Synthesis and Hypoglycemic Activity of 2-(ω-Substituted Alkylamino)-2-imidazolines

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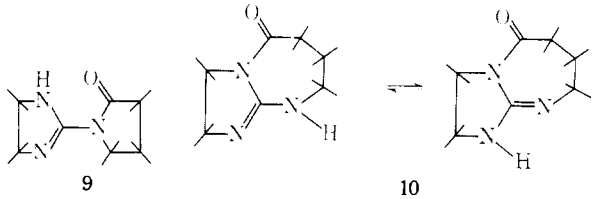
In connection with our search[1] for an effective hypoglycemic agent, we prepared a series of 2-(ω-hydroxyalkylamino)-2-imidozolines, 2-(ω-carboxyalkylamino)-2-imidazolines, and several derivatives of the latter. Although some of these compounds had been previously described in the scientific literature,[2] we were unable to find any information regarding their effect on blood sugar in animals.

The imidazoline moiety was introduced into these compounds by the convenient reaction of 2-methylmercapto-2-imidazoline with the appropriate amino derivative.[3] The acids **1** and **5** (Table I) were esterified following the method decribed by Garmaise, *et al.*,[2b] using MeOH instead of EtOH, and the ester hydrochlorides were converted to the corresponding amide hydrochlorides **3** and **6** by ammonolysis.

When **5** was allowed to react with methanolic HCl and the resulting ester HCl was treated with NaOMe, a product was obtained which gave elementary analytical values corresponding to **9** and **10**. The nmr spectrum of the cyclized product in $CDCl_3$ was consonant with structure **9**. It exhibited a singlet at 6.73 ppm for NH, another singlet at 3.60 ppm attributable to the four protons attached to the two methylene carbons in the imidazoline ring, a triplet at 3.8–4.10 ppm integrating for two protons of the C_5-methylene in the pyrrolidone ring, and, finally a multiplet at 2.0–2.8 ppm corresponding to the remaining four protons.



9 **10**

The 2-(ω-substituted alkylamino)-2-imidazolines in Table I and 1-(imidazolin-2-yl)-2-pyrrolidone (**9**) were evaluated for their hypoglycemic activity in male Charles River CD rats and in male albino rabbits following the procedure described by Ludwig, *et al.*[1] Only one compound, 2-(2-hydroxyethylamino)-2-imidazoline (**4**), produced a significant lowering of blood sugar. It was active in rats at 300–600 mg/kg. None of the compounds showed significant hypoglycemic activity in rabbits up to 600 mg/kg.

Experimental Section[4]

2-(Carboxymethylamino)-2-imidazoline (1) and 2-(3-carboxypropylamino)-2-imidazoline monohydrate (5) were prepared in 57 and 52% yields, respectively, by the procedure (method C) described by Garmaise, *et al.*[2b]

2-(Carbomethoxymethylamino)-2-imidazoline hydrochloride (2) was prepared from 50 g (0.35 mole) of **1**, 19.3 g (0.53 mole) of dry HCl in 150 ml of MeOH, and 415 ml of C_6H_6 following the procedure of Garmaise, *et al.*[2b] The yield of product after four recrystallizations from *i*-PrOH was 36 g (53%).

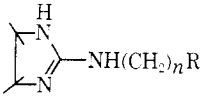
2-(Carbamoylmethylamino)-2-imidazoline Hydrochloride (3).—Liquid NH_3 (86.5 g) was added with stirring to 25.8 g (0.133 mole) of **2** over a period of 3 hr. The mixture was transferred with precooled MeOH (60 ml) to a pressure bottle, allowed to warm to room temperature, and maintained under pressure overnight. The MeOH was removed *in vacuo* and the residue was recrystallized (MeOH–Et_2O); yield of purified product 76%.

The corresponding amide **6** was obtained in a similar manner by the esterification of **5** followed by ammonolysis of the crude ester.

2-(2-Hydroxyethylamino)-2-imidazoline Hydrochloride (4).—A solution of 29 g (0.25 mole) of 2-methylmercapto-2-imidazoline, and 15 g (0.25 mole) of ethanolamine in 300 ml of MeOH was heated under reflux for 3 hr and then concentrated to dryness. The residual oil was treated with dilute HCl and the solvent was allowed to evaporate over a period of 24 hr. The semicrystalline solid was dissolved in warm PrOH, treated with *i*-Pr_2O to the cloud point, and chilled, yielding 10 g of crude product purified by crystallization (BuOH–Me_2CO).

2-(3-Hydroxypropylamino)-2-imidazoline hydrochloride (7) and 2-(4-hydroxybutylamino)-2-imidazoline hydrochloride (8) were obtained by the method discribed by McKay and Kreling.[2c]

TABLE I



No.	*n*	R	Salt	Mp, °C	Recrystn solvent	Formula	Analyses
1	1	COOH		279–280 dec[a]	EtOH–H_2O	$C_5H_9N_3O_2$	C, H, N
2	1	$COOCH_3$	HCl	157–159 dec	*i*-PrOH	$C_6H_{12}ClN_3O_2$	C, H, Cl, N, OCH_3
3	1	$CONH_2$	HCl	180.5–182.5	MeOH–Et_2O	$C_5H_{11}ClN_4O$	C, H, Cl, N
4	2	OH	HCl	95–97.5	*n*-BuOH–Me_2CO	$C_5H_{12}ClN_3O$	C, H, Cl, N
5	3	COOH		227–227.5[b]	MeOH	$C_7H_{13}N_3O_2 \cdot H_2O$[c]	C, H, N
6	3	$CONH_2$	HCl	125–127 dec	MeOH–Et_2O	$C_7H_{15}ClN_4O$	C, H, Cl, N
7	3	OH	HCl	102.5–105[d]	MeOH–EtOAc	$C_6H_{14}ClN_3O$	C, H, Cl, N
8	4	OH	HCl	106–109	EtOH	$C_7H_{16}ClN_3O$	C, H, Cl, N

[a] Lit.[2a] mp 293° dec. [b] Lit.[2b] mp 224–225°. [c] Loss on drying; calcd, 9.52; found, 9.67. [d] Lit.[2c] mp 95–96°.

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(2) (a) A. F. McKay and W. G. Hatton, *J. Am. Chem. Soc.*, **78**, 1618 (1956); (b) D. L. Garmaise, S. O. Winthrop, G. A. Grant, and A. F. McKay, *Can. J. Chem.*, **34**, 743 (1956); (c) A. F. McKay and M. E. Kreling, British Patent 826,837 (1960).

(3) S. R. Aspinall and E. J. Bianco, *J. Am. Chem. Soc.*, **73**, 602 (1951).

(4) Melting points were determined using a Thomas–Hoover melting point apparatus and are uncorrected. Elementary analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.3% of the theoretical values.

1-(2-Imidazolin-2-yl)-2-pyrrolidone (9).—2-(3-Carboxypropylamino)-2-imidazoline (33.7 g) was esterified according to the procedure described for **2**, and the ester HCl (33.7 g, oil) was treated with a solution of 7.9 g of NaOMe in 150 ml of MeOH. The NaCl was removed by filtration and the filtrate was evaporated to dryness. The solid residue was extracted with PrOH in a Soxhlet extractor. The PrOH solution was concentrated to about 80 ml, Et_2O was added to cloud point, and the mixture was chilled to obtain 9.73 g of product, mp 107.5–109°. *Anal.* ($C_7H_{11}N_3O$) C, H, N.

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Potential Antidiabetics. Benzimidazole-2-sulfonylglycamide Derivatives

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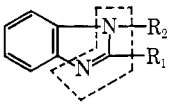
Benzimidazole derivatives of type **1** where R_1 = H, Me, Et, and *n*-Pr, and R_2 = $CH_3C_6H_4SO_2$, $C_{10}H_7SO_2$, etc., are reported to possess hypoglycemic activity.[1-3] These compounds when compared with chloropropamide, tolbutamide, etc., indicate that an aromatic nucleus (homocyclic or heterocyclic) carrying a side chain $-SO_2NHCONRR'$ plays an important role in the production of potent antidiabetic drugs. The basic moiety seen in benzimidazoles (as is shown within block lines **1**) coupled with the high antidiabetic activity exhibited by benzimidazole[2] prompted us to synthesize possible hypoglycemic agents derived from in the benzimidazole series (**2**) see Table I).



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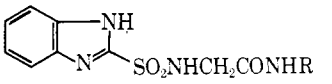

2, R = alkyl or aryl

TABLE I

No.	R	Mp,[a] °C	Recrystn solvent[c]	Yield, %	Formula[b]
1	C_6H_5	147	A	65	$C_{15}H_{16}N_4O_4S$
2	CH_3	186	A	35	$C_{10}H_{12}N_4O_3S$
3	C_2H_5	150–151	B	46	$C_{11}H_{14}N_4O_3S$
4	*n*-C_3H_7	192	A	38	$C_{12}H_{16}N_4O_3S$
5	*n*-C_4H_9	220–222	A	42	$C_{13}H_{20}N_4O_4S$

[a] Melting points were taken in open capillaries in sulfuric acid bath and are uncorrected. [b] Analyses for C, H, N were within ±0.4% of the theoretical values. [c] A = EtOH, B = dilute EtOH.

Experimental Section

2-Benzimidazolesulfonyl Chloride.—2-Mercaptobenzimidazole[3] (20 g) in 800 ml of 20% AcOH was cooled in an ice bath and Cl_2 was passed first slowly then vigorously for 50–55 min.[4] The product was filtered quickly.

Benzimidazole-2-sulfonylglycine.—The acid chloride was added immediately to a solution containing 10 g of glycine and 450 ml of 10% NaOH solution. The solution was stirred vigorously and was kept at room temperature overnight to complete the reaction. It was filtered and the filtrate was acidified to pH 2 with dilute HCl when sulfonylglycine precipitated. It was filtered, washed (cold H_2O), and collected; mp 214°.

Benzimidazole-2-sulfonylglycamide.—A mixture of 1 mole of the above sulfonylglycine and slightly more than 1 mole of alkyl- or arylamines was refluxed for 1–2 hr. When cooled the mixture was washed (5% Na_2CO_3 solution, 5% HCl, H_2O).

Pharmacology.—The compounds were studied for their hypoglycemic action in albino rats of either sex weighing 150–200 g, fasted for 18 hr (water was allowed *ad lib*). The blood sugar was determined by collecting blood (0.1 ml) from the tail of the rats and determined by the method of Folin and Wu.[5]

A suspension of 250 mg/kg of the test compounds in gum acacia was administered orally to six groups of rats. The blood sugar was determined after 3, 6, and 24 hr. At the end of 6 hr food weighed in grams was given to all of the rats and 18-hr blood sugar was again determined, *i.e.*, 24 hr after the drug administration. All of the test drugs and the reference drug, tolbutamide, were administered at 250 mg/kg (see Table II).

Compounds **1–3** and **5** have no significant hypoglycemic action; compound **4** at the doses tested reduced the blood sugar signifi-

TABLE II

BLOOD SUGAR DETERMINATION

Test compd	No. of animals	Initial blood sugar, mg/100 ml	Blood sugar (mg/100 ml) level after 3 hr	6 hr	24 hr
Control	5	101.94 ± 5.2[a]	98.68 ± 5.2	97.54 ± 5.1	105.5 ± 1.4
1	5	104.40 ± 1.2	99.98 ± 1.6	98.22 ± 1.8	99.67 ± 1.6
2	5	103.50 ± 1.7	99.54 ± 1.8	98.32 ± 1.2	99.87 ± 1.4
3	5	101.40 ± 1.9	98.74 ± 1.6	97.12 ± 1.09	99.46 ± 1.2
4	5	97.90 ± 2.1	90.04 ± 6.0	79.22 ± 2.01 ($P < 0.001$)	95.86 ± 4.5
5	5	107.62 ± 2.1	106.64 ± 3.1	116.60 ± 4.10	110.04 ± 2.01
Tolbutamide	5	94.51 ± 3.1	95.19 ± 6.2	59.56 ± 4.45 ($P < 0.001$)	84.53 ± 2.2

[a] Mean ± standard error.

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