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).

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

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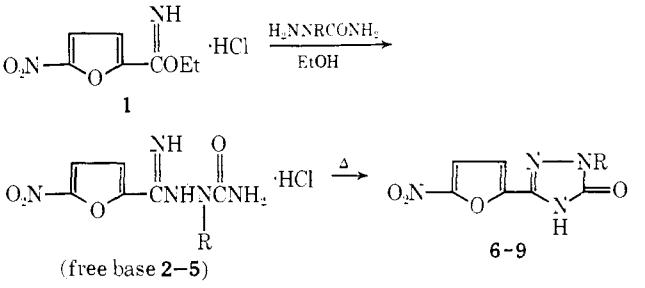
As part of our investigation of the potential antibacterial properties of nitrofuryl heterocycles, methods were evaluated for the preparation of nitrofuryl 1,2,4-triazole derivatives. An earlier paper presented our explorations of 3-alkyl-5-(5-nitro-2-furyl)-1,2,4-triazoles.[3] This note presents our 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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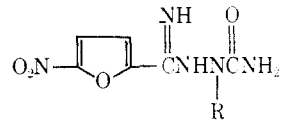
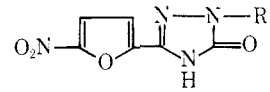
(9) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(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.

TABLE I



No.	R	Mp, °C	Yield, %	Recrystn solvent	Formula[a]
2	H	274–275	51	DMF–MeCN	$C_6H_7N_5O_4$
3	CH_3	195–196	64	MeOH or DMF	$C_7H_9N_5O_4$
4	CH_2CH_3	173–174	60	H_2O	$C_8H_{11}N_5O_4$
5	CH_2CH_2OH	181–182	40	MeOH	$C_8H_{11}N_5O_5$



6	H	277–279	78	H_2O	$C_6H_4N_4O_4$
7	CH_3	275–276	73	H_2O	$C_7H_6N_4O_4$
8	CH_2CH_3	243–244	56	AcOH	$C_8H_8N_4O_4$
9	CH_2CH_2OH	263–264	38	AcOH	$C_8H_8N_4O_5$

[a] All compounds analyzed for C, H, and N within ±0.40% of the theoretical values.

TABLE II

ANTIBACTERIAL TESTING OF 3-(5-NITRO-2-FURYL)-Δ^2-1,2,4-TRIAZOLIN-5-ONES

	Minimal inhibitory concentration, μg/ml[a]								
No.	Mi-6[b]	Es-2	Ps-10	Pr-12	SaD-13	StA-1	StB-12	Er-4	Ae-6
6	200	10	>200	>200	100	12.5	100	12.5	>200
7	25	3.1	>200	>200	6.25	25	>200	3.1	200
8	25	12.5	>100	>100	12.5	100	>100	6.25	>100
9	6.25	0.38	>50	>50	3.1	50	>50	3.1	>50
Nitrofurazone[c]	12.5	3	>100	100	3	6	12.5	12.5	100

[a] Minimal inhibitory concentration is the lowest concentration of compound that prevents visible growth after 24 hr of incubation. [b] The Norwich Pharmacal Co. strain number: Mi-6 = *Staphylococcus aureus*, Es-2 = *Escherichia coli*, Ps-10 = *Pseudomonas aeruginosa*, Pr-12 = *Proteus vulgaris*, SaD-13 = *Salmonella typhosa*, StA-1 = *Streptococcus pyogenes*, StB-12 = *Streptococcus agalactiae*, Er-4 = *Erysipelothrix insidiosa*, Ae-6 = *Aerobacter aerogenes*. [c] Furacin(R), for comparison.

The mixture was cooled to room temperature and filtered. The orange solid was washed successively with H_2O, *i*-PrOH, and Et_2O and then air dried. A warm solution of the crude salt in DMF was diluted with MeCN and kept at room temperature until crystallization was complete. Conversion of the salt into the free base **2** was effected with aqueous Na_2CO_3 solution.

Compounds **3–5** were prepared similarly from **1** and the appropriately 2-substituted semicarbazides except that the crude salts were obtained by dilution of the reaction mixtures with Et_2O.

3-(5-Nitro-2-furyl)-Δ^2-1,2,4-triazolin-5-one (6).—A solution of 60 g (0.28 mol) of **2**·HCl in 450 ml of $PhNO_2$ was refluxed for 15 min, cooled, and diluted with 400 ml of Et_2O. The dark solid was filtered off, washed with Et_2O, and dried.

Compounds **7–9** were prepared similarly from the appropriate intermediates **3–5**.

Acknowledgments.—The authors are grateful to Mr. G. Gustin and Mr. M. Tefft for the elemental analyses and to Mrs. P. Curtis for the nmr spectra.

Synthesis of 1-Phenyl-2-styryl-3,5-dioxopyrazolidines as Antiinflammatory Agents

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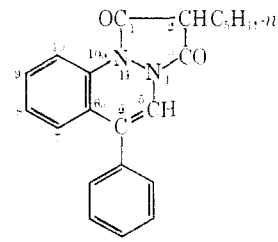
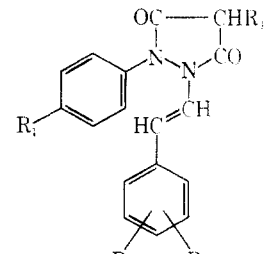
A series of 1-phenyl-2-styryl-3,5-dioxopyrazolidine derivatives was synthesized for antiinflammatory testing, and it was found that some of these compounds were more potent inhibitors than phenylbutazone or oxyphenbutazone in the carrageenin-induced foot edema test in rats.

In a previous paper,[1] it was reported that 1,2-pentylmalonyl-1,2-dihydro-4-phenylcinnoline (I) showed potent antiinflammatory activity. This prompted us to prepare 1-phenyl-2-styryl-3,5-dioxopyrazolidines (II), because the intrinsic antiinflammatory activity of I might be due to the presence of a 3,5-dioxopyrazolidine ring and the activity might be kept when the C_6–C_{8a} bond of I is cleaved. Based on this hypothesis, various derivatives of II have been prepared for antiinflammatory tests.[2]



I



II

Compounds (II) based on the same concept were recently suggested to have antiinflammatory activity, though their synthesis has not been described.[3]

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