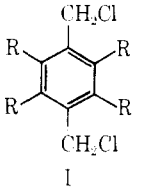
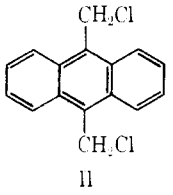


I



II

other *p*-bis(chloromethyl) models. All may be represented by I; the simple benzene derivative (I, R = H) is inactive but the durene derivative (I, R = CH_3) has enough steric resemblance to the highly active II to impart activity to the simple benzene ring. In the hexachloro compound (I, R = Cl) the bulky halogen atoms have an equivocal effect; the trend to higher toxicity may mask any latent antitumor activity.

Two additional points of interest concerning the properties of the compounds in Table I arise: (1) the ICH_2 derivatives are less active biologically than the corresponding $ClCH_2$ hydrocarbons under the testing conditions, although much more reactive chemically as alkylating agents; (2) the $ClCH_2$ compounds of Table I (A) as well as the last compound in Table I (B) show strong activity *vs.* the S-37 ascites tumor, against which N mustards including HN2, have never shown more than borderline activity (a "degree" of 1.5 to 1.8). The S mustards in Table II are also much more active as a group in this test than any N mustards ever tested in this laboratory, an indication that a wider spectrum of activity may be realized in this area.

When our initial studies demonstrated the exceptional antitumor activity of some of our monofunctional alkylating agents, we postulated that this behavior was actually following a bifunctional pattern in which cross-linkage was being accomplished through the reactivity of the monofunctional mustard moiety combined with the action of the polycyclic components of these agents. This belief has been supported by the work of Lerman[10] and of Boyland and Green,[11] among others, who present evidence for intercalation of comparable moieties into the DNA helix. Further support has come from the discovery, by a large number of workers, of strong mutagenic activity of our monofunctional nitrogen mustard derivatives of polynuclear heterocyclics in various organisms; Ames and Whitfield's work[12] reviews some of these. It has also been found that monofunctional S mustards derived from polynuclear hydrocarbons possess mutagenic frame shift activity in *Neurospora*[13] comparable with that of the N mustard-heterocyclic aromatic combination.

Acknowledgment.—The authors thank Mrs. G. Bates for assistance in the animal studies.

(10) L. S. Lerman, *J. Cellular Comp. Physiol., Suppl. 1*, **64**, 1 (1964).
(11) E. Boyland and B. Green, *Brit. J. Cancer*, **16**, 507 (1962); *J. Med. Biol.*, **9**, 589 (1964).
(12) B. N. Ames and H. J. Whitfield, Jr., *Cold Spring Harbor Symp. Quant. Biol.*, **31**, 221 (1966).
(13) Personal communication from Dr. H. V. Malling.

Notes

Nitrofuryl Heterocycles. X.[1] Analogs of 6-(5-Nitro-2-furyl)-*as*-triazine-3,5(2H,4H)-dione

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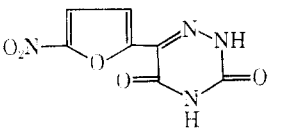
In a previous note from this laboratory, Hayes[2] reported the synthesis and antibacterial activity of 6-(5-nitro-2-furyl)-*as*-triazine-3,5(2H,4H)-dione (I). Since I was also excreted to a significant extent in the urine of the mouse, rat, and monkey, the compound was of interest as a potential urinary tract antibacterial agent. On this basis, the structure of I was modified at positions 2 through 5 in an attempt to enhance biologic activity.

Most of the compounds reported herein were prepared by modifications of the general *as*-triazine-3,5-dione synthesis used by Hayes to prepare I. The



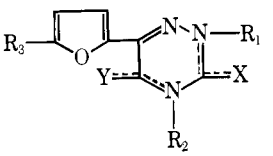
I

remaining compounds were prepared by modifications of the procedures reviewed by Erickson.[3] Table I summarizes the compounds prepared.

Compounds **15–36** were screened for urinary tract activity by measuring the per cent of the oral dose excreted in rat urine following a 24-hr collection period using both antibacterial (*Escherichia coli*) and uv spectrometric assay techniques. These data are summarized in Table II. Using I as a standard, it can be seen from the data in Table II that none of the analogs of I was excreted as well as the parent compound in the urine of rats. The most active analog prepared was the 3-thio compound, **29**, which showed about one-half the urinary excretion of I. Compounds **17**, **21**, **22**, **24**, and **28** were excreted significantly in the urine as measured by uv assay but not by antibacterial assay, an observa-

(1) For the previous paper in this series see H. R. Synder, Jr., and L. E. Banjamin, *J. Med. Chem.*, **13**, 164 (1970).
(2) K. Hayes, *ibid.*, **7**, 819 (1964).
(3) J. G. Erickson in The "Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, Chapter 2.

TABLE I



No	R_1	R_2	R_3	X	Y	Mp, °C	Yield, %	Recrystn solvent	Formula[a]
1	CH_3	H	H	O	O	134.5–136	51.5	MeOH	$C_8H_7N_3O_3$
2	C_3H_7	H	H	O	O	184.5–185	25.3	Aq EtOH	$C_{10}H_{11}N_3O_3$
3	*i*-C_3H_7	H	H	O	O	235–235.5	9.5	Aq EtOH	$C_{10}H_{11}N_3O_3$
4	*i*-C_4H_9	H	H	O	O	196.5–197.5	17	MeOH	$C_{11}H_{13}N_3O_3$
5	CH_2CH_2OEt	H	H	O	O	136–137	28	EtOH	$C_{11}H_{13}N_3O_4$
6	$CH_2CH{=}CH_2$	H	H	O	O	193.5–194.5	22.8	EtOH	$C_{10}H_9N_3O_3$
7	H	CH_3	H	O	O	239.5–240.5	36	MeOH	$C_8H_7N_3O_3$
8	H	H	H	S	O	320	99	NH_3–HCl	$C_7H_5N_3O_2S$
9	CH_3	H	H	S	O	246–247	100	AcOH	$C_8H_7N_3O_2S$[b]
10	H	CH_3	H	S	O	261–262.5	90.5	NH_3–HCl	$C_8H_7N_3O_2S$
11		H	H	SCH_3	O	260–261.5	85	MeOH	$C_8H_7N_3O_2S$
12		H	H		O	349–350	100	AcOH	$C_{11}H_{12}N_4O_2$
13		H	H		O	325	59	DMF	$C_{11}H_{12}N_4O_3$
14		H	H	NHAc	O	307–308	52.2	Aq AcOH	$C_9H_8N_4O_3$
15	CH_3	H	NO_2	O	O	264–265	52.2	AcOH	$C_8H_6N_4O_5$
16	C_2H_5	H	NO_2	O	O	246–248	98.4	AcOH	$C_9H_8N_4O_5$
17	C_3H_7	H	NO_2	O	O	195–196.5	35.2	Aq AcOH	$C_{10}H_{10}N_4O_5$
18	*i*-C_3H_7	H	NO_2	O	O	218.5–219	44.2	Aq AcOH	$C_{10}H_{10}N_4O_5$
19	*i*-C_4H_9	H	NO_2	O	O	202–203	31.9	*i*-PrOH	$C_{11}H_{12}N_4O_5$
20	CH_2CH_2OEt	H	NO_2	O	O	181.5–182.5	49.2	EtOH	$C_{11}H_{12}N_4O_6$
21	$CH_2CH{=}CH_2$	H	NO_2	O	O	174–175	16.5	Aq AcOH	$C_{10}H_8N_4O_5$
22	H	CH_3	NO_2	O	O	240.5–241.5	50.2	Aq AcOH	$C_8H_6N_4O_5$
23	CH_3	CH_3	NO_2	O	O	215–215.5	12.5	EtOH–MeCN	$C_9H_8N_4O_5$
24	CH_2OH	CH_2OH	NO_2	O	O	126–127	45	10% aq H_2CO	$C_9H_8N_4O_7 \cdot 0.5H_2O$
25	CH_2CH_2N-*i*-Pr_2	CH_2CH_2N-*i*-Pr_2	NO_2	O	O	98–99.5	11	Aq EtOH	$C_{23}H_{38}N_6O_5$[c]
26	CH_2COPh	CH_2COPh	NO_2	O	O	188–189	50.8	Aq DMF	$C_{23}H_{16}N_4O_7$
27	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	NO_2	O	O	102–103	86.2	EtOH	$C_{13}H_{12}N_4O_5$
28	H	H	NO_2	O	H_2	244–245.5	70	Aq AcOH	$C_7H_6N_4O_4$
29	H	H	NO_2	S	O	249–250	62.4	Aq DMF	$C_7H_4N_4O_4S$[d]
30	CH_3	H	NO_2	S	O	210–212	22.5	AcOH	$C_8H_6N_4O_4S$
31	H	CH_3	NO_2	S	O	210–211	59.5	DMF	$C_8H_6N_4O_4S$
32		H	NO_2	SCH_3	O	311–312	41.4	Aq DMF	$C_8H_6N_4O_4S$
33		H	NO_2		O	340	33.6	DMF	$C_{11}H_{11}N_5O_4$
34		H	NO_2		O	330	30.9	DMF	$C_{11}H_{11}N_5O_5$
35	H	H	NO_2	NH	O	350	60	Aq DMF	$C_7H_5N_5O_4$
36		H	NO_2	NHAc	O	334–334.5	20	DMF	$C_9H_7N_5O_5$

[a] Analyses for C, H, and N unless otherwise noted. [b] Analyses for C, H, S. [c] Calcd: C, 57.22; found: C, 57.85. [d] Calcd: C, 35.00 found: C, 35.67.

tion which suggests the excretion of inactive or less active metabolites.

Experimental Section[4]

2-Furanglyoxylic Acid 4-Methylsemicarbazone.—A hot solution of 112 g (0.80 mol) of 2-furanglyoxylic acid[2] in 500 ml of MeOH was treated with charcoal and filtered. To the filtrate was added 75.5 g (0.85 mol) of 4-methylsemicarbazide and 10 ml of concentrated HCl. The resulting solution was refluxed with stirring for 1.5 hr, treated with charcoal, and filtered. Upon cooling the filtrate at 0° overnight, the product separated as yellow crystals in 141 g (83.5%) yield, mp 167.5–169° dec (MeOH). *Anal.* ($C_8H_9N_3O_4$) C, H. Calcd: N, 19.90. Found: N, 20.66.

2-Furanglyoxylic acid thiosemicarbazone was prepared similarly in 87.7% yield from 2-furanglyoxylic acid and thiosemicarbazide, mp 165.5–166.5° (H_2O–EtOH). *Anal.* ($C_7H_7N_3O_3S$) C, H, N.

2-Furanglyoxylic acid 4-methylthiosemicarbazone was prepared similarly in 75% yield from 2-furanglyoxylic acid and 4-methylthiosemicarbazide, mp 154–154.5° dec (H_2O–EtOH). *Anal.* ($C_8H_9N_3O_3S$) C, H, N.

2-Furanglyoxylic Acid Guanylhydrazone.—A mixture of 42.0 g (0.30 mol) of 2-furanglyoxylic acid and 34.0 g (0.31 mol) of aminoguanidine hydrochloride (prepared by bubbling dry HCl through an EtOH suspension of 0.31 mol of aminoguanidine carbonate) in 500 ml of H_2O was heated on a steam bath for 0.5 hr with stirring. Charcoal was added and the mixture was filtered. The addition of solid Na_2CO_3 precipitated the colorless product which was filtered off, washed with H_2O, and dried to give 29.5 g (50.4%), mp 350° dec (H_2O–EtOH). *Anal.* ($C_7H_6N_4O_2$) C, H, N.

6-(2-Furyl)-4-methyl-*as*-triazine-3,5(2H,4H)-dione (7).—To a solution of 15.4 g (0.67 g-atom) of Na in 500 ml of absolute EtOH were added 141 g (0.67 mol) of 2-furanglyoxylic acid 4-methylsemicarbazone and 1.2 l. of propylene glycol. The resulting solution was refluxed with stirring overnight and concentrated under reduced pressure until a solid began to separate, when the reaction mixture was diluted with 300 ml of hot H_2O. When the

(4) All melting points were taken in a capillary (Mel-Temp) melting apparatus and are corrected. The compounds reported herein had satisfactory analyses within ±0.4% of the theoretical values for the elements indicated unless otherwise noted. Ir spectra were determined on a Perkin-Elmer Model 21 spectrophotometer as Nujol mulls.

TABLE II

No.	Uv absorption: λ_{max}, nm.	Uv absorption: A	Uv absorption: Solvent[a]	MIC, μg/ml[b]: *E. coli*	Urinary excretion, rat: Dose, mg/kg	Urinary excretion, rat: % excreted in urine	
15	366	768	A	<1.5	10	>6.6[c]	5.5[d]
16	365	736	B	5	100	0	0
17	365	704	B	12.5	10	1.8	30.3
18	370	672	A	12.5	100	0	0
19	367.5	645	B	25	100	0	0
20	365	608	B	50	100	0	0
21	365	701	B	6.25	10	2.7	25.6
22	375.5	742	A	<1.2	10	<1.1	10.2
23	367.5	725	A	0.38	10	<0.07	5.1
24	357	595	C	12.5	10	1.6	11.2
25	362.5	591	D	>50	100	0	0
26	357.5	449	E	0[e]	100	0	0
27	365	611	B	7.5[e]	100	0	0
28	365	630	C	2.2	10	3.3	20.4
29	380	730	A	12.5	10	23.9	26.1
30	390	824	B	1.5	100	0	0
31	390	838	A	18[e]	10	<0.1	8.3
32	360	602	E	6.25	100	7.6	6.3
33	370	576	F	>20	100	0	0
34	367	549	A	>20	100	0	0
35	360	737	A	>50	100	0	0
36	355	680	A	25	100	0	0
I	357.5	760	A	3.1	10	50.2	42.8

[a] A = 2% DMF–H_2O, B = 5% (95% EtOH)–H_2O, C = H_2O, D = 95% EtOH, E = 2% DMF–95% EtOH, F = 10% DMF–H_2O. [b] Minimum inhibitory concentration is the lowest concentration of compound that prevents visible growth after 24-hr incubation. [c] Per cent of oral dose as determined by antibacterial assay against *E. coli*; 24-hr urine collection. [d] Per cent of oral dose as determined by uv spectroscopy; 24-hr urine collection. Uv curves of excreted urine resemble that for drugs administered. [e] Impregnated paper disks (30 μg). Zone diameters in mm include the 6-mm disk, except negative reactions are recorded as 0.

resultant solution was poured into 2 l. of ice–H_2O containing 300 ml of concentrated HCl, the product precipitated.

Compound **10** was cyclized similarly from 2-furanglyoxylic acid 4-methylthiosemicarbazone.

6-(2-Furyl)-3-thio-*as*-triazine-3,5(2H,4H)-dione (8).—A suspension of 20.0 g (0.09 mol) of 2-furanglyoxylic acid thiosemicarbazone in 300 ml of H_2O was adjusted to pH 7–8 by the addition of 10 *N* NaOH solution. An additional 5 ml of base was added, after which the solution was refluxed for 3 hr. The solution was chilled thoroughly and acidified with AcOH to precipitate the product which was filtered off; ir 3150 (NH), 1690 cm^{-1} (CO).

3-Acetamido-6-(2-furyl)-*as*-triazin-5(4H)-one (14).—A suspension of 100 g (0.51 mol) of 2-furanglyoxylic acid guanylhydrazone in 500 ml of pyridine was treated with 150 ml of Ac_2O. The stirred mixture was heated briefly on a steam bath to initiate an exothermic reaction. After cooling for about 20 min, heating on a steam bath was resumed for 2 hr. The mixture was poured into 2.5 l. of ice–H_2O and allowed to stand for 2 hr to precipitate the product which was filtered off.

6-(2-Furyl)-2-methyl-*as*-triazine-3,5(2H,4H)-dione (1).—A 5-l. flask was charged with 138 g (3.0 mol) of $MeNHNH_2$, 1.5 l. of H_2O, and 250 g (3.1 mol) of KNCO. To this stirred solution 8 *N* HCl was added dropwise at 25° during about 5 hr until the solution remained slightly acidic (pH 6). This solution was kept overnight at 25° after which it was acidified to pH 2 with concentrated HCl. This freshly prepared 2-methylsemicarbazide solution (1 l.) was mixed with 42.0 g (0.31 mol) of 2-furanglyoxylic acid. The resultant solution was stirred at 25–30° for 2 hr after which pH 11 was obtained by the addition of aqueous KOH. The alkaline solution was heated on a steam bath with stirring for 1 hr, chilled thoroughly, and acidified with concentrated HCl to precipitate the product which was filtered off.

Compounds **2–6** and **9** were prepared similarly from the appropriately substituted hydrazine.

6-(2-Furyl)-3-methylthio-*as*-triazin-5(4H)-one (11).—A solution of 140 g (1.0 mol) of 2-furanglyoxylic acid and 100 g (1.1 mol) of thiosemicarbazide in 1 l. of MeOH containing 2 ml of concentrated HCl was refluxed with stirring for 0.5 hr. Methyl iodide (150 g, 1.05 mol) was added in small portions through the condenser at such a rate that flooding of the condenser was minimized. Refluxing was then continued for 6 hr. After chilling the mixture thoroughly, the precipitated product was filtered off; ir 3130 (NH), 1625 cm^{-1} (CO).

6-(2-Furyl)-3-pyrrolidino-*as*-triazin-5(4H)-one (12).—A solution of 100 g (0.48 mol) of **11** in 600 ml of pyrrolidine was refluxed for 22 hr. The liberated MeSH was captured in an aqueous NaOH trap. The mixture was then poured into 4 l. of ice–H_2O and acidified with concentrated HCl to precipitate the product which was filtered off; ir 3120 (NH), 1630 cm^{-1} (CO).

Compound **13** was prepared similarly from **11** and morpholine.

6-(5-Nitro-2-furyl)-2-methyl-*as*-triazine-3,5(2H,4H)-dione (15).—To 600 ml of Ac_2O was added dropwise with stirring at 25–30° a solution of 20 drops of concentrated H_2SO_4 in 44 ml of concentrated HNO_3 (sp gr 1.42). The resulting solution was kept at 25–30° with intermittent cooling for 15 min after which 43.6 g (0.23 mol) of **1** was added in small portions during 5 min. Cooling was necessary to keep the temperature at 25–30°. After completing the addition, stirring was continued at 30° for 10 min and then at 45° for 5 min. The cooled solution was poured into 3 l. of ice–H_2O and stirred until the product crystallized. The crude product was filtered off and washed thoroughly with cold H_2O; ir 1717, 1680 (CO), 1518, 1345 (NO_2), 1015, 967 cm^{-1} (nitrofuran).

Caution should be used in following this procedure, since the reaction may be quite exothermic.

By means of a similar procedure, **16–23**, **32**, and **33–34** (compound **34** prepared at <5° in the absence of H_2SO_4) were prepared from the appropriate furyl compound.

2,4-Dimethyl-6-(5-nitro-2-furyl)-*as*-triazine-3,5(2H,4H)-dione (23).—To a stirred suspension of 0.22 mol of NaH (mineral oil suspension) in 300 ml of dry DMF was added in small portions 50.0 g (0.22 mol) of I.[2] After the ensuing reaction had subsided (*ca.* 1 hr), 85 g (0.67 mol) of Me_2SO_4 and 22.4 g (0.22 mol) of $CaCO_3$ were added. The resulting mixture was heated with stirring at *ca.* 107° for 24 hr. The hot mixture was poured into 3 l. of ice–H_2O and the container scratched to induce crystallization. The product was filtered off and washed with cold H_2O; ir 1720, 1670 (CO), 1515, 1352 (NO_2), 1032 and 972 cm^{-1} (nitrofuran).

By means of a similar procedure compounds **25–27** were prepared from I and the appropriately substituted alkyl halide.

2,4-Bis(hydroxymethyl)-6-(5-nitro-2-furyl)-*as*-triazine-3,5-(2H,4H)-dione Hemihydrate (24).—A mixture of 22.4 g (0.10 mol) of I and 12.0 g (0.40 mol) of paraformaldehyde in 300 ml of H_2O containing 2 ml of concentrated HCl was refluxed for 45 min during which time solution became nearly complete. The hot mixture was filtered and the filtrate was chilled causing a gum to separate. After several days in the cold the gum crystallized. The product was filtered off and recrystallized from

10% formalin solution; ir 3575 (OH), 1720, 1650 (CO), 1530, 1340 (NO_2), 1020 and 965 cm^{-1} (nitrofuran).

4,5-Dihydro-6-(5-nitro-2-furyl)-*as*-triazin-3(2H)-one (28).—Extreme caution should be used during the performance of this reaction. An ice–H_2O bath should be available.

A 500-ml three-neck flask, fitted with a thermometer and a stirrer, was charged with 10.0 g (0.06 mol) of finely pulverized 4,5-dihydro-6-(2-furyl)-*as*-triazine-3(2H)-one[5] and 300 ml of $CHCl_3$. The suspension was heated to boiling with stirring and then allowed to cool to 50°. With continued stirring, 15 ml of concentrated HNO_3 (sp gr 1.42) was added slowly in about 1-ml portions. When the addition was completed (*ca.* 5 min), the stirrer was temporarily stopped. A globular material accumulated on the $CHCl_3$ surface. The instant coalescence began (observed by vigorous bubbling with evolution of brown fumes), the stirrer was started, and an ice–H_2O bath was raised around the flask. After chilling the dark red homogeneous solution to 10°, 150 ml of cold H_2O was added in one portion. The product separated instantly as yellow crystals which were filtered off, washed thoroughly with cold H_2O, and air dried; ir 3225 (NH), 1695 (CO), 1515, 1345 (NO_2), 1023 and 962 cm^{-1} (nitrofuran).

6-(5-Nitro-2-furyl)-3-thio-*as*-triazine-3,5(2H,4H)-dione (29).—To 400 ml of cold (10°) concentrated H_2SO_4 was added 60.0 g (0.30 mol) of **8** in portions with stirring. After cooling to −5°, a chilled solution of 25 ml of concentrated HNO_3 (sp gr 1.42) in 40 ml of concentrated H_2SO_4 was added dropwise with stirring at such a rate that the temperature was kept below −5°. The addition required 30–40 min. Stirring was continued below 0° for 1 hr after which the mixture was poured cautiously into 3 l. of ice–H_2O. The crystallized product was filtered off and washed thoroughly with H_2O; ir 3150 (NH), 1682 (CO), 1515, 1343 (NO_2), 1018 and 967 cm^{-1} (nitrofuran).

By means of a similar procedure compounds **30** and **31** were prepared from **9** and **10**, respectively.

3-Acetamido-6-(5-nitro-2-furyl)-*as*-triazin-5(4H)-one (36). To 160 ml of fuming (90%) HNO_3 was added 22.4 g (0.11 mol) of **14** in small portions with stirring below 10°. The solution was kept in the cold for 0.5 hr after which it was poured cautiously into 1 l. of ice–H_2O. The crystallized product was filtered off and washed thoroughly with cold H_2O; ir 3150 (NH), 1700, 1638 (CO), 1528, 1360 (NO_2), 1020 and 967 cm^{-1} (nitrofuran).

3-Imino-6-(5-nitro-2-furyl)-*as*-triazine-3,5(2H,4H)-dione (35).—A suspension of 70.0 g (0.30 mol) of **36** in 1 l. of 20% aqueous HCl was refluxed for 6 hr. The solution was cooled and the tan solid filtered off and washed with H_2O; ir 3420 (NH), 1655 (C=N), 1625 (CO), 1528, 1340 (NO_2), 1015 and 967 cm^{-1} (nitrofuran).

Acknowledgments.—I am grateful to Mr. G. Gustin and Mr. M. Tefft for the elemental analyses, to members of the Chemotherapy Division for the screening results, to Mr. W. O. Smith for assistance in the preparation of the compounds, and to Mr. B. F. Stevenson and associates for large scale synthetic support.

(5) D. G. Holland and E. D. Amstutz, *Rec. Trav. Chim.*, **83**, 1047 (1964).

Nitrofuryl Heterocycles. XI.[1] 3-(5-Nitro-2-furyl)-Δ^2-1,2,4-triazolin-5-ones.

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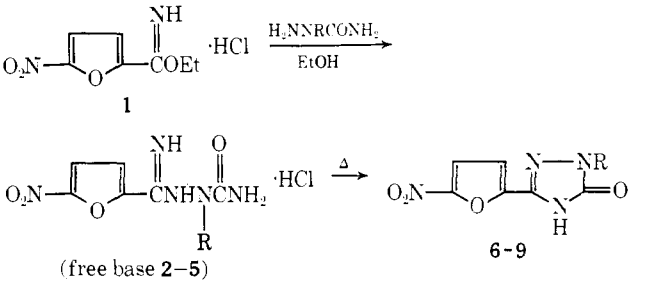
As part of our investigation of the potential antibacterial properties of nitrofuryl heterocycles, methods were evaluated for the preparation of nitrofuryl 1,2,4-triazole derivatives. An earlier paper presented our explorations of 3-alkyl-5-(5-nitro-2-furyl)-1,2,4-triazoles.[3] This note presents our work on the preparation and testing of 3-(5-nitro-2-furyl)-Δ^2-1,2,4-triazolin-5-ones.

Initial routes to this ring system by decarboxylative cyclization of 2-furanglyoxylic acid semicarbazone[1] in alkaline KI–I_2 solution, ring closure of 2-furaldehyde semicarbazone with either $FeCl_3$ or $K_3Fe(CN)_6$, thermal or P_2O_5 dehydration of 2-furoic acid semicarbazide,[4] or alkaline rearrangement of 2-amino-5-(2-furyl)-1,3,4-oxadiazole[5,6] proved undesirable. However, by a modification of the method of Pesson, *et al.*,[7] the intermediate 5-nitro-*N*-uredio-2-furamidine hydrochlorides, obtained from the reaction of ethyl 5-nitro-2-furimidate hydrochloride (**1**)[8] with various semicarbazides, readily cyclized in refluxing $PhNO_2$ to give the Δ^2-1,2,4-triazolin-5-ones **6–9**. Difficulties in purification made it necessary to characterize the 5-nitro-*N*-ureido-2-furamidine hydrochlorides as their free bases (**2–5**). With the exception of **2** the free bases failed to cyclize when heated to 200° in $PhNO_2$.



Although cyclization of the 5-nitro-*N*-ureido-2-furamidines could lead to the isomeric 2-amino- or 2-imino-1,3,4-oxadiazole structures, the presence of carbonyl absorption at 1690 cm^{-1} in the ir and their failure to form HCl salts indicated that **6–9** are best represented by the Δ^2-1,2,4-triazolin-5-one structure. The nmr spectra of compounds **6–9** were also consistent with this structure assignment. Finally, an authentic sample of 2-amino-5-(5-nitro-2-furyl)-1,3,4-oxadiazole[9] was prepared from 5-nitro-2-furoylhydrazine and CNBr. It showed no absorption in the 1670–1790 cm^{-1} region and showed a depression of the melting point on admixture with **6**.

Table I summarizes the physical properties of the compounds prepared. The antibacterial testing data, obtained by standard procedures, on compounds **6–9** are summarized in Table II.

Experimental Section[10]

5-Nitro-*N*-ureido-2-furamidine (2).—A mixture of 100 g (0.45 mol) of **1**,[8] 34 g (0.45 mol) of semicarbazide, and 800 ml of absolute EtOH was heated at 50–60° for 30 min with occasional stirring.

(1) For the previous paper in this series see H. A. Burch, *J. Med. Chem.*, **13**, 288 (1970).

(2) To whom inquires concerning this paper should be addressed.

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(4) H. L. Yale, K. A. Losee, F. M. Perry, and J. Bernstein, *J. Amer. Chem. Soc.*, **76**, 2208 (1954).

(5) H. L. Yale and K. Losee, *J. Med. Chem.*, **9**, 478 (1966).

(6) J. C. Howard and H. A. Burch, *J. Org. Chem.*, **26**, 1651 (1961).

(7) M. Pesson, S. Dupin, and M. Antoine, *Bull. Soc. Chim. Fr.*, 1364 (1962).

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

(9) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(10) All melting points were determined in open capillaries using a Mel-Temp melting point apparatus and are corrected. Ir spectra were determined as Nujol mulls on a Perkin–Elmer Model 135 Infracord. The nmr spectra were obtained on a Varian A60A instrument using Me_4Si as an internal standard.