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]

PRICE TRUITT AND J. T. WITKOWSKI

Department of Chemistry, North Texas State University, Denton, Texas 76203

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Although several 1-(N_1N-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$_2$R

	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	$C_7H_{13}ClN_2O_2$	N

TABLE II

QUATERNARY SALTS, RR$_2'$N$^+$CH$_2$CONHCONHR″

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	$C_8H_{18}IN_3O_2$	CHN
$C_6H_5CH_2$	$(CH_2)_4$	H	Cl	185–186	41	$C_{14}H_{20}ClN_3O_2$	N
p-$NO_2C_6H_4CH_2$	$(CH_2)_4$	H	Br	171–172	88	$C_{14}H_{19}BrN_4O_4$	CHN
p-$NO_2C_6H_4CH_2$	$(CH_2)_5$	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	$C_{19}H_{28}BrN_4O_4$	CHN
p-$NO_2C_6H_4CH_2$	$(CH_2)_4$	Et	Br	191–192	74	$C_{16}H_{23}BrN_4O_4$	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	$C_{14}H_{21}BrN_4O_4$	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 ±0.4% of the theoretical values.

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

WILLIAM J. HAGGERTY, JR., AND C. C. CHENG

Midwest Research Institute, Kansas City, Missouri 64110

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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

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(3) P. F. Wiley, *J. Amer. Chem. Soc.*, **71**, 1310 (1949).

(4) T. Takahashi, H. Fujimura, and K. Okamura, *Yakugaku Zasshi*, **82**, 1597 (1962); *Chem. Abstr.*, **59**, 611c (1963).

(5) T. Takahashi and K. Ogiu; Japan Patent 6173 (1961); *Chem. Abstr.*, **58**, P10247a (1963).

(6) Y. Matsuo; *Yakugaku Zasshi*, **83** (5) 480 (1963); *Chem. Abstr.*, **59**, 7401e (1964).

(7) These tests were arranged through Dr. Ed Elslager of Parke, Davis and Co., Ann Arbor, Mich.

(8) F. A. Neva, M. F. Malone, and B. R. Meyers, *J. Trop. Med. Hyg.*, **10**, 140 (1961).

(9) F. Hawking, *Trans. Roy. Soc. Trop. Med. Hyg.*, **40**, 345 (1946).

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

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(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.