4$	A (24)	H_2O	262–263 dec	68	C, H, N
15	NH_2	C_6H_5	$C_{14}H_{11}N_3$	B (2)	Et cellosolve	252–254	67	*c*
16	NH_2	*p*-C_6H_4-OCH_3	$C_{15}H_{13}N_3O$	B (1)	*n*-BuOH	263–265	96	C, H, N
17	NH_2	2-Furyl	$C_{12}H_9N_3O$	B (3)	C_6H_6	199–201	84	C, H, N
18	NH_2	2-Thienyl	$C_{12}H_9N_3S$	B (1)	EtOH	230–231	75	C, H, N, S
19	NH_2	$SO_2C_6H_5$	$C_{14}H_{11}N_3O_2S$	B (24)	EtOH	235–237 dec	88	C, H, N, S
20	*m*-C_6H_4-CF_3	H	$C_{15}H_9F_3N_2$·H_2O	A (24)	Petr ether	129–131	91	C, H, F, N
21	3-Pyridyl	CN	$C_{14}H_8N_4$	A (0.5)	EtOH	261–263	80	C, H, N
22	CH_3	$SO_2C_6H_5$	$C_{15}H_{12}N_2O_2S$	A (24)	*n*-PrOH	171–173	49	C, H, N, S
23	CH_3	CH_3	$C_{10}H_{10}N_2$	B (24)	EtOAc	140–142	27	C, H, N
24	C_6H_5	H	$C_{14}H_{10}N_2$	B (24)	EtOAc	115–116	89	*d*
25	3-Pyridyl	H	$C_{13}H_9N_3$	B (1)	C_6H_6	144–145	61	C, H, N
26	OH	CN	$C_9H_5N_3O$	A (0.5)	Et cellosolve	>300	76	C, H, N
27	OH	$COOCH_3$	$C_{10}H_8N_2O_3$	A (24)	MeOH	219–220	86	C, H, N
28	OH	$CONH_2$	$C_9H_7N_3O_2$	A (24)	H_2O	>300	95	C, H, N
29	Cl	CN	$C_9H_3ClN_3$	C	EtOH	>300	70	C, H, Cl, N
30	OCH_3	CN	$C_{10}H_7N_3O$	D	*n*-BuOH	193–195 dec	77	C, H, N
31	$NHCH_3$	CN	$C_{10}H_8N_4$	E	*n*-PrOH	238–239	90	C, H, N
32	$N(CH_3)_2$	CN	$C_{11}H_{10}N_4$	E	H_2O	172–174	76	C, H, N
33	$NHCH_3$	$CONH_2$	$C_{10}H_{10}N_4O$·H_2O	F	H_2O	257–258 dec	80	C, H, N
34	$N(CH_3)_2$	$CONH_2$	$C_{11}H_{12}N_3O$	F	*n*-PrOH	235–237 dec	36	C, H, N
35	NH_2	CN	$C_9H_6N_4$	*d*	Et cellosolve	260–262	*d*	*d*
36	NH_2	$CSNH_2$	$C_9H_8N_4S$	G	EtOH	265–268 dec	98	C, H, N, S
37	NH_2	$C(=NH)NHNH_2$	$C_9H_{10}N_6$	H	H_2O	218–220 dec	69	C, H, N
38	$N(COCH_3)_2$	CN	$C_{13}H_{10}N_4O_2$	I	EtOH	179–180	49	C, H, N
39	NH_2	COOH	$C_9H_7N_3O_2$	*d*	MeOH	>300	*d*	*d*

40	NH_2	H	$C_8H_7N_3$	Et_2O	139–140	*d*	
41	NH_2	$COOCH_3$	$C_{10}H_9N_3O_2$	J	Abs EtOH	191–192 dec	66	C, H, N
42	NH_2	$CONHNH_2$	$C_9H_9N_5O$	K	Abs EtOH	>300	85	C, H, N
43	NH_2	$CONHNHCH_3$	$C_{10}H_{11}N_5O$	K	EtOH	199–201 dec	47	C, H, N
44	NH_2	$CONHC(=NH)NH_2$	$C_{10}H_{10}N_6O\cdot H_2O$	K	H_2O	>300	85	C, H, N
45	NH_2	$CONHC(=NH)NHCH_2C_6H_5$	$C_{17}H_{16}N_6O\cdot 1.5H_2O$	K	*n*-PrOH	>300	65	C, H, N
46	NH_2	*s*-Triazinyl	$C_{11}H_{10}N_6\cdot 0.5H_2O$	K	EtOH	>300	75	C, H, N
47	OH	$SO_2C_6H_5$	$C_{14}H_{10}N_2O_3S$	L	Et cellosolve	294–296 dec	75	C, H, N, S
48	3-Pyridyl	$CONH_2$	$C_{14}H_{10}N_4O$	F	DMF	255–257 dec	46	C, H, N
49	OH	$CONHNH_2$	$C_9H_8N_4O_2\cdot H_2O$	K	EtOH	>300	84	C, H, N
50	$NHCOCH_3$	$CONH_2$	$C_{11}H_{10}N_4O_2$	*e*	Et cellosolve	>300	*e*	*e*
51	C_6H_5	CN	$C_{15}H_9N_3$	*d*	Abs EtOH	224–225	*d*	*d*
52	C_6H_5	$CONH_2$	$C_{15}H_{11}N_3O$	F	EtOH	233–234	51	C, H, N

[a] Under method the capital letters relate to the general procedures given in the Experimental Section. [b] Under method the values in parentheses are reflux times (hour) for the corresponding reaction. [c] Under method, yield and analyses "*c*" indicates that the preparation and analyses are described in ref 2. [d] Under method, yield and analyses "*d*" indicates that the preparation and analyses are described in ref 3. [e] Previously reported; see ref 5.

Table II. Compounds Active in Rat Saline-Loaded Screen

Compd	Increase from control (% of load excreted) 2 mg/kg	15 mg/kg	Act. as compared to triamterene 2 mg/kg	15 mg/kg
3[a]	60.0	67.5	2.96	1.27
3a[a]	62.9	75.0	3.00	1.41
7[b]	–	60.0	–	1.06
8[b]	–	57.6	–	1.02
10[a]	–	26.1	–	0.49
28[b]	–	36.6	–	0.61
34[b]	–	23.4	–	0.41
35[a]	–	61.7	–	1.16
42[a]	–	53.2	–	1.00
44[a]	34.5	49.6	1.64	0.94
51[b]	–	52.4	–	0.92
Triamterene[a]	21.0	53.0	1.00	1.00
Triamterene[b]	33.4	56.7	1.00	1.00

[a] 32 control groups excreted an average of 53.57% of the volume of the saline load with a standard deviation of 10.3%; a dash indicates an insignificant response of less than 20.6% above control. [b] 26 control groups excreted an average of 73.40% of the volume of the saline load with a standard deviation of 11.5%; a dash indicates an insignificant response of less than 23.0% above control.

England) are reported by symbols of the elements, analytical results were within 0.4% of the calculated value. Infrared spectra were obtained with a Unicam SP200G spectrometer. NMR spectra were recorded with a Varian T-60 spectrometer. Mass spectral data were obtained on an AEI-MS 12 mass spectrometer. Infrared, NMR, and mass measurements were determined for all reported compounds and were considered consistent with the assigned structures.

2-Amino-1,8-naphthyridine-3-carboxamide Hydrochloride Monohydrate (3a). A well-stirred solution of 7.52 g (40 mmol) of **3** in hot MeOH was treated with a stream of HCl gas for 5 min. The mixture was cooled and the resulting precipitate filtered to yield 7.7 g (79%) of cream solid which recrystallized from MeOH as pale yellow needles, mp 290 °C dec. Anal. ($C_9H_8N_4O\cdot HCl\cdot H_2O$) C, H, Cl, N.

General Procedure. A mixture of 2-aminonicotinaldehyde (**4**)[2,4] (3.0 mmol) and the appropriate reagent (6.0 mmol) in absolute EtOH with either piperidine (method A) or 10% aqueous NaOH (method B) as catalyst was heated under reflux for the stated time (Table I). The naphthyridines were obtained in the recorded yield by direct filtration or on evaporation, trituration with a suitable solvent, and filtration.

Method A. 2-Amino-*N*-propyl-1,8-naphthyridine-3-carboxamide (7). A mixture of 0.366 g (3.0 mmol) of **4**, 0.857 g (6.0 mmol) of *N*-propylcyanoacetamide, and 0.075 g (0.75 mmol) of piperidine in 5.0 ml of absolute EtOH was heated under reflux for 24 h. Cooling and filtering yielded 0.55 g (80%) of a yellow solid which recrystallized from C_6H_6 as yellow needles, mp 165–166 °C. Anal. ($C_{12}H_{14}N_4O$) C, H, N.

Method B. 2-Amino-*N*,*N*-dimethyl-1,8-naphthyridine-3-carboxamide (10). A mixture of 0.366 g (3.0 mmol) of **4**, 0.672 g (6.0 mmol) of *N*,*N*-dimethylcyanoacetamide, and 0.4 ml (1.0 mmol) of 10% aqueous NaOH in 5.0 ml of absolute EtOH was heated under reflux for 3 h. The reaction mixture was cooled to yield 0.365 g (56%) of yellow solid which recrystallized from absolute EtOH as pale yellow needles, mp 228–230 °C. Anal. ($C_{11}H_{12}N_3O$) C, H, N.

Method C. 2-Chloro-3-cyano-1,8-naphthyridine (29). An ice-cold solution of 1.71 g (10.0 mmol) of **26** in concentrated HCl was treated with acetone to precipitate the corresponding HCl salt which was subsequently heated under reflux for 1 h in $POCl_3$. The excess $POCl_3$ was removed by distillation and the residue treated with an ice–water mixture. The resulting solution was treated with Na_2CO_3 to precipitate 1.33 g (70%) of a tan solid which recrystallized from EtOH as cream flakes, mp >300 °C. Anal. ($C_9H_4ClN_3$) C, H, Cl, N.

Method D. 3-Cyano-2-methoxy-1,8-naphthyridine (30). A mixture of 0.61 g (3.2 mmol) of **29** and 0.074 g (3.2 mg-atoms)

Table III. Diuretic and Saluretic Effects of 2-Amino-1,8-naphthyridine-3-carboxamide (3) and Its Hydrochloride Salt (3a)

	Determination of the 6-h cumulative excretion													
Dose ip, mg/kg	Mean excretion, ml		Increase over control, %		Na^+, mequiv		K^+, mequiv		Ca^{2+}, mequiv		Na^+/K^+		Na^+/Ca^{2+}	
	3	3a	3	3a	3	3a	3	3a	3	3a	3	3a	3	3a
2.5	6.2	4.8	342	100	0.38	0.29	0.30	0.12	0.019	0.014	1.39	2.97	19.9	22.0
12.5	4.3	4.4	207	83	0.37	0.38	0.18	0.08	0.014	0.013	2.22	4.66	25.6	29.0
6.25	4.3	5.7	207	138	0.34	0.45	0.16	0.11	0.017	0.027	2.10	4.20	20.4	20.6
3.13	4.0	5.5	185	129	0.30	0.34	0.13	0.13	0.013	0.020	2.36	2.97	24.2	21.3
Control		2.4				0.09		0.07		0.003		1.28		36.6
1.6	3.3	6.6	136	83	0.19	0.38	0.11	0.16	0.012	0.008	1.68	2.32	16.3	46.7
0.8	4.2	5.6	200	56	0.22	0.39	0.16	0.12	0.011	0.009	1.26	3.47	18.4	43.1
0.4		4.9		36		0.31		0.10		0.009		3.63		36.0
0.2		5.3		47		0.30		0.15		0.007		2.36		40.2
0.1		3.5		−3		0.20		0.14		0.005		1.52		51.3
Control	1.4	3.6			0.10	0.17	0.10	0.16	0.005	0.010	0.89	1.18	19.1	49.3

of Na metal in 6.0 ml of absolute MeOH was heated under reflux for 1 h. The mixture was stored at 0 °C for 24 h. The 0.45 g (77%) of solid which separated was collected by filtration and recrystallized from *n*-BuOH as cream needles, mp 193–195 °C dec. Anal. ($C_{10}H_7N_3O$) C, H, N.

Method E. 3-Cyano-2-dimethylamino-1,8-naphthyridine (32). A stirred suspension of 0.76 g (4.0 mmol) of **29** in *n*-PrOH was treated with gaseous dimethylamine for 2 h at room temperature. Cooling and filtration gave 0.60 g (76%) of a yellow solid which recrystallized from H_2O as yellow needles, mp 172–174 °C. Anal. ($C_{11}H_{10}N_4$) C, H, N.

Method F. 2-Dimethylamino-1,8-naphthyridine-3-carboxamide (34). A mixture of 0.792 g (4.0 mmol) of **32**, 1.792 g of KOH, 1.4 ml of H_2O, and 7.0 ml of EtOH was heated under reflux for 1 h. The excess solvent was removed and the residue treated with H_2O to yield 0.313 g (36%) of yellow solid which recrystallized from *n*-PrOH as yellow needles, mp 235–237 °C dec. Anal. ($C_{11}H_{12}N_3O$) C, H, N.

Method G. 2-Amino-1,8-naphthyridine-3-thiocarboxamide (36). A well-stirred suspension of 0.51 g (3.0 mmol) of **35**[3] in 1.5 ml of $N(CH_2CH_3)_3$ and 15.0 ml of pyridine was treated with H_2S gas for 4 h. The resulting solution was treated with ice–water to precipitate 0.60 g (98%) of a yellow solid which recrystallized from EtOH as bright yellow needles, mp 265–268 °C dec. Anal. ($C_9H_8N_4S$) C, H, N, S.

Method H. 2-Amino-1,8-naphthyridine-3-carboxamidic Acid Hydrazone (37). A mixture of 0.51 g (3.0 mmol) of **35** and 4.0 ml of $NH_2NH_2 \cdot H_2O$ was refluxed together for 1–2 min. The reaction mixture was rapidly cooled and the resulting yellow solid collected by filtration yielded 0.42 g (69%) which recrystallized from H_2O as yellow needles, mp 218–220 °C dec. Anal. ($C_9H_{10}N_6$) C, H, N.

Method I. 3-Cyano-2-diacetylamino-1,8-naphthyridine (38). A suspension of 0.51 g (3.0 mmol) of **35** in 6.0 ml of acetic anhydride was heated under reflux for 0.5 h. The mixture was cooled and the resulting tan solid collected by filtration yielded 0.37 g (49%) which recrystallized from EtOH as cream needles, mp 179–180 °C. Anal. ($C_{13}H_{10}N_4O_2$) C, H, N.

Method J. Methyl 2-Amino-1,8-naphthyridine-3-carboxylate (41). A mixture of 100.0 ml of MeOH and 10.0 ml of H_2SO_4 was added dropwise to 6.0 g (32.0 mmol) of **39**[3] in 50.0 ml of concentrated H_2SO_4. The resulting solution was heated under reflux for 3 h with an occasional addition of 100.0 ml of MeOH. The excess solvent was removed; the residue was poured over ice and extracted several times with $CHCl_3$. The combined extracts dried (Na_2SO_4) and the $CHCl_3$ was removed to yield 3.96 g (66%) of ester which recrystallized from absolute EtOH as yellow needles, mp 191–192 °C dec. Anal. ($C_{10}H_9N_3O_2$) C, H, N.

Method K. 2-Amino-3-(2,4-diamino-6-*s*-triazinyl)-1,8-naphthyridine Hemihydrate (46). A mixture of 0.406 g (2.0 mmol) of 41, 0.202 g (2.0 mmol) of biguanide, and 10.0 ml of absolute methanol was refluxed together for 1 h. The resulting yellow precipitate was collected by filtration to yield 0.38 g (75%) which recrystallized from EtOH as yellow needles, mp >300 °C. Anal. ($C_{11}H_{10}N_8 \cdot 0.5H_2O$) C, H, N.

Method L. 2-Hydroxy-3-phenylsulfonyl-1,8-naphthyridine (47). A solution of 0.285 g (1.0 mmol) of 19 in 22.0 ml of 2 N HCl was treated with 0.5 g of $NaNO_2$ in 20.0 ml of H_2O at room temperature for 0.5 h. The resulting yellow solid was filtered to yield 0.214 g (75%) which recrystallized from ethyl cellosolve as pale yellow needles, mp 294–296 °C dec. Anal. ($C_{14}H_{10}N_2O_3S$) C, H, N, S.

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