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2,3-Disubstituted 1,6-Naphthyridines as Potential Diuretic Agents

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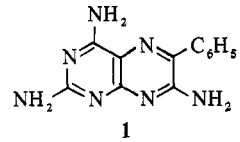
A series of 2,3-disubstituted 1,6-naphthyridines was synthesized either directly from 4-aminonicotinaldehyde or by subsequent reaction of the bicyclic products. The title compounds were prepared because of their relationship to triamterene (**1**). Most were active in a saline-loaded rat screen at 15 mg/kg but inactive at 2 mg/kg (ip). 2-Methylamino-3-(3-pyridyl)- (**9**), 2-methylamino-3-cyano- (**12**), and 2-amino-3-cyano- (**21**) 1,6-naphthyridines displayed diuretic activity comparable to **1** but markedly less than 2-amino-1,8-naphthyridine-3-carboxamide hydrochloride monohydrate (**3**). Structure–activity relationships of the title compounds are discussed and comparisons are made to **1** and **3**.

The clinical need for a potassium-sparing diuretic has resulted in series of papers appearing on the synthesis and preliminary screening of various nitrogen heterocyclic systems,[1] especially pteridines[2,3] and pyrazines.[4] Of two series of pteridines widely investigated, 2,4,7-triamino-6-phenylpteridine (**1**) and 4,7-diamino-2-phenylpteridine-6-carboxamide (**2**) were the most potent diuretics found.[2] The former (**1**), triamterene, also has potent potassium-sparing properties.[5] It was concluded that the major site for drug-receptor interaction in **1** was N-1 or N-8 or both and that the phenyl ring may enhance hydrophobic binding.[2] Since **1** contains many electron-donating amino groups and electron-withdrawing aza atoms, which are probably not essential for drug-receptor interactions, some were deleted in the molecules being investigated in the present work. A series of 1,8-naphthyridines, of which 2-amino-1,8-naphthyridine-3-carboxamide hydrochloride monohydrate (**3**) is the most potent, has been shown to possess diuretic and antikaliuretic activity in rats.† Since in the naphthyridine systems the electronic effects in the ground state of N-6 and N-8 atoms at N-1 are approximately the same,[6] it came of interest to screen a series of 2,3-disubstituted 1,6-naphthyridines to gain further insight into which aza atoms are essential for activity.



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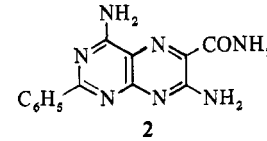

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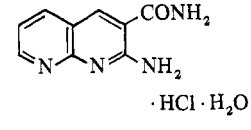


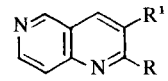
3

Synthesis. The methods for preparing several of the 2-amino compounds appearing in Table I have been described previously; these are **21** and **28–39**.[7] The procedure involved an application of the classical Friedlander method:[8] condensation of substituted acetonitriles with 4-aminonicotinaldehyde in boiling alcohol with an appropriate base catalyst. Similar procedures were employed in preparing **4**, **5**, **40**, and **41**, in which 4-aminonicotinaldehyde was condensed with ethyl cyanoacetate, ethyl 3-pyridylacetate, methyl ethyl ketone, and benzoylacetonitrile, respectively. In the case of ethyl cyanoacetate and benzoylacetonitrile the products did not result from cyclization into the nitrile group which was anticipated by analogy to classical Friedländer reactions with *o*-aminobenzaldehyde.[9,10]

Since in preliminary screening **21**, **28**, and **33** showed

†E. M. Hawes, D. K. J. Gorecki, and D. D. Johnson, unpublished results.

Table I. Chemical Properties and Diuretic Activity of 2,3-Disubstituted 1,6-Naphthyridines

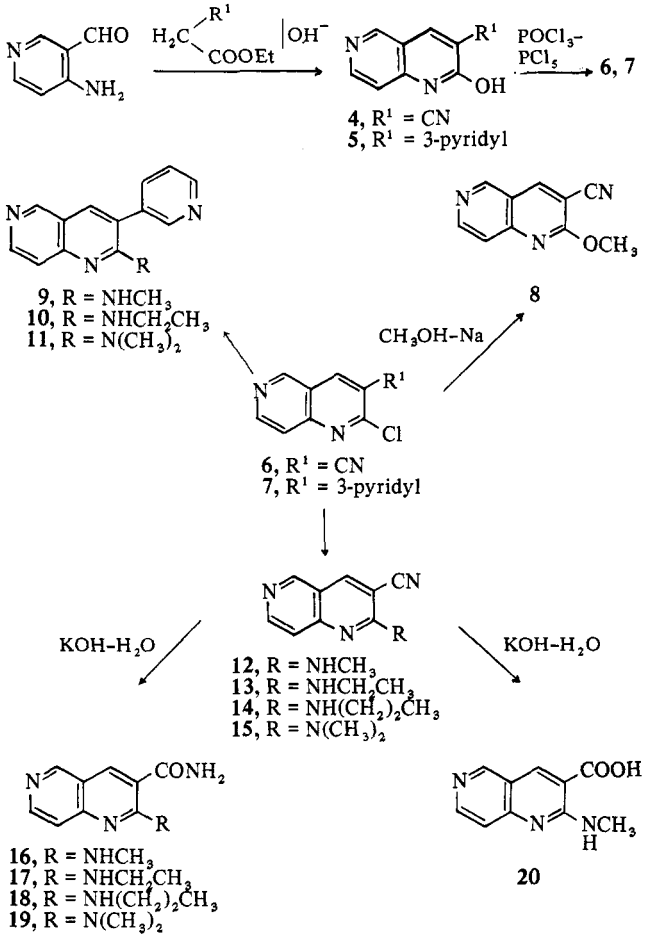


No.	R	R¹	Formula	Recrystn solvent	Mp, °C	Yield,[a] %	Analyses[a]	Pharmacological results[b] Increase from control expressed as % of load excreted 2 mg/kg	15 mg/kg
4	OH	CN	$C_9H_5N_3O$	Dilute HCl–Na_2CO_3	>300	92	C, H, N	–	21.2
5	OH	3-Pyridyl	$C_{13}H_9N_3O$	*n*-BuOH	>300	65	C, H, N		
6	Cl	CN	$C_9H_4ClN_3$	Petroleum ether[c]	>300	89	C, H, Cl, N	–	–
7	Cl	3-Pyridyl	$C_{13}H_8ClN_3$	Petroleum ether[c]	162–163 dec	97	C, H, Cl, N		
8	OCH_3	CN	$C_{10}H_7N_3O$	H_2O	186–189	87	C, H, N	–	32.4
9	$NHCH_3$	3-Pyridyl	$C_{14}H_{12}N_4$	H_2O	182–184	89	C, H, N	–	45.4
10	$NHCH_2CH_3$	3-Pyridyl	$C_{15}H_{14}N_4$	C_6H_6	172–174	92	C, H, N	29.8	–
11	$N(CH_3)_2$	3-Pyridyl	$C_{15}H_{14}N_4$	Petroleum ether[d]	130–132	87	C, H, N	–	–
12	$NHCH_3$	CN	$C_{10}H_8N_4$	*n*-PrOH	269–272 dec	92	C, H, N		
13	$NHCH_2CH_3$	CN	$C_{11}H_{10}N_4$	H_2O	162–164	68	C, H, N		
14	$NH(CH_2)_2CH_3$	CN	$C_{12}H_{12}N_4$	*n*-PrOH	182–184	86	C, H, N		
15	$N(CH_3)_2$	CN	$C_{11}H_{10}N_4$	H_2O	164–168	93	C, H, N	–	23.3
16	$NHCH_3$	$CONH_2$	$C_{10}H_{10}N_4O$	H_2O	229–231	79	C, H, N	–	66.0
17	$NHCH_2CH_3$	$CONH_2$	$C_{11}H_{12}N_4O$	H_2O	227–229	65	C, H, N	22.0	22.7
18	$NH(CH_2)_2CH_3$	$CONH_2$	$C_{12}H_{14}N_4O$	H_2O	179–182	65	C, H, N	–	22.0
19	$N(CH_3)_2$	$CONH_2$	$C_{11}H_{12}N_4O$	H_2O	214–217	65	C, H, N	–	–
20	$NHCH_3$	COOH	$C_{10}H_9N_3O_2 \cdot H_2O$	EtOH	>300	87	C, H, N	–	25.7
21	NH_2	CN	$C_9H_6N_4$	EtOH	>300	*a*	*a*	23.3	92.9
22	NH_2	$CSNH_2$	$C_9H_8N_4S$	EtOH	294–297 dec	97	C, H, N, S	–	22.1
23	NH_2	$C(=NH)NHNH_2$	$C_9H_{10}N_6$	H_2O	240–242 dec	65	C, H, N	33.3	35.6
24	NH_2	COOH	$C_9H_7N_3O_2$	Dilute Na_2CO_3–AcOH	340–345 dec	95	H, N; C[e]	–	65.8
25	NH_2	$COOCH_3$	$C_{10}H_9N_3O_2$	Absolute EtOH	210–212 dec	70	C, H, N		
26	NH_2	$CONHNH_2$	$C_9H_9N_5O$	MeOH	268–269 dec	83	C, H, N	–	–
27	NH_2	$CONHC(=NH)NH_2$	$C_{10}H_{10}N_6O \cdot H_2O$	H_2O	>300	75	C, H, N	–	–
28	NH_2	$CONH_2$	$C_9H_8N_4O$	EtOH	294–295 dec	*a*	*a*	–	38.3
29	NH_2	$CONHCH_3$	$C_{10}H_{10}N_4O$	Absolute EtOH	264–266	*a*	*a*	–	29.5
30	NH_2	$CONH(CH_2)_2N(C_2H_5)_2$	$C_{15}H_{21}N_5O$	Petroleum ether[c]	124.5–126	*a*	*a*	–	–
31	NH_2	$CONH(CH_2)_2$-c-$N(CH_2CH_2)_2O$	$C_{15}H_{19}N_5O_2$	C_6H_6	181–183	*a*	*a*	–	–
32	NH_2	*p*-$C_6H_4NO_2$	$C_{14}H_{10}N_4O_2$	*n*-BuOH	267–270	*a*	*a*	–	39.7
33	NH_2	3-Pyridyl	$C_{13}H_{10}N_4$	C_6H_6	188–190	*a*	*a*	–	42.3
34	NH_2	C_6H_5	$C_{14}H_{11}N_3$	C_6H_6	214.5–217	*a*	*a*	–	–
35	NH_2	2-Furyl	$C_{12}H_9N_3O$	C_6H_6	183–184 dec	*a*	*a*	–	–
36	NH_2	2-Thienyl	$C_{12}H_9N_3S$	Absolute EtOH	163–165	*a*	*a*	–	29.5
37	NH_2	3-Indolyl	$C_{16}H_{12}N_4$	Absolute EtOH	276–278	*a*	*a*	–	–
38	NH_2	H	$C_8H_7N_3$	C_6H_6	238–239	*a*	*a*	–	29.3
39	NH_2	CH_3	$C_9H_9N_3$	H_2O	265–267	*a*	*a*	22.7	33.6
40	CH_3	CH_3	$C_{10}H_{10}N_2$	Petroleum ether[d]	112–114	54	C, H, N	–	27.6
41	C_6H_5	CN	$C_{15}H_9N_3$	EtOH	202–203	71	C, H, N		
42	C_6H_5	$CONH_2$	$C_{15}H_{11}N_3O$	H_2O	239–240	74	C, H, N	–	–
43	$NHCOCH_3$	CN	$C_{11}H_8N_4O$	*n*-PrOH	>300	73	C, H, N	–	22.1
44	$NHCOCH_3$	$CONH_2$	$C_{11}H_{10}N_4O_2$	EtOH	>300	81	C, H, N	–	–
Triamterene								22.0	54.2
2								–	51.9
3								63.9	76.0
Hydrochlorothiazide								60.9	84.8

[a] Under yield and analyses "*a*" indicates that the preparation and analyses of the compound are described in ref 7. [b] A dash indicates an insignificant response of less than 22.0% above control; a blank indicates that the compound was not tested. [c] Bp 100–120° [d] Bp 60–80° [e] C: calcd, 57.14; found, 56.61.

significant diuretic activity it seemed reasonable to prepare series of 3-cyano, 3-carbamoyl, and 3-pyridyl compounds in which the 2 substituent was varied. The simplest approach was to prepare an intermediate from which the required compounds could be obtained by nucleophilic displacement. The 2-chloro derivatives appeared to be satisfactory for this purpose. Treatment of **4** and **5** with PCl_5 in refluxing $POCl_3$ gave the required chloronitriles (**6** and **7**) in good yield (Scheme I). Due to the strong electron-attracting in-

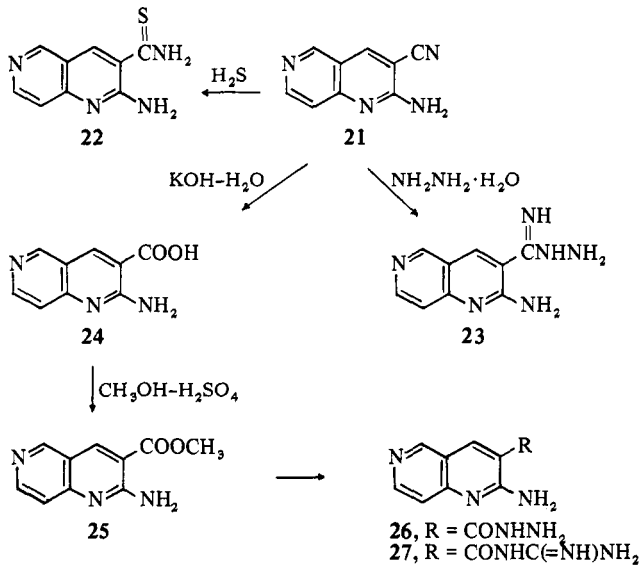
Scheme I



fluence of the aza atoms and the 3 substituents, nucleophilic displacement of the halogen occurred readily. Treatment of **7** with gaseous alkylamines readily provided the 3-pyridyl compounds **9–11**. Similarly, **6** on treatment with sodium methoxide or gaseous alkylamines afforded the nitriles **8** and **12–15**. Simple aqueous KOH hydrolysis of the latter four compounds yielded the required amides **16–19**. A similar conversion of nitrile to carboxylic acid was successful in forming **20** (Scheme I). The acetyl derivatives **43** and **44** were routinely synthesized by treating the 2-amino-3-nitrile **21** and 2-amino-3-amide **28**, respectively, with boiling acetic anhydride.

2-Amino-3-cyano-1,6-naphthyridine (**21**) proved to be a versatile intermediate for the synthesis of 2-amino-3-substituted compounds which could not be directly obtained *via* the Friedländer method (Scheme II). Thus, treatment of **21** with H_2S gas in pyridine resulted in the formation of the thioamide **22**, while reaction with hydrazine hydrate readily formed the amidrazone **23**. Hydrolysis of **21** to the acid **24** followed by esterification afforded the methyl ester **25** which was used in amination procedures to prepare the hydrazide **26** and the guanidine **27**. The amide derivative

Scheme II



42 of 3-cyano-2-phenyl-1,6-naphthyridine was prepared by aqueous KOH hydrolysis.

Structure–Activity Relationships. The results for a saline-loaded rat screen are shown in Table I and a brief description of the procedure is given in the Experimental Section. In further testing shown in Table II the most active compound, **21**, has been shown to possess no antikaliuretic activity. In this screen there was no artificial oral loading and the rats were allowed water *ad libitum* during the period of the experiment.

Of the 35 1,6-naphthyridines screened by the saline-loaded rat screen, 21 showed significant diuretic activity at 15 mg/kg, but of these only four at 2 mg/kg. Compared to the reference compounds for both dose levels, three (**9, 12, 21**) displayed potency comparable to triamterene, while six (**9, 12, 16, 21, 24, 33**) were as potent as **2**; however, the 1,8-naphthyridine (**3**) was the most potent compound screened in the present work. Only the latter (**3**) was as potent as hydrochlorothiazide.

Many 2-amino-3-substituted compounds were screened in which there was a wide variation in electronic features at the 3 position. Of the 3-aryl compounds **32–37** the π-deficient system containing compounds, **32** and **33**, displayed the greatest activity. With substituents other than aryl, marked activity was present in the nitrile (**21**), hydrazone (**23**), carboxylic acid (**24**), and carboxamide (**28**).

Compounds **21, 24, 28,** and **33** were selected for further investigation. Alkyl substitution of the carboxamide moiety in **28** resulted in reduced activity (**29–31**), although the statistical significance of this in the case of **29** is questionable. Compounds **30** and **31**, which were completely devoid of activity, were screened because of their relationship to active pteridines.[3] Alkyl substitution of the amino group in **21** and **24** markedly reduced activity (**12, 15, 20**), but with **28** and **33** the monomethyl derivatives were at least as active (**16, 9**) while further alkyl substitution also reduced activity (**10, 11, 17–19**). Acetylation reduced activity (**43, 44**) as did complete replacement of the 2-amino group with other functional groups (**4, 6, 8, 42**).

That a wide selection of substituents in the 2 and 3 positions led to active compounds is best displayed by the 2,3-dimethyl derivative **40** which is an analog of active pteridines.[2] This wide variation in active structural characteristics is reminiscent of the pteridines[2] and indicates that

Table II. Diuretic and Saluretic Effects of 2-Amino-3-cyano-1,6-naphthyridine (21)

Dose ip, mg/kg	Determination of the 6-hr cumulative excretion							
	Mean excretion, ml	Increase over control, %	Na^+, mequiv	K^+, mequiv	Ca^{2+}, mequiv	Na^+/K^+	Na^+/Ca^{2+}	pH
25	5.6	133	0.64	0.31	0.009	1.85	59.60	6.5
12.5	6.7	179	0.66	0.39	0.009	1.69	73.33	6.6
6.25	5.9	146	0.51	0.31	0.009	1.65	56.61	6.5
3.2	2.7	12.5	0.17	0.16	0.004	1.06	42.50	6.8
1.6	1.8	−25	0.14	0.17	0.004	1.87	53.66	6.6
Control	2.4		0.16	0.17	0.003	0.94	53.33	6.5

in the 1,6-naphthyridines screened, even though far less complex, the essential electronic features for drug-receptor interaction were retained. This tends to suggest that only N-1 is essential for binding to the receptor site. However, the general lower diuretic activity of the 1,6-naphthyridines as compared to the pteridines and to **3** indicates that N-8 enhances drug-receptor interaction.

Experimental Section

Diuretic Screening. The diuretic activity was evaluated by a modification of the classical method of Lipschitz[11] using saline-loaded rats. Adult male albino rats of the Wistar strain weighing between 225 and 275 g were fasted overnight (18 hr) with H_2O allowed *ad libitum*. The rats were divided into groups of eight, one control group and one group for each dose level of test compound; 2 and 15 mg/kg were the doses chosen. Each rat received an oral load of 2.4 ml of 0.9% NaCl/100 g of body weight administered by means of a graduate syringe fitted with a stomach tube. Each desired mg/kg dose of test compound was prepared separately so that the mg/kg dose was in 1.0 ml of saline. The saline-drug solution or suspension was administered to each rat intraperitoneally. The control group received 1 ml/kg of 0.9% NaCl intraperitoneally. The rats were placed in metabolism cages and urine was collected and recorded for a 6-hr period. The results were expressed in terms of the per cent of volume of the saline-load excreted during the 6-hr period.

$$\frac{\text{volume of urine (8 rats)}}{\text{volume of saline load (8 rats)}} \times 100$$

It was found that 25 control groups excreted an average of 52.58% of the volume of the saline load with a standard deviation of 11.04%. Thus, those results greater than 22% above control are regarded as significant within 95% confidence limits.[5]

Synthesis.‡ **2-Hydroxy-3-cyano-1,6-naphthyridine (14).** A mixture of 2.44 g (0.02 mol) of 4-aminonicotinaldehyde, 4.52 g (0.04 mol) of ethyl cyanoacetate, 0.50 ml (0.005 mol) of piperidine, and 50 ml of absolute EtOH was refluxed together for 1 hr. The 3.15 g (92%) of pale yellow solid which separated was collected by filtration and reprecipitated from dilute HCl with Na_2CO_3, mp >300°. *Anal.* ($C_9H_5N_3O$) C, H, N.

2-Chloro-3-cyano-1,6-naphthyridine (6). To a well-stirred mixture of 25.65 g of PCl_5 in 100 ml of $POCl_3$ was added 5.13 g (0.03 mol) of 2-hydroxy-3-cyano-1,6-naphthyridine **(4).** The reaction mixture was refluxed for 1 hr and then a portion of the $POCl_3$ was removed by distillation. Upon cooling the pale yellow solid was filtered and treated with an ice-water mixture. This resulting suspension was basified with Na_2CO_3 and extracted several times with $CHCl_3$. The extracts were dried (Na_2SO_4) and the $CHCl_3$ was removed to yield 4.58 g (89%) of yellow solid which recrystallized from petroleum ether (100–120°), mp >300°. *Anal.* ($C_9H_4ClN_3$) C, H, Cl, N.

2-Methoxy-3-cyano-1,6-naphthyridine (8). A mixture of 0.57 g (0.003 mol) of **6** and 0.069 g (0.003 g-atom) of Na metal in 5.0 ml of absolute MeOH was heated under reflux for 1 hr. The 0.48 g (87%) of solid which separated was collected by filtration and recrystallized from H_2O as pale yellow needles, mp 186–189°. *Anal.* ($C_{10}H_7N_3O$) C, H, N.

‡Satisfactory spectra were obtained in all cases for structural determination: ir as KBr pellets on a Unicam SP200 g spectrometer; nmr on a Varian T-60 spectrometer. Melting points were determined in capillary tubes on a Gallenkamp block and are uncorrected. Where analyses (Dr. Strauss, Oxford, England) are indicated only by symbols of the elements, analytical results were within 0.4% of their values.

2-Methylamino-3-cyano-1,6-naphthyridine (12). A suspension of 0.76 g (0.004 mol) of **6** in 25.0 ml of *n*-PrOH was stirred at room temperature for 1 hr while a stream of anhydrous $MeNH_2$ gas was passed into the reaction mixture. Filtration gave 0.68 g (92%) of a yellow solid which recrystallized from *n*-PrOH as yellow needles, mp 269–272° dec. *Anal.* ($C_{10}H_8N_4$) C, H, N.

2-Methylamino-1,6-naphthyridine-3-carboxamide (16). A mixture of 0.200 g (0.0011 mol) of **12,** 0.400 g of KOH, 0.75 ml of H_2O, and 5.0 ml of EtOH was heated under reflux for 5.0 min. The excess solvent was removed and the residue treated with water to yield 0.175 g (79%) of solid which recrystallized from H_2O as yellow needles, mp 229–231°. *Anal.* ($C_{10}H_{10}N_4O$) C, H, N.

2-Amino-1,6-naphthyridine-3-thiocarboxamide (22). A suspension of 0.34 g (0.002 mol) of **21** in 1.0 ml of $N(CH_2CH_3)_3$ and 10.0 ml pyridine was stirred at room temperature for 2 hr while a stream of H_2S gas was passed into the reaction mixture. The reaction mixture was treated with ice-water yielding 0.395 g (97%) of a cream solid which recrystallized from EtOH as yellow needles, mp 294–297° dec. *Anal.* ($C_9H_8N_4S$) C, H, N, S.

2-Amino-1,6-naphthyridine-3-carboximidic Acid Hydrazone (23). A mixture of 0.34 g of **21** and 4.0 ml of $NH_2NH_2 \cdot H_2O$ was refluxed together for 5 min. The mixture was cooled and the yellow solid collected by filtration yielded 0.26 g (65%) which recrystallized from H_2O as yellow needles, mp 240–242° dec. *Anal.* ($C_9H_{10}N_6$) C, H, N.

2-Amino-1,6-naphthyridine-3-carboxylic Acid (24). A mixture of 13.0 g (0.076 mol) of **21,** 26.0 g of KOH, 120 ml of H_2O, and 200 ml of EtOH was heated under reflux for 14 hr. The excess solvent was removed and the residue treated with H_2O. Acidification with AcOH yielded 13.7 g (95%) of a pale solid which was purified by reprecipitation from dilute Na_2CO_3, mp 340–345° dec. *Anal.* ($C_9H_7N_3O_2$) unsatisfactory analytical figures were obtained.

Methyl 2-Amino-1,6-naphthyridine-3-carboxylate (25). A mixture of 250.0 ml of MeOH and 25.0 ml of H_2SO_4 was added dropwise to a mixture of 10.0 g (0.053 mol) of **24** in 80.0 ml of concentrated H_2SO_4. The resulting solution was heated under reflux for 3 hr while every 0.75 hr an additional 100.0 ml of MeOH with a little H_2SO_4 was added The excess solvent was removed, the residue was poured over ice and neutralized with Na_2CO_3 and extracted several times with $CHCl_3$, and the extracts were dried (Na_2SO_4). The $CHCl_3$ was removed to yield 7.55 g (70%) of ester which recrystallized from absolute EtOH as cream needles. mp 210–212° dec. *Anal.* ($C_{10}H_9N_3O_2$) C, H, N.

2-Amino-1,6-naphthyridine-3-carboxylic Acid Hydrazide (26). A mixture of 1.00 g (0.0049 mol) of **25** and 15 ml of $NH_2NH_2 \cdot H_2O$ was heated under reflux for 0.5 hr The resulting solid was collected by filtration to yield 0.83 g (83%) which recrystallized from MeOH as white needles, mp 268–269° dec. *Anal.* ($C_9H_9N_5O$) C, H, N.

2-Amino-*N*-amidino-1,6-naphthyridine-3-carboxamide (27). Guanidine HCl (0.76 g, 0.008 mol) was added to a solution of 0.184 g (0.008 g-atom) of Na metal in 10.0 ml of anhydrous MeOH and was allowed to stir for 5 min upon which 0.406 g (0.002 mol) of **25** was added. The mixture was refluxed for 1 hr and the solvent removed. The cream solid was treated with H_2O and filtered to yield 0.37 g (80%) of product which recrystallized from H_2O as cream flakes, mp >300°. *Anal.* ($C_{10}H_{10}N_6O \cdot H_2O$) C, H, N.

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2-Azabicyclo[2.2.2]octane Derivatives as Conformational Analogs of Local Anesthetics†

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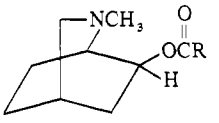
The importance of conformational factors in the production of local anesthesia by the *p*-aminobenzoate esters, particularly procaine, was examined through the synthesis of the *p*-aminobenzoate esters of the cis and trans isomers of 5- and 6-hydroxy-2-methyl-2-azabicyclo[2.2.2]octane. One of these isomers, the *p*-aminobenzoate ester of *trans*-6-hydroxy-2-methyl-2-azabicyclo[2.2.2]octane, produced three times the duration of action of procaine in the intradermal wheal assay in guinea pigs. The syntheses, stereochemical assignments, and pharmacological results are presented.

The concept that blockade of nerve impulses by local anesthetics is a consequence of interactions of the local anesthetic with a biological receptor site located in a structurally distinct area on the cell membrane has generated a significant degree of recent interest.[1,2] While attempts to correlate physicochemical properties of local anesthetics have been reported, it is only recently that the importance of conformational effects has been studied. It has been suggested that a gauche conformation of the ethanolamine linkage of procaine is an important feature in its ability to block conduction of the nerve impulse.[3] Quantum mechanical calculations have been performed by the method of perturbative configuration interaction using localized orbitals on model local anesthetics representing the methanolamine, ethanolamine, propanolamine, and anilide structures.[4] The stable conformations calculated for the ester anesthetics indicated an optimum separation of 4.1–4.2 Å between the basic nitrogen and carbonyl oxygen atoms. This observation did not hold true for the anilide series. In a recent study designed to clarify conformational aspects of local anesthetics, Boots and Boots reviewed previous efforts directed toward testing conformational isomers and reported their results of conformationally restricting the flexibility of the propanolamine chain through its incorporation, in part, into the norbornane ring system.[5] Differences in activity between the two epimers studied were observed, the most potent epimer being the one in which the amine and alcohol functions occupy the exo positions of the norbornane ring. More recently, a series of 1-alkyl-3-benzoyl-3-acyloxypiperidines was tested for local anesthetic activity and toxicity.[6] These derivatives can be formally considered as ethanolamines which are restricted in a preferred gauche conformation. The procaine analog of this series was eight times more active and 16 times more toxic than procaine.

We wish to report here the synthesis and local anesthetic activity of 2-azabicyclo[2.2.2]octane analogs of local anesthetics in order to examine conformational effects of both the ethanolamine and propanolamine series of local anesthetics within the same "conformationally rigid" ring framework. Compounds **1** and **3** can be considered as conformational analogs of procaine in which the N-C-C-O grouping is restricted in gauche and trans conformations, respectively. Compounds **2** and **4** represent similarly restricted conformers of the corresponding propanolamine series.



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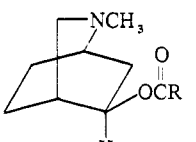

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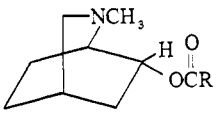

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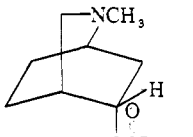

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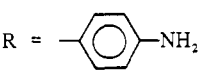

Chemistry. The key intermediates in the synthesis of the esters **1–4** were, of course, the corresponding alcohols **5–8.** While syntheses of several of these alcohols had been previously reported, we noted some inconsistencies in structural assignments on repetition of these reactions. Two basic approaches were utilized and are shown in Schemes I and II. The synthesis of **5, 6,** and **8** was accomplished (Scheme I) through a modification of the procedure reported by DeGraw and Kennedy.[7] Oxidation of the olefin obtained from 1,3-cyclohexadiene and methylene bisurethane with *m*-chloroperoxybenzoic acid gave a mixture of epoxides which was not separated. Reduction of the epoxide mixture with Red-Al gave three different alcohols, **5, 6,** and **8,** in a ratio of 1:4.5:4.5 based on glc. DeGraw and Kennedy reported only

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