Scheme I

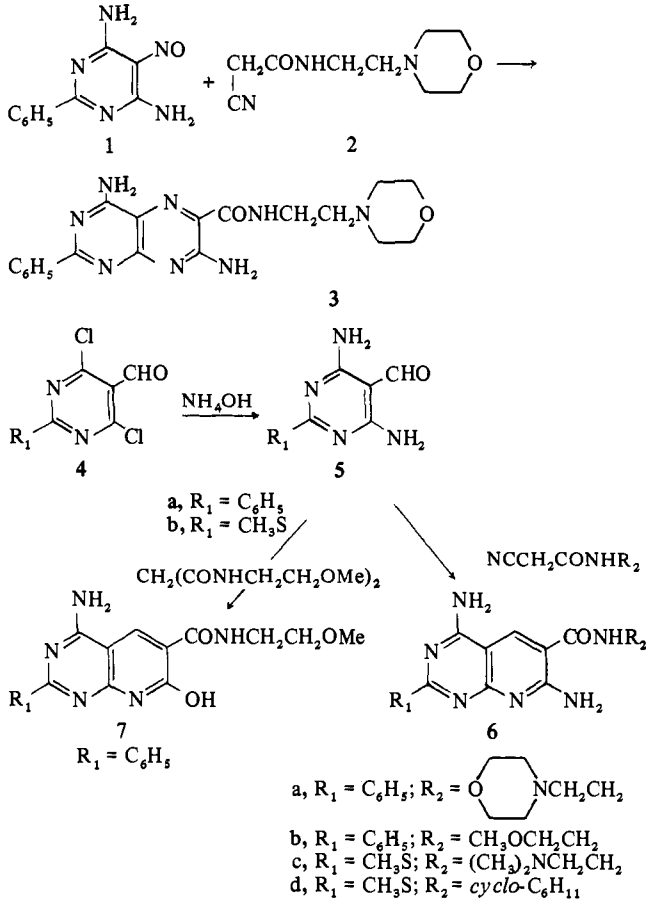

Table I. Substituted Pyrido[2,3-*d*] pyrimidine-6-carboxamides

No.	R_1	R_2	Recrystn solvent[a]	Mp, °C	Yield, %	Formula
6a	C_6H_5	$(CH_2)_2N$(morpholino)	A	299–300	50	$C_{20}H_{23}N_7O_2$
b	C_6H_5	$(CH_2)_2OCH_3$	B	258–261	10	$C_{17}H_{18}N_6O_2$
c	CH_3S	$(CH_2)_2N(CH_3)_2$	B	297–300	29	$C_{13}H_{19}N_7OS$
d	CH_3S	*cyclo*-C_6H_{11}	A	>360	30	$C_{15}H_{20}N_6OS$

[a] A = aq DMF, B = EtOH.

electronic difference to nullify the diuretic effect previously observed.

Experimental Section†

4,6-Diamino-2-phenyl-5-pyrimidinecarboxaldehyde (5a). To 50 ml of concd NH_4OH in a pressure flask was added 15 g of 4,6-dichloro-2-phenyl-5-pyrimidinecarboxaldehyde.[2] The mixt was heated on a steam bath for 1 hr and a sufficient quantity of EtOH was added to solubilize it. Heating was cont for an addl hour. The reaction mixt was cooled in ice and the cryst product deposited amounted to 9.5 g. A portion was recrystd from EtOH for analysis, mp 217–218°. *Anal.* $C_{11}H_{10}N_4O$.

†Melting points were detd in capillary tubes (Thomas-Hoover mp apparatus) and are uncor. Where analyses are indicated only by empirical formulas, analytical results for C, H, N, and S (where applicable) were within ±0.4% of theory. Ir spectra were obtd in KBr discs using a Perkin-Elmer (Model 21) spectrophotometer and are compatible with the assigned structures. The NHC=O bands for 6a–d and 7 ranged from 6.06 to 6.14 μ.

4,6-Diamino-2-methylthio-5-pyrimidinecarboxaldehyde (5b) was prepd in the same fashion as **5a**. From 15 g of 4,6-dichloro-2-methylthio-5-pyrimidinecarboxaldehyde[4] and 80 ml of concd NH_4OH was obtd 10 g of **5b**. The analytical sample, mp 228–230°, was obtd by recrystn from MeOH. *Anal.* $C_6H_8N_4OS$.

The following procedure typifies the method used for preparing **6b–d**.

4,7-Diamino-*N*-(2-morpholinoethyl)-2-phenylpyrido[2,3-*d*]-pyrimidine-6-carboxamide (6a). To 0.69 g of Na in 100 ml of EtOH was added 6.1 g of **4a** and 5.9 g of 2-cyano-*N*-(2-morpholinoethyl)acetamide. The reaction mixt was heated under reflux for 20 min, during which time a yellow ppt was deposited. The mixt was then cooled in ice and filtered under suction. The product amounted to 5.9 g. The analytical sample was obtd by recrystn of a portion from aq DMF.

4-Amino-7-hydroxy-*N*-(2-methoxyethyl)-2-phenylpyrido-[2,3-*d*] pyrimidine-6-carboxamide (7). To a soln contg 0.7 g of Na in 60 ml of abs EtOH was added 6.1 g of **5a** and 5.9 g of *N,N'* bis(2-methoxyethyl)malonamide. The reaction mixt was heated under reflux with stirring for 3 hr and then cooled in ice. The yellow ppt which formed was collected on a filter and recrystd from aq DMF; yield 2 g, mp >360°. *Anal.* $C_{17}H_{17}N_5O_3$.

Acknowledgments. The authors are indebted to Mr. Bruce Hofmann and staff for the analytical results and to Dr. Marvin E. Rosenthale for the diuretic assays.

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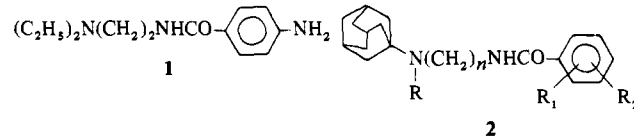
Synthesis and Antiarrhythmic Activity of Some *N*-(Adamantylaminoalkyl)benzamides[1]

V. L. Narayanan* and F. J. Sweeney

The Squibb Institute for Medical Research, New Brunswick, New Jersey 08903. *Received October 15, 1971*

The publication by Yung, *et al.*,[2] concerning the synthesis of novel analogs of procaine amide (**1**) prompts us to report our efforts in this direction. Recently several reports have appeared describing the synthesis and biological activity of a variety of adamantane derivatives.[3] Our paper describes the synthesis and antiarrhythmic activity of a series of *N*-(adamantylaminoalkyl)benzamides (**2**).



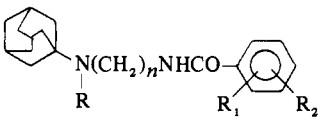
1

2
R = H, C_2H_5
n = 2, 3
R_1 = H, Cl, CH_3
R_2 = NH_2, NO_2

Chemistry. Routes to the preparation of the key intermediates *N*-(1-adamantyl)-*N*-ethylethylenediamine (**6**) and *N*-(1-adamantyl)-1,3-propanediamine (**8**), required for the final synthesis of the *N*-(adamantylaminoalkyl)benzamides (**2**) are outlined below.

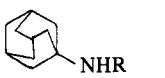
Refluxing a suspension of 1-acetamidoadamantane[4] (**3**) with an excess of LAH in Et_2O afforded an 80% yield of *N*-ethyl-1-adamantylamine (**4**). Treatment of **4** with a large excess of aziridine gave only starting material. However, the reaction of **4** with aziridine tosylate gave a mixture of

Table I

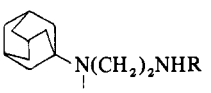


No.	n	R	R_1	R_2	Recrystn solvent	Mp, °C	Formula	Analysis
13	2	C_2H_5	H	p-NO_2	MeCN	191-193	$C_{21}H_{29}N_3O_3 \cdot HCl$	C, H, N, Cl
14	2	C_2H_5	H	p-NH_2	MeCN	280-282	$C_{21}H_{31}N_3O \cdot HCl$	C, H, N
15	2	C_2H_5	o-Cl	p-NO_2	MeCN	193-196	$C_{21}H_{28}ClN_3O_3 \cdot HCl$	C, H, N, Cl
16	2	C_2H_5	o-Cl	p-NH_2	MeCN	241-243	$C_{21}H_{30}ClN_3O \cdot HCl$	C, H, N, Cl
17	2	C_2H_5	m-CH_3	p-NO_2	MeCN	223-225	$C_{22}H_{31}N_3O_3 \cdot HCl$	C, H, N, Cl
18	2	C_2H_5	m-CH_3	p-NH_2	MeCN	274-275	$C_{22}H_{33}N_3O \cdot HCl$	C, H, N, Cl
19	2	C_2H_5	H	o-NO_2	MeCN	228-230	$C_{21}H_{29}N_3O_3 \cdot HCl$	C, H, N, Cl
20	2	C_2H_5	H	o-NH_2	MeCN	252-254	$C_{21}H_{31}N_3O \cdot HCl$	C, H, N, Cl
21	3	H	H	p-NO_2	MeOH-C_6H_6	294-297	$C_{20}H_{27}N_3O_3 \cdot HCl$	C, H, N, Cl
22	3	H	H	p-NH_2	MeOH-Et_2O	274-277	$C_{20}H_{29}N_3O \cdot 2HCl$	C, H, N, Cl
23	3	H	o-Cl	p-NO_2	MeOH-Et_2O	239-242	$C_{20}H_{26}ClN_3O_3$	C, H, N
24	3	H	o-Cl	p-NH_2	MeOH-MeCN	264-266	$C_{20}H_{28}ClN_3O_3 \cdot HCl$	C, H, N, Cl
25	3	H	m-CH_3	p-NO_2	MeOH-Et_2O	270-272	$C_{21}H_{29}N_3O_3 \cdot HCl$	C, H, N, Cl
26	3	H	m-CH_3	p-NH_2	MeCN-Et_2O	225-228	$C_{21}H_{31}N_3O \cdot 2HCl$	C, H, N
27	3	H	H	o-NO_2	MeCN	270-273	$C_{20}H_{27}N_3O_3 \cdot HCl$	C, H, N, Cl
28	3	H	H	o-NH_2	MeCN	229-231	$C_{20}H_{29}N_3O \cdot HCl$	C, H, N, Cl
29	3	H	H	m-NO_2	MeCN	253-254	$C_{20}H_{27}N_3O_3 \cdot HCl$	C, H, N, Cl
30	3	H	H	m-NH_2	MeCN	268-271	$C_{20}H_{29}N_3O \cdot 2HCl$	C, H, N, Cl

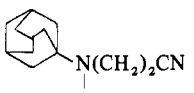
products from which **5** was obtained in 27% yield by simple crystallization from Et_2O-hexane. The reduction of **5**, using Na in liquid NH_3 in a mixture of Et_2O and THF, furnished an excellent yield (80%) of **6**.



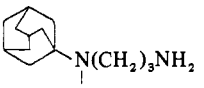
3, R = $COCH_3$
4, R = C_2H_5



5, R = Ts
6, R = H



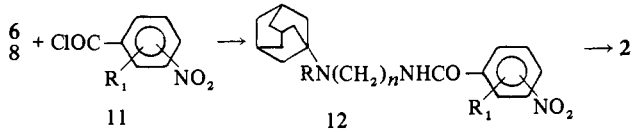
7, R = H
9, R = $COCH_3$



8, R = H
10, R = C_2H_5

In an effort to synthesize the diamine **10**, the alkylation of **3** with β-chloropropionitrile was attempted under different reaction conditions, but without success. The cyanoethylation of **3** using Triton B also failed. As an alternate route, 1-adamantaneamine was refluxed with a large excess of acrylonitrile in the presence of 10% of its weight of H_2O to give, exclusively, the monocyanoethylated compd **7**. Acetylation of **7** by refluxing with excess Ac_2O gave **9**. Efforts to reduce **9** to the diamine **10** by refluxing with LAH in Et_2O led, instead, to the isolation of adamantyl-*N*-ethylamine (**4**) in excellent yields (90%). This is an interesting case of an elimination initiated by a hydride ion. However, the reduction of **7** with LAH in Et_2O at room temperature gave an 85% yield of *N*-(1-adamantyl)-1,3-propanediamine (**8**).

The reaction of the diamines **6** and **8** with the properly substituted nitrobenzoyl chlorides **11** yielded the nitrobenzamides **12**. Catalytic reduction of **12** using PtO_2, gave



11 **12**

R = H, C_2H_5
n = 2, 3
R_1 = H, Cl, CH_3

Table II. Antiarrhythmic Activity in Mice

Compd	Activity	Toxicity
1	1	1
14	5	1.5
16	3	5
18	3	4
20	2	4
22	2	3
24	3	2
26	2	3
28	2	2
30	2	2

the desired *N*-(adamantylaminoalkyl)benzamides (**2**). The compounds synthesized are listed in Table I.

Pharmacological Results. The antiarrhythmic activity of these compounds was determined in mice by a test that measures the ability of the compound to antagonize $CHCl_3$-induced ventricular fibrillation.[5] The compound is injected ip into albino mice and the animals are placed in a $CHCl_3$ chamber. After respiratory arrest, the heart is exposed quickly and the quantal responses are recorded, based on visual observation of the heart. In addition, the ip LD_{50} in mice is also determined. All compounds are compared with procaine amide, which has an ip ED_{50} of 75 mg/kg and an ip LD_{50} of 325 mg/kg in this test. The results are summarized in Table II.

All compounds show enhancement of antiarrhythmic activity, accompanied by an increase in toxicity. The first member of the series, **14**, shows the most favorable therapeutic ratio, three times that of procaine amide. The antiarrhythmic activity of **14** was confirmed in three dogs, in which it had 3 times the activity of procaine amide. However, unlike procaine amide, **14** prolongs the duration of the QRS interval in the electrocardiogram.

Experimental Section

Melting points were detd on a Thomas-Hoover Uni-Melt apparatus and are uncor. The results of elemental analyses were within ±0.4% of the theoretical values, unless otherwise indicated.

N-**Ethyl-1-adamantylamine (4).** To a well-stirred suspension of 25 g of LAH in 1000 ml of dry Et_2O, 19.3 g (0.1 mole) of 1-acetamidoadamantane[4] (**3**) was added in portions, and the mixt was heated under reflux overnight. The reaction mixt was cooled and

25 ml of H_2O, followed by 75 ml of 2 *N* NaOH and 20 ml of H_2O, was added dropwise. The pptd solid was filtered and washed thoroughly with Et_2O. The combined ext was dried ($MgSO_4$), concd, and distd to give 14.2 g (79%) of **4**, bp 102–104° (7.0 mm), solidifies to a low-melting solid. *Anal.* ($C_{12}H_{21}N$) C, H, N.

The picrate of **4** was obtd as tiny yellow crystals from EtOH, mp 253–256° dec. *Anal.* ($C_{18}H_{24}N_4O_7$) C, H, N.

***N*-[2-[(1-Adamantyl)ethylamino]ethyl]-*p*-toluenesulfonamide (5).** To a mixt of 4.31 g (0.1 mole) of ethyleneimine and 10.12 g (0.1 mole) of Et_3N in 150 ml of dry C_6H_6 cooled to −5°, a soln of 19.07 g (0.1 mole) of TsCl in 200 ml of dry $CHCl_3$ was added during 1 hour. After stirring for 0.5 hr, dry Et_2O was added and the pptd solid was removed by filtration and washed with Et_2O. The combined ext was concd to a syrup at room temp and dissolved in 100 ml of dry C_6H_6. To the above soln of aziridine tosylate, a soln of 17.93 g (0.1 mole) of **4** in 100 ml of dry C_6H_6 was added at 20°, and the mixt was then refluxed for 6 hr. Evapn of the solvent *in vacuo* gave a thick syrup. Et_2O (500 ml) was added, and after filtration of the solids, the Et_2O ext was concd, 100 ml of hexane was added, and the mixt was allowed to stand for 2 hr, whereupon 10.3 g (27%) of solid sepd, mp 90–92°. An analytical sample was obtd as white crystals from C_6H_6–hexane, mp 92–93°. *Anal.* ($C_{21}H_{22}N_2O_2S$) C, H, N. Evapn of the hexane soln yielded 8.5 g of the starting material **4**.

***N*-(1-Adamantyl)-*N*-ethylethylenediamine (6).** To a soln of 3.76 g (0.01 mole) of **5** in a mixt of 25 ml of Et_2O and 75 ml of THF, 100 ml of liq NH_3 was added under a Dry Ice condenser. Freshly cut Na was added with stirring during 0.5 hr till a permanent blue color appeared. After stirring of the soln for 2 hr, 5 g of solid NH_4Cl was added and the excess NH_3 was allowed to evap. The solid was filtered and extd thoroughly with Et_2O. The combined Et_2O exts were concd to give 2.1 g (98%) of **6** as a thick oily liq. The salt of **6** with 1 mole of *p*-aminobenzoic acid crystd from MeCN as white needles, mp 159–160°. *Anal.* ($C_{21}H_{33}N_3O_2$) C, H, N.

3-(1-Adamantylamino)propionitrile (7). To a soln of 10 g of adamantylamine in 100 ml of acrylonitrile, 1 ml of H_2O was added and the mixt was heated under reflux overnight. Evapn of the excess acrylonitrile gave a thick liquid which solidified to give 12.3 g (95%) of a glassy solid. An analytical sample distd at 165–175° (0.6–0.7 mm). *Anal.* ($C_{13}H_{20}N_2$) C, H, N.

***N*-(1-Adamantyl)-1,3-propanediamine (8).** To a well-cooled suspension of 3.8 g of LAH in 200 ml of dry Et_2O, a soln of 20.4 g (0.1 mole) of **7** was added dropwise at room temp. After this addn, the reaction mixt was stirred at room temp for 3 hr. With cooling, 4 ml of H_2O was added, followed by 3 ml of 5 *N* NaOH soln, and 14 ml of H_2O. The Et_2O layer was decanted, and the solid cake was washed with several portions of Et_2O. The Et_2O layers were combined, dried ($MgSO_4$), and evapd, to yield 17.1 g (85%) of **8**. The dioxalate melted at 238–239°. *Anal.* ($C_{13}H_{24}N_2 \cdot 2(COOH)_2$) C, N; calcd: H, 7.27; found: H, 6.79.

The prepn of compds in Table I is exemplified by the following typical procedure.

***N*-[2-[(1-Adamantyl)ethylamino]ethyl]-*p*-nitrobenzamide·HCl (13).** To a soln of 1.11 g (0.005 mole) of **6** in 50 ml of dry $CHCl_3$, a soln of 0.03 g (0.005 mole) of *p*-O_2NBzCl in 25 ml of dry $CHCl_3$ was added dropwise at room temp and the mixt was refluxed for 4 hr. Evapn of the $CHCl_3$ gave a solid, which crystd on the addn of Et_2O, yielding 1.6 g (80%) of **13** as brownish white crystals. A sample crystd from MeCN melted at 191–193°. *Anal.* ($C_{21}H_{29}N_3O_3 \cdot HCl$) C, H, N, Cl.

***N*-[2-[(1-Adamantyl)ethylamino]ethyl]-*p*-aminobenzamide·HCl (14).** A soln of 1.2 g (0.003 mole) of **13** in 50 ml of EtOH was reduced in a Parr hydrogenator, using 0.12 g of PtO_2 as catalyst. Evapn of the solvent, after filtration of the catalyst, gave a solid that was crystd from MeCN to yield 0.78 g (69%) of **14** as pink-white crystals, mp 280–282°. *Anal.* ($C_{21}H_{31}N_3O \cdot HCl$) C, H, N.

Acknowledgment. The authors are indebted to Dr. J. Bernstein for his suggestions and encouragement during this investigation, to Mr. J. High and Dr. R. Laffan of our Pharmacology Department for the data on antiarrhythmic activity in mice, and to Dr. V. Lanzoni of the Boston University of Medicine for the corresponding data for dogs. The authors wish to thank Mr. J. Alicino and his staff for the microanalyses.

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New Compounds

Some Cyclic Derivatives of 2-Cyclohexylamino-1-phenylethanol

W. J. Irwin,* D. L. Wheeler, and N. J. Harper

Department of Pharmacy, University of Aston in Birmingham, Gosta Green, Birmingham B4 7ET, England.
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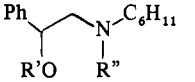
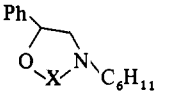
Our interest in derivatives of β-aminoethanols[1,2] for a general screening program has led us to study some 5-membered (**2**)[3-5] and 6-membered (**3**)[6,7] cyclic compounds derived from 2-cyclohexylamino-1-phenylethanol (**1a**).

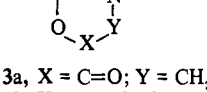
Some preliminary screening results on mice which also include 2-phenethylamino-1-phenylethanol (**4**) and 3-phenethyl-5-phenyloxazolidine (**5**), are presented in Table II. No potentiation of subthreshold doses of pentobarbital was observed with any derivative prepared in this investigation and the most interesting compound appeared to be 2-cyclohexylamino-1-phenylethanol (**1a**).



1a, R' = R" = H
b, R' = H; R" = NH_2
c, R' = H; R" = NHCOPh
d, R' = R" = $COCH_2Ph$
e, R' = H; R" = CH_2CH_2Ph



2a, X = CH_2
b, X = S=O



3a, X = C=O; Y = CH_2
b, X = Y = C=O
c, X = C=S; Y = NH
d, X = C=S; Y = NMe