

1-(2-Imidazolin-2-yl)-2-pyrrolidone (9).—2-(3-Carboxypropyl-amino)-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, Et₂O was added to cloud point, and the mixture was chilled to obtain 9.73 g of product, mp 107.5–109°. *Anal.* (C₇H₁₁N₃O) C, H, N.

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Potential Antidiabetics. Benzimidazole-2-sulfonylglycamide Derivatives

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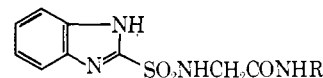
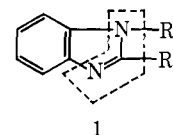
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Benzimidazole derivatives of type **1** where R₁ = H, Me, Et, and *n*-Pr, and R₂ = CH₃C₆H₄SO₂, C₁₀H₇SO₂, etc., are reported to possess hypoglycemic activity.^{1–3} These compounds when compared with chlorpropamide, tolbutamide, etc., indicate that an aromatic nucleus (homocyclic or heterocyclic) carrying a side chain –SO₂NHCONRR' plays an important role in the pro-

duction 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 benzimidazole² prompted us to synthesize possible hypoglycemic agents derived from in the benzimidazole series (**2**) see Table I).



2. R = alkyl or aryl

Experimental Section

2-Benzimidazolesulfonyl Chloride.—2-Mercaptobenzimidazole³ (20 g) in 800 ml of 20% AcOH was cooled in an ice bath and Cl₂ 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 H₂O), 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% Na₂CO₃ solution, 5% HCl, H₂O).

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 I

No.	R	Mp. ^a °C	Recrystn solvent ^c	Yield, %	Formula ^b
1	C ₆ H ₅	147	A	65	C ₁₅ H ₁₆ N ₄ O ₄ S
2	CH ₃	186	A	35	C ₁₀ H ₁₂ N ₄ O ₄ S
3	C ₂ H ₅	150–151	B	46	C ₁₁ H ₁₄ N ₄ O ₄ S
4	<i>n</i> -C ₃ H ₇	192	A	38	C ₁₂ H ₁₆ N ₄ O ₄ S
5	<i>n</i> -C ₄ H ₉	220–222	A	42	C ₁₃ H ₂₀ N ₄ O ₄ S

^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.

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	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	84.53 ± 2.2

^a Mean ± standard error.

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