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

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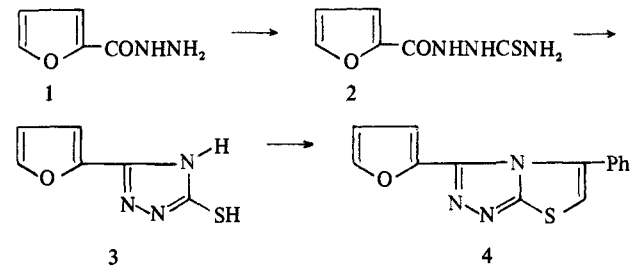
Received August 27, 1971

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-phenythiazolo[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.

recorded by physiograph. The test material was administered by ip in 5% acacia suspension at 2 dose levels, 50 and 100 mg/kg. The volume of injection was 1.5 ml at both dose levels. A control injection of acacia suspension was also done at this volume. Pressure levels were determined just prior to injection and at 15-min intervals following for a period of 105 min. Table I presents data from the control rate and the 3 rats receiving the test compound.

References

(1) K. T. Potts and H. R. Burton, *J. Org. Chem.*, 31, 251 (1966).
(2) S. C. Boots and C. C. Cheng, *J. Heterocyclic Chem.*, 4, 272 (1967).
(3) C. C. Cheng and L. R. Lewis, *ibid.*, 1, 260 (1964).
(4) M. M. Kochhar, *ibid.*, in press.

Antibacterial Activity of 6-(5-Membered heteroarylacetamido)penicillanic Acids

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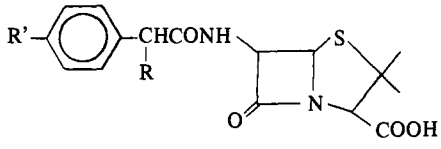
Analog synthesis[1] has been fruitful in obtaining semisynthetic penicillins with widely differing antibacterial spectra (for recent reviews on penicillins see ref 2). Thus, the insertion of a polar substituent into the phenylacetic acid moiety of penicillin G, **1**, has a profound effect on the activity of the penicillin.



1, R = H; R' = H
2, R = NH_2; R' = H
3, R = CO_2H; R' = H
4, R = H; R' = NH_2

The introduction of a free amino group into the "side chain" of penicillin G gives **2**† or **4**, penicillins with enhanced Gram-negative antibacterial activity, which also retain the Gram-positive activity of **1**.[2b,2d,3] The presence of CO_2H produces a broad-spectrum penicillin **3**,‡ clinically effective in treating infections caused by *Pseudomonas* and *Proteus* strains resistant to ampicillin.[4]

Another way in which the properties of the phenylacetic acid moiety in **1** can be altered is by replacing the Ph ring by an heteroaromatic ring. The 2- and 4-pyridylmethylpenicillins were reported to have better Gram-negative activities than **1**.[5] The 5-membered heteroaryl compds comprise a number of ring systems contg N, O, and S (occasionally Se) as part of the ring, and as a result provide a wide range in size and polarity. Since each ring and the CH_2 group of the acetic acid chain can be further substituted, a large variety of acetic acids are possible. This note describes the results obtained from penicillins derived from the heteroarylacetic acids, without additional substitution of the CH_2 group. The methods of preparation of the acetic acids and the derived penicillins are described in the Exptl Section.

Results and Discussion

In Table I the MIC values of **2** and the heteroarylmethyl penicillins against various bacteria are compared with those of **1**, measured under the same conditions.§,[6] The number of dilutions by which the MIC differs from that of **1** is given, + indicating that it is more active, – that it is less active, and = that it is as active. All of these penicillins show good Gram-positive antibacterial activity, but the activity against Gram-negative organisms show a greater spread of values, with **9**, **10**, **17**, and **33** being similar to **2**. Isomerism within a particular class of penicillin causes considerable variation in activity levels. This effect is quite evident with the isothiazoles **8**, **9**, and **10**; the 1,2,3-thiadiazoles **16**, **17**, **18**, and **19**; and the tetrazoles **25–45**. In the case of the tetrazoles the 1,5 isomers (**31**, **33**, **36**, **40**, and **42**) are more active than the 2,5 isomers (**32**, **34**, **37**, **41**, and **43**). This effect is probably a reflection of the differences in polarity between the isomers. The more polar the side-chain acid the better the Gram-negative antibacterial activity. Many of these penicillins are also more stable than **1** to acid.

Experimental Section#

Preparation of Heteroarylacetic Acids. The following general methods were used for the prepn of the side-chain acids.

A. From the Formic Acids. The heteroaryl carboxylic acids were converted to the acetic acids using the Arndt–Eistert synthesis.[7,8]

1,2,3-Thiadiazole-4-acetic Acid. 1,2,3-Thiadiazole-4-carbonyl chloride[9] with excess CH_2N_2 gave the diazo ketone (87%), mp 145–148° dec, which was converted to ethyl 1,2,3-thiadiazole-4-acetate (30%) [bp 105–109° (0.6 mm)] by a 20-hr reflux with EtOH–Ag_2O. Hydrolysis gave the acid (67%), mp 146–148°. *Anal.* ($C_4H_4N_2O_2S$) C, H, N, S.

5-Methyl-1,2,3-thiadiazole-4-acetic Acid. The acid chloride (71%), bp 75–77° (0.4 mm), of 5-methyl-1,2,3-thiadiazole-4-carboxylic acid[10] with excess CH_2N_2 gave the diazo ketone (90%), mp 85–89°, which was converted to ethyl 5-methyl-1,2,3-thiadiazole-4-acetate (60%) [bp 100–105° (0.2 mm)] by a 2.5-hr reflux with EtOH–Ag_2O. Hydrolysis gave the acid (75), mp 91–93°. *Anal.* ($C_5H_6N_2O_2S$) C, H, N.

4-Methyl-1,2,3-thiadiazole-5-acetic Acid. The acid chloride (88%), bp 35° (0.4 mm), of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid[11] with excess CH_2N_2 gave the diazo ketone (75%), mp 55–57°, which was converted to methyl 4-methyl-1,2,3-thiadiazole-5-acetate (44%) [bp 115–117° (1.5 mm)] by a 4-hr reflux with MeOH–Ag_2O. Hydrolysis gave the acid (93%), mp 163–165° dec. *Anal.* ($C_5H_6N_2O_2S$) C, H, N, S.

B. From the Aldehydes. Cleavage of the aldehyde–rhodanine condensation product gave the acetic acid.[12]

C. From Methyl Heteroaryl Compds. The lateral lithiation of certain Me compds offers a convenient route to the acetic acids.[13]

D. From the Halomethyl Compds. These compds were obtd by the chloromethylation of the heteroaryl compd[14] or by bromination of the Me compds using NBS.[15,16] The halomethyl compds were converted to the acetic acids *via* the cyanomethyl derivs.[14,17-19]

E. From the Heteroaryl Methyl Ketones. These ketones were converted to the 4-heteroaryl-1,2,3-thiadiazoles[9,11] which underwent base-catalyzed ring opening to the 2-heteroarylalkynyl 1-thioether. These alkynyl thioethers were hydrolyzed to the acetic acids.[11]

F. From the NH Azoles. Haloacetic esters N-alkylate azoles contg an NH group in the ring, to form the *N*-acetic esters which can be hydrolyzed to the acids. In many of these alkylations a mixt of isomers may result. The tetrazoles, for example, produced both the 1- and the 2-acetic esters, which were sepd by distn, and the isomer structure was established from its nmr spectrum.[20]

G. Direct Synthesis. The heterocyclic compd was synthesized with a potential acetic acid group present. The starting material in most of these synthesis was cyanoacetic ester[20-22] or acetoacetic ester.[23]

2-Methyloxazole-4-acetic Acid. A mixt of ethyl γ-bromoacetoacetate (1 mole), NaAcO (2 mole), and HAcO (300 ml) was heated with stirring on a steam bath for 3 hr. NH_4AcO (3 moles) was added, and the mixt was heated for 1 hr more. The HAcO was re-

†D-(–) form, ampicillin from Bristol Labs, Syracuse, N. Y.
‡Carbenicillin from Beecham Labs.

§The penicillins were tested for their antibacterial activity by the late Dr. A. Gourevitch and his associates in the Microbiology Dept. of Bristol Labs, Syracuse, N. Y.

#For the instruments used see ref 7. All new acids were analyzed as indicated and the results were within ±0.4% of the calcd values.