

## Synthetic Antibacterials. I. Nitrofurylvinyl-*s*-triazine Derivatives

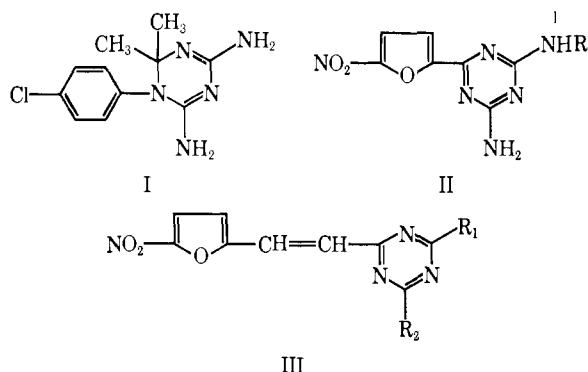
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The preparation of several 2,4-disubstituted 6-[(5-nitro-2-furyl)vinyl]-*s*-triazines and 2,4-diamino-6-(5-nitro-2-furyl)-*s*-triazines is described. Some members of the series display high antibacterial activities *in vitro* against gram-positive and gram-negative organisms.

1-*p*-Chlorophenyl-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine (I), a metabolite of chlorguanide ( $N^1$ -*p*-chlorophenyl- $N^5$ -isopropylbiguanide), was reported to have high antimalarial activity.<sup>1</sup> Some 2,4-diamino-6-(5-nitro-2-furyl)-*s*-triazines (II) showed antibacterial activity against gram-positive and gram-negative organisms.<sup>2</sup> These facts prompted us to investigate systematic syntheses of the *s*-triazine derivatives in an effort to obtain useful antibacterial agents. Our initial efforts have been directed toward the preparation of the vinylogs (III) of II in expectation of enhanced activity.<sup>3</sup> This paper describes the synthesis



of several 2,4-disubstituted 6-[(5-nitro-2-furyl)vinyl]-*s*-triazines (III), and the antibacterial testing data for these and other derivatives are discussed.

**Chemistry.**—The condensation of ethyl 5-nitro-2-furylacrylate with substituted biguanide was first tried to obtain III, but all attempts under various conditions were unsuccessful, starting materials being recovered in every case. Therefore, the general procedure, which consists of treatment of 5-nitrofurfural with *s*-triazines possessing an active methylene group, has been carried out to produce these vinylogs (III).

The key intermediates, *s*-triazine derivatives, were prepared by the following methods. 2,4-Dichloro-6-methyl-*s*-triazine (IV) was obtained from cyanuric chloride and MeMgBr according to the procedure described by Hirt, *et al.*<sup>4</sup> Amination of IV with amines at low temperature gave the 2-amino-4-chloro-6-methyl-*s*-triazines (V).<sup>5</sup> Displacement of the chloro group

in V by alkoxides proceeds smoothly to give the 2-alkoxy-4-amino-6-methyl-*s*-triazines (VI). Compound V was converted to 2,4-diamino-6-methyl-*s*-triazines (VII) by further amination with appropriate amines at higher temperature. On the other hand, the general procedure of Overberger, *et al.*,<sup>6</sup> was also followed in the preparation of 2-alkyl-4,6-diamino-*s*-triazines (VII) from alkylbiguanides and esters. Condensation of 1,1-dimethylbiguanide hydrochloride and ethyl acetate in the presence of sodium ethoxide afforded the corresponding *s*-triazine along with a by-product, which proved to be identical with 1,1-dimethylbiguanide acetate. 2-Amino-4-cyanomethyl-6-dimethylamino-*s*-triazine was prepared by displacement of the chlorine of 2-amino-4-chloromethyl-6-dimethylamino-*s*-triazine<sup>7</sup> with KCN. The *s*-triazines that were prepared are listed in Table I.

Treatment of the *s*-triazines with 5-nitrofurfural led to the formation of desired vinylogs (III). The reaction was generally performed by heating the reactants in AcOH or Ac<sub>2</sub>O in the presence or absence of catalysts such as concentrated H<sub>2</sub>SO<sub>4</sub> or KOAc. Using the *s*-triazines substituted with primary amine as starting materials and Ac<sub>2</sub>O for this condensation, the acetyl derivatives were isolated. The latter were hydrolyzed to the corresponding amino derivatives by boiling in alcoholic HCl. When 2,4-diamino-6-[ $\alpha$ -alkyl- $\beta$ -(5-nitro-2-furyl)vinyl]-*s*-triazines were refluxed with Ac<sub>2</sub>O, the diacetyl derivatives were formed, which were converted to the monoacetyl derivatives by boiling for 16 hr in a mixture of water and DMF (see Scheme I). The physical and analytical properties of 2,4-disubstituted 6-[(5-nitro-2-furyl)vinyl]-*s*-triazines are summarized in Table II.

For the purpose of the comparison in activity with their respective vinylogs four nitrofuryl-*s*-triazines were prepared: 2,4-diamino,<sup>2a</sup> 2-amino-4-methylamino-, 2-amino-4-dimethylamino-, and 2-amino-4-isopropylamino-6-(5-nitro-2-furyl)-*s*-triazines<sup>2b</sup> (Table III).

**Screening Results.**—The antibacterial activities of the compounds herein reported against *Escherichia coli* 0-55, *Staphylococcus aureus* 209P, *Bacillus subtilis* PCI 219, *Proteus vulgaris* HX-19, and *Aerobacter aerogenes* were tested *in vitro*. As can be seen from Table IV, most of these compounds possess activity against both gram-negative and gram-positive organisms. The data for 2,4-diamino(5-nitro-2-furyl)-*s*-triazines were listed in Table V for the comparison. From these data the following observations are apparent: (1) com-

synthesized 2-amino-4-chloro-6-methyl-*s*-triazine by the cyclization of  $N,N'$ -dicyanoacetamide using dry HCl in acetone.

(6) C. G. Overberger, F. W. Michelotti, and P. M. Carabateas, *J. Am. Chem. Soc.*, **79**, 941 (1957).

(7) S. L. Shapiro, E. S. Isaacs, V. A. Parrino and L. Freedman, *J. Org. Chem.*, **26**, 68 (1961).

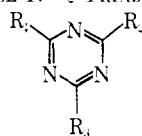
(1) H. C. Carrington, A. F. Crowther, and G. J. Stacey, *J. Chem. Soc.*, 1017 (1954).

(2) (a) R. U. Schock, U. S. Patent 2,885,400 (1959); (b) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(3) Several examples suggest the fact that the introduction of a conjugated double bond between the nitrofuryl group and the end group of the side chain may result to enhance the *in vitro* activity. For example, see T. Takahashi, H. Saikachi, S. Yoshina, and C. Mizuno, *Yakugaku Zasshi*, **69**, 284 (1949); *Chem. Abstr.*, **44**, 5372 (1950), and T. Sasaki, *Chem. Pharm. Bull. (Tokyo)*, **2**, 104 (1954).

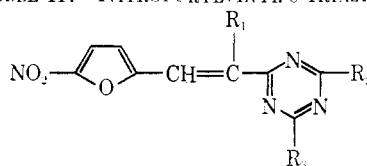
(4) R. Hirt, H. Nidecker, and R. Bechtold, *Helv. Chim. Acta*, **33**, 1365 (1950).

(5) R. Huffman and F. C. Schaeffer, *J. Org. Chem.*, **28**, 1816 (1963). They

TABLE I: *s*-TRIAZINES

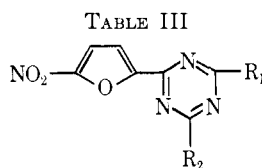
R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield, %	Mp, <sup>f</sup> °C	Recrystn solvent	Formula	Analyses
CH <sub>3</sub>	NH <sub>2</sub>	Cl	57 <sup>a</sup>	204 <sup>a</sup>	CHCl <sub>3</sub>	C <sub>4</sub> H <sub>4</sub> ClN <sub>4</sub>	C, H, N
CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	Cl	74 <sup>a</sup>	85	(CH <sub>3</sub> ) <sub>2</sub> CO-H <sub>2</sub> O	C <sub>6</sub> H <sub>6</sub> ClN <sub>4</sub>	C, H, N
CH <sub>3</sub>	NHCH <sub>3</sub>	NH <sub>2</sub>	33 <sup>b</sup>	210	MeOH	C <sub>5</sub> H <sub>5</sub> N <sub>5</sub>	N
CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	65 <sup>a</sup>	187-188 <sup>b</sup>	MeOH	C <sub>6</sub> H <sub>11</sub> N <sub>5</sub>	C, H, N
			30 <sup>b</sup>				
CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	86 <sup>a</sup>	45 <sup>c</sup>	Petr ether	C <sub>8</sub> H <sub>16</sub> N <sub>6</sub>	
C <sub>2</sub> H <sub>5</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	49 <sup>b</sup>	146-147	EtOH	C <sub>7</sub> H <sub>15</sub> N <sub>5</sub>	N
C <sub>3</sub> H <sub>7</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	28 <sup>b</sup>	121-122	C <sub>3</sub> H <sub>6</sub>	C <sub>8</sub> H <sub>15</sub> N <sub>5</sub>	C, H, N
CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	44 <sup>b</sup>	140-141	MeOH	C <sub>12</sub> H <sub>15</sub> N <sub>5</sub>	C, H, N
	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	76 <sup>b</sup>	125	EtOH-H <sub>2</sub> O	C <sub>10</sub> H <sub>13</sub> N <sub>5</sub> O	C, H, N
CH <sub>2</sub> Cl	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	52 <sup>b</sup>	173 <sup>d</sup>	EtOH	C <sub>6</sub> H <sub>10</sub> ClN <sub>4</sub>	
CH <sub>2</sub> CN	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	85 <sup>e</sup>	158	AcOEt	C <sub>7</sub> H <sub>10</sub> N <sub>6</sub>	C, H, N
CH(CH <sub>3</sub> ) <sub>2</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	37 <sup>b</sup>	150-151	EtOH-H <sub>2</sub> O	C <sub>8</sub> H <sub>13</sub> N <sub>5</sub>	C, H, N
CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	OCH <sub>3</sub>	90 <sup>d</sup>	87	MeOH-H <sub>2</sub> O	C <sub>7</sub> H <sub>12</sub> N <sub>5</sub> O	C, H, N
CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	OC <sub>2</sub> H <sub>5</sub>	92 <sup>d</sup>	62-63	MeOH-H <sub>2</sub> O	C <sub>8</sub> H <sub>14</sub> N <sub>5</sub> O	C, H, N
CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	OCH(CH <sub>3</sub> ) <sub>2</sub>	64 <sup>d</sup>	59-61	MeOH-H <sub>2</sub> O	C <sub>9</sub> H <sub>16</sub> N <sub>5</sub> O	C, H, N
CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	OC <sub>4</sub> H <sub>9</sub>	58 <sup>d</sup>	43	MeOH-H <sub>2</sub> O	C <sub>10</sub> H <sub>18</sub> N <sub>5</sub> O	C, H, N
C <sub>2</sub> H <sub>5</sub>	NH <sub>2</sub>	NH <sub>2</sub>	96 <sup>e</sup>	300-302 <sup>h</sup>	H <sub>2</sub> O	C <sub>8</sub> H <sub>7</sub> N <sub>5</sub>	
C <sub>3</sub> H <sub>7</sub>	NH <sub>2</sub>	NH <sub>2</sub>	52 <sup>e</sup>	200-202 <sup>i</sup>	H <sub>2</sub> O	C <sub>9</sub> H <sub>11</sub> N <sub>5</sub>	N

<sup>a</sup> Prepared by amination of 2,4-dichloro-6-methyl-*s*-triazine with appropriate amines. <sup>b</sup> Prepared by the condensation of an alkylbiguanide with an ester. <sup>c</sup> Prepared by the reaction of 2-amino-4-chloromethyl-6-dimethylamino-*s*-triazine with potassium cyanide. <sup>d</sup> Prepared by replacement of a chloro group of 2-chloro-4-dimethylamino-6-methyl-*s*-triazine with a sodium alkoxide. <sup>e</sup> Prepared by thermal cyclization of acylguanidine, see ref *k*. <sup>f</sup> All melting points are uncorrected. <sup>g</sup> Lit.<sup>5</sup> mp 206-207°. <sup>h</sup> Lit.<sup>5</sup> mp 192-193°. <sup>i</sup> Lit.<sup>6</sup> mp 45-46°. <sup>j</sup> Lit.<sup>7</sup> mp 176-179°. <sup>k</sup> J. K. Simons and W. Weaver [U. S. Patent 2,408,694 (1946)] reported subl > 230°. <sup>l</sup> Lit.<sup>8</sup> mp 195°.

TABLE II: NITROFURYLVINYL-*s*-TRIAZINES

No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield, %	Mp, <sup>h</sup> °C	Recrystn/ solvent	Formula	Analyses
1	H	NHCH <sub>3</sub>	NH <sub>2</sub>	58 <sup>a</sup>	219 <sup>i</sup> dec	3% HCl-EtOH	C <sub>10</sub> H <sub>11</sub> ClN <sub>6</sub> O <sub>3</sub> <sup>m</sup>	N
2	H	N(CH <sub>3</sub> ) <sub>2</sub>	NHCOCH <sub>3</sub>	80 <sup>b</sup>	199	EtOH <sup>k</sup>	C <sub>15</sub> H <sub>14</sub> N <sub>6</sub> O <sub>4</sub>	C, H, N
3	H	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	86 <sup>c</sup>	219 <sup>i</sup> dec	EtOH <sup>l</sup>	C <sub>11</sub> H <sub>13</sub> ClN <sub>6</sub> O <sub>3</sub> <sup>m</sup>	C, H, N
4	H	N(CH <sub>3</sub> ) <sub>2</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	30 <sup>b</sup>	211	EtOH-CHCl <sub>3</sub>	C <sub>19</sub> H <sub>16</sub> N <sub>6</sub> O <sub>2</sub>	N
5	CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	28 <sup>d</sup>	222-224	<i>n</i> -PrOH-(CH <sub>3</sub> ) <sub>2</sub> CO <sup>l</sup>	C <sub>12</sub> H <sub>14</sub> N <sub>6</sub> O <sub>3</sub>	C, H, N
6	CH <sub>3</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NHCOCH <sub>3</sub>	82 <sup>e</sup>	124-125 dec	EtOH <sup>k</sup>	C <sub>14</sub> H <sub>16</sub> N <sub>6</sub> O <sub>4</sub>	N
7	C <sub>2</sub> H <sub>5</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	11 <sup>d</sup>	185 dec	EtOH <sup>k</sup>	C <sub>13</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub>	C, H, N
8	C <sub>2</sub> H <sub>5</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NHCOCH <sub>3</sub>	90 <sup>e</sup>	139-140 dec	<i>n</i> -PrOH-MeOH	C <sub>15</sub> H <sub>18</sub> N <sub>6</sub> O <sub>4</sub>	C, H, N
9	C <sub>6</sub> H <sub>5</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	78 <sup>d</sup>	195 dec	<i>n</i> -PrOH <sup>l</sup>	C <sub>17</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub>	C, H, N
10		N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	66 <sup>j</sup>	165	EtOH-H <sub>2</sub> O	C <sub>15</sub> H <sub>14</sub> N <sub>6</sub> O <sub>4</sub>	C, H, N
11	Cl	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	29 <sup>d</sup>	244	C <sub>6</sub> H <sub>6</sub>	C <sub>19</sub> H <sub>11</sub> ClN <sub>5</sub> O <sub>3</sub>	C, H, N
12	CN	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	34 <sup>d</sup>	244	C <sub>6</sub> H <sub>6</sub>	C <sub>12</sub> H <sub>11</sub> N <sub>6</sub> O <sub>3</sub>	C, H, N
13	H	N(CH <sub>3</sub> ) <sub>2</sub>	OCH <sub>3</sub>	20 <sup>b</sup>	244	CHCl <sub>3</sub>	C <sub>12</sub> H <sub>13</sub> N <sub>6</sub> O <sub>4</sub>	C, H, N
14	H	N(CH <sub>3</sub> ) <sub>2</sub>	OC <sub>2</sub> H <sub>5</sub>	33 <sup>b</sup>	169	EtOH	C <sub>13</sub> H <sub>15</sub> N <sub>6</sub> O <sub>4</sub>	C, H, N
15	H	N(CH <sub>3</sub> ) <sub>2</sub>	OCH(CH <sub>3</sub> ) <sub>2</sub>	17 <sup>b</sup>	174-175	EtOH	C <sub>14</sub> H <sub>17</sub> N <sub>6</sub> O <sub>4</sub>	N
16	H	N(CH <sub>3</sub> ) <sub>2</sub>	OC <sub>4</sub> H <sub>9</sub>	15 <sup>b</sup>	138	EtOH <sup>l</sup>	C <sub>15</sub> H <sub>19</sub> N <sub>6</sub> O <sub>4</sub>	C, H, N
17	H	NH <sub>2</sub>	NH <sub>2</sub>	66 <sup>d</sup>	>300	DMF <sup>l</sup>	C <sub>9</sub> H <sub>8</sub> N <sub>6</sub> O <sub>3</sub>	C, H, N
18	CH <sub>3</sub>	NH <sub>2</sub>	NH <sub>2</sub>	64 <sup>d</sup>	>300	AcOH	C <sub>10</sub> H <sub>10</sub> N <sub>6</sub> O <sub>3</sub>	C, H, N
19	CH <sub>3</sub>	NHCOCH <sub>3</sub>	NHCOCH <sub>3</sub>	87 <sup>e</sup>	260	AcOH	C <sub>14</sub> H <sub>14</sub> N <sub>6</sub> O <sub>5</sub>	C, H, N
20	C <sub>6</sub> H <sub>5</sub>	NH <sub>2</sub>	NH <sub>2</sub>	69 <sup>d</sup>	238 dec	EtOH <sup>l</sup>	C <sub>11</sub> H <sub>12</sub> N <sub>6</sub> O <sub>3</sub>	C, H, N
21	C <sub>2</sub> H <sub>5</sub>	NH <sub>2</sub>	NHCOCH <sub>3</sub>	94 <sup>e</sup>	258	DMF	C <sub>13</sub> H <sub>14</sub> N <sub>6</sub> O <sub>4</sub>	C, H, N
22	C <sub>2</sub> H <sub>5</sub>	NHCOCH <sub>3</sub>	NHCOCH <sub>3</sub>	77 <sup>e</sup>	260	EtOH	C <sub>14</sub> H <sub>16</sub> N <sub>6</sub> O <sub>5</sub>	N

<sup>a</sup> Condensation using Ac<sub>2</sub>O and then hydrolysis with alcoholic 8% HCl. <sup>b</sup> Condensation using Ac<sub>2</sub>O. <sup>c</sup> Hydrolysis of **2** with alcoholic 8% HCl. <sup>d</sup> Condensation using glacial AcOH and concentrated H<sub>2</sub>SO<sub>4</sub>. <sup>e</sup> Acetylation with Ac<sub>2</sub>O. <sup>f</sup> Condensation using Ac<sub>2</sub>O and KOAc. <sup>g</sup> Hydrolysis of **22** with aqueous DMF (1:1). <sup>h</sup> All melting points are uncorrected. <sup>i</sup> Hydrochloride. <sup>j</sup> All compounds were yellow needles unless noted otherwise. <sup>k</sup> Brown powder or crystals. <sup>l</sup> Yellow prisms or plates. <sup>m</sup> HCl salt.



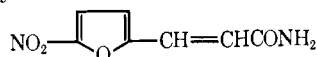
No.	R <sub>1</sub>	R <sub>2</sub>	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses
23	NH <sub>2</sub>	NH <sub>2</sub>	69	>300 <sup>d</sup>	DMF <sup>a</sup>	C <sub>7</sub> H <sub>6</sub> N <sub>6</sub> O <sub>3</sub>	N
24	NHCH <sub>3</sub>	NH <sub>2</sub>	67	236-239	MeOH-Me <sub>2</sub> CO <sup>b</sup>	C <sub>8</sub> H <sub>8</sub> N <sub>6</sub> O <sub>3</sub>	C, H, N
25	N(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	41	287	MeOH-DMF <sup>c</sup>	C <sub>9</sub> H <sub>10</sub> N <sub>6</sub> O <sub>3</sub>	C, H, N
26	NHCH(CH <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	22	196-197 <sup>e</sup>	EtOH <sup>c</sup>	C <sub>10</sub> H <sub>10</sub> N <sub>6</sub> O <sub>3</sub>	

<sup>a</sup> Yellow powder. <sup>b</sup> Brown powder. <sup>c</sup> Yellow needles. <sup>d</sup> Lit.<sup>2a</sup> mp >300°. <sup>e</sup> Lit.<sup>2b</sup> mp 197-197.5°.

TABLE IV  
*In Vitro* ANTIBACTERIAL ACTIVITY OF 5-NITROFURYLVINYL-*s*-TRIAZINES

No.	Min inhib concn, µg/ml <sup>a</sup>				
	<i>E. coli</i> 0-55	<i>S. aureus</i> 209P	<i>B. subtilis</i> PCI 219	<i>P. vulgaris</i> HX-19	<i>A. aerogenes</i>
1	0.25	1	0.1	5	10
2	>20	2.5	2.5	40	>40
3	1	10	0.5	>5	>5
4	>1.56	>1.56	>1.56	>1.56	>1.56
5	3.13	1.56	0.78	>25	>25
6	6.25	0.78	0.195	>25	>25
7	>25	25	3.13	>25	>25
8	>25	6.25	1.56	>25	>25
9	>25	>25	6.25	...	...
10	>25	12.5	1.56	...	...
11	>12.5	>12.5	6.25	>12.5	...
12	>25	25	25	>25	...
13 <sup>b</sup>	...	...	...	...	...
14	>12.5	6.25	1.56	>12.5	>12.5
15	>12.5	12.5	0.78	>12.5	>12.5
16	>3.13	>3.13	>3.13	>3.13	>3.13
17	0.5	0.25	0.5	5	2.5
18	1.56	0.78	0.195	12.5	3.13
19	3.13	1.56	1.56	>25	25
20	12.5	3.13	0.39	>25	25
21	>25	>25	>25	>25	>25
22	>25	6.25	0.78	>25	>25
5-Nitro-2-furanaacrylamide <sup>c</sup>	1.56	3.13	0.78	25	6.25

<sup>a</sup> Minimum inhibitory concentration is the lowest concentration of compound that prevents visible growth after 48 hr of incubation at 37°. <sup>b</sup> Could not be tested due to low solubility in the common solvents. <sup>c</sup> This compound (see structure below) is stronger than nitrofurazone in the *in vitro* activity.



pounds **1**, **3**, **5**, **6**, **17-20** possess high antibacterial activity; the excellent activity of **1**, **17**, and **18** against *P. vulgaris* is especially noteworthy; (2) insertion of a vinyl group between the two hetero rings enhances clearly the *in vitro* activity (compare **1**, **3**, and **17** with **24**, **25**, and **23**); (3) there is no significant difference in activity between amino compounds and their acetyl derivatives.

### Experimental Section

The preparation given below are the representative of the procedure indicated in Tables I-III.

**2-Amino-4-chloro-6-methyl-*s*-triazine.**—Alcoholic 12% NH<sub>3</sub> (18.5 g, 0.12 mole) was added dropwise over a period of 1.5 hr to a stirred solution of 2,4-dichloro-6-methyl-*s*-triazine (5 g, 0.03 mole) in 70 ml of C<sub>6</sub>H<sub>6</sub>. After stirring at room temperature for 2.5 hr longer, the precipitate which had separated was collected and crystallized from CHCl<sub>3</sub>, providing a white powder (2.5 g, 57%).

**2-Chloro-4-dimethylamino-6-methyl-*s*-triazine.**—Aqueous 20% NH(CH<sub>3</sub>)<sub>2</sub> (17 ml, 0.076 mole) was added dropwise over 1 hr to a stirred solution of 2,4-dichloro-6-methyl-*s*-triazine (10 g, 0.06 mole) in a mixture of 70 ml of Me<sub>2</sub>CO and 60 ml of H<sub>2</sub>O. The

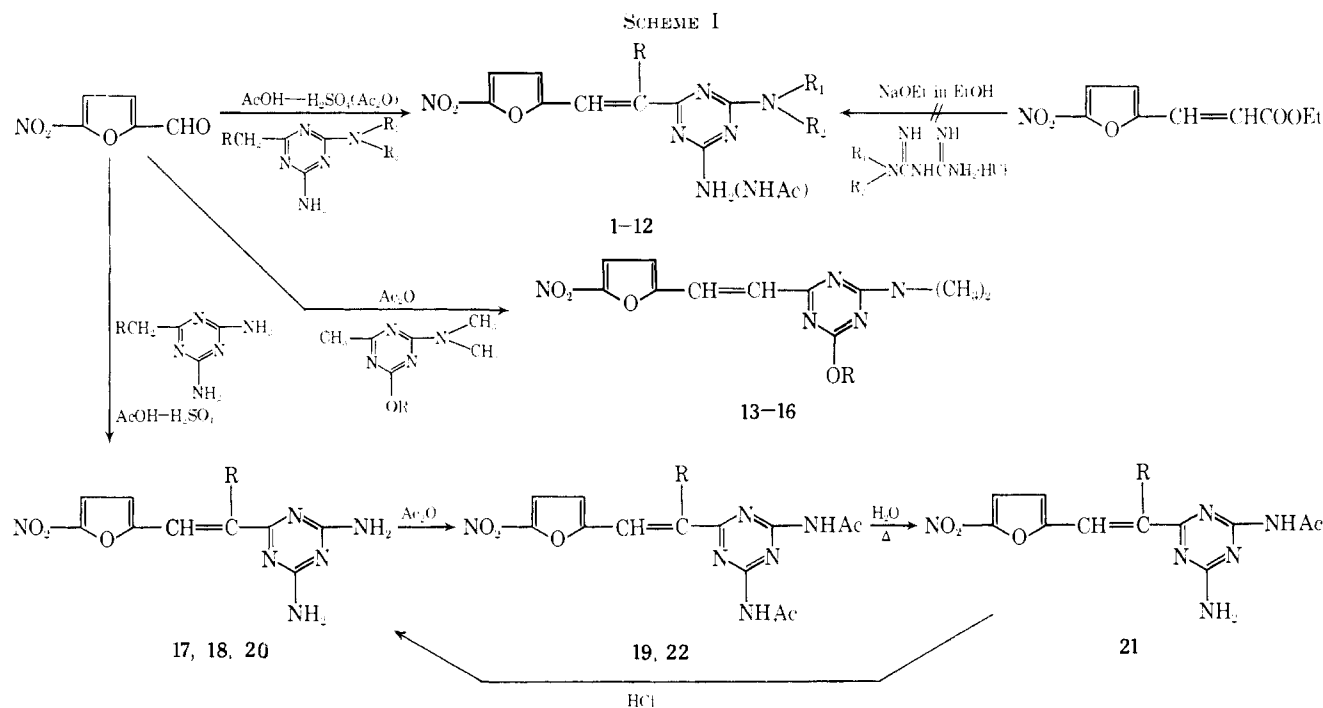
TABLE V  
*In Vitro* ANTIBACTERIAL ACTIVITY OF  
5-NITROFURYL-*s*-TRIAZINES

No.	Min inhib concn, µg/ml <sup>a</sup>				
	<i>E. coli</i> 0-55	<i>S. aureus</i> 209P	<i>B. subtilis</i> PCI 219	<i>P. vulgaris</i> HX-19	<i>A. aerogenes</i>
23	12.5	12.5	25	>25	>25
24	5	5	2.5	50	25
25	>20	>20	1	>40	>40
26	50	10	2.5	50	50
5-Nitro-2-furanaacrylamide <sup>b</sup>	1.56	3.13	0.78	25	6.25

<sup>a</sup> Minimum inhibitory concentration is the lowest concentration of compound that prevents visible growth after 48 hr of incubation at 37°. <sup>b</sup> See footnote c in Table IV.

temperature of the reaction mixture was maintained below 5°. On adding K<sub>2</sub>CO<sub>3</sub> (4.2 g, 0.03 mole) under stirring, crystals began to separate immediately. After stirring at 0-5° for 1 more hr, the product was filtered off and recrystallized from Me<sub>2</sub>CO-H<sub>2</sub>O; white needles (7.8 g, 74%) were obtained.

**2-Amino-4-dimethylamino-6-methyl-*s*-triazine** (a).—1,1-



Dimethylbiguanide hydrochloride (3.4 g, 0.02 mole) was neutralized with Na (0.46 g, 0.02 g-atom) in 35 ml of dry MeOH. The resulting NaCl was filtered, and AcOEt (1.8 g, 0.02 mole) was introduced and refluxed for 5 hr. Cooling gave colorless prisms (0.9 g, 30%) which were filtered off and recrystallized (MeOH).

The filtrate was evaporated to dryness, and the residue was recrystallized from MeOH to give colorless prisms melting at 219°. This compound was ascertained to be 1,1-dimethylbiguanide acetate, an authentic sample of which was obtained from 1,1-dimethylbiguanide and AcOH. *Anal.* (C<sub>6</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>) C, H, N.

(b) 2-Amino-4-chloro-6-methyl-*s*-triazine (2 g, 0.014 mole) was heated in alcoholic 20% Me<sub>2</sub>NH (5 g, 0.02 mole) under pressure at 100° for 5 hr. The reaction mixture was evaporated to dryness, and the residue was recrystallized from MeOH to give colorless prisms (1.4 g, 65%).

**2-Amino-4-dimethylamino-6-furfuryl-*s*-triazine.**—Na (0.27 g, 0.012 g-atom) was dissolved in 40 ml of dry MeOH. 1,1-Dimethylbiguanide hydrochloride (2 g, 0.012 mole) was then added, the resulting NaCl was filtered, ethyl 2-furylacetate (1.8 g, 0.012 mole) was introduced, and the mixture was heated at reflux for 5 hr. It was then evaporated to dryness and the residue was recrystallized (C<sub>6</sub>H<sub>6</sub>) to give white crystals (2 g, 76%).

**2-Amino-4-cyanomethyl-6-dimethylamino-*s*-triazine.**—To a stirred suspension of 2-amino-4-chloromethyl-6-dimethylamino-*s*-triazine (1.4 g, 0.0075 mole) in 100 ml of EtOH was added dropwise a solution of KCN (1.1 g, 0.008 mole) in 1 ml of H<sub>2</sub>O. After heating at reflux for 4.5 hr, the reaction mixture was evaporated to dryness. Crystallization from AcOEt gave pale yellow crystals (1.1 g, 85%).

**2-Amino-4-dimethylamino-6-[ $\alpha$ -methyl- $\beta$ -(5-nitro-2-furyl)-vinyl]-*s*-triazine (5).**—2-Amino-4-dimethylamino-6-ethyl-*s*-triazine (3.1 g, 0.019 mole) was dissolved in 60 ml of AcOH including 6 ml of concentrated H<sub>2</sub>SO<sub>4</sub>. To this solution 5-nitrofurfural (2.7 g, 0.019 mole) was added and heated at 100° for 3 hr. The

reaction mixture was diluted with 200 ml of H<sub>2</sub>O and the separated sulfate was filtered off. The sulfate was neutralized with aqueous 10% NH<sub>3</sub> to yield free base, which was recrystallized from *n*-PrOH-Me<sub>2</sub>CO to give yellow prisms (1.5 g, 28%).

**2-Ethoxy-4-dimethylamino-6-[ $\beta$ -(5-nitro-2-furyl)-vinyl]-*s*-triazine (14).**—2-Ethoxy-4-dimethylamino-6-methyl-*s*-triazine (2 g, 0.011 mole) and 5-nitrofurfural (1.5 g, 0.011 mole) were dissolved in 15 ml of Ac<sub>2</sub>O and the solution was heated for 4 hr at around 130°. On cooling, yellow crystals (1.19 g, 33%) separated. Crystallization (EtOH) gave yellow needles.

**2,4-Diacetamido-6-[ $\alpha$ -ethyl- $\beta$ -(5-nitro-2-furyl)-vinyl]-*s*-triazine (21).**—2,4-Diamino-6-[ $\alpha$ -ethyl- $\beta$ -(5-nitro-2-furyl)-vinyl]-*s*-triazine (0.2 g, 0.0007 mole) was heated under reflux with 5 ml of Ac<sub>2</sub>O for 1.5 hr. On cooling, the diacetyl compound (0.2 g, 77%) separated. Recrystallization (EtOH) gave yellow crystals.

**2-Acetamido-4-amino-6-[ $\alpha$ -ethyl- $\beta$ -(5-nitro-2-furyl)-vinyl]-*s*-triazine (20).**—A solution of 2,4-diacetamido-6-[ $\alpha$ -ethyl- $\beta$ -(5-nitro-2-furyl)-vinyl]-*s*-triazine (0.17 g, 0.0005 mole) in 20 ml of H<sub>2</sub>O-DMF (1:1) was heated at reflux for 16 hr. After cooling, the product was removed by filtration and purified by recrystallization from DMF to give pale yellow needles (0.15 g, 94%).

**2-Amino-4-dimethylamino-6-(5-nitro-2-furyl)-*s*-triazine (23).**—A solution of 1,1-dimethylbiguanide (0.65 g, 0.005 mole) and methyl 5-nitro-2-furoate (0.86 g, 0.005 mole) in 20 ml of MeOH was allowed to stand at room temperature for 3 hr. The yellow product which separated was collected by filtration and recrystallized from MeOH-DMF (1:3) to give yellow needles (0.5 g, 41%).

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