

Notes

**Nitrones. 5.^{1a} Vinylogs of
 α -(5-Nitro-2-heteroaryl)-N-substituted Nitrones**

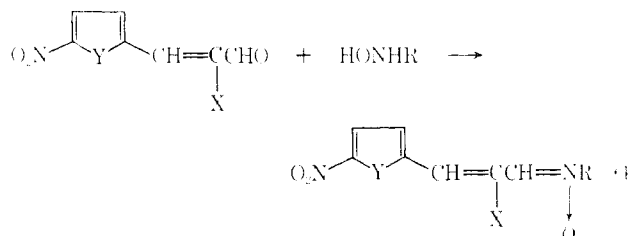
HYUN K. KIM* AND RONALD E. BAMBURY

Hess & Clark, Division of Richardson-Merrell
 Inc., Ashland, Ohio 44805

Received July 13, 1970

In previous reports on nitrones² we discussed the preparation and chemotherapeutic activity of α -(5-nitro-2-furyl)-N-aryl-, N-cycloalkyl-, N-alkyl-, and N-hydroxyalkylnitrones. This paper describes the preparation of nitrofuryl- and nitrothienylnitrones in which a vinyl or α -bromovinyl moiety is inserted between the nitroaryl and the nitrone group. The biological effect ensuing from this type of structural variation has been

Compounds **1-16** were obtained in 7-99% yield by the reaction of β -(5-nitro-2-furyl)acrolein,⁵ β -(5-nitro-2-furyl)- α -bromoacrolein,⁶ or their analogs in the thiophene series,⁴ and N-substituted hydroxyalamines in a manner similar to the nitrofurylnitrones,² according to eq 1.



X, Y, and R (see Table I).

TABLE I
 α -[2-(5-NITRO-2-HETEROARYL)VINYL]-N-SUBSTITUTED NITRONES

Compd	Y	X	R	Prepn method	Mp, °C	Recrystn solvent	Yield, ^a %	Formula ^b
1	O	H	CH ₃	A	175-176 dec	Abs EtOH	41	C ₈ H ₉ N ₃ O ₄ ^c
2	O	H	C ₂ H ₅	B	104-106	Et ₂ O	52	C ₉ H ₁₀ N ₂ O ₄
3	O	Br	CH ₃	A	170-171	CH ₃ NO ₂	43	C ₈ H ₇ BrN ₂ O ₄
4	O	Br	C ₂ H ₅	B	178-179 dec	CHCl ₃	36	C ₉ H ₉ BrN ₂ O ₄
5	O	H	CH ₂ CH ₂ OH	B	188-190 dec	CH ₃ NO ₂ -EtOH	73	C ₉ H ₁₀ N ₂ O ₅
6	O	Br	CH ₂ CH ₂ OH	B	160-161	Abs EtOH	20	C ₉ H ₉ BrN ₂ O ₅
7	O	H	CH ₂ CH ₂ OAc	B	146-147	C ₆ H ₆ -hexane	32	C ₁₁ H ₁₂ N ₂ O ₆
8	O	Br	CH ₂ CH ₂ OAc	B	124-125	C ₆ H ₆ -hexane	36	C ₁₁ H ₁₁ BrN ₂ O ₆
9	O	H	CH ₂ CH ₂ OEt	B	117-118	Abs EtOH	49	C ₁₁ H ₁₄ N ₂ O ₇
10	S	Br	CH ₃	A	169-170	Abs EtOH	7	C ₈ H ₇ BrN ₂ O ₃ S
11	S	H	CH ₂ CH ₂ OH	B	162-163	95% EtOH	42	C ₉ H ₁₀ N ₂ O ₄ S
12	S	Br	CH ₂ CH ₂ OH	B	160-162	Abs EtOH	38	C ₉ H ₉ BrN ₂ O ₄ S
13	S	H	C ₆ H ₁₁ ^d	C	125-127	C ₆ H ₆ -Et ₂ O	36	C ₁₃ H ₁₆ N ₂ O ₃ S
14	O	H	C ₆ H ₅	C	182 dec	CH ₃ NO ₂	74	C ₁₃ H ₁₀ N ₂ O ₄
15	S	H	C ₆ H ₅	C	182	CH ₃ NO ₂	99	C ₁₃ H ₁₀ N ₂ O ₃ S
16	O	H		C	210 dec	CH ₃ NO ₂	43	C ₁₂ H ₉ N ₃ O ₄

^a Yield of purified product. ^b All compounds were analyzed for C, H, N, and where applicable halogen; analytical results obtained varied within $\pm 0.4\%$ of the calculated values. ^c Reported subsequent to our work, Dai-nippon Pharmaceutical Co., Ltd., British Patent 1,105,007 (1968); *Chem. Abstr.*, **69**, 86809 (1968). ^d Cyclohexyl.

studied for other classes of nitrofurfural³ and nitrothienal⁴ derivatives. In general the effect found was an increase in antibacterial activity and/or a decrease in toxicity. Based on these reports it was hoped that similar biological effects would be obtained in the nitrone series.

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(2) (a) H. K. Kim and R. E. Bambury, *J. Med. Chem.*, **12**, 719 (1969); (b) H. K. Kim, H. K. Yaktin, and R. E. Bambury, *ibid.*, **13**, 238 (1970); (c) H. K. Kim, R. E. Bambury, and H. K. Yaktin, *ibid.*, **14**, 301 (1971).

(3) T. Takahashi, H. Saikachi, S. Yoshina, and C. Mizuno, *Yakugaku Zasshi*, **69**, 284 (1949); *Chem. Abstr.*, **44**, 5372 (1950). H. Saikachi, *J. Amer. Chem. Soc.*, **80**, 3642 (1958). H. Saikachi and H. Ogawa, Japanese Patent 17,981 (1962).

(4) G. Carrara, R. Ettorre, F. Fava, G. Rolland, E. Testa, and A. Vecchi, *J. Amer. Chem. Soc.*, **76**, 4391 (1954).

Screening Results.⁷—An examination of the data in Table II indicates that insertion of a double bond or α -halogenated double bond between the nitrofuryl ring and nitrone group did increase *in vitro* antimicrobial activity. The *in vitro* activities of **1** and **5** are greater than those of α -(5-nitro-2-furyl)-N-methylnitrone (**17**)^{2b} and α -(5-nitro-2-furyl)-N-(2-hydroxyethyl)-nitrone (**18**).^{2c}

The compounds were tested in the feed against a

(5) K. Venters, S. Hillers, and A. Lazdins, *Litr. PSR Zinat. Akad. Vestis*, **87** (1961); *Chem. Abstr.*, **56**, 14194 (1962).

(6) H. Ishida, T. Namerikawa, A. Matsuda, and Y. Kawamura, Japanese Patent 10,524 (1956); *Chem. Abstr.*, **52**, 15590 (1958).

(7) The *in vitro* and *in vivo* biological data were obtained using methods described previously.^{2b}

TABLE II

Compd	In Vitro ANTIMICROBIAL ACTIVITY, MIN INHIB CONCEN, $\mu\text{g/ml}$								
	SG ^a	ST	SA	SAG	BS	EC	AF	CA	
1	0.1	<0.01	<0.01	0.1	1	1	10	10	
3		1	100		100	10		1	
5	1	1	1	1	0.1	1	100	>100	
6	1	1	0.1	1	1	1	10	10	
7	1	1	1	0.1	1	10	100	100	
8	10	10	1	1	1	10	10	10	
12		100	10		1	100		100	
14		>100	100		100	>100		>100	
15	>100	>100	>100	>100	>100	>100	>100	>100	
16	100	100	10	100	10	100	100	>100	
17	100	100	>100	100	100	>100	1	10	
18	1	10	1	1	1	10	100	100	

^a SG = *Salmonella gallinarum*, ST = *S. typhimurium*, SA = *Staphylococcus aureus*, SAG = *Streptococcus agalactiae*, BS = *Bacillus subtilis*, EC = *Escherichia coli*, AF = *Aspergillus fumigatus*, CA = *Candida albicans*.

Salmonella choleraesuis infection in mice. In this test **1** and **5** were the most active of the series, but less active than **17** and **18**. The α -halogenated derivatives **3**, **4**, **6**, and **8** showed less *in vivo* antibacterial activity. Thus, the enhanced *in vitro* activity did not extend to an *in vivo* system. Replacement of a 5-nitro-2-furyl with a 5-nitro-2-thienyl group also decreased *in vivo* activity. Insufficient data are available, at present, to discuss the effect of the vinyl group on the toxicity of the series.

Surprisingly, **5** showed appreciable anticoccidial activity against *Eimeria acervulina* and *E. maxima* in chickens when administered in the feed at high levels (0.033%). The activity fell off rapidly at lower levels (0.0165, 0.0085, and 0.004%). This was particularly true with *E. acervulina* where activity was measurable only at 0.033%. Compound **5** also gave measurable protection against a mixed infection of *E. adenoides* and *E. melagrimitis* in turkeys. This pattern of activity is in contrast to that of **18** which showed no anticoccidial activity at any level.

Experimental Section⁸

Starting Materials.— β -(5-Nitro-2-furyl)acrolein,⁵ β -(5-nitro-2-furyl)- α -bromoacrolein,⁶ β -(5-nitro-2-thienyl)acrolein,⁴ β -(5-nitro-2-thienyl)- α -bromoacrolein,⁴ and hydroxylamines,² not commercially available, were prepared by the methods described in the literature.

α -[2-(5-Nitro-2-heteroaryl)vinyl- or 1-bromovinyl]-*N*-substituted Nitrones. **Method A.**—The *N*-alkylhydroxylamine·HCl (0.01 mole) was added portionwise to a warm soln of β -(5-nitro-2-furyl)acrolein (0.01 mole) in abs EtOH (20 ml) contg NaHCO₃ (0.015 mole) and stirred overnight at room temperature. The mixture was worked up in the usual manner² and the results are shown in Table I.

Method B.—The same procedure as above was used except that 5 molar equiv of hydroxylamino alcohol oxalate was used.

Method C.—A mixture of β -(5-nitro-2-furyl)acrolein (0.005 mole) and the *N*-substituted hydroxylamine (0.005 mole) in C₆H₆ (20 ml) (**13**, **14**, **15**) or in a mixture (64 ml) of THF-EtOH (5 : 2) (**16**) was refluxed 0.5 hr using a Dean-Stark water separator. After cooling, the solid was filtered off and recrystd to afford the orange-red to red nitrones (Table I).

Acknowledgment.—We are indebted to W. E. Meredith, D. R. Filson, J. R. Challey, and C. A. Johnson for the biological data.

(8) 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. Evaporation of solvents was done under reduced pressure using a rotary evaporator.

Novel Substrate of Adenosine Deaminase^{1a}

HOWARD J. SCHAEFFER,^{*1b} S. GURWARA, ROBERT VINCE,
AND S. BITNER

Department of Medicinal Chemistry,
State University of New York at Buffalo,
Buffalo, New York 14214

Received October 5, 1970

The structural features that determine whether a compound will be a substrate or an inhibitor of an enzyme are often difficult to untangle. For calf intestinal mucosal adenosine deaminase, it is well known that a variety of changes can be made in the carbohydrate moiety of adenosine analogs without loss of substrate activity.² For example, in addition to the 9- β -D-ribo configuration of adenosine (**1**), it is known that 9- β -D-arabino-, -xylo-, and -lyxofuranosyladenines (**2**, **3**, **4**) are all substrates of adenosine deaminase.² Furthermore, the 2'- and 3'-OH groups of adenosine do not play a critical role in substrate activity for it has been found that 2'-deoxy-, 3'-deoxy-, and even 2',3'-dideoxyadenosine (**5**, **6**, **7**) undergo deamination with adenosine deaminase.² The 5'-OH group of adenosine and its analogs does, however, play a special role in the deamination reaction since the 5'-deoxynucleosides of adenine (**8**) do not undergo deamination with adenosine deaminase unless a properly positioned OH group is present at C-3' as in 9-(5-deoxy- β -D-xylofuranosyl)adenine (**9**) such that the 3'-OH group can assume the function of the 5'-hydroxyl group of adenosine.^{2a,d,f}

Based on these observations, we decided to synthesize an acyclic analog of adenosine containing several functional groups which appear to be important for substrate activity. The compound selected for preparation was 9-(2-hydroxyethoxymethyl)adenine (**10**).

(1) (a) This work was supported by Grant T-337D from the American Cancer Society and by a Public Health Service Training Grant 5-T1-GM-00555 from the Division of Medical Sciences, Bethesda, Md. (b) Wellcome Research Laboratories, Burroughs Wellcome & Co., Research Triangle Park, North Carolina 27709.

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