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	$C_{13}H_{10}ClN_2O_6S$
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).

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(2) N. Sharghi and I. Lalezari, *ibid.,* **11**, 612 (1966).

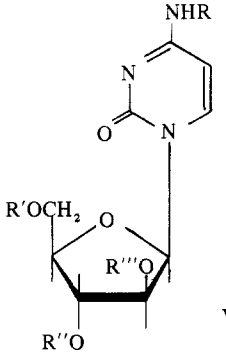
†Melting points were taken on a Kofler hot stage microscope. The ir spectra were determined with a Leitz Model III spectrograph (KBr). Nmr spectra were obtained on a Varian A60A instrument using Me_4Si as internal standard. Mass spectra were recorded on a Varian Mat 111 instrument.

Acyl Derivatives of 1-β-D-Arabinofuranosylcytosine†

John A. Montgomery* and H. Jeanette Thomas
Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205. *Received August 2, 1971*

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



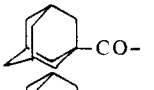
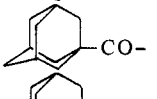
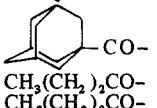
I, R = R′ = R″ = R‴ = H
II, R = H; R′ = R″ = R‴ = CH_3CO–
III, R = R″ = R‴ = H; R′ =  –CO–
IV, R′ = R″ = R‴ = H; R =  –CO–
V, R″ = R‴ = H; R′ = R =  –CO–
VI, R‴ = H; R = R′ = R″ = $CH_3(CH_2)_2CO$–
VII, R = R‴ = H; R′ = R″ = $CH_3(CH_2)_2CO$–
VIII, R = H; R′ = R″ = R‴ = $CH_3(CH_2)_2CO$–
IX, R = R′ =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

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Table I. Activity of the Butyryl Derivatives of Ara-C against Leukemia L1210[a]

No.	Name	Treatment: Dose, mg/kg[b]	Treatment: Schedule	Host wt. change $\Delta T/\Delta C$	Life-Span: T	Life-Span: C	Life-Span: % increase
VII	1-(3,5-Di-*O*-butyryl-β-D-arabinofuranosyl)-cytosine	400	qd 2-6	−2.9/+2.1			Toxic
		200	qd 2-6	−3.7/+2.1	15.2	8.9	70
		134	qd 2-6	−0.6/+2.0	13.8	8.5	62
		60	qd 2-6	+0.7/+2.0	15.6	8.5	83
VIII	1-(2,3,5-Tri-*O*-butyryl-β-D-arabinofuranosyl)-cytosine	450	qd 2-6	−0.7/+1.8	>25.0	9.1	>174[c]
		300	qd 2-6	−0.4/1.8	20.6	9.1	126
		200	qd 2-6	−0.2/2.0	19.4	8.5	128
		135	qd 2-6	+0.2/2.0	13.5	8.5	58
		80	qd 2-6	+0.7/2.0	13.0	8.5	52
		40	qd 2-6	−0.7/2.3	12.2	9.0	27
IX	1-(2,3,5-Tri-*O*-butyryl-β-D-arabinofuranosyl)-N^4-butyrylcytosine	600	Day 1 only	+0.4/+1.8	11.7	9.2	27
		400	Day 1 only	+1.0/+1.8	10.8	9.2	17
		266	Day 1 only	+1.3/+1.8	10.7	9.2	16
		177	Day 1 only	+1.2/+1.8	9.3	9.2	1

[a] 10^5 cells injected intraperitoneally. [b] Injected intraperitoneally. [c] Two 30-day survivors from six treated animals.

acid. This procedure was also used to prepare the tri-*O*-acetyl derivative II of ara-C and ^{3}H-labeled II for use in pharmacological studies.

Screening Data. Results of the evaluation of the butyryl derivatives of ara-C are given in Table I. The tetrabutyryl compd IX was essentially inactive when given as a single dose. Both the di-*O*-butyryl and the tri-*O*-butyryl compds (VII and VIII) were active on a chronic schedule, but the tri-*O*-butyryl compound VIII is clearly less toxic and more active; in fact, it gave two 30-day survivors at the highest dose tested. These results also show that the tri-*O*-butyryl compd VIII is superior to both ara-C and its tri-*O*-acetyl derivative II when they are given on a chronic schedule,[5] but it is inferior to both 1-(5-*O*-adamantoyl-β-D-arabinofuranosyl)cytosine[6] and to ara-C given on its optimal schedule[7] (see above), indicating that tri-*O*-acyl derivatives of longer chain length may be desirable for optimal activity.

Experimental Section

Uv spectra were detd in the solvents specified with a Cary Model 14 spectrophotometer, the ir spectra were detd in pressed KBr disks with a Perkin-Elmer Model 521 spectrophotometer, and the pmr spectrum was detd in DMSO-d_6 with a Varian A60-A spectrophotometer. Melting points were taken on a Mel-Temp and are uncorrected.

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)cytosine (II). A soln of 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-N^4-acetylcytosine[4] (411 mg, 1.00 mmole) and picric acid (411 mg, 1.80 mmoles) in MeOH (20 ml) was refluxed for 1 hr and then evapd to dryness *in vacuo*. A soln of the resulting yellow residue in 95% aq Me_2CO (25 ml) was stirred with enough Dowex 1-X8 (carbonate) ion-exchange resin to remove the picric acid and give a colorless soln. The soln was evapd to dryness and the resulting residue crystd from EtOAc–Et_2O. A soln of this cryst material in $CHCl_3$ (50 ml) was washed with H_2O (50 ml). The H_2O layer was then extd 6 times with $CHCl_3$ (50 ml each). The $CHCl_3$ exts were combined, dried ($MgSO_4$), and evapd to dryness. The residue, a white glass, crystd from EtOAc–Et_2O: yield, 200 mg (54%); mp 189–190°; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl 277 (13.2), pH 7, 233 (7.72), 269 (8.93), 0.1 *N* NaOH, 274 (9.80); $\bar{\nu}_{max}$ (cm^{-1}): 3445, 3320, 3120 (NH), 1735, 1655 (C=O), 1605, 1525 (C=C, C=N). These figures are in agreement with published data.[4]

In a similar manner, 128 mg (40%) of ^{3}H-labeled II was prepd from ^{3}H-labeled ara-C.

1-(5-*O*-Adamantoyl-β-D-arabinofuranosyl)cytosine (III). A. A soln of 1-(5-*O*-adamantoyl-β-D-arabinofuranosyl)-N^4-adamantoylcytosine (6.80 g, 11.5 mmoles) and hydrazine hydrate (3.0 ml, 48.0 mmoles) in pyridine–AcOH (90 ml of 4:1 v/v) was left for 48 hr at room temp and poured into H_2O (1200 ml). The ppt that immediately formed was collected by filtration after cooling several hours. This solid was triturated first with several portions of Et_2O and then $CHCl_3$. A soln of the insol material in MeOH (300 ml) was evapd to 100 ml. The solid was recrystd from EtOH: yield, 974 mg (21%); mp 299–301° dec.

The analytical sample was obtd from a previous run by recrystn from MeOH. It was dried for 20 hr at 100° (0.07 mm) over P_2O_5: mp 299–300° dec [lit.[7] 300–301°]; λ_{max} nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 280 (13.4); pH 7, 271 (9.35), 0.1 *N* NaOH (unstable); $\bar{\nu}_{max}$ (cm^{-1}): 3460 (OH), 3340, 3270, 3230 (NH), 2905, 2850 (CH), 1695, 1655 (C=O), 1635, 1605, 1525 (C=C, C=N). *Anal.* ($C_{20}H_{27}N_3O_6$) C, H, N.

B. A soln of 1-(5-*O*-adamantoyl-β-D-arabinofuranosyl)-N^4-adamantoylcytosine (638 mg, 10.8 mmoles) and picric acid (638 mg, 27.9 mmoles) in MeOH (25 ml) was refluxed for 5 hr, dild with H_2O (5 ml), and stirred with Dowex 1-X8 (carbonate) ion-exchange resin until colorless. The resin was then removed by filtration and washed several times with hot MeOH. The combined filtrate and wash were evapd to dryness *in vacuo*. The residue obtd was triturated with two 20-ml portions of acetone. The acetone-insol material then crystd from MeOH as a white solid: yield 200 mg (51%); mp 298–299° dec.

1-β-D-Arabinofuranosyl-N^4-adamantoylcytosine (IV). A suspension of 1-β-D-arabinofuranosylcytosine hydrochloride (527 mg, 1.00 mmole) and Et_3N (405 mg, 4.00 mmoles) in anhyd dioxane (40 ml) was stirred for 15 min. A soln of adamantoyl chloride (397 mg, 2.00 mmoles) in dioxane (10 ml) was added to the suspension over a 30-min period. The reaction mixt was stirred at room temp for 20 hr, dild with H_2O (2 ml), stirred for 30 min, and evapd to dryness *in vacuo* below 35°. The residue crystd from MeOH–EtOAc: yield 205 mg (22%); mp 234–236° dec with sintering at 130°. The analytical sample was obtd by recrystn from MeOH. It was dried at 100° (0.07 mm) over P_2O_5: λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 241 (9.48), 311 (15.7), pH 7, 248 (15.9), 299 (9.18), 0.1 *N*, NaOH (unstable); $\bar{\nu}_{max}$ (cm^{-1}): 3465 (broad) (OH, NH), 2900, 2850 (CH), 1705, 1640 (C=O), 1550, 1480 (C=C, C=N). *Anal.* ($C_{20}H_{27}N_3O_6 \cdot H_2O$) C, H, N.

1-(5-*O*-Adamantoyl-β-D-arabinofuranosyl)-N^4-adamantoylcytosine (V). To a soln of 1-β-D-arabinofuranosylcytosine hydrochloride (4.28 g, 16.28 mmoles) in pyridine (300 ml) was added, with stirring and cooling, a soln of adamantoyl chloride (6.48 g, 32.56 mmoles) in 20 ml of C_6H_6 over a 30-min period. After another 15 min in the cold, the soln was left for 20 hr at room temp, dild with H_2O (16 ml), stirred for 30 min, and evapd to dryness at less than 45°. A soln of the residue in $CHCl_3$ (150 ml) was washed 3 times with satd $NaHCO_3$ soln (100 ml), 2 times with H_2O (100 ml), dried ($MgSO_4$), and evapd to dryness *in vacuo*. The residue was triturated several times with petr ether and then pptd as a gel from EtOAc (30 ml). A white solid was obtd: yield 8.15 g (85%); mp 185° dec. The analytical sample was obtd from a previous run. It was dried at 78° (0.07 mm) over P_2O_5 for 20 hr: mp 185° dec; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 247 (11.4), 307 (11.2); $\bar{\nu}_{max}$ (cm^{-1}): 3400 (broad) (OH), 3410 (NH), 2900, 2850 (CH), 1725 (sh), 1710, 1650 (C=O), 1620, 1550, 1480 (C=C, C=N). *Anal.* ($C_{31}H_{41}N_3O_7 \cdot 1.4H_2O$) C, H, N.

1-(3,5-Di-*O*-butyryl-β-D-arabinofuranosyl)-N^4-butyrylcytosine (VI). To a soln of 527 mg (2.00 mmoles) of 1-β-D-arabinofuranosylcytosine hydrochloride in pyridine (25 ml) was added, with cooling and stirring, a soln of butyryl chloride (852 mg, 8.00 mmoles) in C_6H_6 (5 ml) over a 30-min period. The reaction soln was left in the cold another 15 min. Then, after 20 hr at room temp, it was

dild with H_2O (4 ml), stirred for 30 min at room temp, and evapd to dryness at less than 45°. A soln of the residue in $CHCl_3$ (50 ml) was washed 3 times with satd $NaHCO_3$ soln (50 ml), 2 times with H_2O (50 ml), dried ($MgSO_4$), and evapd to dryness *in vacuo*. The residue crystd from EtOAc: yield 335 mg (37%). The analytical sample was obtd by recrystn from EtOAc. It was dried at 100° (0.07 mm) over P_2O_5 for 20 hr: mp 203–204°; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 242 (9.80), 308 (14.2), pH 7, 248 (16.2), 297 (9.40), 0.1 *N* NaOH, 275 (9.74), 303 (sh) (4.35); $\bar{\nu}_{max}$ (cm^{-1}): 3400 (broad) (OH), 3320 (NH), 2965, 2930, 2875 (CH), 1730, 1720, 1655 (C=O), 1605, 1580, 1480 (C=C, C=N); δ in ppm: 0.9 (m, CH_3), 1.6 and 2.4 (m, CH_2 of butyryl), 4.3 (m, $C_2'H$, $C_4'H$, and $C_5'H_2$), 5.0 (t, $C_3'H$), 6.0 and 6.1 (overlapping d, $C_2'OH$ and $C_1'H$), 7.2 and 7.9 (AB pair, C_5H and C_6H), 10.8 (s, NH). These assignments were verified by spin decoupling. *Anal.* ($C_{21}H_{31}N_3O_8$) C, H, N.

1-(3,5-Di-*O*-butyryl-β-D-arabinofuranosyl)cytosine (VII). A soln of 1-(3,5-di-*O*-butyryl-β-D-arabinofuranosyl)-N^4-butyrylcytosine (1.18 g, 2.51 mmoles) and picric acid (1.18 g, 5.10 mmoles) in MeOH (100 ml) was refluxed for 1 hr and stirred with enough Dowex 1-X8 (carbonate) ion-exchange resin to give a colorless soln. Evapn of the soln to dryness gave a white glass. A $CHCl_3$ soln of the glass was washed with H_2O, dried ($MgSO_4$), and evapd to dryness *in vacuo*. The residue crystd from EtOAc: yield 640 mg (66%); mp 166–167°; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 212 (9.55), 278 (13.2); pH 7, 230 (sh) (7.83), 270 (9.18); 0.1 *N* NaOH, 230 (sh) (7.83), 273 (9.53); $\bar{\nu}_{max}$ (cm^{-1}): 3420, 3345, 3230, 3115 (NH), 2965, 2935, 2905, 2875 (CH), 1735, 1660, 1640 (C=O), 1620, 1605, 1525, 1485 (C=C, C=N). *Anal.* ($C_{17}H_{25}N_3O_7$) C, H, N.

1-(2,3,5-Tri-*O*-butyryl-β-D-arabinofuranosyl)cytosine (VIII). A soln of 1-(2,3,5-tri-*O*-butyryl-β-D-arabinofuranosyl)-N^4-butyrylcytosine (4.84 g, 9.25 mmoles) and picric acid (4.84 g, 11.1 mmoles) in MeOH (200 ml) was refluxed for 1 hr and evapd to dryness *in vacuo*. A soln of the yellow residue in 95% aq Me_2CO (100 ml) was stirred with enough Dowex 1-X8 (carbonate) ion-exchange resin to give a colorless soln. Evapn of the soln to dryness gave a syrup that crystd from Et_2O. A soln of the cryst product in $CHCl_3$ (100 ml) was washed with 0.1 *N* H_2SO_4 (100 ml), satd $NaHCO_3$ soln (100 ml), and then H_2O (100 ml), dried ($MgSO_4$), and evapd to dryness *in vacuo*. The residue crystd from Et_2O: yield, 3.20 g (76%); mp 127–129°. The analytical sample was obtd from a previous run by recrystn from Et_2O and dried at 78° (0.07 mm) over P_2O_5 for 8 hr: mp 126–127°; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 277 (13.2); pH 7, 233 (7.67), 269 (8.88); 0.1 *N* NaOH, 274 (10.0); $\bar{\nu}_{max}$ (cm^{-1}): 3445, 3320, 3265, 3125 (NH), 2965, 2935, 2875 (CH), 1760, 1735, 1655 (C=O), 1605, 1525, 1495, 1475 (C=C, C=N). *Anal.* ($C_{21}H_{31}N_3O_8$) C, H, N.

1-(2,3,5-Tri-*O*-butyryl-β-D-arabinofuranosyl)-N^4-butyrylcytosine (IX). A soln of 1-β-D-arabinofuranosylcytosine hydrochloride (3.00 g, 10.8 mmoles) in pyridine (300 ml) contg butyric anhydride (7.86 ml, 47.7 mmoles) was heated at 80–85° for 2 hr. Another 1.86 ml of butyric anhydride was added and heating continued for 1 hr. The soln was then evapd to 60 ml and poured into ice water (300 ml). The resulting mixt was extd 3 times with $CHCl_3$ (200 ml). The $CHCl_3$ ext was extd 2 times with satd $NaHCO_3$ soln (300 ml), then H_2O (300 ml), dried ($MgSO_4$), and evapd to dryness *in vacuo*. Crystn of the residue from Et_2O–petr ether gave a white solid: yield 4.85 g (86%); mp 91–93°. The analytical sample was obtd from a previous run by recrystn from Et_2O–petr ether. It was dried at 78° (0.07 mm) over P_2O_5 for 20 hr: mp 91–93°; λ_{max} nm ($\epsilon \times 10^{-3}$): 0.1 *N* HCl, 248 (12.3), 301 (8.85); pH 7, 249 (15.9), 297 (8.26); 0.1 *N* NaOH, 274 (9.73), 305 (sh) (3.51); $\bar{\nu}_{max}$ (cm^{-1}): 3230 (NH), 2965, 2930, 2875 (CH), 1730, 1665 (C=O), 1610, 1550, 1480 (C=C, C=N). *Anal.* ($C_{25}H_{37}N_3O_9$) C, H, N.

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Antibacterial Activity of *o*-Amino-*N*-hydroxybenzenesulfonamides†

Ned D. Heindel,* C. C. Ho Ko, Richard B. Birrer, and Joseph R. Merkel

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015. *Received July 9, 1971*

Several reports in the chemical literature have demonstrated the potentiating effect of an NOH moiety on the antibacterial properties of an arylsulfonamide. For example, *N*-hydroxybenzenesulfonamide is more potent against *Mycobacterium tuberculosis* than is benzenesulfonamide[1] and several N^4-acyl-N^1-hydroxybenzenesulfonamides are more effective against β-hemolytic streptococci in mice than is sulfanilamide itself.[2] Furthermore, the SO_2NHOH grouping is well known as a chelator of metal ions[3,4] a property which might be expected to be reflected in enhanced antibacterial effects.[5] However, N^1-hydroxysulfanilamide appears less active than the nor-OH counterpart *in vitro* but of equivalent activity *in vivo* by virtue of a metabolic conversion of sulfanilamide.[6] Tests against *Escherichia coli*[7] and other microorganisms[8] have shown that *o*- and *m*-aminobenzenesulfonamides, lacking the NOH on the sulfonamide group, do not inhibit bacterial growth.

Thus, our observation of significant antibacterial potency in several *o*-amino-*N*-hydroxysulfonamides, appears as a striking example of the activity promoting effects of an NOH function. We have prepared these materials (**1**, **2**, **4**, **5**, **6**) through the intermediacy of the *o*-aminobenzenesulfonyl chlorides and their subsequent reaction with hydroxylamines (H_2NOR) to yield both *N*-OH and *N*-OMe systems. Employing a cyclization method previously applied to ortho-substituted carboxamides and dimethyl acetylenedicarboxylate,[9,10] the 1,2,4-benzothiadiazine (**7**) was prepared. Methylation of this heterocyclic with aq Me_2SO_4 yielded **3**. By a technique described by Wei, *et al.*[11] for condensation of aldehydes with *o*-amino-*N*-hydroxybenzenesulfonamides, *p*-nitrobenzaldehyde and the 2-amino-4,5-dichloro-*N*-hydroxybenzenesulfonamide (**1**) gave the 1,2,4-benzothiadiazine (**8**) in 90% yield.

Biological Activity. Compounds were applied to penicillin assay disks (Schleicher and Schuell Co., 12 mm diam) as either solution or suspension in 95% EtOH to achieve a concn of 4 mg/disk of test substance. The disks were then air-dried and placed on the surface of brain heart infusion agar medium (Difco) which had been seeded with the test organism. The assay plates were incubated at 37° and inhibition zones were measured after 24 and 48 hr (see Table I).

A free *o*-NH_2 and an SO_2NHOR appear to be essential for inhibitory activity since neither the heterocyclics, **7** and **8**, nor the *N*,*N*-Me_2N analog, **3**, displayed any measurable

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