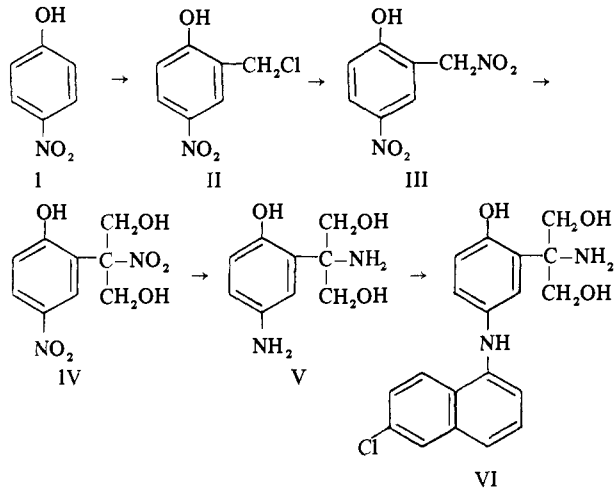
Scheme I. Scheme of Syntheses



with 4,7-dichloroquinoline, a brownish intractable product was obtained. However when IV was treated similarly it gave VI in 33% yield. Apparently an aliphatic NO_2 can be reduced by hydrazine and Raney Ni, although in lower yield, provided the NO_2 is attached to a quaternary C.

Experimental Section†

2-(α-Nitromethyl)-4-nitrophenol (III). (a) Using $AgNO_2$. To a slurry of 40 g (0.264 mole) of $AgNO_2$ in 100 ml of dry Et_2O, cooled to 0° and stirred, was added dropwise over 1 hr 37.5 g (0.2 mole) of 2-hydroxy-5-nitrobenzyl chloride (II)[3] dissolved in 100 ml of dry Et_2O. Stirring was contd in the dark at 0° for a total of 25 hr. The reaction mixt was filtered, the Ag salt washed with dry Et_2O, and the combined filtrate was evapd under reduced pressure leaving a yellow solid residue which on recrystn from Et_2O–C_6H_6 gave 30 g of III (76%), mp 152.5°. *Anal.* ($C_7H_6N_2O_5$) C, H.

(b) Using $NaNO_2$. II (18.7 g, 0.1 mole) dissolved in 50 ml of DMF was added dropwise with stirring to 12 g (0.178 mole) of dry $NaNO_2$ and 13.3 g of dry urea dissolved in 150 ml of DMF and cooled to −60°. Stirring was contd for 5 hr after which the mixt was poured into 500 ml of ice H_2O and extd with three 50-ml portions of Et_2O. The combined ext was dried (Na_2SO_4), and the solvent was removed *in vacuo* giving 10 g of crude III (50%). Recrystn from Et_2O–C_6H_6 gave 9.6 g of III, mp 152°.

2-Nitro-2-(2-hydroxy-5-nitrophenyl)propane-1,3-diol (IV). (a) Eight grams (0.1 mole) of 40% HCHO in 8 ml of dry dioxane was added dropwise over 1 hr to 10 g (0.05 mole) of III in 24 ml of dry dioxane contg 40 mg of $Ca(OH)_2$ in fine suspension. After stirring for 40 hr at 29°, the dioxane soln was dild with H_2O and extd with three 10-ml portions of Et_2O. The Et_2O ext was washed with satd brine and dried (Na_2SO_4). When Et_2O was removed *in vacuo* a thick oily residue was obtd which on crystn from Et_2O–C_6H_6 gave 9.7 g (74%) of IV, mp 115°. *Anal.* ($C_9H_{10}N_2O_7$) C, H, N.

(b) Using $(C_2H_5)_3N$. To a stirred soln contg 2 g (0.01 mole) of III and 1.6 g (0.02 mole) of 40% HCHO in 5 ml of dioxane was added dropwise over 30 min 0.1 ml of $(C_2H_5)_3N$ in 2 ml of dry dioxane. The color of the soln during addn changed from yellow to orange. Stirring was contd for 1.5 hr at 29°. IV was isolated as in a, yield 1.43 g (54%), mp 115°.

4-[3'-(α,α-Dihydroxymethylaminomethyl)-4'-hydroxyphenylamino]-7-chloroquinoline (VI). Using Zn and H_2SO_4. H_2SO_4 (112 ml, 30%) was added with vigorous stirring over 10 hr to a mixt of 5.2 g (0.02 mole) of IV and 24 g of Zn dust in 64 ml of 95% EtOH. Agitation was contd for another 1–2 hr. Excess Zn was filtered off and the pH of the filtrate was adjusted to 3 with NH_3. An equiv quantity of 4,7-dichloroquinoline (3.9 g) was added to the filtrate and the mixt was heated on a water bath for 1.5 hr. After cooling, the soln was made alk with NH_3 pptg the free amine and $Zn(OH)_2$. The gel-like ppt was filtered, washed with H_2O, and extd twice with cold EtOH, and once by digestion with hot EtOH. The combined EtOH ext was concd to 15 ml *in vacuo* and on addn of H_2O, VI sepd as a yellow solid, yield 3.8 g (52%). The solid was recrystd from EtOH–H_2O, mp 130–132°. The sulfate had mp 241–245° dec. *Anal.* ($C_{18}H_{18}ClN_3O_3 \cdot SO_4 \cdot 3H_2O$) C, H, N.

(b) Raney Ni(W_2) (1.5 g) was added to 5 ml of an EtOH soln of 0.5 g of IV (0.0012 mole) and 0.4 ml of NH_2NH_2 (0.008 mole) and the mixt was gradually brought to reflux. Successive portions of Raney Ni were added over 1.5 hr and finally excess Ni to decomp unreacted NH_2NH_2. The soln was filtered, the pH was adjusted to 3 with EtOH–HCl, and the amine, without isolation, was condensed with 4,7-dichloroquinoline as in a. The condensed product (0.23 g, 33%) as a free base was isolated with an ir spectrum identical with that of VI obtd by method a.

Pharmacology. Antimalarial Activity. The minimum effective dose of VI (HCl salt) against *Plasmodium berghei* in mice, detd according to the method of Thurston,[8] was found to be 10 mg/kg. The quinine equivalent is 5.8.

†All melting points 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.

References

(1) S. S. Walkenstein, N. Chumakow, and J. Seifter, *J. Pharmacol.*, 115, 16 (1955).
(2) D. E. Pearson and J. C. Craig, *J. Med. Chem.*, 10, 737 (1967).
(3) C. A. Buehler, F. K. Kirchner, and G. F. Deebel, *Org. Synth.*, 20, 59 (1940).
(4) N. Kornblum, B. Taub, and H. E. Ungnade, *J. Amer. Chem. Soc.*, 76, 3209 (1954).
(5) N. Kornblum, *Org. React.*, 12, 101 (1962).
(6) D. Balcom and A. Furst, *J. Amer. Chem. Soc.*, 75, 4334 (1953).
(7) H. B. Hass and E. F. Riley, *Chem. Rev.*, 32, 402 (1942).
(8) J. P. Thurston, *Brit. J. Pharmacol.*, 8, 162 (1953).

Hill Reaction Inhibitors. 3. Conformational Aspects of Ureas†

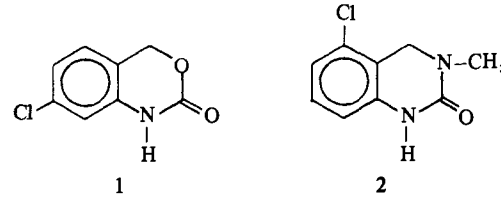
Sharon G. Boots, Marvin R. Boots,*

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

and Donald E. Moreland

Plant Science Research Division, Agricultural Research Service, U.S. Department of Agriculture, Crop Science Department, North Carolina State University, Raleigh, North Carolina 27607.
Received July 22, 1971

In earlier reports,[1,2] efforts were described to assess the conformational requirements of carbamate and urea inhibitors of the Hill reaction. The previous chemical systems (**1**, **2**) involved fixed geometry of the carbamate and ureido groups. In each case the Ph ring, the N atom, and the C=O carbon atom were essentially coplanar, thus defining the overall shape of the molecule. The cyclic carbamate and urea (**1**, **2**) were inactive while the corresponding linear systems *m*-$ClC_6H_4NHCOXCH_3$ (X=O; NCH_3) were active. The inactivity of **1** and **2** may be attributed



1 **2**

to the fact that the carbamate and ureido groups are in a conformation that prevents them from binding to the receptor. An alternative explanation involves the conformation of th Ph ring which is restricted in the cyclic

†Presented before the Division of Pesticide Chemistry, at the 162nd National Meeting of the American Chemical Society, Washington, D.C., Sept 1971. The investigations of D. E. Moreland were supported in part by the United States Public Health Service Grant ES 00044.

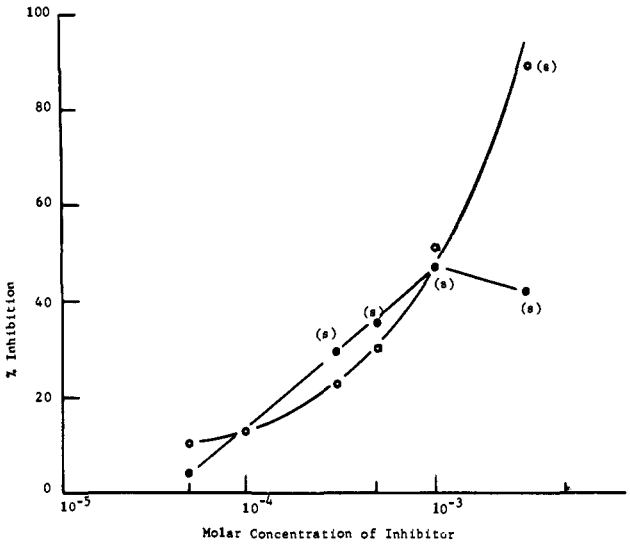
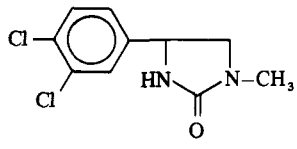


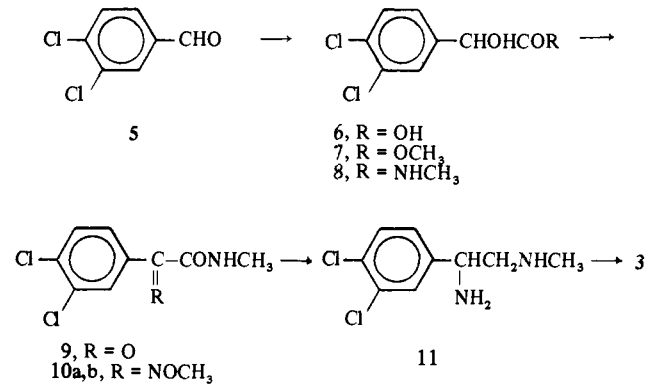
Figure 1. Effects of (●) cyclic urea (3) and the (○) linear urea (4) on the photoreduction of ferricyanide by spinach chloroplasts under nonphosporylating conditions (s = saturation of reaction mixture).

systems (1, 2). In order to distinguish between these two possibilities the synthesis and biological evaluation of 3 were undertaken. The cyclic urea 3 has the same fixed geometry about the ureido function as 2, but possesses a freely rotating Ph ring in contrast to the restricted Ph ring in 2. With a freely rotating Ph ring, 3 may assume a suitable conformation which allows binding to the active site of the receptor. The corresponding linear urea, 3,4-$Cl_2C_6H_3CH_2NHCON(CH_3)_2$ (4), was also prepared. Both the cyclic (3) and linear urea (4) were equally inhibitory to the Hill reaction up to the concentration (10^{-3} *M*) that produced approximately 50% inhibition (see Figure 1). However, at concentrations above 3×10^{-4} *M* the cyclic urea (3) saturated the reaction mixture. Under conditions of saturation, because of crystallization or salting-out of the inhibitor, the exact concentration responsible for the observed inhibition is not known.[3] These results indicate the the cis conformation of the ureido group can effectively bind to the receptor. Thus, the inactivity of the cyclic carbamate and urea (1 and 2) appears to be the result of the inability of Ph ring to assume a conformation that is suitable for binding.



3

Chemistry. Treatment of 5 with HCN in Et_2O, generated from NaCN-HCl, followed by heating with HCl afforded the carboxylic acid 6. Esterification using MeOH-H_2SO_4 yielded the ester 7 which upon treatment with $MeNH_2$ in DME-H_2O gave the desired amide 8. Oxidation of 8 with DMSO-Ac_2O afforded the keto amide 9 which was readily converted into a 3:2 mixture of isomeric *O*-methyl oximes (10a, b). The ir and nmr spectra of 10a and 10b were very similar, therefore, no stereochemical assignment can be made at this time. Reduction of 10a,b with B_2H_6 gave the diamine 11. Cyclization of 11 using 1,1′-carbonyldiimidazole afforded the desired cyclic urea 3.



Experimental Section‡

1-(3,4-Dichlorobenzyl)-3-dimethylurea (4). To a soln of 8.80 g (0.05 mole) of 3,4-$Cl_2C_6H_3CH_2NH_2$ and 5.05 g (0.05 mole) of Et_3N in 20 ml of C_6H_6 was added dropwise with cooling, a soln of 5.35 g (0.05 mole) of $(CH_3)_2NCOCl$ in 20 ml of C_6H_6. The mixt was allowed to stand at 25° for 3 days, then was added to C_6H_6 and H_2O. The org phase was washed (5% HCl, H_2O, satd aq NaCl), then dried (Na_2SO_4). The solvent was removed *in vacuo* to afford 12.0 g (97%) of a white solid 4, mp 85–86° (lit.[4] mp 87.2–88.4°).

3,4-Dichloromandelic Acid (6). The procedure of Barthel, *et al.*,[5] was used. To a suspension of 12.0 g (0.25 mole) of NaCN and 35 g (0.20 mole) of 3,4-$Cl_2C_6H_3CHO$ in 100 ml of Et_2O, was added dropwise at 15° 30 ml of concd HCl. Water was added to dissolve the pptd NaCl and the Et_2O layer was separated. The Et_2O was removed *in vacuo*, then 60 ml of concd HCl was added to the residue. The mixt was heated on the steam bath with mechanical stirring for 4 hr. The mixt was extd with Et_2O. The organic phase was washed with a 5% NaOH soln. The basic layer was adjusted to pH 2 with 5% HCl and then was extd with Et_2O. The organic phase was washed (H_2O, satd NaCl), then dried (Na_2SO_4). The solvent was removed *in vacuo* to afford 28.6 g (64%) of 6 as a white solid, mp 112–116° (lit.[6] mp 113–115°).

Methyl 3,4-Dichloromandelate (7). A mixt of 54 g (0.25 mole) of 6, 205 ml of MeOH, and 20.5 g of concd H_2SO_4 was heated at reflux for 22 hr. Approximately 100 ml of MeOH was removed *in vacuo*, then the mixt was poured onto ice. The mixt was extd with Et_2O. The organic phase was washed (H_2O, 5% NaOH soln, H_2O, satd aq NaCl) then dried (Na_2SO_4). The solvent was removed *in vacuo* to afford 41.4 g (71%) of 7. Recrystallization from Et_2O-petroleum ether (bp 60–75°) afforded an analytical specimen, mp 72–74°. *Anal.* ($C_9H_8Cl_2O_3$) C, H.

3,4-Dichloro-*N*-methylmandelamide (8). A mixt of 8.0 g (0.032 mole) of 7, 128 ml of 40% aq $MeNH_2$ soln, and 40 ml of dimethoxyethane (DME) was stirred at 25° for 18 hr. The soln was poured into H_2O, adjusted to pH 2 with a 5% HCl soln, then extd with Et_2O. The organic phase was washed (H_2O, satd aq NaCl) then dried (Na_2SO_4). The Et_2O was removed *in vacuo* to afford 7.29 (90%) of 8 as white prisms, mp 121–122° (lit.[7] mp 121–122°).

3,4-Dichlorophenyl-α-oxo-*N*-methylacetamide (9). The procedure of Albright and Goldman[8] was used. A soln of 8.2 g (0.035 mole) of 8, 105 ml of DMSO, and 69 ml of Ac_2O was stirred at 25° for 20 hr. The mixt was poured onto ice, then extd with Et_2O. The org phase was washed (H_2O, 5% NaOH soln, satd aq NaCl) and then dried (Na_2SO_4). The solvent was removed *in vacuo* to yield 5.4 g (60%) of 9, mp 128–130°. Recrystn from Et_2O-petroleum ether afforded an analytical specimen of 9 as white needles, mp 129.5–130°. *Anal.* ($C_9H_7Cl_2NO_2$) C, H, N.

***O*-Methyl 3,4-Dichlorophenyl-α-oxo-*N*-methylacetamide Oxime (10).** The procedure of Feuer and Braunstein[9] was employed. A soln of 2.15 g (0.0093 mole) of 9, 0.924 g (0.011 mole) of $NH_2OCH_3 \cdot HCl$, 50 ml of dry Py, and 50 ml of 100% EtOH was heated at reflux for 24 hr. The mixt was poured onto ice–HCl and then was extd with Et_2O. The org phase was washed (H_2O, satd aq NaCl), then dried (Na_2SO_4). The solvent was re-

‡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 compounds were consistent with the proposed structures.

moved *in vacuo* to give 2.23 g (92%) of **10** as a white solid. Recrystn from Et_2O–petroleum ether afforded isomer **10a**, 1.34 g, as white needles, mp 147–149°, as a first crop and isomer **10b**, 0.890 g, as white prisms, mp 86–90°, as a second crop. Two recrystns from Et_2O-petroleum ether afforded an analytical specimen of isomer **10a**, mp 150–151°. *Anal.* ($C_{10}H_{10}Cl_2N_2O_2$) C, H, N. Two recrystns from petroleum ether afforded an analytical specimen of **10b**, mp 92–94°. *Anal.* ($C_{10}H_{10}Cl_2N_2O_2$) C, H, N.

3,4-Dichloro-α-[(methylamino)methyl]benzylamine (11). The procedures of Boots, *et al.*[2] and Feuer and Braunstein[9] were modified. To a suspension of 2.23 g (8.54 mmoles) of **10a,b** and 800 mg (21.4 mmoles) of $NaBH_4$ in 45 ml of DME was added dropwise over 30 min, while cooling in an ice-salt bath, 3.7 ml (28.2 mmoles) of BF_3–Et_2O in 20 ml of DME. The mixt was stirred at 25° for 1 hr, then was heated at reflux for 2 hr. The mixt was cooled in an ice bath, then 3 ml of H_2O was added cautiously, followed by 15 ml of a 5% HCl soln. The mixt was then heated at reflux for 1 hr. The DME was removed *in vacuo*, and the residue was added to Et_2O and H_2O. The organic phase was washed with a 5% HCl soln, then the aqueous acidic ext was made basic with a 5% NaOH soln, the extd with Et_2O. The organic phase was washed (H_2O, satd aq NaCl), then dried (Na_2SO_4). The solvent was removed *in vacuo* to give 1.49 g (80%) of **11** as a colorless liquid. The dihydrochloride was recrystd from EtOH–EtOAc, mp 265–268°. *Anal.* ($C_9H_{14}Cl_4N_2$) C, H, N.

1-Methyl-4-(3,4-dichlorophenyl)-2-imidazolidinone (3). The procedure of Wright[10] was used. A soln of 760 mg (3.47 mmoles) of **11** and 562 mg (3.47 mmoles) of 1,1'-carbonyldiimidazole (Aldrich Chemical Co.) in 20 ml of dry THF was allowed to stand at 25° for 24 hr. The mixt was extd with EtOAc. The organic phase was washed (H_2O, 5% HCl soln, H_2O, saturated aqueous NaCl) and then dried (Na_2SO_4). The solvent was removed *in vacuo* to afford 660 mg of a yellow solid. Two recrystns from EtOAc–petroleum ether afforded 325 mg (41%) of **3** as a white solid, mp 137–140°. One additional recrystallization afforded an analytical specimen of **3**, mp 141–142°. *Anal.* ($C_{10}H_{10}Cl_2N_2O$) C, H, N.

Biological Assays. Effects of **3** and **4** on the photolytic activity (Hill reaction) of freshly isolated spinach (*Spinacia oleracea* L.) chloroplasts under nonphosphorylating conditions were measured by previously described techniques.[2]

Acknowledgment. The authors are indebted to Mrs. G. G. Hussey for technical assistance with the biological assays.

References

(1) M. R. Boots, *J. Med. Chem.*, 12, 426 (1969).
(2) M. R. Boots, S. G. Boots, and D. E. Moreland, *ibid.*, 13, 144 (1970).
(3) N. E. Good, *Plant Physiol.*, 36, 788 (1961).
(4) A. R. Surrey, U.S. Patent 3,388,158 (1968); *Chem. Abstr.*, 69, 86597 (1968).
(5) W. F. Barthel, J. Leon, and S. A. Hall, *J. Org. Chem.*, 19, 485 (1954).
(6) Belgium Patent 619,160 (1962); *Chem. Abstr.*, 59, 9905c (1963).
(7) G. Pagani, A. Baruffini, P. Borgna, and F. Gialdi, *Farmaco, Ed. Sci.*, 22, 1019 (1967).
(8) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 87, 4214 (1965).
(9) H. Feuer and D. M. Braunstein, *J. Org. Chem.*, 34, 1817 (1969).
(10) W. B. Wright, Jr., *J. Heterocycl. Chem.*, 2, 41 (1965).

Bicyclic Triazoles. 1. 3-(2-Furyl)-5-phenylthiazolo-2,3-*c*]-*s*-triazole

Man M. Kochhar* and B. B. Williams

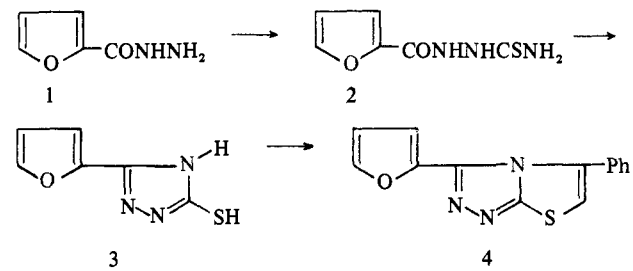
School of Pharmacy, Auburn University, Auburn, Alabama 36830.
Received August 27, 1971

Pyrido-*s*-triazoles have been shown to have antineoplastic activity.[1] This observation prompted us to synthesize bicyclic triazole, 3-(2-furyl)-5-phenylthiazole[2,3-*c*]-*s*-triazole (**4**), as illustrated in the accompanying scheme.

Table I. Effect of 3-(2-Furyl)-5-phenylthiazolo[2,3-*c*]-*s*-triazole on Mean Arterial Blood Pressure in Rats

Dose, mg/kg	Mean arterial pressure, mm: Preinjection	15 min	30 min	45 min	60 min	75 min	90 min	105 min
Control	150	150	150	160	158	155	155	155
50	130	140	142	140	140	138	135	130
50	130	150	160	156	150	130	130	130
100	150	150	180	180	178	150	150	150

2-Furoylthiosemicarbazide[2,3] was cyclized under basic conditions to 3-(2-furyl)-1,2,4-triazole-5-thiol (**3**). The reaction period (4–6 hr) seems to be essential.[2]



The characteristic feature of 1,2,4-triazole is the stability of the nucleus, an inherent property of its aromatic nature. Reaction of 5-thiol-1,2,4-triazole (**3**) with 2-halogeno ketone was found to be an effective route for the synthesis of bicyclic system, 3-(2-furyl)-5-phenylthiazole-[2,3-*c*]-*s*-triazole. 3-Substitution of the 1,2,4-triazole nucleus has a pronounced effect on the ease of ring closure.[4] Thus **4** was obtained by treating **3** with $PhCH_2COBr$.

The effect of **4** on mean arterial blood pressure was evaluated in male Sprague-Dawley rats. The lower dose level induced a rise in pressure in both the test subjects with return to preinjection pressure level within the period of observation. The higher dose level induced an increase in pressure which persisted for a longer period at its maximum level but which also within the 105-min observation period had returned to preinjection level. The rat which received the control acacia injection showed a very slight pressure alteration of short duration.

Experimental Section†

2-Furoylthiosemicarbazide (**2**)[2] was recrystallized from MeOH: 200–201 degrees; yield, 80%. *Anal.* ($C_6H_7N_3O_2S$): C, H, N.

3-(2-Furyl)-1,2,4-triazole-5-thiol (3). A soln of **2** (1.85 g; 0.01 mole) in KOH (10%; 20 ml) was refluxed for 6 hr and then kept overnight at room temp. The alkaline solution was acidified with glacial AcOH (pH 6.0). The solid was removed by filtration, washed (H_2O), and dried. The crude material on recrystallization from EtOH gave 1.5 g (90%) of **3**: mp 271–272°. *Anal.* ($C_6H_5N_3OS$): C, H, N.

3-(2-Furyl)-5-phenylthiazolo[2,3-*c*]-*s*-triazole (4). A solution of **3** (1.67 g; 0.01 mole), $PhCH_2COBr$ (1.99 g; 0.01 mole), and abs EtOH (100 ml) was refluxed for 8 hr. The solvent was evapd under reduced pressure, washed (H_2O), and dried. Recrystallization from EtOH afforded a pure sample: mp 151–152°; yield, 1.3 g (50%). *Anal.* ($C_{14}H_9N_3OS$): C, H, N.

Pharmacologic Assay. The effect of **4** on mean arterial blood pressure was evaluated in male Sprague-Dawley rats (320–450 g) by use of a Narco Biosystems linear-core electrosphygmograph and

†Reported melting points are uncorrected. A Thomas Hoover Uni-Melt apparatus was used for melting point determinations. Galbraith Laboratories Inc., Knoxville, Tenn., conducted the elemental analysis.