needles, mp 160°. *Anal.* ($C_{11}H_{11}N_5O_4$) C, H, N. Compound **8** decomposed with evolution of AcOH when kept at 25°.

Treatment of 6-Hydroxylaminopurine Triacetate (8) with AcO_2H.—To a solution of **8** (0.27 g) in Ac_2O (3 ml) 30% H_2O_2 (0.4 ml) dissolved in Ac_2O (4 ml) was added and the mixture was kept at 25° for 3 weeks. Evaporation to dryness *in vacuo* resulted in the recovery of the starting material **8**, mp 158°.

Similar treatment of 6-hydroxylaminopurine (0.3 g) in Ac_2O (10 ml) and 30% H_2O_2 (0.4 ml) gave no oxidation product, and the starting material was recovered. Reaction with trifluoroacetic acid and H_2O_2 in Ac_2O gave hypoxanthine. Chloroperbenzoic acid[15] in ether and 6-hydroxylaminopurine after 3 weeks gave no reaction and the purine was recovered unchanged.

6-Mercaptopurine 3-Oxide (1) and NH_2OH.—6-Mercaptopurine 3-oxide[7b] (**1**, 0.20 g, 1.2 mmoles) was suspended in a solution of 0.6 *M* ethanolic NH_2OH (200 ml) and $NH_2OH \cdot HCl$ (20 mg). The mixture was refluxed for 6 hr. Upon evaporation to dryness *in vacuo*, **1** was recovered unchanged.

Biological Activity.—6-Hydroxylaminopurine 3-oxide (**4**) has been tested in the screening program of the Divisions of Applied Therapy and Experimental Chemotherapy. It showed no toxicity when administered to mice at 200 mg/kg, but was found toxic at 300 mg/kg (no survivors in control mice after 7 days). The kidneys of these animals presented a normal aspect, and no crystalline deposit was detected on microscopic observation.

In cell suspension culture, **4** caused very slight inhibition (10%) at 30 μg/ml of leukemia L5178Y/Ca55. At the dosage level of 150 and 100 mg/kg/day for 10 days, **4** prolonged slightly (increased life span: +23 and +24%, respectively) the survival time of mice with leukemia LE1210S. At 100 mg/kg for 7 days, **4** failed to inhibit the growth of Sarcoma 180 and Ridgway osteogenic sarcoma in mice.

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Nitrones. I. α-(5-Nitro-2-furyl)-N-arylnitrones

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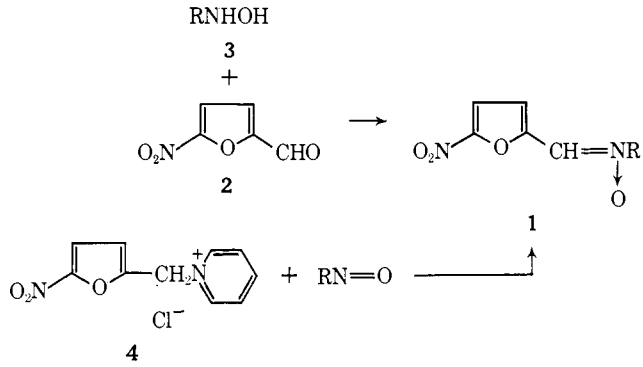
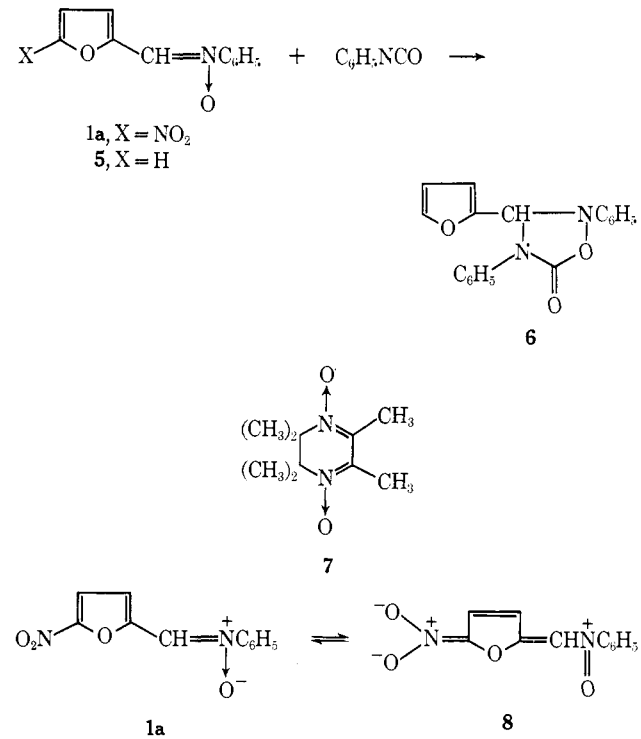
In the course of studies for new antibacterial agents based on nitrofuran,[1] we synthesized a number of the title compounds.[2] At the outset of this work only one nitrofurylnitrone was reported;[3a] subsequently, however, several reports have appeared.[3b-d]

We report here several additional nitrofurylnitrones (**1**) and evidence for the back polarization of the nitrone group.

Nitrones **1a–c**, **f**, and **g** were obtained in 41–64% yield by reaction of 5-nitrofurfural (**2**) and the corresponding N-arylhydroxylamine (**3**).[4] Nitrones **1a**, **d**, and **e** were prepared in 35–83% yield by the Kröhnke reaction[5] (Table I).



An attempt to cyclize **1a** with phenyl isocyanate in a 1,3 cycloaddition[6] was unsuccessful; the starting material was recovered completely. Yet when α-furyl-N-phenylnitrone (**5**) was treated similarly, the expected cycloaddition product **6** was obtained in good yield. We could find only one other example of thermal inertness in a 1,3 cycloaddition reaction of this type and this involved the cyclic α-dinitrone **7**.[7] We believe that since nitrophenylnitrones undergo the 1,3 cycloaddition[8] the inability of **1a** to do so is good evidence for "back polarization" as depicted in **1a** ⇌ **8**.



Screening Results.—The compounds described above were tested against *Salmonella choleraesuis* (mice)

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(2) For a general review on nitrones see J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964); G. R. Delpierre and M. Lamchen, *Quart. Rev.* (London), **19**, 329 (1965).

(3) (a) α-(5-Nitro-2-furoyl)-N-(*p*-dimethylaminophenyl)nitrone was reported by N. Saldabols and S. Hillers, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.*, 585 (1963); *Chem. Abstr.*, **61**, 4297 (1964); (b) for structures related to **1** see Dainippon Pharmaceutical Co., Ltd., British Patent 1,105,-007 (1968); *Chem. Abstr.*, **69**, 86809 (1968); (c) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. France*, 4179 (1967); (d) α-(5-Nitro-2-furyl)-N-benzhydrylnitrone was reported by E. Bellasio, F. Parravicini, T. La Noce, and E. Testa, *Farmaco* (Pavia), *Ed. Sci.*, **23**, 372 (1968); *Chem. Abstr.*, **69**, 10143 (1968).

(4) The N-arylhydroxylamines mentioned in this report were prepared by the procedure of H. E. Baumgarten, A. Staklis, and E. M. Miller [*J. Org. Chem.*, **30**, 1203 (1965)], of E. C. Taylor and P. K. Loeffler [*ibid.*, **24**, 2035 (1959)], and of P. K. Chang [*J. Med. Chem.*, **8**, 884 (1965)].

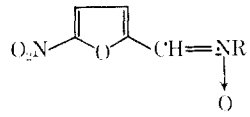
(5) F. Kröhnke, *Ber.*, **71**, 2583 (1938).

(6) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).

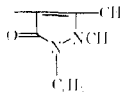
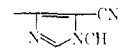
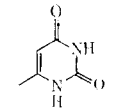
(7) M. Lamchen and T. W. Mittag, *J. Chem. Soc., C*, 1917 (1968).

(8) G. Cum, M. C. Aversa, and N. Uccella, *Gazz. Chim. Ital.*, **98**, 782 (1968); *Chem. Abstr.*, **69**, 77144 (1968).

TABLE I



1

Compd	R	Method	Mp, °C[a]	Yield,[b] %	Formula	Analyses[c]
1a	C_6H_5	A, B	175[d]	52, 56[e]	$C_{11}H_8N_2O_4$	
1b	p-$CH_3SO_2C_6H_4$	A	195–196	52[f]	$C_{12}H_{10}N_2O_6S$	C, H, N, S
1c	p-BrC_6H_4	A	170–171	64[f]	$C_{11}H_7BrN_2O_4$	C, H, Br, N
1d	p-$(CH_3)_2NC_6H_4$	B	204–205	83[f]	$C_{13}H_{13}N_3O_4$	C, H, N
1e		B	184–185	35[f]	$C_{16}H_{14}N_4O_5$	C, H, N
1f		A	235	57[f]	$C_{10}H_7N_3O_4$	C, H, N
1g		A	253–255	41[g]	$C_9H_6N_4O_6$	[h]

[a] All samples decomposed on melting. [b] Yield is of the analytical sample. [c] Where analyses are indicated by the symbols of the elements, analytical results obtained for these elements were within ±0.4% of the calculated values. [d] Lit. mp 178°[3c] and 180–181°.[3b] [e] Recrystallized from MeOH. [f] Recrystallized from $MeNO_2$. [g] Recrystallized from dioxane. [h] *Anal.* Calcd: C, 40.61; H, 2.27; N, 21.05. Found: C, 41.11; H, 2.75; N, 20.58.

and *Eimeria tenella* (chicks). Drugs were given in a powdered diet for 16 days at doses ranging from 25 to 240 mg/kg/day for the bacterial screen and 8 days at a dose of 97.9 mg/kg/day for the coccidial screen. None of the compounds displayed *in vivo* activity. These compounds showed slight *in vitro* antibacterial activity against representative bacteria (*Staphylococcus aureus*, *Streptococcus agalactiae*, and *Bacillus subtilis*) as shown in Table II.

TABLE II

In Vitro ANTIBACTERIAL ACTIVITY[a,b]

	Min inhib concn, μg/ml		
Compd	*S. aureus*	*S. agalactiae*	*B. subtilis*
1a	100	100	100
1b	10	>100	10
1c	100	10	100
1d	>100	>100	>100
1e	10	100	>100
1f	100	100	100

[a] A serial, tenfold, tube dilution assay was employed. [b] These compounds also had activity at 100 μg/ml or more against *Salmonella gallinarum*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Escherichia coli*.

Experimental Section[9]

α-(5-Nitro-2-furyl)-N-arylnitrones. Method A.—A mixture of 5-nitrofurfural (2.82 g, 0.02 mole) and the corresponding N-arylhydroxylamine[4] (0.02 mole) in dry PhH (40 ml) for **1a** and **c**, dry THF (45 ml) for **1b**, and a mixture of ethanol–THF (280 ml, 5:2) for **1f** was refluxed for 0.5 hr using a Dean–Stark water separator. After cooling, the solid was filtered off and recrystallized to afford pure nitrones. In the case of **1g**, DMF was used and the mixture was heated at 60° under nitrogen for 1 hr.

Method B.—5-Nitrofurfuryl chloride[10] (1.62 g, 0.01 mole) in dry PhH (10 ml) containing pyridine (3.96 g, 0.05 mole) was heated at 85° overnight. After cooling the pyridinium salt was filtered off, washed (Et_2O), and crystallized from EtOH to give 1-(5-nitrofurfuryl)pyridinium chloride (**4**, 1.95 g, 81%), mp 191° dec. An analytical sample, mp 198–200° dec, was obtained by recrystallization from $MeNO_2$. *Anal.* ($C_{10}H_9ClN_2O_3$) C, H, Cl, N.

Morpholine (0.44 g, 0.005 mole) was added dropwise to a solution of **4** (1.20 g, 0.005 mole) and the corresponding aromatic nitroso compound (0.005 mole) in EtOH. After 10–20 min the solid was filtered off and dried in air to give nitrones which were purified by recrystallization.

Methyl 4-Hydroxylaminophenyl Sulfone.—A solution of methyl 4-nitrophenyl sulfone (12.88 g, 0.064 mole) in 75% EtOH (100 ml) was stirred with Zn dust (9.00 g, 94% purity, 0.13 g-atom) and a solution of 6–8 ml of saturated aqueous NH_4Cl. After the mixture had begun to boil, more NH_4Cl (3.48 g, 0.065 mole) in H_2O (23 ml) was added dropwise (7 min) while maintaining the temperature at 85–90°. Stirring was continued at this temperature 10 min more. After rapid cooling to *ca* 0°, the precipitated Zn salt was filtered off and washed with hot 95% EtOH (15 ml). The combined filtrate and washings were concentrated to one-third of the original volume and chilled at 0°. Filtration gave 5.80 g (48%) of a white solid, mp 139–143°. An analytical sample, mp 152–153°, was obtained by recrystallizing the material twice from 95% EtOH; ν_{max} 3300, 3247 (NHOH), 1325, 1282, and 1136 cm^{-1} (SO_2); nmr (DMSO-d_6) τ 0.98 and 1.22 (2 s, 2 H, NHOH, exchangeable with D_2O), 2.65 (q, 4 H, J = 7 cps, C_6H_4), and 6.90 (s, 3 H, SO_2CH_3). *Anal.* ($C_7H_9NO_3S$) C, H, N, S.

2,4-Diphenyl-3-furyl-1,2,4-oxadiazolidin-5-one (6).—To a solution of **5**[11] (9.36 g, 0.05 mole) in dry PhH (50 ml) was added phenyl isocyanate (11.91 g, 0.1 mole) in PhH (25 ml) and the mixture was refluxed for 3 hr. After cooling, the solvent was removed and the residue was triturated with petroleum ether (bp 60–70°, 100 ml) and dried to give a white solid (10.80 g, 71%), mp 107–111° dec. Recrystallization of the product from EtOH gave **6** (6.10 g, 40%): mp 122–124°; ν_{max} 1748 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.42 and 2.60 (q + s, 11.3 H, furan-H_3 and two C_6H_5), 3.38 (d, 1.1 H, furan-H_4), 3.54 and 3.66 (q + s, 1.9 H, furan-H_2 and methine). *Anal.* ($C_{18}H_{14}N_2O_3$) C, H, N.

Attempted Cycloaddition of 1a.—When **1a** was refluxed 48 hr as above only starting material was recovered (100%).

(9) Melting points were taken in open capillary tubes using a Thomas–Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Ir spectra were obtained with a Beckman IR-5 ir spectrophotometer using KBr pellets. Nmr spectra were obtained with a Varian A-60 spectrometer, using Me_4Si as an internal standard; s, signifies singlet; d, doublet; and q, quartet. Evaporation of solvents was done under reduced pressure using a rotating evaporator.

(10) H. Gilman and R. R. Burtner, *Iowa State Coll. J. Sci.*, **6**, 389 (1932).

(11) (a) E. Bamberger, *Ber.*, **57**, 2082 (1924); (b) P. Grammaticakis, *Bull. Soc. Chim. France*, 965 (1951).