NEW COMPOUNDS

Synthesis of *N*-Aryl-*N'*-2-(thiazolyl-, -naphthothiazolyl-, -benzothiazolyl)guanidine Hydrochlorides

P. K. Srivastava

Surgical Research Laboratory, Institute of Medical Sciences, Banaras Hindu University, Varanasi-5, India

S. C. Mehra*

Bareilly College, Bareilly (U.P.), India

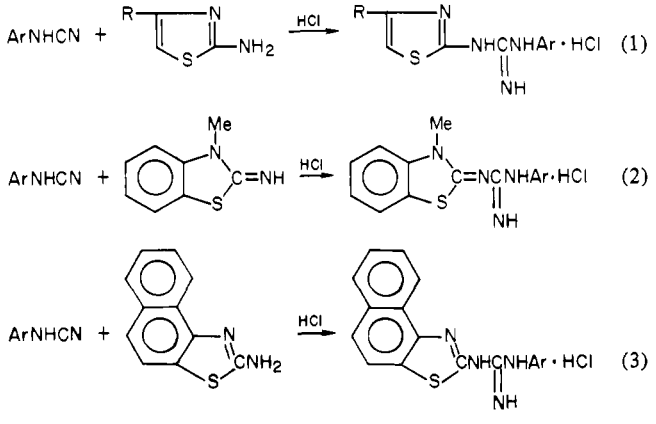
Various thiazoles, naphthothiazoles, and benzothiazoles are condensed with arylcyanamides to yield *N*-aryl-*N'*-2-(thiazolyl-, -naphthothiazolyl-, -benzothiazolyl)guanidine hydrochlorides.

The occurrence of antimalarial activity in certain diguanides (*1*) stimulated the search for other therapeutically useful members of this series. This led to the discovery of compounds of high antibacterial activity, especially among a series of bis(diguanides) (*5*). Dyer and Johnson (*2*) prepared a series of nitro and amino derivatives of triphenylguanidine, and their pharmacological study in the chemotherapy of tuberculosis was reported.

In view of the great therapeutic activities of substituted guanidine derivatives, it seemed desirable to synthesize some guanidines with various cyclic modifications of the parent structure.

In this communication a very satisfactory route to synthesize *N*-aryl-*N'*-2-(thiazolyl-, -naphthothiazolyl-, -benzothiazolyl)-guanidine hydrochlorides has been found. This was previously carried out by the condensation of *N*-aryl-*N'*-2-(thiazolyl-, -naphthothiazolyl-, -benzothiazolyl)thioureas with ammonia in the presence of lead oxide (*3*, *4*).

The synthesis of *N*-aryl-*N'*-2-(thiazolyl-, -naphthothiazolyl-, -benzothiazolyl)guanidine hydrochlorides was carried out by the condensation of arylcyanamides with various thiazoles, benzothiazoles, and naphthothiazoles in the presence of hydrogen chloride. This can be represented as shown below.

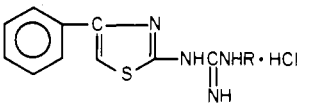


N-Phenyl-*N'*-2-(4-phenylthiazolyl)guanidine Hydrochloride

In an ice-cooled ethereal solution of phenylcyanamide (3.5 g) dry hydrogen chloride was passed for about 3 min. The phenylamidine chloride which separated as a sticky mass was dissolved in acetone. To this solution was added a solution of 2-amino-4-phenylthiazole (4 g) in acetone. The *N*-phenyl-*N'*-2-(4-phenylthiazolyl)guanidine hydrochloride which separated was filtered and washed with warm acetone and crystallized from hydrochloric acid, mp 195–197 °C, yield 5 g. Anal. Calcd for $C_{16}H_{14}N_4S$·HCl: N, 16.93; S, 9.69. Found: N, 16.75; S, 9.58. This hydrochloride on treatment with liquid ammonia afforded a base, mp 135–136 °C. Aqueous solution of guanidine hydrochloride, when treated with picric acid, afforded a picrate, mp 215–216 °C.

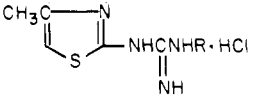
Similarly other *N*-aryl-*N'*-2-(4-phenylthiazolyl)guanidine hydrochlorides were prepared by the condensation of 2-amino-4-phenylthiazole with various arylcyanamides in the presence

Table I. Condensation of Arylcyanamides with 2-Amino-4-phenylthiazole: Formation of *N*-Aryl-*N'*-2-(4-phenylthiazolyl)guanidine Hydrochlorides



No.	Nature of R	% yield	Mp, °C	Mp of free base, °C	Mp of picrate, °C
1	Phenyl-	75	195–197	135–136	215–216
2	*o*-Tolyl-	75	193–194	146	207
3	*m*-Tolyl-	78	130–132	138	218–220
4	*p*-Tolyl-	80	185–187	142	
5	*o*-Anisyl-	78	183–185	141	198
6	*m*-Anisyl-	80	179–180	143	210–212
7	*p*-Anisyl-	75	168–170	140	185–187
8	*p*-Phenetyl-	79	125–127	149–150	
9	*p*-Chlorophenyl-	62	134–135	147	200–202

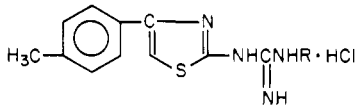
Table II. Condensation of Arylcyanamides with 2-Amino-4-methylthiazole: Formation of *N*-Aryl-*N'*-2-(4-methylthiazolyl)guanidine Hydrochlorides



No.	Nature of R	% yield	Mp, °C	Mp of picrate, °C
1	Phenyl-	75	158–162	205–207
2	*o*-Tolyl-	60	153–155	
3	*m*-Tolyl-	65	149–150	220–222
4	*p*-Tolyl-	70	158–160	225–227
5	*o*-Anisyl-	65	152–154	240
6	*m*-Anisyl-	70	160–162	235–236
7	*p*-Anisyl-	65	154–156	210–213
8	*p*-Phenetyl-	75	165–166	224
9	*m*-Chlorophenyl-	62	147–149	213–215

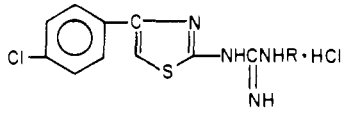
0021-9568/78/1723-0177$01.00/0

Table III. Condensation of Arylcyanamides with 2-Amino-4-*p*-tolylthiazole: Formation of *N*-Aryl-*N'*-2-(4-*p*-tolylthiazolyl)guanidine Hydrochlorides



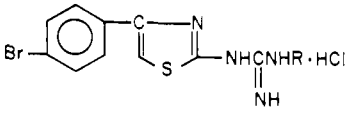
No.	Nature of R	% yield	Mp, °C	Mp of free base, °C	Mp of picrate, °C
1	Phenyl-	80	199–201	136	208–210
2	*o*-Tolyl-	70	220–222	142	226
3	*m*-Tolyl-	68	210–212	125–126	207
4	*p*-Tolyl-	60	225–227	131	
5	*o*-Anisyl-	55	242–244	138–144	203–205
6	*m*-Anisyl-	65	179–181	114–116	216–217
7	*p*-Anisyl-	78	232–234	151	220
8	*p*-Phenetyl-	62	219–220	147–148	215
9	*m*-Chlorophenyl-	58	207–209	122–123	

Table IV. Condensation of Arylcyanamides with 2-Amino-4-*p*-chlorophenylthiazole: Formation of *N*-Aryl-*N'*-2-(4-*p*-chlorophenylthiazolyl)guanidine Hydrochlorides



No.	Nature of R	% yield	Mp, °C	Mp of free base, °C	Mp of picrate, °C
1	Phenyl-	72	173–175	139	243–245
2	*o*-Tolyl-	58	153–155	183	217 dec
3	*m*-Tolyl-	65	165–167	168–169	230
4	*p*-Tolyl-	70	153–156	156–157	240–242
5	*o*-Anisyl-	50	203–204	165	
6	*m*-Anisyl-	68	115–117	134	
7	*p*-Anisyl-	65	198–200	158–159	229
8	*p*-Phenetyl-	67	169–170	160	236
9	*m*-Chlorophenyl-	58	160–162	143–144	212

Table V. Condensation of Arylcyanamides with 2-Amino-4-*p*-bromophenylthiazole: Formation of *N*-Aryl-*N'*-2-(4-*p*-bromophenylthiazolyl)guanidine Hydrochlorides



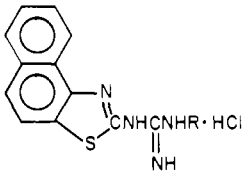
No.	Nature of R	% yield	Mp, °C	Mp of free base, °C	Mp of picrate, °C
1	Phenyl-	58	109–112	174–175	218–220
2	*o*-Tolyl-	55	97–100	165	221–222
3	*m*-Tolyl-	60	112–114	143	237
4	*p*-Tolyl-	62	107–109	154	229–232
5	*o*-Anisyl-	50	115–117	175	210–212
6	*m*-Anisyl-	52	116–118	162–163	241–243
7	*p*-Anisyl-	58	119–121	183–184	236
8	*p*-Phenetyl-	54	122–124	138–139	250 dec
9	*m*-Chlorophenyl-	60	113–114	185	

of hydrogen chloride (see Table I).

In the same manner various *N*-aryl-*N'*-2-(4-*p*-tolyl-, -4-*p*-chlorophenyl-, -4-*p*-bromophenyl-, -naphtho-, -3-methylbenzothiazolyl)guanidine hydrochlorides were synthesized. The results have been summarized in Tables II–VII.

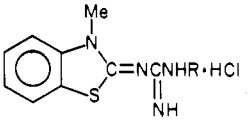
The analyses for nitrogen and sulfur were performed on all the compounds prepared and in no case did these analyses differ from the calculated values by more than 2.35%.

Table VI. Condensation of Arylcyanamides with 2-Aminonaphthothiazole: Formation of *N*-Aryl-*N'*-2-(naphthothiazolyl)guanidine Hydrochlorides



No.	Nature of R	% yield	Mp, °C	Mp of free base, °C
1	Phenyl-	75	260–262	185
2	*o*-Tolyl-	80	253–255	191
3	*m*-Tolyl-	78	184–186	177
4	*p*-Tolyl-	75	203–205	175
5	*o*-Anisyl-	78	195–196	179
6	*m*-Anisyl-	60	190–192	169–170
7	*p*-Anisyl-	70	185–187	152
8	*p*-Phenetyl-	60	180–182	165–166
9	*m*-Chlorophenyl-	85	175–177	186

Table VII. Condensation of Arylcyanamides with 2-Imino-3-methylbenzothiazole: Formation of *N*-Aryl-*N'*-2-(3-methylbenzothiazolyl)guanidine Hydrochlorides



No.	Nature of R	% yield	Mp, °C	Mp of free base, °C
1	Phenyl-	75	238–240	130–131
2	*o*-Tolyl-	55	245 dec	180
3	*m*-Tolyl-	68	230–232	154
4	*p*-Tolyl-	80	209–211	169
5	*o*-Anisyl-	58	225–227	118
6	*m*-Anisyl-	70	205–207	125
7	*p*-Anisyl-	60	210–212	136
8	*p*-Phenetyl-	58	229–232	128–130
9	*m*-Chlorophenyl-	68	208–210	139–140

Biological Screening

A few compounds of each series have been sent for biological testing. The results of testing received so far are as follows: *N*-*p*-chlorophenyl-*N'*-2-(4-phenylthiazolyl)guanidine hydrochloride and *N*-*p*-tolyl-*N'*-2-(4-phenylthiazolyl)guanidine hydrochloride (Table I, compound 9 and 4) have shown analgesic activity, *N*-*p*-chlorophenyl-*N'*-2-(4-phenylthiazolyl)guanidine hydrochloride has also been found to possess antimalarial activity (Table I compound no. 9).

Pharmacological screening of these compounds was carried out by Dr. J. J. Denton, Lederle Laboratories, Pearl River, N.Y.

Literature Cited

(1) Curd, F. H. S., Rose, F. L., *J. Chem. Soc.*, 729 (1946).
(2) Dyer, E., Johnson, T. B., *J. Am. Chem. Soc.*, **54**, 777 (1932).
(3) Malik, W. U., Srivastava, P. K., Mehra, S. C., *J. Med. Chem.*, **11**, 1268 (1968).
(4) Malik, W. U., Srivastava, P. K., Mehra, S. C., *J. Chem. Eng. Data*, **19**, 183 (1974).
(5) Rose, F. L., Swain, G., *J. Chem. Soc.*, 4422 (1956).

Received for review June 8, 1977. Accepted November 7, 1977.