**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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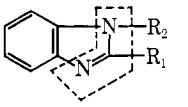
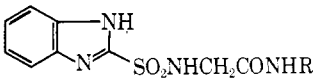
Benzimidazole derivatives of type **1** where $R_1$ = H, Me, Et, and *n*-Pr, and $R_2$ = $CH_3C_6H_4SO_2$, $C_{10}H_7SO_2$, etc., are reported to possess hypoglycemic activity.[1-3] These compounds when compared with chloropropamide, tolbutamide, etc., indicate that an aromatic nucleus (homocyclic or 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).



**1**



**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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cantly after 6 hr ($P < 0.001$) under conditions at which tolbutamide had a very good hypoglycemic activity.

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## Conformational Aspects of Ureas in the Inhibition of the Hill Reaction[1a]

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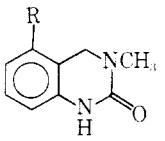
In an earlier report[2] an effort was described to assess the conformational requirements of carbamate inhibitors of the Hill reaction. This study involves a similar approach which attempts to correlate the geometry of the =NCONHPh moiety with inhibition of the Hill reaction. Two cyclic ureas (**1**, **2**) with fixed con-



1, R = H
2, R = Cl

formations were synthesized and assayed. The corresponding linear ureas[3] $m$-$RC_6H_4NHCON(CH_3)_2$ [R = H (**3**), R = Cl (**4**)] were also assayed so that a direct comparison could be made.

**Chemistry.**—Treatment of the appropriate isatoic anhydride with an aqueous solution of $MeNH_2$ gave the corresponding 2-amino-N-methylbenzamide (**5**). Reduction of **5** with diborane gave the corresponding 2-amino-N-methylbenzylamine (**6**). Fusion of **6** with urea gave the desired cyclic ureas (**1**, **2**).

The N,N-dimethylureido group, $(Me)_2NCONH$, is planar because of resonance and may exist in two possible conformations (A, B) depending on the position of the C=O group with respect to the amido hydrogen

$$(CH_3)_2NCONHR \rightleftharpoons (CH_3)_2NCONHR$$
A, *cis* B, *trans*

atom. This suggests the possibility that one or both conformational forms could be involved in binding to a receptor. In attempting to assess this factor, two cyclic ureas (**1**, **2**) which exist solely as the *cis* conformer were prepared and assayed. Compounds **1** and **2** were inactive at $3 \times 10^{-4}$ $M$, whereas $I_{50}$ values of $1.5 \times 10^{-5}$ and $2.7 \times 10^{-6}$ $M$ were obtained for **3** and **4**, respectively. The inactivity of **1** and **2** may be attributed to the fact that the ureido group is in a conformation that prevents it from binding to the receptor. An alternative explanation involves the conformation of the Ph ring, which is restricted in the cyclic urea system. This restriction is not required in the linear ureas (**3**, **4**), and the Ph ring may assume a conformation that allows binding to the active site of the receptor.

### Experimental Section[4]

**2-Amino-N-methylbenzamide (5a).**—The procedure of Clark and Wagner[5] was modified. A solution of 40.8 g (0.25 mole) of isatoic anhydride, 100 ml (1.3 moles) of 40% aqueous $MeNH_2$, and 400 ml of $H_2O$ was allowed to stand at 25° for 15 min. The mixture was extracted with EtOAc. The organic phase was washed (10% aqueous $Na_2CO_3$, $H_2O$, saturated aqueous NaCl) then dried ($MgSO_4$). The solvent was removed *in vacuo* to give 22.3 g (60%) of **5a**, mp 77–79° (lit.[6] mp 79–80°).

**2-Amino-6-chloro-N-methylbenzamide (5b)** was prepared analogously. The crude **5b** (27 g, 56%), mp 126–128°, was recrystallized twice from EtOAc–petroleum ether (60–75°) to afford an analytical specimen as white needles, mp 130–131°. *Anal.* ($C_8H_9ClN_2O$) C, H, N.

**2-Amino-N-methylbenzylamine (6a).**—To a mixture of 9 g (0.06 mole) of **5a** and 4.1 g (0.11 mole) of $NaBH_4$ in 90 ml of dimethoxyethane (DME) was added dropwise with stirring at 25° over a 1-hr period, 20.4 g (0.14 mole) of $BF_3$–$Et_2O$ in 30 ml of DME. The mixture was stirred an additional 22 hr at 25°, then poured onto an ice–HCl mixture. It was extracted with $Et_2O$, then the acidic aqueous phase was made basic with NaOH solution and extracted with EtOAc. The organic phase was washed ($H_2O$, saturated aqueous NaCl), then dried ($Na_2SO_4$). The solvent was removed *in vacuo* to afford 7.6 g of a liquid. Distillation yielded 4.5 g (55%) of **6a** as a colorless liquid, bp 116–118° (10 mm) (lit.[7] bp 114–118° (10 mm)).

**2-Amino-6-chloro-N-methylbenzylamine (6b)** was prepared similarly. Crude **6b** was distilled to yield 2.2 g (65%) of colorless liquid, bp 155–157° (10 mm). *Anal.* ($C_8H_{11}ClN_2$) C, H, N.

**3-Methyl-3,4-dihydro-2(1H)-quinazolinone (1).**—The procedures of Short and Swett[8] and Martell and Frost[9] were modified. A mixture of 0.60 g (4.4 mmoles) of **6a** and 0.53 g (8.8 mmoles) of urea was heated at 195° for 40 min. The resulting white mass was washed ($H_2O$), then dried to afford 0.55 g (77%) of a white solid (**1**), mp 198–205°. Three recrystallizations from EtOAc afforded an analytical specimen as white needles, mp 198–202°. *Anal.* ($C_9H_{10}N_2O$) C, H, N.

**3-Methyl-5-chloro-3,4-dihydro-2(1H)-quinazolinone (2)** was prepared similarly. Crude **2** (2.4 g, 92%), mp 195–200°, was recrystallized three times from EtOAc to afford an analytical specimen as white needles, mp 208–212°. *Anal.* ($C_9H_9ClN_2O$) C, H, N.

**Biological Assays.**—The molar concentration of the ureas required to reduce the photolytic activity of the isolated chloroplasts by 50% ($I_{50}$ value) was determined by previously described techniques,[10] except that ferricyanide reduction was measured colorimetrically at 420 mμ following precipitation of chloroplast protein with trichloroacetic acid.

Determinations were performed in duplicate with three separate chloroplast extractions from Alaska pea leaves (*Pisum sativum* L.). Data are presented (see Introduction) as the arithmetic averages of the individual determinations.

(1) (a) Presented before the Division of Medicinal Chemistry, at the Southeastern Regional Meeting of the American Chemical Society, Richmond, Va., Nov, 1969. The investigtions of D. E. Moreland were supported in part by Public Health Service Grant ES 00044. (b) To whom inquiries concerning this work should be addressed.

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(3) The linear ureas (**3**, **4**) were supplied by E. I. duPont de Nemours and Company, Inc. Wilmington, Del.

(4) Melting points, determined with a Thomas–Hoover capillary melting point apparatus, are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir and nmr data of all the compounds were consistent with the proposed structures.

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