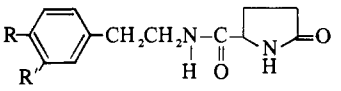
Table I. L-5-Oxo-2-pyrrolidinecarboxamides



No.	R	R′	Mp, °C[a]	Crystn solvent[b]	Yield, %	$[\alpha]^{26}D$	1% in solvent	Formula[c]
1	H	OH	133-134	AE	60	−16.7	E	$C_{13}H_{16}N_2O_3$
2	OH	OH	182.5-184.5[d]	E	77	−4.2	D	$C_{13}H_{16}N_2O_4$
3	MeO	OH	151-151.5	A	74	−1.3	D	$C_{14}H_{18}N_2O_4$
4	OH	MeO	150-151	A	65	−5.3	D	$C_{14}H_{18}N_2O_4$
5	MeO	MeO	131-133	A	36	−39.7	C	$C_{15}H_{20}N_2O_4$
6	H	$PhCH_2O$	138-140	A	73	−29.6	C	$C_{20}H_{22}N_2O_3$
7	$PhCH_2O$	MeO	95-97	A	63	−28.8	C	$C_{21}H_{24}N_2O_4$
8	MeO	$PhCH_2O$	144.5-145.5	EA	42	−28.7	C	$C_{21}H_{24}N_2O_4$
9	$PhCH_2O$	$PhCH_2O$	104-106	A	89	−24.7	C	$C_{27}H_{28}N_2O_4$

[a] Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. [b] A, MeCN; EA, EtOAc; E, EtOH; C, $CHCl_3$; D, DMF. [c] Analyses for C, H, and N were within ±0.4% of the theoretical values. [d] Subsequent to this work, this compound has been described in German Patent 2,153,825 issued to Hoffmann-La Roche (May 1972).

increased brain levels of the amine. Such an increase with dopamine purportedly is helpful in the treatment of Parkinson's disease.[2] Accordingly, the compounds described in Table I were prepared and tested as follows.

Pharmacology. The compounds were screened in groups of three male CF No. 1 mice by the method of Irwin[3] using apomorphine, a dopamine-like compound that passes the blood-brain barrier as a standard.

Four types of stereotyped behavior were seen after apomorphine: continual sniffing, head-searching, rearing, or chewing movements. Because these movements were occurring simultaneously in various combinations, it was not possible to score the intensity or duration of each of the movements. Therefore, a quantal measure had to be used. A maximum combination of three of these movements was found after high doses of apomorphine (*e.g.*, sniffing, head-searching, and rearing) and this was used as the criterion for significant stereotypy. Any mouse that showed a combination of any three of the four movements (continual sniffing, rearing, head-searching, or chewing) was considered to have exhibited significant stereotypy. For apomorphine all three mice in each group receiving 30, 100, or 300 mg/kg po exhibited significant stereotypy whereas apomorphine was inactive at 10 mg/kg po in the three mice tested at this dose. The ED_{50} for apomorphine was estimated graphically as 54.0 mg/kg. No confidence limits could be calculated because of the steepness of the slope of the dose-response curve.

Groups of three mice received 100 mg/kg po of each test compound and none of the compounds reported met the defined criterion for significant stereotypy in any of the mice tested. The enzymatic hydrolysis of these compounds was not studied and whether or not they cross the blood-brain barrier is unknown but their lack of activity relative to apomorphine discouraged further work.

Experimental Section

The compounds in Table I were prepared by heating a 5% excess of the appropriate amine and methyl L-pyroglutamate at 60-100° until an ir spectrum of the mixture indicated the reaction was essentially complete. The product was recrystallized directly or, if necessary, was first purified by washing a $CHCl_3$ solution with dilute HCl, $NaHCO_3$, and H_2O. The benzyl groups were hydrogenolyzed with Pd/C in alcohol in the usual manner.

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Antifertility Activity of Some β-Amino Alcohols[1]

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The addition of a basic ether side chain to a variety of both steroidal[2] and nonsteroidal estrogens[3] confers a significant degree of antifertility activity to these compounds. It has been shown that this effect is caused primarily by an antiestrogenic activity produced by the addition of the basic side chain.[3,4] However, no study of the antifertility effect of the amino alcohols themselves corresponding to these side chains had yet been reported and a study of the activity of these compounds was undertaken.

Some simple amino alcohols were prepared, and one of them, 2-(isopropylamino)ethanol (**2**), exhibited an unexpectedly high degree of antifertility activity. On this basis, the series was extended to include a variety of amino alcohols and related compounds in order to determine the structural features necessary for activity in this type of compound. Those compounds showing significant antifertility activity are listed in Table I, and those with weak activity as well as the inactive compounds which were previously unreported on the literature are tabulated in Table II.†

The structure of **2** can be considered as being comprised of four distinct "parts," each of which was varied in turn, keeping the other three constant in order to determine the relative importance of each to the antifertility activity.

Hydroxyl Group. The hydroxyl group was replaced by

†A complete listing of all compounds tested in this series will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-73-736.

Table I

No.	R	Bp, °C (mm)	Method[a]	Dose, mmol/kg/day	No. pregnant
				RCH_2CH_2OH	
1		110–111 (10)	B	0.025	9
				0.05	2
				0.075	0
2	*i*-PrNH-	*b*	A	0.025	10
				0.05	2
				0.10	0
3		*c*	C	0.05	9
				0.10	2
				0.20	0
4	c-C_4H_7-NH-	88.5–90 (9)	A, B	0.10	10
				0.25	1
				0.50	0
5	c-C_5H_9-NH-	*d*	A	0.20	7
				0.40	1
				0.50	0
6	*t*-Bu-NH-	*e*	D	0.20	10
				0.40	1
7	c-C_4H_8N-	*f*	D	0.25	9
				0.50	1
				1.00	0
8	c-C_4H_8NNH-	83–91 (3)[g]	B	0.25	8
				0.50	1[h]
9	*sec*-Bu-NH-	*i*	A	0.25	10
				0.50	8
				0.75	5
10	Me_2NNH-	96–97 (45)[j]	C	0.42	8
				1.20	1
11	CH_2=$CHC(CH_3)HNH$-	75–76 (19)	B	1.0	1

[a] A = reductive alkylation; B = hydride reduction of oxalamide; C = miscellaneous; D = purchased. [b] H. Matthes, *Justus Liebigs Ann. Chem.*, **315**, 104 (1901). [c] F. Winternitz and R. M. Thakkar, *Bull. Soc. Chim. Fr.*, 646 (1952). [d] J. R. Reasenberg and S. D. Goldberg, *J. Amer. Chem. Soc.*, **67**, 933 (1945). [e] R. E. Holmen and D. D. Carroll, *ibid.*, **73**, 1859 (1951). [f] A. Lespagnol and J. Deprey, *Bull. Soc. Chim. Fr.*, 606 (1961). [g] Calcd: C, 55.35; N, 21.52. Found: C, 54.69; N, 20.72. [h] Toxic. One of seven survivors was pregnant. [i] A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **64**, 1503 (1942). [j] Calcd: C, 46.13; N, 26.90. Found: C, 46.70; N, 24.46.

a variety of functional groups of which only esters showed any degree of comparable activity. Presumably the activity of these could be accounted for by hydrolysis to the parent amino alcohol in the intestine. Replacing the proton of the hydroxyl group with the more acidic acetylenic proton of isopropylpropargylamine[5] caused a complete loss of activity. The presence of the hydroxyl group is apparently essential for the compound to have significant antifertility activity.

Carbon Chain. Lengthening the carbon chain or adding any type of substituent to either carbon atom completely destroyed the antifertility activity. Oxidation of either methylene group to a carbonyl group (in the hope of finding an active metabolite) also caused complete loss of activity. The ethylene group appears to be an essential part of the active molecule.

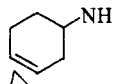
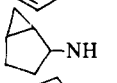
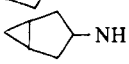
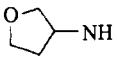
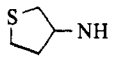
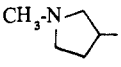
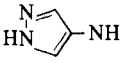
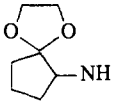
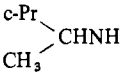
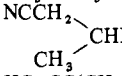
Alkyl Substituent. Very slight changes in the structure of this substituent can completely change the activity of the molecule (compare the inactive cyclohexyl and tetrahydrofuryl derivatives with the very active cyclopentyl compound), and we have been unable to explain satisfactorily the structure-activity relationships that have been found. Although many of these compounds were inactive, some of the closer analogs did retain some of the activity of **2**. Four of them, the cyclobutyl (**4**), the cyclopentyl (**5**), and the two cyclopentenyl (**1** and **3**) compounds, had activity on about the same level as **2**. A certain amount of steric bulk is necessary in this substituent, as shown by the inactive *n*-alkyl-substituted derivatives. However, it seems obvious that steric bulk is more detrimental to the activity as its distance from the nitrogen atom increases [compare the relative activities of the 1-, 2-, and 3-methylcyclopentyl analogs and the *sec*-butyl (**9**) *vs.* the *tert*-butyl (**6**) compound]. The inactivity of the cyclohexyl and cyclohexenyl derivatives is also probably due to the added bulk of the 4-carbon, in comparison with the very active cyclopentyl and cyclopentenyl analogs. Heteroatoms in the alkyl group destroy activity, probably because the increased polarity alters the solubility pattern in the animal or facilitates metabolism to an inactive metabolite.

Third Nitrogen Substituent. N-Methylation or N-acetylation of **2** caused a loss of activity, although the *N*-carbethoxy derivative did retain some of the potency of the parent amine. The cyclic carbamate was inactive, however. One tertiary amine (**7**) was found to have a relatively high degree of antifertility activity, although several of its close analogs were inactive. Replacing the nitrogen with a sulfur atom to give the sulfide corresponding to **2**, β-hydroxyethyl isopropyl sulfide,[6] caused a complete loss of activity.

Chemistry. Two general synthetic routes were used to prepare the majority of the amino alcohols. Reductive alkylation (method A) of the appropriate ketone or aldehyde with ethanolamine served well for the preparation of many analogs of **2** in which the alkyl group on the nitrogen atom was varied. On the other hand, for those analogs for which the parent amine was available or could be synthesized, a new method for fabricating the β-hydroxyethyl group needed to be devised. We found that SN2 displacement of bromoethanol or bromoethyl acetate was undependable, although a few of the analogs were prepared in this manner. The ethyl oxalamide of the parent amine could be easily prepared with freshly distilled ethyloxalyl chloride.‡ The resulting ethyl oxalamide could then be readily reduced

‡ We were able to show by means of vpc analysis that upon standing ethyloxalyl chloride disproportionated to oxalyl chloride and diethyl oxalate.

Table II

RCH_2CH_2X				
R	X	Bp, °C (mm)	Method[a]	Activity[b]
i-PrNH	Cl·HCl	187.5–188.5[c]	C	I
i-PrNH	OMe·HCl	100.5–102[c]	A	I
i-PrNH	OCH_2CH_2NH-*i*-Pr	98 (12)	A	I
i-PrNH	OAc·HCl	124–125[c]	C	E
i-PrNH	$OC(=O)(CH_2)_{14}CH_3$·HCl	107–108[c]	C	E
i-PrNH	$NHSO_2CH_3$·HCl	123–124[c]	C	I
i-PrNH	OSO_2OH	261.5–262.5[c]	C	I[d]
EtNH	OH	*e*	D	P
n-PrNH	OH	*f*	B	P
c-C_3H_5-NH	OH	72–73 (9)	B	P
c-C_5H_9-NH	$OC(=O)(CH_2)_{14}CH_3$·HCl	130–132[c]	C	E
1-Me-c-C_5H_8-NH	OH	59 (0.1)	B	P
2-Me-c-C_5H_8-NH	OH	102–103 (9)	A	P
3-Me-c-C_5H_8-NH	OH	108–109 (9)	A	I
c-C_5H_9-CH_2NH	OH	126–127 (14)	C	I
	OH	133–135 (19)	B	I
	OH	117–119 (6)	A	I
	OH	112–114 (5)	A	I
	OH	86–88 (0.2)	A	I
	OH	41.5–46[c]	C	I
	OH	122–130 (5)	B	I
	OH	119.5–120.5[c]	B	I
	OH	94–95 (0.25)	B	I
	OH	111 (7)	A	I
	OH	91 (6)	A	I
$HOCH_2C(CH_3)HNH$	OH	95 (0.1)	B	I
$CF_3C(CH_3)HNH$	OH	94–95.5 (43)	C	I
	OH	122–127 (2)	C	I
$HC{\equiv}CC(CH_3)HNH$	OH	84–87 (6)	C	I
Et_2N	OH	*g*	D	P
i-PrNAc	OAc	130–131 (9)	C	I
i-$PrNCO_2Et$	OAc	78–79 (0.5)	C	P
i-PrNCONHPh	OH	133–134[c]	C	I

[a] A = reductive alkylation; B = hydride reduction of oxalamide; C = miscellaneous; D = purchased. [b] E = completely effective at ≤1 mmol/kg/day; P = partially or completely effective at doses between 1 and 3 mmol/kg/day; I = ineffective at 1 mmol/kg/day. [c] Corrected melting point of a solid. [d] Ineffective at 0.5 mmol/kg/day. [e] L. Knorr and W. Schmidt, *Ber.*, **31**, 1072 (1898). [f] H. Matthes, *Justus Liebigs Ann. Chem.*, **315**, 104 (1901). [g] A. Ladenburg, *Ber.*, **14**, 1876 (1881).

with lithium aluminum hydride (method B) to give the desired amino alcohol. In the case of the allylic amines, the amides had to be reduced instead with alane, for reduction with lithium aluminum hydride reduced the double bonds, affording the corresponding propylamines. This reduction of allylic amines appears to be without precedent in the chemical literature, although the lithium aluminum hydride reduction of allylic alcohols and other similar functions is well known. (For several examples of this type of reduction, see ref 7.)

A few analogs were synthesized by reduction of the appropriate imine or oxazolidine with sodium cyanoborohydride. The aminothiol was prepared by the ring opening of ethylene sulfide with isopropylamine, and 3-isopropylamino-2-methyl-2-propanol was synthesized by opening the corresponding epoxide with isopropylamine. The cyano derivative

was formed by a Michael addition of ethanolamine to 3-butenonitrile.

Biology.[§] The 11 amino alcohols showing significant antifertility activity are listed in Table I in decreasing order of potency. These compounds appear to affect fertility in at least two ways: through an arrest in development of the preimplantation embryo and by prevention of postimplantation development. Although all the active members of the series are probably capable of both actions, rather surprising differences in the antifertility profiles were observed. At lower dose levels the isopropylamino (**2**) and pyrrolidino (**7**) derivatives did not alter the number of implantation sites but did prevent postimplantation embryonic development. At higher doses the isopropylamino (**2**), but not the pyrrolidino (**7**), compound had a deleterious effect on preimplantation development and thus prevented the appearance of implantation sites. The cycloalkylamino analogs **1** and **3-5** produced only the latter effect, that of preventing the appearance of implantation sites. Further studies on the biological actions of these compounds, which are described in a separate report,[8] suggest that the active members of this series of compounds possess, to varying degrees, rather specific embryotoxic effects and an action on the endometrium which precludes effective support for fetal development.

These amino alcohols represent the simplest structural type yet found which possesses significant antifertility activity. Their complete lack of estrogenic or other hormonal action and the apparent duality of the antifertility effects make them attractive candidates for further study.

Experimental Section[#]

Preparation of Amino Alcohols. Method A. Reductive Alkylation. A solution of 0.70 mol of the appropriate primary amine and 0.80 mol of the desired ketone in 100 ml of absolute EtOH was treated with 0.50 g of PtO_2 and hydrogenated at 2 atm at room temperature until hydrogen uptake ceased (1 equiv). The catalyst was removed by filtration and the product isolated by distillation through a Vigreux column at reduced pressure.

Method B. Reduction of Ethyl Oxalamides. A solution of 0.13 mol of the desired primary amine and 30 g of Et_3N in 500 ml of Et_2O was added over a 20-min period to a cooled, stirred solution of 19.1 g (0.14 mol) of ethyloxalyl chloride in 300 ml of ether. The stirred mixture was allowed to warm to room temperature over the next 45 min, and the salts were then removed by filtration. The Et_2O was removed under reduced pressure, and the residual oil, the ethyl oxalamide, was used directly for reduction. A solution of this oil in 300 ml of dry THF was dripped slowly into a mixture of 11.7 g (0.33 mol) of $LiAlH_4$ (AlH_3, prepared from $LiAlH_4$ and one-third of an equivalent of $AlCl_3$, was used in some cases, especially those containing a double bond conjugated with the nitrogen atom) in 300 ml of THF, and the mixture was stirred and refluxed overnight. The reaction mixture was worked up in the usual manner, and the pure amino alcohol was obtained by distillation under reduced pressure.

2-(Isopropylamino)ethyl Hydrogen Sulfate. A cooled solution of 10.3 g of 2-(isopropylamino)ethanol (**2**) in 50 ml of CCl_4 was treated slowly with 11.6 g of chlorosulfonic acid, keeping the temperature below 10°. After addition was complete, the mixture was allowed to warm to room temperature and kept there for 2 hr. The precipitate was collected and recrystallized twice from 95% EtOH, affording 8.9 g of product, mp 261.5–262.5°.

2-(3-Tetrahydrothienylamino)ethanol. A solution of 8.25 g of tetrahydrothiophen-3-one[9] and 4.71 g of 2-aminoethanol in 175 ml of absolute EtOH was treated with 5.07 g of sodium cyanoborohydride and 6.58 ml of 12 *N* HCl. The mixture was stirred at room temperature for 40 hr and then concentrated under reduced pressure. The residue was treated with K_2CO_3 solution and extracted with EtOAc. The extract was dried over Na_2SO_4 and concentrated. The residue was distilled twice under reduced pressure, affording 3.0 g of product, bp 87–88° (0.10 mm), which later solidified to a waxy solid, mp 41.5–46°.

2-[(2,2,2-Trifluoro-1-methylethyl)amino]ethanol. A solution of 38.5 ml of 2-aminoethanol in 1000 ml of CH_2Cl_2 was cooled to −30° and stirred while 77.2 g of trifluoroacetone was added, followed by 80 g of 4A molecular sieves. The mixture was stirred at −30° for 3 hr and then allowed to warm to room temperature and left ovenight. The filtered solution was concentrated and distilled under reduced pressure, affording 29.6 g of 2-methyl-2-trifluoromethyloxazolidine, bp 58–59° (5 mm).

A solution of this oxazolidine in 50 ml of Et_2O was added to a cooled solution of 7.6 g of $LiAlH_4$ in 250 ml of Et_2O, and the mixture was stirred overnight at room temperature. After work-up in the usual manner, the product was distilled, affording 18.0 g of amino alcohol, bp 94–95.5° (43 mm).

2-(2-Cyano-1-methylethylamino)ethanol. A solution of 40.0 g of 3-butenonitrile in 100 ml of dioxane was treated with 0.30 g of KO-*t*-Bu and then with 45.0 g of 2-aminoethanol. The mixture was left at room temperature for 0.5 hr and then refluxed for 15 hr. The mixture was distilled under reduced pressure, affording 52.6 g of crude product, bp 122–127° (2 mm).

2-(2,2-Dimethylhydrazino)ethanol. A cooled solution of 50 ml of *unsym*-dimethylhydrazine in 150 ml of EtOH was treated with 9.9 g of glycolaldehyde and 0.3 g of *p*-TSA. The solution was stirred with some 4A molecular sieves for 28 hr under an atmosphere of nitrogen. The solution was then filtered, concentrated, and distilled under reduced pressure, affording 14.3 g of the dimethylhydrazone of glycolaldehyde, bp 72–73° (9 mm).

A cooled solution of this hydrazone in 500 ml of absolute EtOH was treated with 8.8 g of sodium cyanoborohydride and then with 11.7 ml of 12 *N* HCl. The mixture was stirred at room temperature for 16 hr and then treated with concentrated K_2CO_3 solution, CH_2Cl_2, and Et_2O. The organic layer was separated and dried well over Na_2SO_4 and then over $CaSO_4$. The solution was concentrated and distilled under reduced pressure, affording 4.0 g of product, bp 96–97° (45 mm).

§ Groups of ten female rats were given the test compounds orally on each of the first six days of pregnancy. Day one of pregnancy was defined as the date of mating, as verified by the presence of vaginal spermatozoa. Aqueous solutions of salts were used *per se*, while the pH of solutions of bases was adjusted to 7 with HCl. The uteri were examined between days 16–18 of pregnancy for the presence and gross appearance of the implantation sites. Animals having one or more normal fetuses were considered to be pregnant.

All compounds listed in the tables were characterized by microanalysis and nmr spectra. In all cases, except the two noted, the analytical figures (C, H, and N) were within acceptable limits (0.4%), and all nmr spectra were consistent with the structures and showed no extraneous peaks.

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Local Anesthetics. Alkylthioalkyl- and Alkylsulfinylalkylaminoacylanilides

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In our studies of aminoacylanilides as local anesthetics we have previously reported a few alkoxyalkylaminoacylanilides.[1] Here we present the results of experiments with some closely related thio analogs.