The present report thus extends the work described earlier[3] and further demonstrates that arylhydroxamic acids are to varying degrees selectively inhibitory to nucleic acid synthesis. An interesting feature noted here is that the majority of the compounds which are active *in vitro* are substituted in the 4 position in relation to the hydroxamic acid group. The demonstrated inhibitory action of 4-hydroxybenzoylhydroxamic acid on growth of experimental tumors[4] suggests that this class of compounds should be subjected to screening in various tumor systems *in vivo*.

Glycylureas and Quaternary Salts[1]

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Received June 16, 1969

Although several 1-(*N*,*N*-dialkylglycyl)ureas have been prepared and tested for analgetic properties,[2-6] it seemed worthwhile to prepare a number of such compounds and to convert them into quaternary salts for further physiological testing.

The reaction of chloroacetyl chloride with urea and substituted ureas according to the procedure of Piggott and Rose[2] was utilized in this work to prepare 1-chloroacetylurea and 1-chloroacetyl-3-alkylureas. The reaction of these compounds with secondary amines gave the desired glycylurea derivatives plus some hydantoin. The quaternary salts were readily prepared by reaction of the dialkylaminoacetylureas with various halides. Attempts to prepare *N*-nitroso derivatives of these urea compounds proved futile.

Physiological Activity.—Representative compounds were tested for antibacterial, antiinflammatory, diuretic, shistosomiasis, and trichomonicidal effects.[7] Compounds **12** and **16** were not active against *Trypanosoma cruzi* in chick embryo tissue culture.[8,9] Compound **10**, 1-butyl-3-(chloroacetyl)urea, was cidal when tested *in vitro* against *Trichomonas vaginalis*. Compound **16** was inactive against *T. cruzi* in mice at 0.25% in diet.

Compounds **15** and **16** failed to show activity against measles virus, polio virus, and herpes virus when tested at 100 μg/ml.[10]

TABLE I

SUBSTITUTED UREAS, $RNHCONHCOCH_2R'$

	R	R'	Mp, °C	Yield, %	Formula	Anal.
1	H	Pyrrolidino	150–151	85	$C_7H_{13}N_3O_2$	CHN
2	H	Morpholino	137–138	68	$C_7H_{13}N_3O_3$	N
3	H	Me_2N	148–150	55	$C_5H_{11}N_3O_2$	N
4	H	n-Bu_2N	123–124	88	$C_{11}H_{23}N_3O_2$	N
5	n-Bu	Pyrrolidino	69–70	65	$C_{11}H_{21}N_3O_2$	CHN
6	n-Bu	Piperidino	78–79	93	$C_{12}H_{23}N_3O_2$	CHN
7	Et	Pyrrolidino	84–85	41	$C_9H_{17}N_3O_2$	N
8	Et	Piperidino	85–86	67	$C_{10}H_{19}N_3O_2$	CHN
9	Et	Morpholino	86–88	50	$C_9H_{17}N_3O_3$	N
10	n-Bu	Cl	115–116	80	$C_7H_{14}ClN_2O_2$	N

TABLE II

QUATERNARY SALTS, $RR_2'N^+CH_2CONHCONHR''$

R	R'	R''	X	Mp, °C	Yield, %	Formula	Anal.
CH_2	n-Bu	H	I	195–196	73	$C_{12}H_{26}IN_3O_2$	N
CH_3	$(CH_2)_4$	H	I	160–161	95	$C_{11}H_{24}IN_3O_2$	CHN
$C_6H_5CH_2$	$(CH_2)_4$	H	Cl	185–186	41	$C_{18}H_{28}ClN_3O_2$	N
p-$NO_2C_6H_4CH_2$	$(CH_2)_4$	H	Br	171–172	88	$C_{18}H_{19}BrN_4O_4$	CHN
p-$NO_2C_6H_4CH_2$	$(CH_2)_4$	n-Bu	Br	179–180	95	$C_{18}H_{27}BrN_4O_4$	CHN
p-$NO_2C_6H_4CH_2$	$(CH_2)_5$	n-Bu	Br	150–155	81	$C_{19}H_{29}BrN_4O_4$	CHN
p-$NO_2C_6H_4CH_2$	$(CH_2)_4$	Et	Br	191–192	71	$C_{16}H_{23}BrN_4O_4$	N
p-$NO_2C_6H_4CH_2$	$(CH_2)_5$	Et	Br	150–151	82	$C_{17}H_{25}BrN_4O_4$	N
p-$NO_2C_6H_4CH_2$	Et	H	Br	174–175	94	$C_{14}H_{19}BrN_4O_4$	N

Experimental Section[11]

1-Alkyl-3-(dialkylglycyl)ureas were prepared by refluxing 1 mol of 1-alkyl-3-chloroacetylurea with 2 mol of dialkylamine or cyclic secondary amine in C_6H_6. The products were recrystallized from MeOH or C_6H_6 (see Table I).

These compounds were converted into quaternary salts by heating with the desired halide in MeCN. The salt precipitated and rarely needed to be recrystallized (see Table II).

(11) Melting points were determined in a Thomas-Hoover melting point apparatus with a calibrated thermometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.1% of the theoretical values.

Antitumor Activity of Some Azine and Hydrazone Derivatives of 1,4-Dimethoxy-2-butanone[1,2]

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Received October 29, 1969

During our investigation of the preparation of certain pyridazine derivatives, three intermediates, 1,4-dimethoxy-2-butanone azine (I), ethyl pyruvate azine with 1,4-dimethoxy-2-butanone (II), and 1,4-dimethoxy-2-butanone hydrazone (III), were prepared and found to possess confirmed activity against Walker 256 (intramuscular, 5WM) tumor system in rats[3] (see Table I).

This interesting activity led us to search the literature for compounds of this type with oncolytic activity. It was found that little information has been published relative to hydrazones as anticancer agents and studies of azines as potential antitumor

(1) Supported by a Grant from Parke, Davis & Company and a Faculty Grant from North Texas State University.

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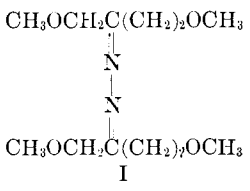
(10) Antiviral screening was carried out by Dr. Frank Schabel, Southern Research Institute, Birmingham, Ala.

(1) This investigation was supported by contract PH 43-65-94 with Chemotherapy, National Cancer Institute, National Institutes of Health.

(2) Presented in part before the Division of Medicinal Chemistry, 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968 (N-055).

(3) Test results were provided by contract screeners of CCNSC.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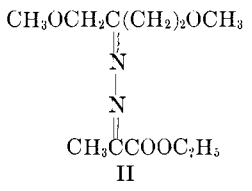
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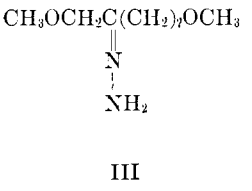
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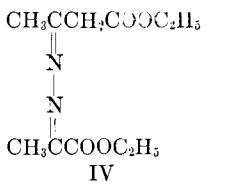
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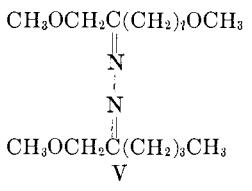
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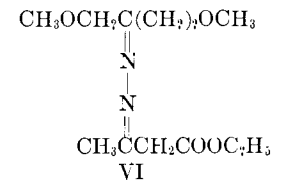
VI

TABLE I

Compounds	Antitumor activity against WA-256: mg/kg	Survivors	Wt. diff., T-C	T/C (%)
I	250	6/6	−27	9
	100	6/6	−14	8
	45	6/6	−9	65
II	200	6/6	−18	18
	100	6/6	−7	72
III	105	6/6	−16	41
	70	6/6	−15	25
	45	6/6	−7	42
	30	6/6	−3	89
1,4-Dimethoxy-4-butanone	400	6/6	−2	60
IV	400	6/6	−3	86

compounds were not reported. Wiley and coworkers[4,5] prepared a series of substituted hydrazones of pyridoxal, indole-3-carboxaldehyde and 2-methoxynaphthaldehyde, but only two of 35 compounds prepared were found to have significant activity against sarcoma 180 in mice.

A survey in the general area of biological activity of azines again revealed little. Some synthetic azine dyes, such as methyl violet and heliotrope, were claimed to have good tuberculostatic effect against human type tubercle bacteria.[6] The molluscacidal activity displayed by azines of certain *p*-benzoquinones[7] was largely attributed to the parent quinones,[7-9] and the well known biological activity of nitrofuran derivatives could possibly be the reason for the antimicrobial activity exhibited by a number of 5-nitro-2-furfural azines.[10,11]

The activity exhibited by compounds I–III is in a way rather unique in that similar activity was not observed by ethyl acetoacetate azine with ethyl pyruvate (IV) nor by 1,4-dimethoxy-2-butanone, the parent compound of I–III. Logically, other azine derivatives of 1,4-dimethoxy-2-butanone, such as compounds V and VI, were prepared for a preliminary structure–activity study. However, the study could not be continued in our laboratory because of the discontinuance of Walker 256 testing system in the general screening.

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Experimental Section

1,4-Dimethoxy-2-butanone Azine (I) and 1,4-Dimethoxy-2-butanone Hydrazone (III).—A solution of 32 g (1 mol) of anhydrous N_2H_4 in 250 ml of anhydrous MeOH was stirred in an ice bath while 33 g (0.25 mol) of 1,4-dimethoxy-2-butanone (prepared by the method of Hennion and Kupiecki[12] from 1,4-butyndiol dimethyl ether[13]) in 50 ml of MeOH was added dropwise over a period of 30 min. The reaction mixture was then stirred at room temperature for 16 hr. Removal of MeOH and excess N_2H_4 followed by fractional distillation gave 22 g (60% yield) of the hydrazone (III), bp 91–92° (5.5 mm), $n^{24}D$ 1.4671, and 11.0 g (17% yield) of the azine (I), bp 138–140° (2.6 mm), $n^{25}D$ 1.4664. *Anal.* ($C_6H_{14}N_2O_4$), C, H, N; ($C_{12}H_{24}N_2O_4$), C, H, N.

Ethyl Pyruvate Azine with 1,4-Dimethoxy-2-butanone (II).—A solution of 16.6 g (0.11 mol) of 1,4-dimethoxy-2-butanone hydrazone (III) in 50 m lof anhydrous MeOH was stirred at 0° while 13.2 g (0.11 mol) of ethyl pyruvate in 50 ml of MeOH was added dropwise over a period of 30 min. The mixture was allowed to stir at room temperature overnight and then distilled to give 19.0 g (70% yield) of the azine, bp 119–120° (0.4 mm), $n^{25}D$ 1.4708. *Anal.* ($C_{11}H_{20}N_2O_4$), C, H, N.

Ethyl acetoacetate azine with ethyl pyruvate (IV) was prepared by a procedure analogous to the foregoing. The product, mp 88–89°, was purified by sublimation at 65° (0.1 mm). *Anal.* ($C_{11}H_{18}N_2O_4$), C, H, N.

1-Methoxy-2-hexanone azine with 1,4-dimethoxy-2-butanone (V) was prepared in an analogous fashion, bp 123–126° (2.3 mm), $n^{25}D$ 1.4628. *Anal.* ($C_{13}H_{26}N_2O_3$), C, H, N.

Ethyl acetoacetate azine with 1,4-dimethoxy-2-butanone (VI) had bp 135–138° (0.35 mm), $n^{25}D$ 1.4938. *Anal.* ($C_{17}H_{22}N_2O_4$), C, H, N.

Acknowledgment.—The authors wish to thank Mr. John Gravatt for his assistance in performing analytical measurements.

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β-Alanyl Thio Esters[1]

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Received October 10, 1969

The introduction of chemically active centers in organic molecules which may serve as alkylating agents has been an area of recent interest in the syntheses of

(1) This investigation was supported in part by National Institutes of Health Research Grant No. CA-08102, National Cancer Institute, and by the North Texas State University Faculty Research Fund.
(2) National Defense Education Act Fellow, Title IV.