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.

References

(1) Abstracts, Division of Medicinal Chemistry, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, MED1 44.
(2) D. K. Yung, L. G. Chatten, and D. P. MacLeod, *J. Pharm. Sci.*, **57**, 2073 (1968).
(3) (a) K. Gerzon, E. V. Krumkalns, R. L. Brindle, F. J. Marshall, and M. A. Root, *J. Med. Chem.*, **6**, 760 (1963); (b) R. T. Rapala, R. J. Kraay, and K. Gerzon, *ibid.*, 8, 580 (1965); (c) W. Korytnyk and G. Fricke, *ibid.*, 11, 180 (1968); (d) V. G. Keizer and J. G. Korsloot, *ibid.*, **14**, 411 (1971); (e) A. N. Voldeng, C. A. Bradley, R. D. Lee, E. L. King, and F. L. Melder, *J. Pharm. Sci.*, **57**, 1053 (1968).
(4) H. Stetter, J. Mayer, M. Schwarz, and C. Wulff, *Ber.*, **93**, 226 (1960).
(5) J. W. Lawson, *J. Pharmacol. Exp. Ther.*, **160**, 22 (1968).

New Compounds

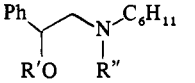
Some Cyclic Derivatives of 2-Cyclohexylamino-1-phenylethanol

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

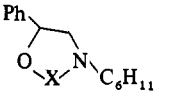
Department of Pharmacy, University of Aston in Birmingham, Gosta Green, Birmingham B4 7ET, England.
Received October 8, 1971

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**).

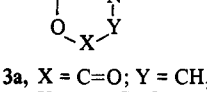
Some preliminary screening results on mice which also include 2-phenethylamino-1-phenylethanol (**4**) and 3-phenethyl-5-phenyloxazolidine (**5**), are presented in Table II. No potentiation of subthreshold doses of pentobarbital was observed with any derivative prepared in this investigation and the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

Table I.

Compd	Formula[a]	Mp, °C	Yield, %	Solvent	Ir, cm^{-1}
1b	$C_{14}H_{22}N_2O$	82–83	52	Petr ether	
1b·HCl	$C_{14}H_{23}ClN_2O$	121–122		EtOH-Et_2O	
1c	$C_{21}H_{26}N_2O_2$	165–166	78	EtOH-petr ether	1630 (C=O)
1d	$C_{30}H_{33}NO_3$	84–85	47	Petr ether	1730 (O–C=O)
					1620 (N–C=O)
1e·HCl	$C_{22}H_{30}ClNO$	163–164	94	EtOH-Et_2O	3200 (OH)
2a·HCl	$C_{15}H_{21}ClNO$	158–159	64	EtOH-Et_2O	1120 (O–C–N)
2b[b]	$C_{14}H_{19}NO_2S$	107–108	15	EtOH	1135 (C=S)
3a·picrate	$C_{22}H_{24}N_4O_9$	180–181	40	C_6H_6	1740 (C=O)
3b[c]	$C_{16}H_{19}NO_3$	126–127	73	Me_2CO-cyclohexane	1745 (O–C=O)
					1665 (N–C=O)
3c	$C_{15}H_{20}N_2OS$	182–183	36	$CHCl_3$-petr ether	1190 (C=S)
3d·HCl	$C_{16}H_{23}ClN_2OS$	148–149	49	EtOH-Et_2O	1170 (C=S)

[a] All compds were analyzed for C, H, and N and were within ±0.4% of the theoretical values. [b] Shown by tlc and nmr to be a mixt of geometrical isomers (5:1) with the cis isomer predominant.[8] [c] Calcd nmr spectrum in C_6H_6 indicates an envelope conformation.[2]

Table II.

		Phenylquinone-induced writhing[b]		Neuropharmacological Tests[b]					
Compd	LD_{50},[a] mg/kg	% inhibition	ED_{50}, mg/kg	Mydriasis, %	Rotating rod, %	Grip strength, %	Hot plate, %	Tonic extension (pentylenetetrazole), %	Death (pentylenetetrazole), %
1a	30–100		23.5	65	20	20	40	100	100
4	30–100		5	–10	0	20	0	0	0
1d	100–300	26.5		0	20	0	0	0	0
1e	100–300	13.3		0	0	0	0	60	20
2a	30–100	44		–16	0	0	0	80	0
5	30–100		10.5	27	0	0	0	0	20
2c	>300	35.7		–30	20	0	0	40	80
3b	>300	0		–26	0	20	0	10	40

[a] Ip. [b] Sc. [c] Dose levels, 1a, 1d, 1e, 2e, and 3b, 100 mg/kg; 2a, 30 mg/kg; 4 and 5, 10 mg/kg.

This showed considerable anticonvulsant properties against pentylenetetrazole (ED_{50} 3–5 mg/kg sc) but was inactive against electroshock and strychnine-induced convulsions. The *N*-phenethyl analog (4) and the cyclic derivatives showed less activity under the test conditions.

Experimental Section

3-Cyclohexyl-5-phenyloxazolidine (2a). The aminoethanol (1a) (2.19 g) and formalin (1 ml, 40%) in EtOH (20 ml) were refluxed for 12 hr to yield the oxazolidine, bp 126–130 (0.3 mm), isolated as its stable hydrochloride.

3-Cyclohexyl-2-oxo-5-phenyl-1,2,3-oxathiazolidine (2b). $SOCl_2$ (2.3 ml), in CH_2Cl_2 (50 ml) was added slowly (15 min) to the aminoethanol (1a) (6.57 g) and Me_3N (11 ml) in CH_2Cl_2 (150 ml). The mixt was stirred (room temp) for 18 hr to yield 2b.

4-Cyclohexyl-6-phenylmorpholin-2-one (3a). Ethyl bromoacetate (3.34 g) in 1,2-dimethoxyethane (5 ml) was added slowly to the aminoethanol 1a (4.38 g) and $NaHCO_3$ (2 g) in 1,2-dimethoxyethane (20 ml) and the mixt was refluxed for 66 hr. The cooled mixt was dild with Et_2O, washed with H_2O, and distd to yield the morpholinone, bp 150–160° (0.7 mm), characterized as its picrate.

4-Cyclohexyl-6-phenylmorpholine-2,3-dione (3b). The aminoethanol 1a (13.57 g), $(COOEt)_2$ (4.38 g), and PhMe (150 ml) were refluxed for 18 hr during which time PhMe was slowly distd from the mixt. Evapn of residual solvent yielded 3b.

1-Cyclohexyl-1-(2-hydroxyphenethyl)hydrazine (1b). The aminoethanol 1a (21.9 g) in 1 *N* HCl (100 ml) at 50° was treated with $NaNO_2$ (10 g) in H_2O (30 ml) and stirred 2 hr. Et_2O extn yielded the *N*-nitroso compd as a yellow oil (20.2 g, 81%) which was reduced with LAH (8 g) in Et_2O (100 ml) to give the hydrazine.

4-Cyclohexyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazine-2-thione (3c). A cold soln of KOH (1.12 g) in H_2O (4 ml) and EtOH (20 ml) was added to the hydrazine 1b (2.34 g) and CS_2 (1.52 g) and the mixt was refluxed for 4 hr. The cooled soln was dild with H_2O (50 ml) and acidified with *N* HCl to ppt 3c. Treatment with Me_2SO_4 yielded the *N*-Me deriv 3d.

1-Cyclohexyl-1-(2-hydroxy-2-phenylethyl)phenethylamine (1e). The aminoethanol 1a (8.7 g), phenylacetyl chloride (13.1 g), and $NaHCO_3$ (10 g) in C_6H_6 (50 ml) refluxed for 4 hr, yielded the *O,N*-diphenylacetyl derivative 1d. Reduction of this amidoester (26.45 g) with LAH (4.6 g) in Et_2O (150 ml) yielded 1e.

Acknowledgment. We wish to thank Organon Laboratories for the award of a Postgraduate Studentship to D. L. Wheeler, and Dr. W. R. Buckett and N. Duff (Organon) for the pharmacological testing data.

References

(1) W. J. Irwin and D. L. Wheeler, *J. Chem. Soc C*, 3166 (1971).
(2) D. L. Wheeler, Ph.D Thesis, University of Aston in Birmingham, Birmingham, England, 1971.
(3) E. Tubaro, *Boll. Chem. Farm.*, 104, 602 (1965).
(4) M. E. Dyen and D. Swern, *Chem. Rev.*, 67, 197 (1967).
(5) G. A. Youngdale, G. W. Duncan, D. E. Emmert, and D. Ledniser, *J. Med. Chem.*, 9, 155 (1966).
(6) H. S. Mosher, M. B. Frankel, and M. Gregory, *J. Amer. Chem. Soc.*, 75, 5326 (1953).
(7) S. Raines and C. A. Kovacs, *J. Med. Chem.*, 11, 854 (1968).
(8) J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, 34, 175 (1969).

Central Nervous System, Antidiuretic, and Some Other Activities of Pyrazoles

H. G. Garg*

Department of Chemistry, University of Roorkee, Roorkee, India.
Received March 5, 1971

A number of pyrazoline-4,5-diones and their functional derivatives[1-5] were tested for CNS[6] and antidiuretic[7] activ-

*Address correspondence to: Harvard University Medical School, Laboratory for Carbohydrate Research, Massachusetts General Hospital, Boston, Massachusetts 02114.