B. Irreversibility of the Disproportionation.—Cystamine dihydrochloride (0.5 mmole) was heated with 0.5 mmole of phenyl disulfide, *o*-chlorophenyl disulfide, or *o*-hydroxymethylphenyl disulfide, as usual for disproportionation experiments, in 10 ml of water at 100° for 72 hr. The three aryl disulfides were recovered unchanged (mixture melting point and infrared spectrum) in yields of 99, 104, and 101%, respectively.

C. Material Balance in the Disproportionation of 2-Aminoethyldithiobenzene Hydrochloride (10).—An aqueous solution of **10** (0.2338 g, 1.054 mmoles) in water (10 ml) was heated at 68° exactly as in the disproportionation of **2-7**, except that a 10-day period was used to assure nearly complete reaction. Phenyl disulfide was extracted with $CHCl_3$; yield, 105.8 mg (92%); mp and mmp 58–59° (infrared spectrum identical with that of phenyl disulfide). Thin layer chromatography was performed on this solid, along with the aqueous phase and appropriate authentic samples, on Eastman Chromagram sheet (Type K 301R; previously activated at 110° for 0.5 hr). Development with 95% acetic acid for 2 hr and exposure to iodine vapor showed one spot with R_f 0.81 (identical with authentic phenyl disulfide) and only two other spots, with R_f values of 0.40 and 0.66 corresponding to the authentic samples of cystamine dihydrochloride and **10**, respectively.

The aqueous phase was evaporated under reduced pressure to a white residue. The residue was rubbed with cold absolute ethanol, which removed **10** but left most of the cystamine salt. Evaporation of the ethanol left crude **10**. Several applications of this procedure finally separated 20.6 mg (13%) of **10**, mp and mmp 127–131°, and 102.6 mg (86%) of cystamine dihydrochloride, mp and mmp 218–220° dec. Infrared spectra for **10** and the cystamine salt were identical with those of authentic material. Since thin layer chromatography showed that only three materials were present and since separation showed these materials to be the two symmetrical disulfides (86–92%) and unchanged **10** (13%, evidently still containing a little cystamine salt), the disproportionation must proceed rather cleanly with rather slight formation of by-products.

Photochemical Disproportionation of Disulfides 2-7 and 9.—Aqueous solutions of 1 mmole of unsymmetrical disulfide in 20 ml of water (0.05 *M*) in 50-ml Pyrex flasks[23] were irradiated at a distance of 12.5 cm with an ultraviolet source (100-w Hanovia ultraviolet lamp, Engelhard Industries Inc., Newark, N. J.) for 25 min at room temperature. Isolations and calculations were done in the same manner described for thermal disproportionation.

Acknowledgment.—We are indebted to Drs. T. R. Sweeney, D. P. Jacobus, and P. Coad for helpful suggestions, as well as for testing and for certain materials mentioned above. The research was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030.

(23) A homogeneous solution of sparingly soluble **9** was prepared by dissolving 1 mmole in 10 ml of hot water, cooling, and diluting with 10 ml more.

Nitrofuryl Heterocycles. I. 5,6-Dihydro-3-(5-nitro-2-furyl)imidazo[2,1-*b*]thiazoles and Acid Addition Salts[1]

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The preparation of several 5,6-dihydro-3-(5-nitro-2-furyl)imidazo[2,1-*b*]thiazoles and acid addition salts is reported and their *in vitro* antibacterial activity is discussed. These compounds are prepared by the condensation of bromomethyl and chloromethyl 5-nitro-2-furyl ketones with ethylenethiourea and C-alkyl-substituted ethylenethioureas. The acid-catalyzed condensation of 5-nitro-2-furaldehyde with chloroacetone produces 3-chloro-4-(5-nitro-2-furyl)-3-buten-2-one. Condensation of 5-nitro-2-furaldehyde with (3-chloro-2-oxopropylidene)triphenylphosphorane yields 1-chloro-4-(5-nitro-2-furyl)-3-buten-2-one which reacts with ethylenethiourea to give the vinylog of the title compound.

Since the introduction of nitrofurazone[2] as a topical antibacterial agent, other nitrofurans have been prepared in an effort to increase activity. This paper describes the synthesis of a new class of nitrofurans, the 5,6-dihydro-3-(5-nitro-2-furyl)imidazo[2,1-*b*]thiazoles and their acid addition salts, which possess enhanced *in vitro* activity, especially against *Proteus vulgaris* and *Pseudomonas aeruginosa* organisms.

Chemistry.—The reaction of ethylenethiourea (**1a**) and *p*-nitrophenacyl bromide to yield 6,7-dihydro-3-(4-nitrophenyl)-5H-imidazo[2,1-*b*]thiazolium bromide was reported by Fefer and King.[3] When this reaction was applied to **1a** using bromomethyl and chloromethyl 5-nitro-2-furyl ketones (**2a**[4] and **2b**,[5] respectively) in refluxing ethanol, or dimethylformamide at steam bath temperature, the imidazothiazoles **3a** and **3b**, respectively, were formed. Neutralization of the salt **3** produced the free base **4** which could be converted to other salts. Because of the good *in vitro* activity of these compounds, several homologs were prepared.

Alkyl substitution on the imidazoline ring carbons was accomplished by using C-alkyl-substituted ethylenethioureas (**1**). The ethylenethioureas were prepared from the appropriately substituted ethylenediamines and carbon disulfide.[6,7] Condensation of these ethylenethioureas with **2a** or **2b** resulted in the products **3a–e** listed in Table I. It is interesting to note that the synthesis of **3c** and **3d**, as well as **3a** and **3b**, proceeded smoothly at steam bath temperature. However, in order to obtain **3e**, it was necessary to carry out the reaction in refluxing Methyl Cellosolve. Furthermore, it should be noted that the methyl and *gem*-dimethyl groups of **3c** and **3d**, respectively, can be on either methylene carbon of the imidazoline ring. Thin layer chromatography in several systems indicate

(1) Presented at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstracts, p 11P.

(2) Furacin®, 5-nitro-2-furaldehyde semicarbazone.

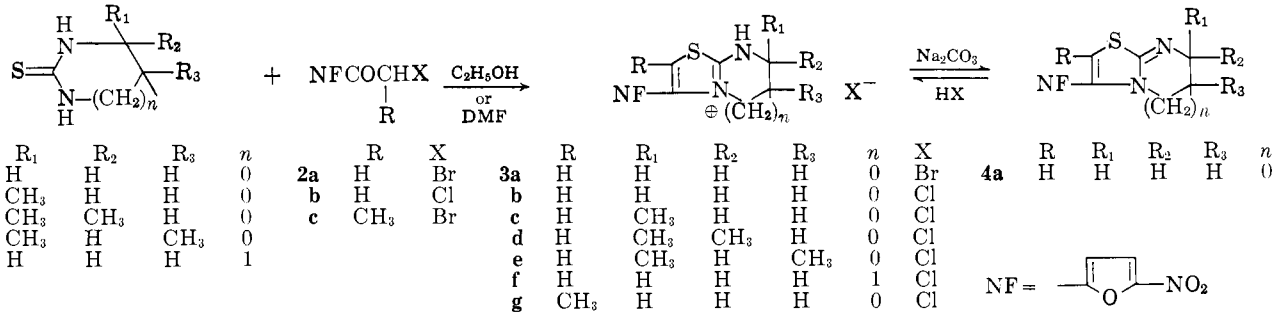
(3) M. Fefer and L. C. King, *J. Org. Chem.*, **26**, 828 (1961).

(4) O. Dann, H. Ulrich, and E. F. Moller, *Z. Naturforsch.*, **7b**, 334 (1952); *Chem. Abstr.*, **47**, 8730*f* (1953).

(5) G. Gever, U. S. Patent 3,111,530 (1963); *Chem. Abstr.*, **60**, 2893 (1964).

(6) A. F. McKay and W. G. Hatton, *J. Am. Chem. Soc.*, **78**, 1618 (1956).

(7) L. Zahlova, *Collection Czech. Chem. Commun.*, **2**, 108 (1930); *Chem. Abstr.* **24**, 2431 (1930).



	R_1	R_2	R_3	n
1a	H	H	H	0
b	CH_3	H	H	0
c	CH_3	CH_3	H	0
d	CH_3	H	CH_3	0
e	H	H	H	1

	R	X
2a	H	Br
b	H	Cl
c	CH_3	Br

	R
3a	H
b	H
c	H
d	H
e	H
f	H
g	CH_3

	R_1	R_2	R_3	n	X
3a	H	H	H	0	Br
b	H	H	H	0	Cl
c	CH_3	H	H	0	Cl
d	CH_3	CH_3	H	0	Cl
e	CH_3	H	CH_3	0	Cl
f	H	H	H	1	Cl
g	H	H	H	0	Cl

	R	R_1	R_2	R_3	n
4a	H	H	H	H	0

NF =

that both compounds are homogeneous. Therefore, although the position of the methyl groups is unknown, the structures of **3c** and **3d** have been assigned arbitrarily. The possibility of *cis* and *trans* isomers of **3e** exists. However, thin layer chromatography in several solvent systems indicated a homogeneous compound.

When tetrahydro-2-pyrimidinethione (**1e**), prepared from 1,3-diaminopropane and carbon disulfide,[3] was condensed with **2b**, the product, after conversion to the chloride salt, was the thiazolopyrimidine **3f**. It was also necessary to carry out this reaction in refluxing Methyl Cellosolve. The condensation of **1a** with the bromoethyl ketone **2c**, prepared by brominating ethyl 5-nitro-2-furyl ketone,[8] gave the product **3g**.

In order to prepare the vinylog of **3b** it was necessary to synthesize the chloromethyl vinyl ketone **5**. Toward this end, chloroacetone (**6**) was condensed with 5-nitro-2-furaldehyde (**7**) in glacial acetic acid solution containing some concentrated sulfuric acid (see Scheme I). It was anticipated that under the acid conditions, the condensation would take place on the methyl group of **6** to give the desired product.[9] Although the material gave satisfactory analytical values, it failed to react with **1a**. In fact, the product behaved in a manner that indicated that the chlorine was very unreactive; *e.g.*, the compound gave a negative test with sodium iodide in acetone. Such would be the case if the condensation had occurred on the methylene carbon of **6** to give a vinyl chloride as in **8**. The nmr spectrum of the condensation product clearly indicated that this compound did indeed have structure **8**. Three singlets at τ 7.5 (3H) (CH_3), 2.7 (2H) (furan protons), and 2.45 (1H) (olefinic proton) were observed. Compound **5** was prepared by the method of Hudson and Chopard.[10] They described the synthesis of the Wittig reagent **9** and its subsequent reaction with carbonyl compounds to give chloromethyl vinyl ketones. When this reaction was applied to **7**, the desired product was obtained in good yield. It is interesting to compare the nmr spectra of **5** and **8**. It may be noted that **5** shows the expected $-CH_2-$ singlet at τ 5.25 (2H) as well as a pair of two overlapping AB quartets (total of 4H) corresponding to the furanoid and olefinic protons. Compound **5** was assigned the *trans* configuration on the basis of the 16-cps coupling constant observed between the two olefinic protons.[11] Condensation of **5** with **1a** proceeded smoothly to yield the vinylog **10**.

Screening Results.—These compounds were screened *in vitro* against a variety of bacteria according to procedures described previously.[12] It can be seen in Table II that all of the compounds possess broad-spectrum activity against both gram-positive and gram-negative organisms. However, the activity of these compounds against *Pseudomonas aeruginosa* and *Proteus vulgaris* is of particular interest. The data for nitrofurazone[2] are included for comparison. From the data shown, the following observations are apparent: (1) all of the compounds are active against *Proteus vulgaris* and *Pseudomonas aeruginosa;* (2) there is little difference in activity between the free base and its salts (compare **3a** and **3b** with **4**); (4) C-methyl substitution and ring expansion cause a decrease in activity (compare **3c**, **3d**, **3e**, **3f**, and **3g** with **3b**); and (4) insertion of a vinyl group (**10**) between the two hetero rings has little effect on activity.

Compounds **3a**, **3b**, and **4** were screened against five additional strains of *Proteus vulgaris* and *Pseudomonas aeruginosa*. From the data listed in Table III it can be seen that the three compounds possess excellent activity against these organisms. Compound **3b**, under the generic name of furazolium chloride, is currently undergoing clinical evaluation, in a water-miscible base of polyethylene glycols, as a topical antibacterial agent.

Experimental Section

All melting points were taken on a micro hot stage (Fisher-Johns) melting apparatus and are uncorrected. The physical and analytical data for compounds **3** are reported in Table I. The nmr spectra were determined on a Varian Model A-60 spectrometer.

6,7-Dihydro-3-(5-nitro-2-furyl)-5H-imidazo[2,1-*b*]thiazolium Bromide (3a).—A mixture of **1a** (20.4 g, 0.2 mole) and **2a**[4] (46.8 g, 0.2 mole) in absolute ethanol (5600 ml) was refluxed for 4 hr. The reaction mixture was cooled and filtered to yield 58.0 g (91%) of product decomposing at 242–244°. The material was recrystallized from methanol (charcoal).

5,6-Dihydro-3-(5-nitro-2-furyl)imidazo[2,1-*b*]thiazole (4).—A solution of **3a** (184 g, 0.58 mole) in water (20 l.) was stirred and neutralized with aqueous $NaHCO_3$ (pH 7.5). The mixture was filtered and the product was washed with water and dried at 65° to yield 137 g (100%) of material melting at 168–171°. A sample was recrystallized from a benzene–hexane mixture (charcoal) to give red needles melting at 171–172° dec.

Anal. Calcd for $C_9H_7N_3O_3S$: C, 45.56; H, 2.98; N, 17.71. Found: C, 45.64; H, 3.02; N, 17.41.

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SCHEME I

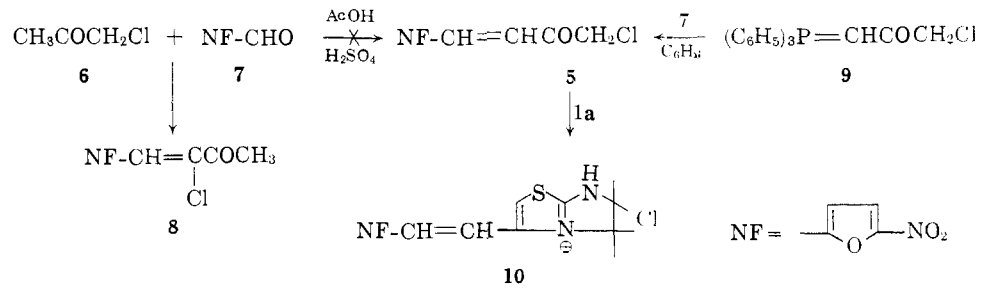
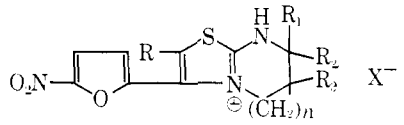


TABLE I: 6,7-DIHYDRO-3-(5-NITRO-2-FURYL)-5H-IMIDAZO[2,1-*b*]THIAZOLIUM HALIDES (**3**)



No.	R	R_1	R_2	R_3	*n*	X	Formula	Mp, °C	Yield,[a] %	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
3a	H	H	H	H	0	Br	$C_9H_8BrN_3O_3S$	244–245	91	33.97	2.53	25.12[b]	34.33	2.58	24.87[b]
b	H	H	H	H	0	Cl	$C_9H_8ClN_3O_3S$	>250 dec	79.5	39.49	2.94	12.96[c]	39.52	3.06	13.22[c]
c	H	CH_3	H	H	0	Cl	$C_{10}H_{10}ClN_3O_3S$	253–254	62	41.74	3.50	11.15	41.94	3.72	11.34
d	H	CH_3	CH_3	H	0	Cl	$C_{11}H_{12}ClN_3O_3S$	258–259	61.2	43.78	4.01	10.63	43.92	4.18	10.72
e	H	CH_3	H	CH_3	0	Cl	$C_{11}H_{12}ClN_3O_3S$	221–222	18	43.78	4.01	10.63	43.58	3.97	10.72
f	H	H	H	H	1	Cl	$C_{10}H_{10}ClN_3O_3S$	242–243	72	41.74	3.50	11.15	41.74	3.65	11.08
g	CH_3	H	H	H	0	Cl	$C_{10}H_{10}ClN_3O_3S$	255 dec	63.2	41.74	3.50	14.60[d]	41.88	3.59	14.43[d]

[a] Over-all yield from the bromomethyl ketone **2**. [b] Value for Br. [c] Value for Cl. [d] Value for N.

TABLE II: *In Vitro* ANTIBACTERIAL ACTIVITY OF 5,6-DIHYDRO-3-(5-NITRO-2-FURYL)IMIDAZO[2,1-*b*]THIAZOLES AND ACID ADDITION SALTS

	Minimal inhibitory concentration, μg/ml[a]								
No.	*Escherichia coli* Es-2[b]	*Salmonella typhosa* SaD-13	*Pseudomonas aeruginosa* Ps-10	*Proteus vulgaris* Pr-12	*Aerobacter aerogenes* Ae-6	*Erysipelothrix insidiosa* Er-4	*Staphylococcus aureus* Mi-6	*Streptococcus pyogenes* StA-1	*Streptococcus agalactiae* StB-12
3a	<0.75	<0.75	25	25		1.5	6.25	6.25	25
3b	<0.75	<0.75	25	25	6.2	1.5	6.2	6.25	25
4	<0.75	<0.75	25	12.5	3.1	1.5	6.2	3.1	25
3c	0.8	0.4	100	50	6.2	6.2	6.0	6.2	50
3d	0.8	0.8	200	200	12.5	12.5	12.5	25	100
3e	0.4	0.75	100	100	6.0	6.0	6.0	12.5	100
3f	1.5	0.6	100	50	25	<1.5	12.0	6.0	25
3g	0.38	1.5	100	25	12.5	1.5	6.0	0.75	12.5
10	0.38	0.38	50	12.5	0.75	0.19	0.75	0.048	1.5
Nitrofurazone[c]	3	3	>100	100	100	12.5	12.5	6	12.5

[a] Minimum inhibitory concentration is the lowest concentration of compound that prevents visible growth after 24 hr of incubation. [b] Eaton Laboratories strain number. [c] For comparison, see J. G. Michels, G. Gever, and P. H. L. Wei, *J. Med. Pharm. Chem.*, **5**, 1042 (1962).

TABLE III

COMPARISON OF COMPOUNDS TESTED *in Vitro vs.* FIVE *Proteus* AND FIVE *Pseudomonas* STRAINS

	24-hr MIC,[b] μg/ml		
Strain no.[a]	**3a**	**3b**	**4**
Proteus			
52	100	50	50
53	50	25	25
54	50	50	50
55	50	25	25
56	50	25	25
Pseudomonas			
38	25	25	25
41	12	<6	6
42	12	<6	6
44	12	<6	6
45	12	<6	6

[a] Eaton Laboratories strain number. [b] Minimum inhibitory concentration is the lowest concentration of the compound that prevents visible growth after 24 hr of incubation.

6,7-Dihydro-3-(5-nitro-2-furyl)-5H-imidazo[2,1-*b*]thiazolium Chloride (3b). Method A.—A hot solution of **4** (80.0 g, 0.336 mole) in methanol was acidified with concentrated HCl (pH ~2). The hot solution was filtered and after chilling the product was collected. The salt was washed with ether and dried at 65° to yield 73.0 g (79.5%) of **3b**, decomposing >250°. The crude product was recrystallized from methanol (charcoal) with no change in the decomposition point.

Method B.—A solution of **1a** (53.9 g, 0.53 mole) and **2b**[5] (100.0 g, 0.53 mole) in dimethylformamide (500 ml) was heated at 95° for 30 min. The mixture was cooled and filtered. The product was washed with methanol and dried at 60° to yield 124.0 g (86%) of **3b**. The infrared and ultraviolet spectra agreed with those of **3b** prepared by method A.

4,4-Dimethyl-2-imidazolidinethione (1c).—Using the method of McKay and Hatton,[6] **1c** was prepared in a 68.0% yield from 1,2-diamino-2-methylpropane and CS_2; mp 118.5–119° (benzene).

Anal. Calcd for $C_5H_{10}N_2S$: C, 46.11; H, 7.74; N, 21.52. Found: C, 46.16; H, 7.80; N, 21.41.

Compounds 3c–f (Table I) were prepared by condensing 4-methyl-2-imidazolidinethione (**1b**),[6] 4,4-dimethyl-2-imidazolidine-

thione (**1c**), 4,5-dimethyl-2-imidazolidinethione (**1d**),[7] and tetrahydro-2-pyrimidinethione (**1e**),[6] respectively, with **2a**. The crude bromide salts were converted to the free bases and then to the chloride salts for characterization. Thin layer chromatography of **3c–e** in several solvent systems indicated that the compounds were homogeneous.

2-Bromo-1-(5-nitro-2-furyl)-1-propanone (2c).—Ethyl 5-nitro-2-furyl ketone[8] (25.0 g, 0.15 mole) was dissolved in warm CCl_4 (200 ml). The solution was kept at 60–70° while bromine (24.0 g, 0.15 mole), dissolved in CCl_4 (50 ml), was added rapidly. Initially there was no reaction. The mixture was refluxed with stirring for 0.5 hr. After this time, the reaction became very exothermic; stirring and heating were stopped until the reaction abated. Then stirring and heating were continued until HBr evolution ceased. The solution was boiled with charcoal for 5 min and filtered. The filtrate was concentrated to *ca.* 50 ml; the product precipitated after the addition of 400 ml of petroleum ether (bp 30–60°). The yield of crude product melting at 56–58° was 24.0 g (65.0%). Recrystallization of a sample from petroleum ether (bp 30–60°) raised the melting point to 59.5–60°.

Anal. Calcd for $C_7H_6BrNO_4$: C, 33.89; H, 2.44; Br, 32.22. Found: C, 34.20; H, 2.48; Br, 32.58.

6,7-Dihydro-2-methyl-3-(5-nitro-2-furyl)-5H-imidazo[2,1-*b*]-thiazolium Chloride (3g).—A mixture of **2c** (124.0 g, 0.5 mole) and **1a** (51.0 g, 0.5 mole) in dimethylformamide (500 ml) was heated at 130–140° for 10 min. The mixture was allowed to cool to room temperature, diluted with ether (400 ml), and filtered to yield 120 g (70.0%) of crude bromide salt. The salt was dissolved in water and neutralized with aqueous Na_2CO_3 solution. The red free base was collected, washed with water, and dried at 100° to yield 86.0 g (95%). A sample of the free base (36.0 g, 0.14 mole) was stirred into concentrated HCl (25 ml) to give a yellow lumpy paste. The paste was stirred with 2-propanol (350 ml), diluted with ether, and filtered. The product was dried at 110° to yield 38.0 g (95%) of crude chloride salt. A portion of the salt (36.0 g) was recrystallized from 2-propanol (10 ml/g) (charcoal) to give 31.0 g of **3a** decomposing at 255° when placed on a preheated melting point block.

3-Chloro-4-(5-nitro-2-furyl)-3-buten-2-one (8).—To a solution of **6** (145.0 g, 1.57 moles) and **7** (141.0 g, 1.0 mole) in acetic acid (500 ml) was added concentrated H_2SO_4 (100 ml) during 10 min at 20–25°. The dark red solution was allowed to stand in the refrigerator for 6 days. The precipitate was collected, washed with 2-propanol, and air dried. The crude material was recrystallized from ethyl acetate (charcoal) to yield 96.0 g (44.5%) of **8** melting at 118–120°. Further recrystallization of the material from 2-propanol raised the melting point to 120–121°.

Anal. Calcd for $C_8H_6ClNO_4$: Cl, 16.45; N, 6.50. Found: Cl, 16.48; N, 6.48.

The nmr spectrum ($CDCl_3$) displayed three singlets at τ 7.5 (3H), 2.7 (2H), and 2.45 (1H).

1-Chloro-4-(5-nitro-2-furyl)-3-buten-2-one (5).—A mixture of **7** (107.0 g, 0.76 mole) and **9**[10] (182.0 g, 0.517 mole) in benzene (1200 ml) was refluxed for 1 hr. The benzene was removed under reduced pressure, and the residue was recrystallized from methanol to yield 92.0 g (82.9%) of crude **5** melting at 134–136°. A portion of the product (70.0 g) was recrystallized from 2-propanol to give 53.0 g of **5** melting at 137–138°.

Anal. Calcd for $C_8H_6ClNO_4$: C, 44.56; H, 2.81; Cl, 16.45. Found: C, 44.64; H, 2.89; Cl, 16.47.

The nmr spectrum (DMSO) showed singlets at τ 5.25 (2H), 3.2, 2.91, 2.72, 2.68, 2.58, 2.30 (overlap), and 2.24 with J = 16 cps.

6,7-Dihydro-3-[2-(5-nitro-2-furyl)vinyl]-5H-imidazo[2,1-*b*]-thiazolium Chloride (10).—A mixture of **1a** (31.0 g, 0.3 mole) and **5** (65.0 g, 0.3 mole) in absolute ethanol (*ca.* 3000 ml) was refluxed for 4 hr. The reaction mixture was cooled and filtered to give 66.0 g of crude **10** decomposing at 245°. Concentration of the filtrate followed by cooling resulted in a second crop of 14.8 g decomposing at 245°; total yield 80.8 g (89.7%). Recrystallization of crude **10** from methanol (charcoal) did not affect the decomposition point.

Anal. Calcd for $C_{11}H_{10}ClN_3O_3S$: C, 44.08; H, 3.36; N, 14.02. Found: C, 44.22; H, 3.58; N, 14.24.

Acknowledgments.—The authors gratefully acknowledge the aid of Mr. George Klein who prepared compound **8**, of Mr. Nicholas Harris who prepared **3b** by method B, and of Mrs. Patricia Curtis, Mr. Frederick Abbott, and Mr. Benjamin Stevenson for the preparation of chemical intermediates. Mr. Grant Gustin and Mr. Marvin Tefft performed the microanalyses. The microbiological data were obtained by Dr. Warren Carey, Mr. Eric Russell, and Mr. Richard Dobson. The nmr spectra were obtained from and interpreted by Professor Jerrold Meinwald of the Chemistry Department, Cornell University.

Nitrofuryl Heterocycles. III.[1] 3-Alkyl-5-(5-nitro-2-furyl)-1,2,4-triazoles and Intermediates

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The synthesis of several N-acylamido-5-nitro-2-furamidines and 3-alkyl-5-(5-nitro-2-furyl)-1,2,4-triazoles is described. The antibacterial testing data for these and other derivatives are discussed.

A continuing search for new chemotherapeutic nitrofurans led to an investigation of 1,2,4-triazole derivatives and intermediates.

Chemistry.—The compounds herein reported were prepared by a modification of the method of Browne and Polya[2] for the synthesis of 3-aryl-5-alkyl-4H-1,2,4-triazoles. Thus, ethyl 5-nitro-2-furimidate hydrochloride[3] was treated with various alkyl hydrazides in the presence of 1 equiv of base to yield N-acylamidoamidines (I). The physical and analytical properties of I are summarized in Table I. Cyclization of the N-acylamidoamidines I was effected readily in refluxing phosphorus oxychloride solution or refluxing glacial acetic acid solution to give the 3-alkyl-5-(5-nitro-2-furyl)-4H-1,2,4-triazoles (II) listed in Table II. These reactions are summarized as shown in Scheme I. In addition, triazole IIa (R = H) was acetylated with acetic anhydride and carbamoylated with methyl isocyanate in dimethylformamide solution to give III and IV, respectively. No satisfactory method was found for establishing the position of ring-nitrogen substitution in III and IV. Alkylation of triazole IIb

(1) For paper II in this series see H. A. Burch and L. E. Benjamin, *J. Med. Chem.*, **9**, 425 (1966).

(2) E. J. Browne and J. B. Polya, *J. Chem. Soc.*, 5149 (1962).

(3) W. R. Sherman and A. Von Esch, *J. Med. Chem.*, **8**, 25 (1965).