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

Acknowledgment.—Thanks are due to the authorities of the Banaras Hindu University for providing the necessary facilities. One of the authors (K. C. D.) is grateful to C.S.I.R., New Delhi, India, for a Junior Fellowship.

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

MARVIN R. BOOTS,[1b] SHARON G. BOOTS,

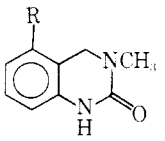
School of Pharmacy, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia 23219

AND DONALD E. MORELAND

Crops Research Division, Agricultural Research Service U. S. Department of Agriculture, Crop Science Department, North Carolina State University, Raleigh, North Carolina 27607

Received August 15, 1969

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 3×10^{-4} M, whereas I_{50} values of 1.5×10^{-5} and 2.7×10^{-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.

(2) M. R. Boots, *J. Med. Chem.*, **12**, 426 (1969).

(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.

(5) R. H. Clark and E. C. Wagner, *J. Org. Chem.*, **9**, 55 (1944).

(6) A. Weddige and M. Körner, *J. Prakt. Chem.*, [2] **36**, 141 (1887); *Chem. Zentr., Zbl.*, **58**, 1375 (1887).

(7) A. R. Osborn and K. Schofield, *J. Chem. Soc.*, 3977 (1956).

(8) J. H. Short and L. R. Swett, *J. Org. Chem.*, **26**, 3428 (1961).

(9) A. E. Martell and A. E. Frost, *J. Am. Chem. Soc.*, **72**, 1032 (1950).

(10) D. E. Moreland and K. L. Hill, *J. Agr. Food Chem.*, **7**, 832 (1959).