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### Nitrofuryl Heterocyclics. 31

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The synthesis and antibacterial properties of some 1-[4-(5-nitro-2-furyl)-2-thiazolyl]hydantoins and -hydrouracils have been described earlier.<sup>2</sup> As part of a search for new chemotherapeutic nitrofurans, the preparation of hyinfections in mice by oral and subcutaneous administration. Although some of these derivatives were active invivo against S. pyogenes (Table II), none was effective against S. aureus.

Nitrofurans 1.27 were also evaluated against *Trichomonas vaginalis in vitro* and in mice.<sup>‡</sup> Most of the compounds had some activity in the *in vitro* screen, and when tested against *T. vaginalis* infections in mice, hydantoins 16, 17, and 21 were found to be *ca*. four times more active than metronidazole.<sup>§</sup> Further experiments showed, however, that none of the compounds appeared in measurable quantities in the urine.

In conclusion, when the nitrofurylthiadiazoles above are compared with the analogous 1-[4-(5-nitro-2-furyl)-2-thiazolyl]hydantoins and -hydrouracils discussed earlier,<sup>2</sup> two points of interest emerge. Firstly, as antibacterial agents the two series have comparable potencies against most organisms in the *in vitro* screen. In vivo, activity against S. aureus and S. pyogenes is relatively widespread among ni-

Table I. In Vitro Antibacterial and Trichomonicidal Activity of Nitrofurans 1-25\*

	Minimum inhibitory concentration, µg/ml								
Compd	Staph. aureus, UC-76	Diplococcus pneumoniae	Strep. pyogenes, C203	Salmonella typhimurium, V-31	Shigella sonnei, C-10	T. vaginalis			
1	1.25	0.31	1.25	2.5	2.5	$>25 \ (6.25)^{b}$			
<b>2</b>	อี	0.16	0.16	20	20	>25			
3	ō	0.16	0.63	10	20	> 25			
4	5	20	0.31	20	20	> 25			
5	0.63	0.31	1.25	2.5	5	6.25			
6	0.63	>20	0.16	20	5	>25 (1.56)			
9	1.25	c	0.63	5	10	>25			
11	2.5	5	0.08	> 20	>20	>25 (6.25)			
13	1.25	e	0.63	>20	>20	25			
15	0.63	>20	0.08	>20	>20	25			
16	1.25	10	0.63	>20	10	25			
17	$\frac{1}{2}, 5$	С	1.25	>20	20	25			
21	5	C	5	>20	>20	>25 (6.25)			
23	1.25	1.25	>20	>20	> 20	>25(6.25)			
24	1.25	10	5	20	20	25			
$\overline{25}$	0.63	1.25	2.5	>20	20	с			

- 'See ref 4 and 5. 'Figures in parentheses indicate 90–99.9 % inhibition at stated levels. Indicates test not done.

dantoin and hydrouracil derivatives of 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (I, R = H) was examined, since it has been established that this latter nitrofuran and related compounds (*e.g.*, I, R = CHO) have potent antibacterial activities.<sup>3</sup>

**Chemistry.** The preparation of ureas II from I (R = H) and various acyl isocyanates, the cyclization of 2- or 3-haloacylureas to the corresponding hydantoins or hydrouracils III with NaH in DMF, and the alkylation of these last compounds to the 3-substituted derivatives IV are described in the Experimental Section.

Screening Results. Nitrofurans 1-27 were tested in vitro against a variety of bacteria according to procedures described previously.<sup>†</sup> It can be seen from Table I, which records the more active compounds, that most of the nitrofurans possessed efficacy against Staphylococcus aureus and Streptococcus pyogenes. Selected compounds were evaluated further against S. aureus and S. pyogenes

Table II. In Vivo Activity<sup>n</sup>

F	S. pyogenes, D <sub>50</sub> (mice), mg/	kg	<i>T. vaginalis</i> , metronidazole equiv,
$\mathbf{Compd}$	ро	sc	$M^{_b}$
2	200	50	с
3	35	50	< 0.25
11	42.5	10.2	С
16	с	c	4
17	C	С	4
21	$C_{-}$	Ċ	2-4

<sup>a</sup>See ref 4 and 5. <sup>*b*</sup> $M = ED_{50}$  of metronidazole  $^{\circ}ED_{50}$  of test compound. <sup>c</sup>Indicates test not done.

trofurylthiazole congeners. and in these compounds hydantoins and hydrouracils (*i.e.*, derivatives equivalent to III and IV) appear to be more active than the acylureas corresponding to II. In thiadiazoles II-IV, however, no compound appears to be effective against *S. aureus in* vivo, and activity against *S. pyogenes in vivo* is of a lower order than that shown by the analogous nitrofurylthiazoles. Finally, as trichomonicidal agents, the nitrofurylthiadiazoles above are very much more potent *in vivo* than the nitrofurylthiazoles discussed earlier.<sup>2</sup> In this respect, maximum activity appears to reside in the nitrothi-

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<sup>&</sup>lt;sup>+</sup> For a description of the general *in vitro* and *in vivo* test procedures, see ref4.

 $<sup>\</sup>ddagger$  For a description of test methods, see ref 5.

<sup>§</sup> Flagyl.

O <sub>2</sub> N O S NHCONHCOR								
Compd	R	Mp, °C	${f Recrystn}\ {f solvent}^a$	Yield, %	Reaction time, hr	Formula		
1	Me	>360	A	74	3	C <sub>9</sub> H <sub>7</sub> N <sub>5</sub> O <sub>5</sub> S		
2	$CH_2Cl$	244–245 dec	C-B	63	1	C <sub>9</sub> H <sub>6</sub> ClN <sub>5</sub> O <sub>5</sub> S		
3	$\mathbf{CHCl}_2$	273 dec	$C-B^b$	68	1	$C_9H_5Cl_2N_5O_5S$		
4	$\mathbf{CH}_{2}\mathbf{Br}$	268–270 dec	В	85	0.5	$C_9H_6BrN_5O_5S$		
5	$\mathbf{Et}$	304–305 dec	Α	78	2.5	$C_{10}H_{0}N_{5}O_{5}S$		
6	$(CH_2)_2Br$	226–227 dec	С	80	1	$\mathrm{C}_{10}\mathrm{H}_8\mathrm{BrN}_5\mathrm{O}_5\mathrm{S}^c$		
7	CH(Me)Br	225–226 dec	Α	82	0.5	$C_{10}H_8BrN_5O_5S$		
8	CH(Et)Br	214 dec	Α	83	5	$\mathrm{C}_{11}\mathrm{H}_{10}\mathrm{BrN}_5\mathrm{O}_5\mathrm{S}^d$		
9	$C(Me)_2Br$	219 dec	Α	82	4	$C_{11}H_{10}BrN_{5}O_{5}S$		
10	Ph	297–298 dec	С	59	2	$C_{14}H_{0}N_{0}O_{0}S$		

	Table	III.	1-Acyl-3-	[5-(5-	-nitro-	2-furyl	l)-1,3	3, <b>4-</b> th	iadiazol	I-2-yl]ureas
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"A, AcOH; B, EtOH; C, DMF. <sup>b</sup>Followed by hot H<sub>2</sub>O wash. <sup>c</sup>C: calcd, 30.8; found, 31.4. <sup>d</sup>C: calcd, 32.7; found, 33.3.

Table IV. 1-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl]hydantoins and -hydrouracils

		0 <sub>2</sub> N 0		<sup>A</sup> C <sup>IO</sup> NH		
			III			
Compd	А	Mp, °C	${f Recrystn}\ {f solvent}^a$	Yield, %	Reaction time, hr (temp, °C)	Formula
11	$CH_2$	308-310 dec	Α	45	0.5 (20)	$C_9H_5N_5O_5S$
12	CH(Me)	283 dec	В	59	2(20)	$C_{10}H_7N_5O_5S$
13	CH(Et)	242–244 dec	С	47	1.5 (20)	$C_{11}H_9N_5O_5S$
14	$C(Me)_2$	266–267 uec	В	41	3 (100)	$C_{11}H_9N_5O_5S$
15	$(CH_2)_2$	310-311 dec	А	86	0.5 (20)	$C_{10}H_7N_5O_5S$

<sup>a</sup>A, DMF, followed by hot H<sub>2</sub>O wash; B, AcOH; C, EtOH.

Table V. 3-Substituted 1-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl] hydantoins and -hydrouracils and -hydrouracils

			0 <sub>2</sub> N 0		C <sup>I</sup> −N−−R		
				IV			
Compd	Α	R	Mp, °C	${f Recrystn} \\ {f solvent}^a$	Yield, %	Reaction time, hr (temp, $^{\circ}C$ )	Formula
16	$\mathbf{CH}_2$	Me	244–245 dec	А	44	1 (20)	$C_{10}H_7N_5O_5S^d$
17	$\mathrm{CH}_2$	$\mathbf{Et}$	204–206 dec	В	41	2 (40)	$C_{11}H_9N_5O_5S$
<b>18</b>	$\mathrm{CH}_2$	$n$ - $\Pr$	221 - 224	Α	56	4 (40)	$C_{12}H_{11}N_{5}O_{5}S$
19	$\mathrm{CH}_2$	n-Bu	230 - 232	Α	50	2(40), 2(60)	$C_{13}H_{13}N_{5}O_{5}S$
<b>20</b>	CH(Me)	Me	241	Α	67	1 (20)	$C_{11}H_0N_0O_0S$
21	CH(Et)	Me	211 - 212	Α	66	1 (20)	$C_{12}H_{11}N_5O_5S$
<b>22</b>	$C(Me)_2$	Me	208 - 210	С	46	1 (20)	$C_{12}H_{11}N_{3}O_{3}S$
23	$(CH_{2})_{2}$	Me	288–290 dec	Α	<b>70</b>	2 (20)	$C_{11}H_0N_0O_0S^c$
<b>24</b>	$(\mathbf{CH}_2)_2$	$\mathbf{Et}$	$207 - 209^{b}$	Α	77	1 (20)	$C_{12}H_{11}N_{2}O_{2}S'$
<b>25</b>	$(CH_2)_2$	n-Pr	220-221°	А	57	1.5 (40)	$C_{13}H_{13}N_{3}O_{3}S$
26	$(\mathbf{CH}_2)_2$	<i>n-</i> Bu	205	Α	61	4.5 (55)	$C_{14}H_{15}N_{2}O_{2}S$
	(CH <sub>2</sub> ) <sub>2</sub>	$n-C_{s}H_{17}$	149	А	67	4.5 (65)	$C_{18}H_{23}N_{5}O_{5}S$

N N

.0

"A, AcOH; B, aqueous DMF; C, aqueous AcOH. <sup>b</sup>Clear at 225°. 'Sinters at 216°. <sup>d</sup>N: calcd, 22.7; found, 22.0. 'C: calcd, 40.9; found, 40.4. <sup>J</sup>C: calcd, 42.7; found, 41.8.

adiazolylhydantoins rather than the ring-enlarged hydrouracils.

### Experimental Section

The physical properties of the compounds prepared are collected in Tables III-V, and the experimental details below relate to these tables.

= Melting points are corrected and were determined in capillary tubes. Analytical results were obtained for C, H, and N for all compounds and unless otherwise stated were within  $\pm 0.4\%$  of the theoretical values. **l-Acyl-3-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]ureas** (II, **Table III).** The appropriate acyl isocyanate (0.055 mol) (prepared by known methods<sup>6</sup> and used, after distillation on the aspirator and measurement of the ir spectra, without further characterization) in THF (35 ml) was added dropwise to a suspension of I (R = H)<sup>7</sup> (0.05 mol) in THF (120 ml), and the mixture was then stirred at room temperature (time given). The product was collected by filtration, washed with Et<sub>2</sub>O, and recrystallized.

1-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl]hydantoins and -hydrouracils (III, Table IV). NaH (50% in oil, 0.01 mol) was added in portions to a suspension of a 2- or 3-haloacylurea (II, R = haloalkyl; 0.01 mol) in DMF (50 ml) at 0° and the mixture was stirred until it became neutral (time/temperature given). Acidification (AcOH) and dilution with  $H_2O$  afforded the crude product, which was recrystallized from the appropriate solvent.

3-Substituted 1-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl]hydantoins and -hydrouracils (IV, Table V). NaH (50% in oil, 0,03 mol) was added in portions to a suspension of the hydantoin or hydrouracil II (0.03 mol) in DMF (60 ml) at 0°, followed by the appropriate alkylating agent. The mixture was then stirred until neutral (time/temperature listed), acidified (AcOH), and diluted with H<sub>2</sub>O. The product was filtered off, washed with H<sub>2</sub>O, dried, and recrystallized.

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# Antimetabolites of Coenzyme Q. 20.† Synthesis of New Alkyl-5,8-quinoxalinequinones as Potential Inhibitors of Coenzyme Q and as Antimalarial Drugs

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The synthesis is described of representative compounds of a new category of alkyl-5,8-quinoxalinequinones as potential antimetabolites of coenzyme Q for testing as antimalarials and other biological activities. In view of the effective antimalarial activity of some of our recently synthesized alkylmercapto-5,8-quinolinequinones,<sup>1</sup> it is of interest to synthesize and bioassay 5,8-quinoxalinequinones, especially those with sulfur-containing side chains. The side chains were designed to impart the necessary lipoidal character to the molecule and toward simulation of the highly lipoidal coenzyme Q.

The initial step in the two-step synthesis of 6-*n*-dodecylmercapto- and 6,7-di-*n*-dodecylmercapto-5,8-quinoxalinequinones (3 and 4, respectively) (Scheme I) consisted of the 1,4 addition of *n*-dodecyl mercaptan to 5,8-quinoxalinequinone in a manner similar to that described by Snell and Weissberger<sup>2</sup> for the syntheses of certain alkylmercaptobenzoquinones. Oxidation of the isolated mono- and dialkylated dihydroxyquinoxalines (1 and 2, respectively) with FeCl<sub>3</sub> gave the alkylated quinoxalinequinones **3** and 4, respectively, in high yield. Attempts to oxidize the dihydroxyquinoxalines with Ag<sub>2</sub>O resulted in extensive decomposition. Acetylation of 6-*n*-dodecylmercapto-5,8dihydroxyquinoxaline (1) with acetic anhydride and  $H_2SO_4$  as catalyst was accomplished to give the corresponding diacetyl derivative 5.

Scheme I



The synthesis of 6- $\omega$ -cyclohexylpentyl-5,8-quinoxalinequinone (6) was effected by treating 5,8-quinoxalinequinone with di- $\omega$ -cyclohexylhexanoyl peroxide in acetic acid (Scheme II). The yield of 6- $\omega$ -cyclohexylpentyl-5,8-quinoxalinequinone (6) was very low.

#### Scheme II



Compounds 2-4 were tested for antimalarial activity against blood-induced *Plasmodium berghei* in mice<sup>3</sup> and were inactive at 640 mg/kg each. Compounds 3 and 4 were tested against *Plasmodium gallinaceum* in the sporozoite-induced chick test<sup>4</sup> and were inactive at 80 mg/kg. Compound 2 was also inactive against *P. gallinaceum* (blood-induced) in the chick<sup>3</sup> at 100 mg/kg. Additional compounds, particularly analogs of 3, merit synthesis and testing.

Compounds 2 and 3 were tested *in vitro* for inhibitory activity in mitochondrial DPNH-oxidase and succinoxidase enzyme systems (Table I). Neither compound showed significant inhibition in DPNH-oxidase at levels of 120 nmol of inhibitor/mg of mitochondrial protein; however, compounds 2 and 3 showed 25 and 29% inhibition, respectively, in succinoxidase at this same concentration level. The mitochondria were prepared by a method similar to that described by Blair.<sup>5</sup>

### **Experimental Section**

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within  $\pm 0.4\%$  of the theoretical values. Nmr spectra were taken on all new compounds and were consistent with the proposed structures.

6-n-Dodecylmercapto- and 6,7-Di-n-dodecylmercapto-5,8dihydroxyquinoxaline (1 and 2, respectively). 5.8-Quinoxalinequinone<sup>6</sup> (1.0 g. 6.24 mmol) in EtOH was treated with n-dodecyl mercaptan (1.5 g, 7.41 mmol). The reaction mixture was stirred