1-Amino-4-aryl-4-piperidinols as Potential Antidepressants

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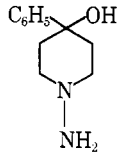
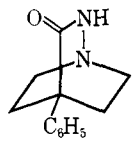
1-Amino-4-phenyl-4-piperidinol is more active than imipramine in animal tests against the depression caused by reserpine. Thirty-six related piperidines have been synthesized and evaluated as potential thymoleptics. Structure–activity relationships are discussed.

In a search for an antidepressant drug of the imipramine type a number of compounds were screened for their ability to prevent the onset of ptosis and hypothermia induced by reserpine in rodents. This test has been advanced as diagnostic of clinically effective thymoleptics.[2] One compound[3] that we found to be more active than imipramine was 1-amino-4-phenyl-4-piperidinol (I), originally prepared by Beckett and Greenhill.[4]

The theme of the present paper is the synthesis of analogs of I and the correlation of structure with antireserpine activity.



I



II

Chemistry.—The nitroso compounds listed in Tables I and II were obtained by nitrosation of the appropriate secondary base and then reduced with zinc and acetic acid[4] to 1-aminopiperidines (Tables III and IV).

An attempt to prepare the amide **10** from the ester **14** with 1-pyrrolidinylmagnesium iodide[5] gave instead the 1,2-diazabicyclo[2.2.2]octanone II.[6]

Reductive alkylation of I with aldehydes or ketones gave **15**, **16**, and **17**. Further reaction of the isopropyl compound **16** with acetaldehyde failed, presumably for steric reasons. The monomethyl compound **19** was obtained by hydrogenation of the methylidene derivative **18**.

The propiophenones **20–22** resulted from amine exchange between the appropriate aminopiperidine and 2-benzoylethyltrimethylammonium iodide.[7]

Mono- and diacyl derivatives of I (Table V) were obtained by conventional methods (see Experimental Section). The diacyl compounds (**33–37**) showed unexpected properties. They did not titrate in acetic acid with perchloric acid. The acyclic imides **33** and **34** had C=O bands at very high frequencies (*ca.* 1715 cm^{-1}) and all compounds showed very strong and unexplained absorption at 1220–1280 cm^{-1}. These features were reproduced in the model compound III and were absent in IV which was a monoacidic base and had an infrared spectrum with normal amide C=O absorption (1670 cm^{-1}) and no major peaks in the 1200–1300-cm^{-1} region. The integrity of the hydroxyl group in the diacyl compounds was shown by a strong band at *ca.* 3640 cm^{-1}.

$(CH_3)_2NN(COCH_3)_2$ III $\qquad$ $Me_2NNHCOCH_3$ IV

In accord with previous work[8] reduction of the monoacyl compounds **27** and **29** with $LiAlH_4$ was unsuccessful. The formyl compound **26** gave **18** in very poor yield. More complex results were obtained with the succinimide **37**. Two molar equivalents of the hydride caused ring fission and, according to the conditions, gave the amide **30** or the alcohol **23**. One molar equivalent gave the pyrrolidinone **32**.

Experimental Section[9]

General Procedure for 1-Amino-4-piperidinols.—The nitrosation and reduction of piperidines were effected essentially as reported by Beckett and Greenhill.[4]

4-Phenyl-1,2-diazabicyclo[2.2.2]octan-3-one (II).—A solution of 8.5 g of ethyl 1-amino-4-phenylisonipecotate (**14**) was refluxed for 2 hr in 90 ml of ether with 1-pyrrolidinylmagnesium iodide (from 4.9 g of pyrrolidine, 8.7 g of methyl iodide, and 1.7 g of Mg). Water was added and the pH was adjusted to 9 with 2 *N* HCl. The aqueous phase was extracted ($CHCl_3$) at pH 7 and the extract was dried ($MgSO_4$) and evaporated to dryness. Crystallization from ethyl acetate gave 1.7 g of white crystals, mp 254–255°, lit.[6] 248.0–249.2° (cor).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.3; H, 7.0; N, 13.85. Found: C, 70.8; H, 6.8; N, 14.2.

1-Dimethylamino-4-phenyl-4-piperidinol (17).—A solution of 5 g of **1** in 20 ml of ethanol was shaken under hydrogen at room temperature and pressure with 5 ml of formalin and 2 g of 10% Pd–C catalyst. After removal of catalyst and solvent the product was crystallized from cyclohexane to give 2.5 g of white crystals, mp 133–134.5°, lit.[4] 137–138°.

The following were similarly prepared.

1-Diethylamino-4-phenyl-4-piperidinol (15).—Hydrochloride mp 232.5–233.5°. *Anal.* Calcd for $C_{15}H_{25}ClN_2O$: C, 63.25; H, 8.85; Cl, 12.4; N, 9.8. Found: C, 63.4; H, 8.8; Cl, 12.3; N, 9.9.

1-Isopropylamino-4-phenyl-4-piperidinol (16).—Hydrochloride mp 211–212°. *Anal.* Calcd for $C_{14}H_{25}ClN_2O$: C, 62.0; H, 8.56; Cl, 13.1; N, 10.3. Found: C, 61.85; H, 8.5; Cl, 13.25; N, 10.2.

1-Methylideneamino-4-phenyl-4-piperidinol (18). Method A.—A mixture of 20 g of **1**, 12 ml of formalin, and 100 ml of ethanol was allowed to stand at room temperature until solution was complete. Evaporation and crystallization from cyclohexane gave 17.9 g of colorless crystals, mp 99–100.5°.

Anal Calcd for $C_{12}H_{16}N_2O$: C, 70.6; H, 7.9; N, 13.7. Found: C, 70.4; H, 7.5; N, 13.75.

(1) To whom correspondence should be addressed.

(2) F. Sulser, J. Watts, and B. B. Brodie, *Ann. N. Y. Acad. Sci.*, **96**, 279 (1962).

(3) Supplied by Dr. W. T. Wakama, University of Nigeria, Nsukka, Nigeria.

(4) A. H. Beckett and J. V. Greenhill, *J. Med. Pharm. Chem.*, **4**, 423 (1961).

(5) H. Ll. Bassett and C. R. Thomas, *J. Chem. Soc.*, 1188 (1954).

(6) P. M. Carabateas, A. R. Surrey, and L. S. Harris, *J. Med. Chem.*, **7**, 293 (1964).

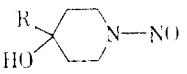
(7) E. M. Fry and E. L. May, *J. Org. Chem.*, **24**, 116 (1959).

(8) R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 1645 (1956).

(9) Melting points were determined on a Townson-Mercer apparatus calibrated for exposed stem. Microanalyses were performed by Alfred Bernhardt, Mülheim, West Germany, and Drs. Weiler and Strauss, Oxford, England.

TABLE I

1-NITROSOPIPERIDINOLS

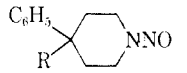


R	Source of parent base	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_4Cl-*p*	*a*	120–121	$C_{11}H_{13}ClN_2O_2$	54.9	5.45	11.6	54.8	5.45	11.5
C_6H_4F-*p*	*a*	107–108	$C_{11}H_{13}FN_2O_2$	58.9	5.8	12.65	58.5	5.6	13.0
$C_6H_4CF_3$-*m*	*b*	122–124	$C_{12}H_{13}F_3N_2O_2$	52.5	4.8	10.2	52.5	5.1	9.9
$CH_2C_6H_3$-3,4-Cl_2	*c*	122–124	$C_{12}H_{14}Cl_2N_2O_2$	49.8	4.9	9.7	49.9	5.0	9.7
$C_6H_4CH_3$-*m*	*d*	102	$C_{12}H_{16}N_2O_2$	65.4	7.3	12.7	65.6	7.3	13.0
$C_6H_5(CH_2)_2$	*e*	112–113	$C_{13}H_{18}N_2O_2$	66.6	7.75	12.0	67.0	7.95	11.85
$C_6H_5(CH_2)_3$	*f*	88–89	$C_{14}H_{20}N_2O_2$	67.7	8.1	11.3	68.1	8.1	10.9

[a] P. A. Janssen, Belgian Patent 577,977 (1959); *Chem. Abstr.*, **54,** 4629 (1960). [b] W. R. Wragg, A. S. F. Ash, and A. M. Creighton, British Patent 948,071 (1960); *Chem. Abstr.*, **61,** 6994 (1964). [c] A. H. Beckett, N. J. Harper, and A. B. Simmonds, British Patent 963,639 (1960); *Chem. Abstr.*, **61,** 8282 (1964). [d] Prepared by catalytic hydrogenolysis of 1-benzyl-4-(*m*-tolyl)-4-piperidinol. The hydrochloride had mp 178–180°. *Anal.* Calcd for $C_{12}H_{18}ClNO$: C, 63.3; H, 8.0; N, 6.15; Cl, 15.6. Found: C, 62.9; H, 8.1; N, 6.3; Cl, 15.1. [e] S. E. Fullerton, Ph.D. Thesis, University of London, 1960. [f] Supplied by Research Laboratorium, Dr. C. Janssen N.V.

TABLE II

4-PHENYL-1-NITROSOPIPERIDINES

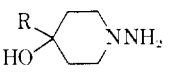


R	Source of parent base	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CH_3O	*a*	78–78.5	$C_{12}H_{16}N_2O_2$	65.3	7.6	12.8	65.4	7.3	12.7
	*b*	159–161	$C_{16}H_{21}N_3O_2$	66.9	7.4	14.6	66.3	7.4	15.0
H	*c*	61.5–62.5	$C_{11}H_{14}N_2O_2$	69.44	7.42	14.73	69.34	7.38	14.81
$HOCH_2$	*d*	*e*							
CH_3CO_2		120–123[f]	$C_{13}H_{16}N_2O_3$	62.89	6.5	11.3	62.7	6.3	11.4
$CO_2C_2H_5$	*g*	44–44.5	$C_{14}H_{18}N_2O_3$	64.1	6.9	10.7	63.8	7.1	10.9

[a] P. A. Janssen, Belgian Patent 615,349 (1962); *Chem. Abstr.*, **59,** 1601 (1963). [b] P. A. Janssen, Belgian Patent 601,228 (1961); *Chem. Abstr.*, **56,** 10,107 (1962). [c] Supplied by Aldrich Chemical Co., Inc. [d] Supplied by Research Laboratorium, Dr. C. Janssen N.V. [e] Not characterized but used directly to prepare the 1-aminopiperidine. [f] Obtained from 1-nitroso-4-phenyl-4-piperidinol with acetic anhydride–pyridine. [g] O. Eisleb, *Ber.*, **74B,** 1433 (1941).

TABLE III

1-AMINOPIPERIDINOLS



No.	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Gradel[a] activity
1	C_6H_5	190–192[b]	$C_{11}H_{16}N_2O$	68.7	8.4	14.55	68.7	8.4	14.1	+++
2	C_6H_4Cl-*p*	163–164[c]	$C_{11}H_{15}ClN_2O$	58.3	6.7	12.4	58.4	6.7	11.6	+
3	C_6H_4F-*p*	190–191	$C_{11}H_{15}FN_2O$	62.8	7.2	13.3	63.3	7.3	13.2	+
4	$C_6H_4CF_3$-*m*	139–140	$C_{12}H_{15}F_3N_2O$	55.4	5.8	10.8	55.2	6.05	10.9	+
5	$CH_2C_6H_3$-3,4-Cl_2	159–161	$C_{12}H_{16}Cl_2N_2O$	52.4	5.9	10.2	52.7	5.7	10.4	+++
6	$C_6H_4CH_3$-*m*	185–187	$C_{12}H_{18}N_2O$	69.9	8.8	13.6	69.8	8.7	13.7	+
7	$C_6H_5(CH_2)_2$	148–150	$C_{13}H_{20}N_2O$	70.85	9.15	12.7	70.4	9.1	12.2	+
8	$C_6H_5(CH_2)_3$	123–126	$C_{14}H_{22}N_2O$	71.75	9.5	11.95	71.75	9.65	11.7	+

[a] +++, high activity (comparable to imipramine); ++, moderate activity; +, low but significant activity; −, negligible or undetectable activity at all doses tested. [b] Mp 188° is quoted in ref 4. [c] G. D. Searle & Co., British Patent 981,262 (1962); *Chem. Abstr.*, **62,** 16202 (1965), quotes mp 165–167°.

Method B.—A suspension of 1 g of **26**, 0.25 g of $LiAlH_4$, and 50 ml of tetrahydrofuran (THF) was refluxed for 8 hr. The complex was decomposed by the addition of water, the THF was removed by distillation *in vacuo*, and the product was extracted ($CHCl_3$). The extract was dried ($MgSO_4$) and evaporated to dryness and the residue was crystallized from a benzene–petroleum ether mixture to give unchanged **26**). The crystallization liquors were evaporated and the residual oil slowly crystallized. Recrystallization from benzene–petroleum ether gave 0.1 g of crude **18**, mp 92°.

1-Methylamino-4-phenyl-4-piperidinol (19).—A solution of 5 g of **18**, 50 ml of THF, and 3 ml of 2-propanol was hydrogenated at room temperature and pressure with 3 g of 10% Pd–C catalyst. Removal of the catalyst and solvent and crystallization of the residue from cyclohexane gave 1.6 g of white crystals, mp 96–99°.

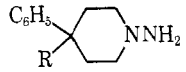
Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.9; H, 8.8; N, 13.6. Found: C, 70.0; H, 8.7; N, 13.7.

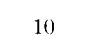
1-[Bis(2-benzoylethyl)amino]-4-phenyl-4-piperidinol (21).—Nitrogen was passed through a mixture of 2.8 g of anhydrous Na_2CO_3, 5 g of **1**, and 16.6 g of 2-benzoylethyltrimethylammonium iodide[19] in 150 ml of dimethylformamide (DMF) for 64 hr. The suspension was poured into water and the product was re-

[19] J. Thesing, A. Müller, and G. Michel, *Ber.*, **88,** 1027 (1955).

TABLE IV

1-AMINO-4-PHENYLPIPERIDINES

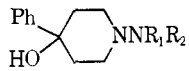


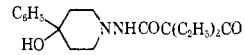
No.	R	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Graded activity[a]
9	CH_3O	198[b]	$C_{12}H_{19}ClNO$	59.35	7.9	11.5	59.5	8.2	11.2	+++
10		229–230[b]	$C_{16}H_{24}ClN_3O$	62.0	7.8	13.55	61.7	7.8	13.1	−
11	H	195–196[b]	$C_{11}H_{17}ClN_2$	62.1	8.05	13.2	62.0	8.05	12.9	−
12	CH_3CO_2	189–190[b]	$C_{13}H_{19}ClN_2O_2$	57.7	7.0	10.35	57.6	7.2	10.5	+++
13	$HOCH_2$	126–128[c]	$C_{12}H_{18}N_2O$	69.9	8.8	13.6	69.8	8.75	13.5	−
14	$CO_2C_2H_5$	179.5–180.5[b,d]	$C_{14}H_{21}ClN_2O_2$	59.0	7.4	9.8	58.6	7.5	9.8	−

[a] See footnote *a*, Table III. [b] Hydrochloride. [c] The hydrochloride, mp 169.5–171.5°, is described by footnote *c*, Table III. [d] The hydrochloride, mp 172–175.5°, is described in footnote *c*, Table III.

TABLE V

1-SUBSTITUTED AMINO-4-PHENYL-4-PIPERIDINOLS



No.	Alkyl derivatives R1	Alkyl derivatives R2	Graded activity[a]	No.	Monoacyl derivatives R1	Monoacyl derivatives R2	Graded activity[a]	No.	Diacyl derivatives R1	Diacyl derivatives R2	Graded activity[a]
15	C_2H_5	C_2H_5	+++	24	$CONH_2$	H	+++	33	CH_3CO	CH_3CO	+
16	H	C_3H_7-*i*	+++	25	$CO_2C_2H_5$	H	+	34	CH_3CO	$CO_2C_2H_5$	+
17	CH_3	CH_3	+++	26	CHO	H	+++	35	$COC(C_2H_5)_2CO$		−
18		CH_2=	+++	27	$C_6H_5CH_2CO$	H	+	36	$COC(CH_3)_2CO$		−
19	H	CH_3	+++	28	$CO_2(CH_2)_2N(CH_3)_2$	H	+	37	$CO(CH_2)_2CO$		−
20	H	$C_6H_5CO(CH_2)_2$	+++	29	CH_3CO	H	++				
21	$C_6H_5CO(CH_2)_2$	$C_6H_5CO(CH_2)_2$	+	30	$HO(CH_2)_3CO$	H	+				
22	CH_3	$C_6H_5CO(CH_2)_2$	+	31		H	−				
23	H	$(CH_2)_4OH$	+	32	$(CH_2)_3CO$		+				

[a] See footnote *a* in Table III.

crystallized twice from benzene–petroleum ether to give 6 g of white crystals, mp 115.5–117°.

Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.3; H, 7.1; N, 6.15. Found: C, 76.7; H, 7.0; N, 6.4.

Similarly was prepared **1-[(2-benzoylethyl)methylamino]-4-phenyl-4-piperidinol (22)**, mp 73–78°.

Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.5; H, 7.7; N, 8.3. Found: C, 74.8; H, 7.65; N, 8.0.

1-[(2-Benzoylethyl)amino]-4-phenyl-4-piperidinol Hydrochloride (20).—Nitrogen was passed for 16 hr through a suspension of 5 g of 1, 4 g of anhydrous Na_2CO_3, and 8.5 g of 2-benzoylethyltrimethylammonium iodide in 100 ml of DMF. The mixture was poured into water and extracted (ether). The ether extract was dried ($MgSO_4$) and treated with dry HCl. The precipitated gum was crystallized from ethyl acetate–methanol (4:1) to give 1.5 g of white crystals, mp 154–155°.

Anal. Calcd for $C_{20}H_{25}ClN_2O_2$: C, 66.5; H, 7.0; Cl, 9.8; N, 7.8. Found: C, 66.75; H, 7.0; Cl, 9.8; N, 7.7.

N-(4-Hydroxy-4-phenylpiperidino)acetamide (29).—A solution of 3.37 g of acetic anhydride, 5.76 g of 1, and 50 ml of pyridine was heated for 3 hr at 100°. Removal of the solvent and crystallization from methanol–ethyl acetate gave 4.9 g of white crystals, mp 198–200°.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C 66.7; H, 7.7; N, 11.9; O, 13.7. Found: C, 67.1; H, 7.7; N, 11.9; O, 13.3.

N-(4-Hydroxy-4-phenylpiperidino)diacetamide (33).—A solution of 100 ml of acetic anhydride and 5.76 g of **1** were heated at 100° for 4.5 hr. Removal of the excess of anhydride and crystallization from benzene–petroleum ether gave 5.5 g of white solid, mp 142–144°.

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.2; H, 7.3; N, 10.1; O, 17.4. Found: C, 65.3; H, 7.2; N, 10.3; O, 17.4.

(4-Hydroxy-4-phenylpiperidino)urea (24).—A solution of 2.7 g of potassium cyanate in 10 ml of water was added to 5.76 g of **1** in 3 ml of acetic acid and 20 ml of water. The solid was filtered off and crystallized from methanol to give 5.1 g of white crystals, mp 204–207°.

Anal. Calcd for $C_{12}H_{17}N_3O_2$: C, 61.24; H, 7.28; N, 17.85. Found: C, 61.54; H, 7.28; N, 17.85.

N-(4-Hydroxy-4-phenylpiperidino)formamide (26).—A mixture of 20 ml of ethyl formate and 1 g of **1** was refluxed for 4 hr. Removal of the solvent and crystallization from ethyl acetate containing a little methanol gave 0.6 g of white crystals, mp 174.5–176.5.

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.4; H, 7.3; N, 12.7. Found: C, 65.6; H, 7.2; N, 12.6.

N-(4-Hydroxy-4-phenylpiperidino)-2-phenylacetamide (27).—A mixture of 6.2 g of **1**, 60 ml of ethylene dichloride, and 20 ml of 5 *N* NaOH was treated at 0° with phenylacetyl chloride. The organic layer was washed (H_2O), dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized from chloroform–petroleum ether to give 3.4 g of colorless solid, mp 153–154°.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.5; H, 7.1; N, 9.0. Found: C, 73.3; H, 7.0; N, 9.0.

4-Hydroxy-4-phenyl-1-piperidinecarbamic Acid Ethyl Ester (25).—A solution of 5.76 g of **1**, 3.24 g of ethyl chloroformate, and 180 ml of pyridine was stirred for 0.5 hr at 0°. The solvent was removed *in vacuo* and the residue dissolved in $CHCl_3$. The solution was washed (H_2O), dried ($MgSO_4$), and evaporated. The residue crystallized from benzene gave 3.5 g of white crystals, mp 123–124°.

Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.6. Found: C, 63.83; H, 7.62; N, 10.57.

N-Acetyl derivative (34), mp 96–96.5° (from cyclohexane–petroleum ether).

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.7; H, 7.2; N, 9.15. Found: C, 63.1; H, 7.3; N, 9.1.

2-Dimethylaminoethyl Ester (28).—A solution of 0.1 g of sodium in 18 g of 2-dimethylaminoethanol was heated with 5 g of **25** at 100° for 6 hr. Removal of the solvent and crystallization from benzene–petroleum ether and then from ethyl acetate–petroleum ether gave 1.9 g of white crystals, mp 155–156°.

Anal. Calcd for $C_{16}H_{25}N_3O_3$: C, 62.5; H, 8.2; N, 13.7. Found: C, 62.8; H, 8.35; N, 13.5.

2,2-Diethyl-N-(4-hydroxy-4-phenylpiperidino)malonimide (35).—A mixture of 9.6 g of **1**, 9.9 g of diethylmalonyl chloride, 11 g of triethylamine, and 100 ml of THF was allowed to stand 3 hr at room temperature. The suspension was filtered and the filtrate was evaporated to dryness. The residue was dissolved ($CHCl_3$) and washed with two 50-ml portions of 2 *N* HCl, 100 ml of 20% KOH, and 100 ml of brine. The dried ($MgSO_4$) extract was evaporated and eluted from a column of silica with benzene–15% ethyl acetate. The product was isolated by evaporation and crystallization from benzene as 0.93 g of white crystals, mp 147–147.5°.

Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.3; H, 7.65; N, 8.85; O, 15.2. Found: C, 68.5; H, 8.1; N, 8.8; O, 15.2.

The acid extracts from this experiment were evaporated and the residue was crystallized from ethanol–chloroform to give 0.95 g of **N,N′-bis(4-hydroxy-4-phenylpiperidino)-2,2-diethylmalonamide dihydrochloride (31)**, mp 198–200°.

Anal. Calcd for $C_{29}H_{42}Cl_2N_4O_4$: C, 59.9; H, 7.3; Cl, 12.2; N, 9.6. Found: C, 60.2; H, 7.7; Cl, 12.1; N, 9.2.

Similarly was prepared **N-(4-Hydroxy-4-phenylpiperidino)-2,2-dimethylmalonimide (36)**, mp 149.5–151°.

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.6; H, 7.0; N, 9.7. Found: C, 66.3; H, 7.1; N, 10.0.

N-(4-Hydroxy-4-phenylpiperidino)succinimide (37).—A mixture of 5 g of **1** and 2.5 g of succinic anhydride was fused at 215° for 0.5 hr. Cooling and crystallization from methanol gave 4.15 g of white crystals, mp 221–222°.

Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.6; H, 6.6; N, 10.2. Found: C, 65.3; H, 6.5; N, 10.35.

4-Hydroxy-N-(4-hydroxy-4-phenylpiperidino)butyramide (30).—A solution of 1 g of **37** in 50 ml of THF was added over 0.25 hr to 0.28 g of $LiAlH_4$ in 20 ml of refluxing THF. After 2 hr the mixture was cooled, 0.7 ml of water was added, and the solid was filtered off. The filtrate was evaporated and the residue was converted into the hydrochloride and recrystallized from ether–ethyl acetate to give 0.3 g of white crystals, mp 177°.

Anal. Calcd for $C_{15}H_{23}ClN_2O_3$: C, 57.25; H, 7.4; Cl, 11.3; N, 8.9. Found: C, 57.0; H, 7.7; Cl, 11.0; N, 8.9.

Extension of the reflux time to 20 hr gave 0.5 g of **4-hydroxy-4-phenyl-1-piperidinebutanol (23)** as the hydrochloride, mp 174–175.

Anal. Calcd for $C_{15}H_{23}ClN_2O_2$: C, 60.0; H, 8.4; Cl, 11.8; N, 9.3. Found: C, 60.3; H, 8.4; Cl, 11.4; N, 9.0.

When the above reaction was carried out with 0.14 g of $LiAlH_4$ for 22 hr and the crude base was recrystallized from acetone–methanol–petroleum ether, 0.25 g of **1-(4-hydroxy-4-phenylpiperidino)-2-pyrrolidinone (32)** was obtained as white crystals, mp 197.5–199°.

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 69.2; H, 7.7; N, 10.8. Found: C, 69.5; H, 7.6; N, 10.6.

Results

Biological Studies.—Antagonism to reserpine-induced depression in animals is shown by (a) CNS stimulants such as amphetamine, (b) monoamine oxidase (MAO) inhibitors, and (c) antidepressants of the imipramine type. Our compounds were not overt stimulants in tests of locomotor activity[10] and did not inhibit MAO in pharmacological[12] or biochemical[13] tests in spite of their hydrazine-like structures.[14]

TABLE VI

Species	Reserpine, dose, mg/kg	Drug	ED_{50}, mg/kg
Mouse	2.0 ip	1	84
		Imipramine	125
Rat	1.8 iv	1	26.3
		Imipramine	79.5

The effects of **1** and imipramine in preventing reserpine-induced ptosis are summarized in Table VI. The drugs were administered orally 2.5 hr before the reserpine, and the ptotic score[15] was recorded 6 hr later.

The anticonvulsant activity of **1** (ED_{50} = 38.5 mg/kg) against the tonic extension of the hind limbs of the mouse induced by maximal electric shock[16] was also comparable to that of imipramine (ED_{50} = 50 mg/kg) as was the ability to inhibit writhing in mice caused by an intraperitoneal injection of phenylquinone.[17] The latter test has been used as a measure of mild analgetic activity. The effective doses (ED_{50}) for **1**, imipramine, and aspirin were 38.0, 28.5, and 27.0 mg/kg, respectively.

Unlike imipramine,[18] **11** had little or no action on the cardiovascular system of anesthetized cats and was devoid of autonomic effects on isolated smooth muscle structures.

Structure–Activity Correlations.—Substitution in the phenyl ring of **1** or separation of the phenyl and piperidine rings by one or more carbon atoms lowered but did not abolish activity (Table III).

Compounds **9** and **12** were as active as **1** but analogs lacking an oxygen function at C-4 were inactive (Table IV). Simple alkyl derivatives (**15–19**) were as effective as **1**, monoacyl compounds (**25–32**) were mainly inferior, and diacyl compounds (**33–37**) were on the whole even less active. However, **24** was an exception.

The persistence of activity over a wide range of structural variants makes it difficult to postulate clear-cut requirements for optimum drug–receptor interaction in terms of simple steric, electronic, or solubility factors.

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