Table III[a]

Compd	Concn, %	Rabbit cornea		Guinea pig cornea	
		Potency	Duration	Potency	Duration
11	1	0.46 (0.37-0.56)	0-23	0.25 (0.17-0.33)	0-14
12	1	0.96 (0.93-1.00)	24-33	0.92 (0.86-0.97)	16-39
	0.50	0.37 (0.28-0.46)	8-12	0.39 (0.29-0.48)	0-13
13	1	0.99 (0.97-1.00)	11-36	0.97 (0.94-1.00)	15-33
	0.50	0.44 (0.34-0.53)	4-15	0.80 (0.72-0.87)	9-18
14	1	1.00	24-63	0.07 (0.02-0.12)	0-6
	0.50	0.95 (0.91-0.99)	16-30	0.00	
16	1	1.00	18-69	0.90 (0.84-0.96)	16-27
	0.50	0.70 (0.61-0.79)	8-27	0.78 (0.70-0.86)	11-18
	0.25	0.17 (0.09-0.24)	0-9	0.09 (0.04-0.15)	0-4
17	1	0.88 (0.81-0.94)	16-29	0.29 (0.20-0.38)	0-28
18	1	1.00	27-156	0.96 (0.93-1.00)	57-143
	0.50	0.96 (0.92-1.00)	17-51	0.87 (0.81-0.93)	18-63
	0.25	0.50 (0.40-0.60)	0-17	0.12 (0.06-0.18)	0-9
19	1	0.96 (0.93-1.00)	69-111	0.00	
	0.50	0.87 (0.80-0.94)	17-39	0.00	
	0.25	0.13 (0.07-0.20)	0-7	0.00	
Cocaine	1	0.95 (0.92-0.98)	16-24	0.61 (0.52-0.70)	8-21
	0.50	0.54 (0.46-0.62)	7-15	0.55 (0.45-0.64)	4-18
	0.25	0.13 (0.08-0.18)	2-6	0.09 (0.04-0.15)	0-5

[a] Surface anesthesia was tested according to the method of Chance and Lobstein,[2] and the anesthetic potency was calcd for the first 18 min.[3] A potency of 1.00 indicates an onset of anesthesia in 1 min and a duration of at least 18 min.

essential materials. Technical assistance by Miss S. Levtov and Mrs. A. Ramazani is gratefully acknowledged.

References

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Synthesis and Antibacterial Activity of 5-Nitro-2-furfurylidene Arylthioacethydrazides and 5-Nitro-2-furfurylidene Arylsulfonylacethydrazides

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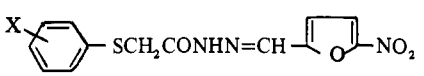
In the course of studies on new antibacterial compounds based on nitrofuran, we have synthesized and screened the title compounds.

Arylthioacetic acid ethyl esters prepared by known methods were treated with hydrazine hydrate to give arylthioacethydrazides. Arylsulfonacethydrazides were prepared similarly from the corresponding arylsulfonylacetic acid ethyl esters. The acethydrazides reacted with 5-nitro-2-furaldehyde afforded the appropriate 5-nitro-2-furfurylidene acethydrazides I and II (see Table II).



I, X_I = H, *m*-F, *p*-CH_3O, *o*-CF_3, *m*-CF_3, *m*-NO_2

II, X_{II} = H, *m*-F, *p*-F, *o*-Cl, *p*-Cl, *o*-CH_3O, *m*-CF_3, *m*-NO_2, *p*-NO_2

New acethydrazides prepared are tabulated in Table I.

Biological Evaluation. Compounds listed in Table II were tested against various Gram-positive and Gram-negative bacteria. Furazolidone was used as a control. The compounds were dissolved in Me_2CO and diluted with H_2O to give a concentration of 250 μ/ml. Paper disks of 9-mm diameter were immersed in the prepared solutions and put on the inoculated penicillin assay seed agar surface.

All compounds were inactive against *Bacillus pyocyaneus* and *Streptococcus β-hemolyticus* at the test concentrations. Compounds **13**, **15**, **20**, and **21** showed slight activities against *Bordetella bronchiseptica* ATCC 4617. Compound **21** showed a hazy inhibition zone with an average value of 12.8 mm against *Proteus vulgaris*. Furazolidone was inactive against the 4 mentioned organisms. The antibacterial activities of the compounds prepared are listed in Table III.

Table I

Compd	Ar	$ArCH_2CONHNH_2$ Mp, °C	Yield, %	Formula[a]
1	$C_6H_5SO_2$	130	68	$C_8H_{10}N_2O_3S$
2	*m*-FC_6H_4S[b]	63	78	$C_8H_9FN_2OS$
3	*m*-$FC_6H_4SO_2$	93	59	$C_8H_9FN_2O_3S$
4	*p*-$FC_6H_4SO_2$	142	61	$C_8H_9FN_2O_3S$
5	*o*-$ClC_6H_4SO_2$	160	64	$C_8H_9ClN_2O_3S$
6	*p*-$ClC_6H_4SO_2$	156	73	$C_8H_9ClN_2O_3S$
7	*m*-$CF_3C_6H_4S$	68	72	$C_9H_9F_3N_2OS$
8	*m*-$CF_3C_6H_4SO_2$	133	61	$C_9H_9F_3N_2O_3S$
9	*m*-$NO_2C_6H_4S$	80	74	$C_8H_9N_3O_3S$
10	*m*-$NO_2C_6H_4SO_2$	155	76	$C_8H_9N_3O_5S$
11	*p*-$NO_2C_6H_4SO_2$	185	66	$C_8H_9N_3O_5S$

[a] All compounds were analyzed for C, H, and the results were satisfactory. Similarly ir, nmr, and mass spectra support the structure assignments. [b] The corresponding ester was prepared according to reference 1.

Table II

$ArCH_2CONHN{=}CH$–(furan)–NO_2

Compd	Ar	Mp, °C	Yield, %	Formula[a]
12	C_6H_5S	130	89	$C_{13}H_{11}N_3O_4S$
13	$C_6H_5SO_2$	180	93	$C_{13}H_{11}N_3O_6S$
14	*m*-FC_6H_4S	185	96	$C_{13}H_{10}FN_3O_4S$
15	*m*-$FC_6H_4SO_2$	187	88	$C_{13}H_{10}FN_3O_6S$
16	*p*-$FC_6H_4SO_2$	180	93	$C_{13}H_{10}FN_3O_6S$
17	*o*-$ClC_6H_4SO_2$	215	95	$C_{13}H_{10}ClN_3O_6S$
18	*p*-$ClC_6H_4SO_2$	205–210	88	$C_{13}H_{10}ClN_3O_6S$
19	*p*-$CH_3OC_6H_4S$	155	82	$C_{14}H_{13}N_3O_5S$
20	*p*-$CH_3OC_6H_4SO_2$	190–210	85	$C_{14}H_{13}N_3O_7S$
21	*o*-$CF_3C_6H_4S$[b]	160	91	$C_{14}H_{10}F_3N_3O_4S$
22	*m*-$CF_3C_6H_4S$	175	88	$C_{14}H_{10}F_3N_3O_4S$
23	*m*-$CF_3C_6H_4SO_2$	186	93	$C_{14}H_{10}F_3N_3O_6S$
24	*m*-$NO_2C_6H_4S$	207	86	$C_{13}H_{10}N_4O_6S$
25	*m*-$NO_2C_6H_4SO_2$	236	88	$C_{13}H_{10}N_4O_8S$
26	*p*-$NO_2C_6H_4SO_2$	210	92	$C_{13}H_{10}N_4O_8S$

[a] See footnote *a* in Table I. [b] The corresponding hydrazide was prepared according to the reference 2.

Table III. Zones of Inhibition

	Av zone size, mm					
Compd	*S. a.*[a]	*S. e.*	*K. p.*	*S. f.*	*S. a.*[+]	*E. c.*
12	15.9[c]	17.8	11.4	11.3	15.2[c]	12.0
13	17.2	18.7	10.1	18.5	16.9	11.4
14	11.7	14.1			12.0	
15	15.4	20.2	9.9	16.6	15.7	10.8
16	14.5	18.7		16.1	13.9	9.8
17	16.3	19.4	9.6	16.0	16.6	10.9
18	16.1	19.4	9.7	15.3	17.0	9.7
19	10.0	14.0			10.7[c]	
20	15.1	18.0		17.8	16.8	9.6
21	16.8[c]	15.6	10.9[b]		18.8[c]	15.0
22	10.2	13.1			11.0	
23	15.4	18.4	9.4	12.0	15.8	
24	10.8	14.7	12.2[b]		13.3	
25	14.0	16.9		14.2	16.4	10.0
26	15.9	19.5		16.5	15.6	10.2
Furazolidone	21.2	25.3	20.6	13.9	22.4	23.4

[a] *S. a.* = *Staphylococcus aureus* ATCC 6538-p, *S. e.* = *Staphylococcus epidermidis* ATCC 12228, *K. p.* = *Klebsiella pneumoniae* ATCC 10031, *S. f.* = *Streptococcus faecalis* ATCC 8043, *S. a.*[+] = *Staphylococcus aureus* coagulase +, *E. c.* = *Excherichia coli.* [b] Inhibition zones were hazy. [c] Edges of inhibition zones were not sharp.

Experimental Section†

Arylthioacethydrazides and Arylsulfonylacethydrazides. To a soln of 0.01 mole of the appropriate ester in 15 ml of EtOH was added 0.011 mole of 99% $N_2H_4 \cdot H_2O$. The reaction mixt was stirred for 0.5 hr, then allowed to stand overnight. After cooling in an ice box, the cryst mass was filtered and recrystd from EtOH–H_2O (see Table I).

5-Nitro-2-furfurylidene Arylthioacethydrazides and Arylsulfonylacethydrazides. To a soln of 0.01 mole of the appropriate hydrazide in 10 ml of EtOH, a hot soln of 0.01 mole of 5-nitro-2-furaldehyde in 10 ml of EtOH was added and the reaction mixt was warmed for 0.5 hr at 50–55°. After cooling, the reaction mixt was filtered and the residue was recrystd from EtOH (see Table II).

References

(1) N. Sharghi and I. Lalezari, *J. Chem. Eng. Data*, 8, 276 (1963).
(2) N. Sharghi and I. Lalezari, *ibid.*, 11, 612 (1966).

†Melting points were taken on a Kofler hot stage microscope. The ir spectra were determined with a Leitz Model III spectrograph (KBr). Nmr spectra were obtained on a Varian A60A instrument using Me_4Si as internal standard. Mass spectra were recorded on a Varian Mat 111 instrument.

Acyl Derivatives of 1-β-D-Arabinofuranosylcytosine†

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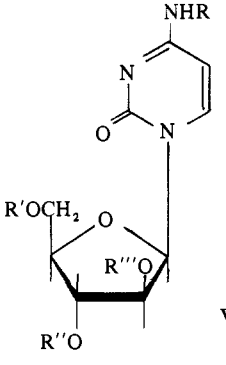
1-β-D-Arabinofuranosylcytosine (I) is an effective anticancer agent against both experimental animal[1] and human[2] tumors, but it is rapidly deaminated in the human,[3] which may adversely affect its clinical utility. 1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)cytosine (II),[4] prepared in an effort to avoid this difficulty and enhance the oral activity of ara-C, was found to be somewhat less effective than the parent compound,[5] but a single dose of 1-(5-*O*-adamantoyl-β-D-arabinofuranosyl)cytosine (III),[6] which appears to be a repository agent, is almost as effective as ara-C on its optimal schedule (3 courses of multiple closely spaced doses with appropriate intervals for host recovery).[7] We desired to prepare tri-*O*-acyl derivatives of ara-C from higher aliphatic acids that might perform more effectively as "depot" agents, but selective O-acylation of ara-C could not be achieved. Treatment of adamantoyl chloride with ara-C in the presence of Et_3N gave only N^4-adamantoyl-1-β-D-arabinofuranosylcytosine (IV), which was also obtained by the reaction of ara-C with adamantanecarboxylic acid in the presence of dicyclohexylcarbodiimide or with adamantanecarboxylic anhydride in pyridine. Neil, *et al.*, did not selectively O-acylate ara-C either, but prepared a compound presumed to be the 5′-*O*,*N*-bisadamantoyl derivative (V), which was hydrolyzed by NaOH in aq MeOH in unspecified yield to the desired 1-(5-*O*-adamantoyl-β-D-arabinofuranosyl)-cytosine (III).[6] Since this method is not applicable to the preparation of tri-*O*-acyl derivatives because of the ease with which the 2′- and 3′-*O*-acyl group are saponified, N-deacylation of V by treatment with picric acid was attempted and was successful. Removal of the picric acid with ion-exchange resin then gave III, which was also prepared from V by treatment with hydrazine in pyridine.[8]

The reaction of ara-C with butyryl chloride gave a tributyryl derivative, but, unfortunately, its uv spectrum indicated that one of the butyryl groups was attached to the amino group—pmr spectroscopy was used to identify this compd as 1-(3,5-di-*O*-butyryl-β-D-arabinofuranosyl)-N^4-butyrylcytosine (VI), which was N-deacylated with picric acid to give 1-(3,5-di-*O*-butyryl-β-D-arabinofuranosyl)cytosine (VII). The desired tri-*O*-butyryl compd VIII was prepared by acylation of ara-C with butyric anhydride followed by N-deacylation of the tetrabutyryl compd IX with picric



1, R = R′ = R″ = R‴ = H
II, R = H; R′ = R″ = R‴ = CH_3CO–
III, R = R″ = R‴ = H; R′ = 1-adamantoyl-CO–
IV, R′ = R″ = R‴ = H; R = 1-adamantoyl-CO–
V, R″ = R‴ = H; R′ = R = 1-adamantoyl-CO–
VI, R‴ = H; R = R′ = R″ = $CH_3(CH_2)_2CO$–
VII, R = R‴ = H; R′ = R″ = $CH_3(CH_2)_2CO$–
VIII, R = H; R′ = R″ = R‴ = $CH_3(CH_2)_2CO$–
IX, R = R′ = R″ = R‴ = $CH_3(CH_2)_2CO$–

†This work was supported by funds from the C. F. Kettering Foundation, and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract Nos. PH43-64-51 and PH43-65-654.