In view of these findings it is surprising that yohimbine and corynanthine (**34**, **35**), which have the opposite configuration of reserpine at position 3 and have a *trans*-D–E ring junction, caused significant release of cardiac norepinephrine-^{3}H. The depletion of norepinephrine stores in brain by yohimbine has been reported.[10]

As in the reserpine series, the ability to release cardiac norepinephrine was lost on epimerization of position 3 (pseudoyohimbine, **37**). Quaternization of the basic nitrogen resulted in loss of activity[3b] as is the case with reserpine. Releasing activity was also observed with 17-β-hydroxyyohimbane (**43**). Study of molecular models did not reveal any obvious spatial correlations between reserpine and yohimbine. In addition, pretreatment with bretylium or cocaine effected drug-induced release (*cf.* Figure 7 in ref 11) differently for reserpine and yohimbine (Table III).

TABLE III
EFFECT OF COCAINE AND BRETYLIUM IN NOREPINEPHRINE RELEASE INDUCED BY RESERPINE AND YOHIMBINE[a]

Blocking agent	Releasing agent	Norepinephrine-^{3}H in heart, % of control
...	...	100
Bretylium	...	94
Cocaine	...	95
...	Reserpine	24
Bretylium	Reserpine	53
Cocaine	Reserpine	23
...	Yohimbine	60
Bretylium	Yohimbine	65
Cocaine	Yohimbine	35

[a] Cocaine or bretylium (20 mg/kg) administered subcutaneously 30 min after prelabeling mouse heart by the intravenous administration of 5 μCi of norepinephrine-^{3}H. Reserpine (1 mg/kg) or yohimbine (5 mg/kg) were administered subcutaneously at 60 min. Mice were sacrificed at 180 min and norepinephrine-^{3}H in heart was determined as described previously.[3a]

Bretylium partially blocked reserpine-induced release but did not significantly alter the release caused by yohimbine. Cocaine had no effect on reserpine-induced release, but markedly potentiated the release induced by yohimbine. The yohimbine–cocaine combination produced severe sympathomimetic effects in mice including piloerection, salivation, and hyperactivity. A similar increase in the toxicity of yohimbine is elicited by other drugs, such as imipramine, which interfere with neuronal uptake of norepinephrine.[10] These observations suggest a different mode of action for reserpine and yohimbine. Continuing studies in this laboratory indicate that the abilities of reserpine and yohimbine to release cardiac norepinephrine are not additive, but rather are partially competitive.[12]

Acknowledgments.—The authors would like to express their deep gratitude to Dr. W. I. Taylor of Ciba for his generosity in providing the majority of these compounds and to Dr. M. von Strandtmann of Warner-Lambert Research Institute for certain yohimbane derivatives. The technical assistance of Mrs. Louise Atwell is gratefully acknowledged.

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A Study of the Toxicity of Several Cyclopentylamino Acid Analogs

C. J. ABSHIRE

Département de Biochimie, Faculté de Médecine, Université Laval, Québec, Canada

Received December 18, 1967

The antibacterial action of 1-aminocyclopentanecarboxylic acid (ACPC)[1–3] and the toxic action in mammals have been reported.[4] This note describes three homologs of ACPC, namely 1-amino-2,5-dimethylcyclopentanecarboxylic acid (I), 1-amino-2-methylcyclopentanecarboxylic acid (II), and 1-amino-3-methylcyclopentanecarboxylic acid (III), and their toxic action on bacteria and mammals.

It was found that III is about 1000 times more toxic to *Escherichia coli* 9723 than ACPC. Compound II is much less toxic than ACPC and I showed no toxicity at all. Of 18 natural amino acids investigated, it was found that isoleucine, leucine, and valine were more powerful reversal agents for III than the others. In each case, elevated concentrations of the natural amino acids caused greater toxicity reversal (see Table I). Smaller differences in concentration gave inconsistent results as the difference in reversal potential was too small.

Concerning toxicity to mice, it was observed that with ACPC (see Figure 1), a remarkable decrease in weight occurred with subsequent death of the animals in 9 days. With III, the animals showed only a minor decrease in weight, with an abrupt weight increase beginning the 4th day after the end of the injections. The other compounds examined were similar to the saline controls.

Experimental Section

Syntheses.—The amino acids were synthesized from the corresponding ketones *via* the hydantoins by a procedure previously described.[5] Compound II was prepared in this manner (mp 295–300°) by L. Nicole.[6] The data of the synthesis of the other compounds appear in Table II.

Bacterial Studies.—A stock culture of *Escherichia coli* 9723 was employed. The salts-glucose medium described by Anderson[7] was modified as described previously[2] before use. The inoculation and incubation methods employed were as described previously.[2] The compounds to be tested were weighed into sterile test tubes and dissolved in sterile water. The solutions were adjusted to pH 7 and added aseptically to the assay tubes. A dilute microbial cell suspension with log-phase cells was utilized for inoculation of the assay; one drop was added to each tube. The incubation was at 37° for 18 hr. The amount of growth was determined turbidimetrically by means of a nephelometer. Utilizing the concentration scale shown in Table III, the toxicity levels for the compounds are indicated. Compound I was not toxic at the highest concentration that solubility would allow in this technique.

Attempts were made to reverse the toxicity of III by 18 natural amino acids: L-alanine, L-arginine, L-aspartic acid, L-cysteine, L-glutamic acid, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-serine, L-

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TABLE I
EFFECT OF VARYING AMOUNTS OF THREE NATURAL AMINO ACIDS ON REVERSAL OF TOXICITY OF 1-AMINO-3-METHYLCYCLOPENTANECARBOXYLIC ACID (III)[a]

III, mg/5 ml	Nephelometer readings: Control a	b	c	10^{-6} a	b	c	10^{-5} a	b	c	10^{-4} a	b	c	10^{-3} a	b	c	10^{-2} a	b	c	10^{-1} a	b	c	1 a	b	c	10 a	b	c	10^{2} a	b	c	10^{3} a	b	c
	Conen of amino acid, μg																																	
0.000	74	60	68	78	62	87	83	61	88	79	60	88	78	63	96	79	64	99	80	62	93	73	58	93	78	55	88	76	59	99	72	60	88
0.001																																	
0.002	81																																
0.005	29	58	70	78	60	82	80	63	81						87																		
0.01	20	26	39	73	41	40	76	47	79		60	79	78	60	79	73	60	83															
0.02	0	0	0	0	2	0	64	1	48	75	46	49	70	25	72	52	40	76	72	60		73	57		49								
0.05				0			3	0	0	6	7	0	6	6	13	4	0	51	16	0	84	19	0		75	41							
0.1							0			0	0		0	0	0	0		0	0		79	9			64	1							
0.2																					51	0		90	33	0		71	50				
0.5																					0			77	3		83	37	39		53		
1																								62	0		70	0	0	81	72	40	
2																								24			43			63	49	7	72
5																								0			12			24	12	2	58
10																											0			0	0	0	4

[a] a = L-valine, b = L-isoleucine, c = L-leucine.

TABLE II
CYCLOPENTYLAMINO ACIDS AND HYDANTOINS

Compd	Mp, °C	Yield, %	Formula[a]	R_f (pyridine–H_2O, 70:30)
ACPC	>300[b]	97	$C_6H_{11}NO_2$	0.77
Hydantoin of ACPC	204–206[c]	83	$C_7H_{10}N_2O_2$	
I	320–322	80	$C_8H_{13}NO_2$	0.83
Hydantoin of I	188–190	74	$C_9H_{14}N_2O_2$	
III	299–300[d]	97	$C_7H_{13}NO_2$	0.82
Hydantoin of III	224–225[e]	99	$C_8H_{12}N_2O_2$	

[a] All compounds were analyzed for N and were within ±0.4% of the theoretical values. [b] T. A. Connors and W. C. J. Ross, *J. Chem. Soc.*, 2119 (1960), reported mp 328–329°. [c] H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 523 (1942), reported mp 204–205°. [d] N. Zelinsky and G. Stadnikoff, *Ber.*, **39**, 1722 (1906), reported mp 299–300°. [e] M. Tiffeneau, B. Tchoubar, Saislambert, and LeTellier-Dupré, *Bull. Soc. Chim. France*, 445 (1947), reported mp 226°.

TABLE III

mg/5 ml		mg/5 ml	
0.001		0.5	
0.002		1	
0.005	← III	2	
0.01		5	← ACPC
0.02		10	
0.05		20	
0.1		50	
0.2		100	← II

threonine, L-tryptophan, L-tyrosine, and L-valine. At 1 mg/5 ml, almost all of these substances caused a toxicity reversal. An investigation was thus carried out at 100 μg/5 ml to determine which substances at lower concentrations would reverse the toxicity. It was found that isoleucine, leucine, and valine were much more powerful reversal agents than the others and were examined further. Table I shows the results where tenfold concentration differences in these particular compounds were employed.

Work with Mice.—The comparative toxicity of the substances in Robidoux albino male mice (20 g) was examined in the following manner. Each of the four compounds was injected at 500 mg/kg; 0.2 ml of a saline solution of the compound at pH 7 was injected intraperitoneally in an aseptic manner once daily for 6 consecutive days; a minimum of six mice were employed for each compound. The animals were then allowed to rest for 8 days, following which they were sacrificed and a brief autopsy was performed. Figure 1 shows the results of the weight changes observed.

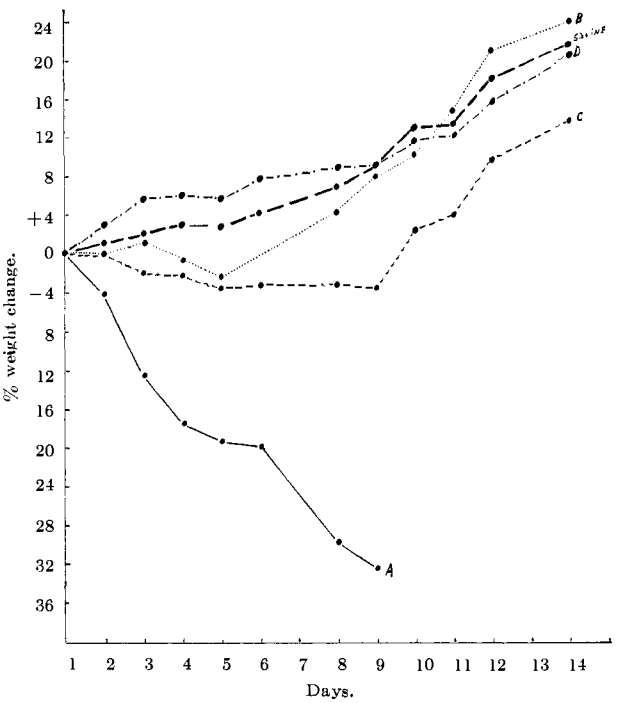

Figure 1.—Weight changes in mice following injections of compounds indicated: A = ACPC, B = compound II, C = compound III, and D = compound I.

Some Arylalkylamino Analogs of Acyclic Analgetics

A. F. CASY AND M. M. A. HASSAN

Faculty of Pharmacy, University of Alberta, Edmonton, Alberta

Received January 19, 1968

Replacement of N-methyl by N-phenethyl in analgetics where the nitrogen atom forms part of an alicyclic system (*e.g.*, morphine, and morphinan, benzomorphan, and 4-phenylpiperidine derivatives) invariably produces a compound of enhanced potency.[1] Data pertaining to the same structural modification in acyclic analgetics are sparse, however, the basic

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