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Nitrofuryl Heterocyclics. 3[1]

Peter J. Islip* and Madelaine R. Johnson

Chemistry Department, Research and Development Division, Parke, Davis and Company, Pontypool, United Kingdom.
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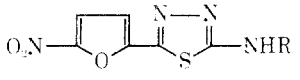
The synthesis and antibacterial properties of some 1-[4-(5-nitro-2-furyl)-2-thiazolyl]hydantoins and -hydrouracils have been described earlier.[2] As part of a search for new chemotherapeutic nitrofurans, the preparation of hydantoin and hydrouracil derivatives of 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (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.[3]



I

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.† 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* infections in mice by oral and subcutaneous administration. Although some of these derivatives were active *in vivo* 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.‡ 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.§ 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,[2] 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 nitrofurylthiazole 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.[2] In this respect, maximum activity appears to reside in the nitrothi-

Table I. *In Vitro* Antibacterial and Trichomonicidal Activity of Nitrofurans **1-25**[a]

	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]
2	5	0.16	0.16	20	20	>25
3	5	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	c	0.63	>20	>20	25
15	0.63	>20	0.08	>20	>20	25
16	1.25	10	0.63	>20	10	25
17	2.5	c	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
25	0.63	1.25	2.5	>20	20	c

[a] See ref 4 and 5. [b] Figures in parentheses indicate 90-99.9% inhibition at stated levels. [c] Indicates test not done.

Table II. *In Vivo* Activity[a]

	S. pyogenes, ED_{50} (mice), mg/kg		*T. vaginalis*, metronidazole equiv, *M*[b]
Compd	po	sc	
2	200	50	c
3	35	50	<0.25
11	42.5	10.2	c
16	c	c	4
17	c	c	4
21	c	c	2-4

[a] See ref 4 and 5. [b] *M* = ED_{50} of metronidazole/ED_{50} of test compound. [c] Indicates test not done.

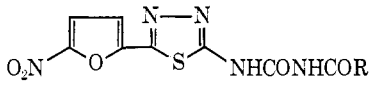
* Author to whom correspondence should be addressed at the Chemical Research Laboratories, Wellcome Research Laboratories, Beckenham, Kent, England.

† For a description of the general *in vitro* and *in vivo* test procedures, see ref 4.

‡ For a description of test methods, see ref 5.

§ Flagyl.

Table III. 1-Acyl-3-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]ureas

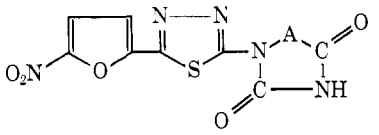


II

Compd	R	Mp, °C	Recrystn solvent[a]	Yield, %	Reaction time, hr	Formula
1	Me	>360	A	74	3	$C_6H_7N_5O_5S$
2	CH_2Cl	244–245 dec	C–B	63	1	$C_6H_6ClN_5O_5S$
3	$CHCl_2$	273 dec	C–B[b]	68	1	$C_6H_5Cl_2N_5O_5S$
4	CH_2Br	268–270 dec	B	85	0.5	$C_6H_6BrN_5O_5S$
5	Et	304–305 dec	A	78	2.5	$C_8H_9N_5O_5S$
6	$(CH_2)_2Br$	226–227 dec	C	80	1	$C_8H_8BrN_5O_5S$[c]
7	CH(Me)Br	225–226 dec	A	82	0.5	$C_8H_8BrN_5O_5S$
8	CH(Et)Br	214 dec	A	83	5	$C_{11}H_{10}BrN_5O_5S$[d]
9	$C(Me)_2Br$	219 dec	A	82	4	$C_{11}H_{10}BrN_5O_5S$
10	Ph	297–298 dec	C	59	2	$C_{14}H_9N_5O_5S$

[a] A, AcOH; B, EtOH; C, DMF. [b] Followed by hot H_2O wash. [c] C: calcd, 30.8; found, 31.4. [d] C: calcd, 32.7; found, 33.3.

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

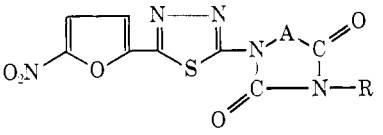


III

Compd	A	Mp, °C	Recrystn solvent[a]	Yield, %	Reaction time, hr (temp, °C)	Formula
11	CH_2	308–310 dec	A	45	0.5 (20)	$C_9H_5N_5O_5S$
12	CH(Me)	283 dec	B	59	2 (20)	$C_{10}H_7N_5O_5S$
13	CH(Et)	242–244 dec	C	47	1.5 (20)	$C_{11}H_9N_5O_5S$
14	$C(Me)_2$	266–267 dec	B	41	3 (100)	$C_{11}H_9N_5O_5S$
15	$(CH_2)_2$	310–311 dec	A	86	0.5 (20)	$C_{10}H_7N_5O_5S$

[a] A, DMF, followed by hot H_2O wash; B, AcOH; C, EtOH.

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



IV

Compd	A	R	Mp, °C	Recrystn solvent[a]	Yield, %	Reaction time, hr (temp, °C)	Formula
16	CH_2	Me	244–245 dec	A	44	1 (20)	$C_{10}H_7N_5O_5S$[d]
17	CH_2	Et	204–206 dec	B	41	2 (40)	$C_{11}H_9N_5O_5S$
18	CH_2	*n*-Pr	221–224	A	56	4 (40)	$C_{12}H_{11}N_5O_5S$
19	CH_2	*n*-Bu	230–232	A	50	2 (40), 2 (60)	$C_{13}H_{13}N_5O_5S$
20	CH(Me)	Me	241	A	67	1 (20)	$C_{11}H_9N_5O_5S$
21	CH(Et)	Me	211–212	A	66	1 (20)	$C_{12}H_{11}N_5O_5S$
22	$C(Me)_2$	Me	208–210	C	46	1 (20)	$C_{12}H_{11}N_5O_5S$
23	$(CH_2)_2$	Me	288–290 dec	A	70	2 (20)	$C_{11}H_9N_5O_5S$[e]
24	$(CH_2)_2$	Et	207–209[b]	A	77	1 (20)	$C_{12}H_{11}N_5O_5S$[f]
25	$(CH_2)_2$	*n*-Pr	220–221[c]	A	57	1.5 (40)	$C_{13}H_{13}N_5O_5S$
26	$(CH_2)_2$	*n*-Bu	205	A	61	4.5 (55)	$C_{14}H_{15}N_5O_5S$
27	$(CH_2)_2$	*n*-C_8H_{17}	149	A	67	4.5 (65)	$C_{18}H_{23}N_5O_5S$

[a] A, AcOH; B, aqueous DMF; C, aqueous AcOH. [b] Clear at 225°. [c] Sinters at 216°. [d] N: calcd, 22.7; found, 22.0. [e] C: calcd, 40.9; found, 40.4. [f] 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 ±0.4% of the theoretical values.

1-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[6] 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)[7] (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_2O, 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 III (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_2O. The product was filtered off, washed with H_2O, 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

Thomas H. Porter, Alexander von Klaudy, and Karl Folkers*

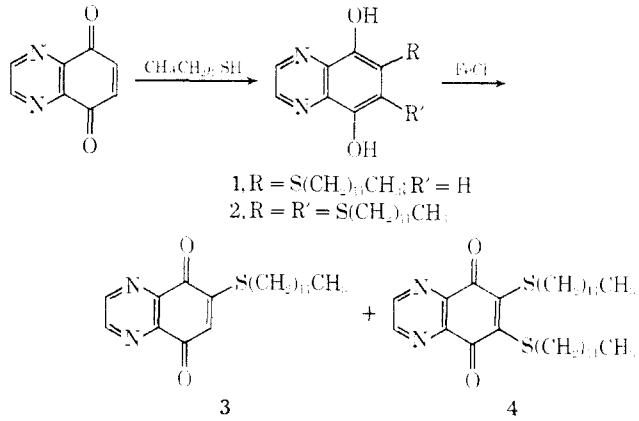
Institute for Biomedical Research, The University of Texas at Austin, Austin, Texas 78712. *Received March 19, 1973*

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,[1] 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[2] for the syntheses of certain alkylmercaptobenzoquinones. Oxidation of the isolated mono- and dialkylated dihydroxyquinoxalines (1 and 2, respectively) with $FeCl_3$ gave the alkylated quinoxalinequinones 3 and 4, respectively, in high yield. Attempts to oxidize the dihydroxyquinoxalines with Ag_2O resulted in extensive decomposition. Acetylation of 6-*n*-dodecylmercapto-5,8-dihydroxyquinoxaline (1) with acetic anhydride and H_2SO_4 as catalyst was accomplished to give the corresponding diacetyl derivative 5.

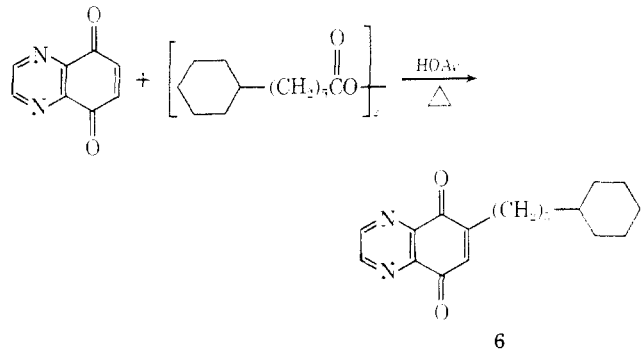
†Coenzyme Q. 163.

Scheme I



The synthesis of 6-ω-cyclohexylpentyl-5,8-quinoxalinequinone (6) was effected by treating 5,8-quinoxalinequinone with di-ω-cyclohexylhexanoyl peroxide in acetic acid (Scheme II). The yield of 6-ω-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[3] and were inactive at 640 mg/kg each. Compounds 3 and 4 were tested against *Plasmodium gallinaceum* in the sporozoite-induced chick test[4] and were inactive at 80 mg/kg. Compound 2 was also inactive against *P. gallinaceum* (blood-induced) in the chick[3] 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.[5]

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 ±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-5,8-dihydroxyquinoxaline (1 and 2, respectively). 5,8-Quinoxalinequinone[6] (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