Notes

Nitrones. 5.[1a] Vinylogs of α-(5-Nitro-2-heteroaryl)-*N*-substituted Nitrones

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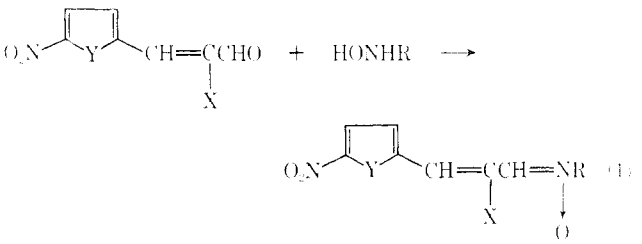
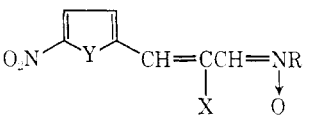
In previous reports on nitrones[2] we discussed the preparation and chemotherapeutic activity of α-(5-nitro-2-furyl)-*N*-aryl-, *N*-cycloalkyl-, *N*-alkyl-, and *N*-hydroxyalkylnitrones. This paper describes the preparation of nitrofuryl- and nitrothienylnitrones in which a vinyl or α-bromovinyl moiety is inserted between the nitroaryl and the nitrone group. The biological effect ensuing from this type of structural variation has been studied for other classes of nitrofurfural[3] and nitrothienal[4] 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.

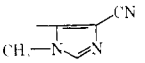
Compounds **1**–**16** were obtained in 7–99% yield by the reaction of β-(5-nitro-2-furyl)acrolein,[5] β-(5-nitro-2-furyl)-α-bromoacrolein,[6] or their analogs in the thiophene series,[4] and N-substituted hydroxylamines in a manner similar to the nitrofurylnitrones,[2] according to eq 1.



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	$C_8H_8N_2O_4$[c]
2	O	H	C_2H_5	B	104–106	Et_2O	52	$C_9H_{10}N_2O_4$
3	O	Br	CH_3	A	170–171	CH_3NO_2	43	$C_8H_7BrN_2O_4$
4	O	Br	C_2H_5	B	178–179 dec	$CHCl_3$	36	$C_9H_9BrN_2O_4$
5	O	H	CH_2CH_2OH	B	188–190 dec	CH_3NO_2–EtOH	73	$C_9H_{10}N_2O_5$
6	O	Br	CH_2CH_2OH	B	160–161	Abs EtOH	20	$C_9H_9BrN_2O_5$
7	O	H	CH_2CH_2OAc	B	146–147	C_6H_6–hexane	32	$C_{11}H_{12}N_2O_6$
8	O	Br	CH_2CH_2OAc	B	124–125	C_6H_6–hexane	36	$C_{11}H_{11}BrN_2O_6$
9	O	H	CH_2CH_2OEt	B	117–118	Abs EtOH	49	$C_{11}H_{14}N_2O_5$
10	S	Br	CH_3	A	169–170	Abs EtOH	7	$C_8H_7BrN_2O_3S$
11	S	H	CH_2CH_2OH	B	162–163	95% EtOH	42	$C_9H_{10}N_2O_4S$
12	S	Br	CH_2CH_2OH	B	160–162	Abs EtOH	38	$C_9H_9BrN_2O_4S$
13	S	H	C_6H_{11}[d]	C	125–127	C_6H_6–Et_2O	36	$C_{13}H_{16}N_2O_3S$
14	O	H	C_6H_5	C	182 dec	CH_3NO_2	74	$C_{13}H_{10}N_2O_4$
15	S	H	C_6H_5	C	182	CH_3NO_2	99	$C_{13}H_{10}N_2O_3S$
16	O	H		C	210 dec	CH_3NO_2	43	$C_{12}H_9N_5O_4$

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

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

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(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).

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(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

In Vitro ANTIMICROBIAL ACTIVITY, MIN INHIB CONCN, μg/ml

Compd	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. adenoeides* 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 Section[8]

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 $NaHCO_3$ (0.015 mole) and stirred overnight at room temperature. The mixture was worked up in the usual manner[2] 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 C_6H_6 (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).

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(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]

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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**).

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