β-Aminopropionohydroxamic Acids and β-Aminopropionic Esters with Hypotensive Properties[1]

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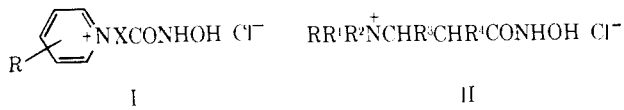
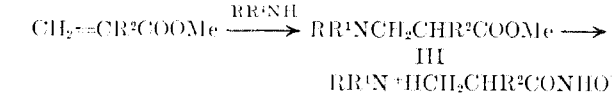
The preparation and biological properties of numerous cyclic and acyclic hydroxamic acids have been reported in the literature and reviewed.[2] Coe[3] has reported that quaternary hydroxamic acids of general structure I [in which R is H or alkyl and X is $(CH_2)_{1,2}$ or $CH(CH_3)$] were active in preventing and reversing some of the physiological effects of cholinesterase inhibition. This observation prompted us to extend our interest in hydroxamic acids to the preparation and pharmacological evaluation of compounds of general structure II, in which the substituents R^2, R^3, and R^4



I II

are H or alkyl and substituents R and R^1, in most instances, are alkyl or a ring system. Preliminary pharmacological evaluations have revealed that some secondary and tertiary amines of general structure II possess interesting properties.

The hydroxamic acids prepared in this study have the structures shown in Table I. As illustrated in the scheme they were all obtained by the interaction of the appropriate amine with methyl or ethyl acrylate or with methyl methacrylate and subsequent treatment of the amino esters (III) so formed with $NH_2OH \cdot HCl$. The



III IV

esters prepared in this study are listed in Table II. They were converted to their water-soluble hydrochlorides prior to pharmacological evaluation.

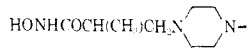
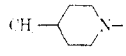
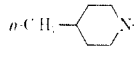
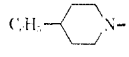
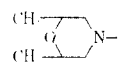
Pharmacology.—Aqueous solutions of each of the hydroxamic acids (Table I) were administered intraperitoneally to groups of six rats in relatively large doses (300 mg/kg). Rats so treated all survived but with some compounds (*e.g.*, **4**, **5**, **6**) they became disorientated, showed neurological effects (*e.g.*, dyspnea), and displayed CNS stimulation followed by depression. Recovery was slow. Compound **6** was most active. When rats were administered 150 mg/kg ip of **6** and then excited mechanically, convulsions of a clonic type occurred from which the rats recovered. When the same compound (100 mg/kg) was administered to cats by subcutaneous injection, the effect on the nictitating membrane was rapid and within 10 min the membrane half-covered the eye. Sudden noise or movement caused convulsions. Recovery was slow but complete.

These observations caused us to evaluate the effect of both the β-aminopropionohydroxamic acids and β-aminopropionates on the blood pressure (carotid artery) of anesthetized cats. This has revealed that all the hydroxamic acids caused a fall in blood pressure, and that nine of the ester hydrochlorides also reduced blood pressure. The exception was ester **12** which surprisingly caused a rise in blood pressure. The compounds were administered *via* the femoral vein and the preliminary pharmacological results are summarized in

TABLE I

β-AMINOPROPIONOHYDROXAMIC ACIDS

$R^1CH_2CHR^2CONHOH \cdot HCl$

No.	R^1	R^2	Mp, °C	Formula[a]
1		H	162–163.5	$C_8H_{17}ClN_2O_2$
2		CH_3	166–167	$C_9H_{19}ClN_2O_2$
3		CH_3	205–207	$C_{12}H_{26}Cl_2N_4O_4$
4		CH_3	147–148	$C_{10}H_{21}ClN_2O_2$
5		CH_3	171.5–173	$C_{12}H_{25}ClN_2O_2$
6		CH_3	199.5–200.5	$C_{15}H_{25}ClN_2O_2$
7		CH_3	156–157	$C_8H_{17}ClN_2O_3$
8		CH_3	196–197	$C_{16}H_{21}ClN_2O_3$
9		CH_3	193–194	$C_{16}H_{21}ClN_2O_2$
10	$C_6H_5CH_2NH$-	H	152–153	$C_{10}H_{14}N_2O_2$[b]

[a] All compounds were analyzed for C, H, N. Analytical results obtained were within ±0.4% of the theoretical values, except where noted. [b] C: calcd, 52.06; found, 52.52.

[1] This research is being supported by Defence Research Board of Canada (8875-05), Medical Research Board of Canada (MA-2993), and Smith Kline and French Inter-American Corp.

(2) R. T. Coutts, *Can. J. Pharm. Sci.*, **2**, 1 (1967).

(3) D. G. Coe, *J. Org. Chem.*, **24**, 882 (1959).

TABLE II
METHYL β-AMINOPROPIONATES[a]
$R^1CH_2CHR^2COOMe$

No.	Reaction time, days	% yield	Bp, °C (mm)	Formula	HCl mp, °C
11[b]	5	74	109–110 (15)[d]	$C_{10}H_{19}NO_2$	183–184
12	5	78	107–108 (18)[e]	$C_{10}H_{19}NO_2$	157–158
13	7	60	138–140 (2)	$C_{14}H_{26}N_2O_4$	203–204.5
14	7	90	66–68 (2)	$C_{11}H_{21}NO_2$	145–146
15	7	80	88–90 (2)	$C_{13}H_{25}NO_2$	164–165
16	7	85	143–145 (2)	$C_{16}H_{23}NO_2$	180–181
17	7	91	120–122 (19)[f]	$C_9H_{17}NO_3$	165–166
18	7	95	76–78 (2)	$C_{11}H_{21}NO_3$	148–149
19	1.25	80	76–78 (2)[g]	$C_{11}H_{21}NO_2$	133–134
20	2	62	100–104 (1)[h]	$C_{11}H_{15}NO_2$	158–159[h]

[a] Substituents R^1 and R^2 in esters **11–20** are identical with those listed for hydroxamic acids **1–10**, respectively, in Table I. [b] Et ester. [c] All compounds were analyzed for C, H. Analytical results obtained were within ±0.3% of theoretical values. [d] J. F. Arens, D. H. Koerts, and P. Plieger, *Rec. Trav. Chim.*, **75**, 1454 (1956), gave bp 106–108° (11 mm). [e] P. Bieber, *Compt. Rend.*, **231**, 291 (1950), gave bp 102–103° (18 mm). [f] A. Vystrcil and S. Hudecek, *Chem. Listy*, **44**, 262 (1950), gave bp 112° (13 mm). [g] D. I. Barron, G. H. Hall, I. L. Natoff, H. F. Ridley, R. G. W. Spickett, and D. K. Vallance, *J. Med. Chem.*, **8**, 836 (1965), gave bp 60° (0.05 mm). [h] P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953), gave bp 145–147° (7 mm) and mp 164–165°, respectively.

Table III. These results show that the duration of action of the hydroxamates is more prolonged than that of the esters.

TABLE III
EFFECT OF β-AMINOPROPIONOHYDROXAMIC ACIDS AND METHYL β-AMINOPROPIONATES ON ARTERIAL BLOOD PRESSURE OF THE ANESTHETIZED CAT[a]

Compd	Dose, mg/kg	Blood pressure fall, mm[b]	Duration,[c] min
1	25	45	5
2	25	60	10
3	25	35	10
4	25	70	10
5	5	40	5
5	10	40	30
5	25	40	120
5	50	55	>120
6	5	70	>80
6	10	65	>120
6	25	90	≫120
7	25	45	5
8	25	25	30
9	25	40	5
10	25	45	>60
11	25	50	5
12	25	(25)[d]	5
13	25	50	15
14	25	30	5
15	25	45	5
16	25	55	10
17	25	45	5
18	25	40	3
19	25	25	10
20	25	25	3

[a] Aqueous solutions were administered intravenously. Averages of at least two results are given. [b] Blood pressure (carotid artery). [c] Time required for blood pressure to return to normal. [d] Rise in blood pressure.

Experimental Section[4]

Esters.—The appropriate acrylate (0.25 mole) and amine (0.25 mole) were dissolved in anhydrous MeOH (50 ml) and heated under reflux for 30 hr to 7 days, as indicated in Table II. The solvent was removed, and the residue was dissolved in Et_2O (100 ml) and extracted with 5% HCl (three 25-ml portions). The aqueous extract was treated with excess 10% NH_3 and re-extracted with Et_2O (three 50-ml portions). The combined Et_2O extract was washed with H_2O and dried (Na_2SO_4), and the Et_2O was removed. The oil which resulted was fractionally distilled and the appropriate fraction was collected (Table II). Each ester was characterized by analysis and by nmr and ir spectra. A C=C stretching band near 1630 cm^{-1} (due to the acrylate starting material) was absent from each spectrum.

Ester hydrochlorides were obtained by adding ethereal HCl to an Et_2O solution of the ester. The hydrochlorides were characterized by their ir spectra. All showed strong $^+$N–H stretching bands in the 2350–2710-cm^{-1} region.[5] Melting points are listed in Table II.

Hydroxamic Acids.—A constantly stirred solution of $NH_2OH \cdot HCl$ (0.02 mole) in MeOH (40 ml) was cooled to 0° and to it was added dropwise, over 0.5 hr, a solution of the ester III (0.02 mole) in dry MeOH (20 ml). Stirring was continued at room temperature for a further 10 hr and then the MeOH was removed *in vacuo*. The resulting semisolid was redissolved in the minimum of dry MeOH and the solution was cooled to 0°. Dry Me_2CO was added until the solution remained cloudy. The products separated on standing, and in all instances the yield of product was in excess of 75% of theory. The hydroxamate hydrochlorides were crystallized from dry MeOH and each was characterized by elemental analysis (Table II) and by ir spectrum. All showed strong carbonyl stretching bands within the range 1650–1680 cm^{-1}.

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(4) Melting points were determined with a Fisher-Johns apparatus. Melting points and boiling points are uncorrected; ir spectra were taken on a Beckman IR10 spectrophotometer and nmr spectra were recorded on a Varian A-60D spectrophotometer. All the hydroxamic acids prepared in this study gave a violet color with ethanolic $FeCl_3$.

(5) W. E. Thompson, R. J. Warren, I. B. Eisdorfer, and J. E. Zarembo *J. Pharm. Sci.*, **54**, 1819 (1965).

Hypoglycemic Esters of 2-Chloroethanol

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In the course of a program unrelated to hypoglycemic agents some chloroalkyl esters of α-keto acids were prepared as intermediates. They were, surprisingly, found to possess hypoglycemic activity in glucose-primed intact fasted rats. Accordingly a study