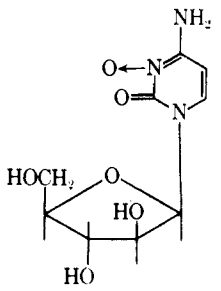
TABLE I
LYMPHOID LEUKEMIA L1210

Host	Dose, mg/kg	Survivors	Animal wt diff ($T - C$)	Tumor evaluation (T/C)	%	Test status
BDF_1	400	6/6	−3.3	11.3/9.0	125	11
BDF_1	40.0	6/6	−1.1	12.3/9.3	132	22P
BDF_1	20.0	6/6	−0.7	12.0/9.3	129	22P
BDF_1	10.0	5/6	−1.8	9.3/9.3	100	22P
BDF_1	5.00	6/6	−0.5	11.5/9.3	123	22P
BDF_1	400	6/6	0.3	16.4/9.8	167	15

itor of this enzyme and to enhance the anticancer effect of Ara-C when both are administered together.[8,9]

These findings prompted us to investigate the rational design of a structural modification of cytosine arabinoside which should provide an increased resistance toward deamination with an increase in anticancer activity. The biological activity of cordycepin, which undergoes a similar enzymatic deamination, can be increased by a facile conversion to cordycepin 1-*N*-oxide.[10] Cordycepin 1-*N*-oxide has been found to be resistant toward this enzymatic deamination and the slow enzymatic reduction back to cordycepin in the tumor cell provides a more efficient administration of cordycepin to the desired site.



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In an attempt to provide similar therapeutic results, cytosine arabinoside 3-*N*-oxide (**1**) was prepared in our laboratory.[11a,b]

Antitumor Evaluation.[12]—The preliminary results obtained from the anticancer testing of cytosine arabinoside 3-*N*-oxide are shown in Table I and evaluation of the activity is in accordance with the criteria of the Cancer Chemotherapy National Service Center. From the testing data available (Table I) at the present time, it is evident that cytosine arabinoside 3-*N*-oxide is a potential inhibitor of lymphoid leukemia L1210.

Experimental Section[13]

Cytosine Arabinoside 3-*N*-Oxide (1).—To a soln of cytosine arabinoside (2.0 g, 8 mmoles)[14] in AcOH (40 ml) at 65° was added *m*-$ClC_6H_4CO_3H$ (5.0 g, 25 mmoles). The reaction mixture was heated at this temp for 1.5 hr and then poured slowly into H_2O (500 ml) with stirring. The insol org acids which pptd were removed by filtration, and the filtrate was evapd to dryness (40°) *in vacuo*. The residue was dissolved in a minimum of 90% aq MeOH and then added dropwise with stirring to EtOAc (300 ml). The granular product was collected by filtration and then triturated with boiling EtOH (25 ml) to remove any traces of starting material. The insol solid was recrystd from a MeOH–EtOAc mixture to give 1.12 g (54%) of product. The *N*-oxide was homogeneous on paper chromatography in solvents A, B, and C and gave a dark red color with $FeCl_3$. An anal. sample was obtained by recrystn from MeOH-EtOAc: mp >150 dec; $[\alpha]^{27}D$ + 109.6° (*c* 1.05, H_2O); λ_{max}^{pH1} 275 nm (ε 9300); λ_{max}^{pH11} 272 (6540), 226.5 (16570); $\lambda_{max}^{H_2O}$ 271 (6480), 223.5 (19600). *Anal.* ($C_9H_{13}N_3O_6$) C, H, N.

The product had R_f values of 0.42, 0.05, and 0.34 on paper chromatography in solvents A, B, and C, resp, as compared with cytosine arabinoside which had R_f values of 0.57, 0.14, and 0.52, resp.

(8) G. W. Camiener, *Biochem. Pharmacol.*, **17**, 1981 (1968).

(9) G. L. Neil, T. E. Moxley and R. C. Manak, Abstracts, Tenth International Cancer Congress, Houston, Texas, May 1970, No. 674.

(10) S. Frederiksen, *Biochim. Biophys. Acta*, **76**, 366 (1963).

(11) (a) This preparation was accomplished by the method of T. J. Delia, M. J. Olsen, and G. B. Brown, *J. Org. Chem.*, **30**, 2765 (1965). (b) G. B. Brown and coworkers have pointed out the chemotherapeutic advantages of *N*-oxides *vs.* the parent compound; see G. Levin and G. B. Brown, *J. Med. Chem.*, **6**, 825 (1963), and G. B. Brown, G. Levin, S. Murphy, A. Sele, H. C. Reilly, G. S. Tarnowski, F. A. Schmid, M. N. Teller, and C. C. Stock, *ibid.*, **8**, 190 (1965).

(12) Testing was performed under the auspices of the Cancer Chemotherapy National Service Center.

(13) Satisfactory anal. data (C, H, N within ±0.4% of theor values) were obtained from Heterocyclic Chemical Corp., Harrisonville, Mo. The melting point was determined on a Thomas-Hoover melting apparatus and is uncorrected. The uv spectra were recorded on a Beckman DK-2 spectrophotometer. The optical rotation was obtained with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Paper chromatograms were run on Whatman No. 1 chromatographic paper using the descending technique. Short-wave uv light (254 nm) was used to detect the spots. Chromatographic solvent systems: A, 1% aq $(NH_4)_2SO_4$–*i*-PrOH, 1:2 (v/v); B, *n*-BuOH satd with H_2O; C, *n*-PrOH–NH_4OH (sp gr 0.90)–H_2O, 6:3:1 (v/v).

(14) The authors wish to thank Drs. H. B. Wood, Jr., and R. E. Engle of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, for the generous gift of cytosine arabinoside monohydrochloride (NSC-63878).

Further Studies in Substituted 4*H*-1,2,4-Triazoles for Possible Hypoglycemic Activity

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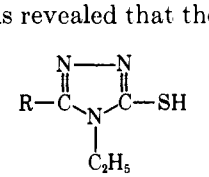
Earlier we reported[1] that 4-ethyl-5-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole-3-thiol (I) and 5-*p*-chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol (II) possess potent and prolonged hypoglycemic activity. Further variations in these compounds revealed that the Et group at position 4 favored this property. The present communication pertains to the replacement of the SH group in po-



I, R = *p*-$H_2NSO_2C_6H_4$
II, R = *p*-ClC_6H_4

(1) M. Y. Mhasalkar, M. H. Shah, S. T. Nikam, K. G. Anantanarayanan, and C. V. Deliwala, *J. Med. Chem.*, **13**, 672 (1970).

TABLE I

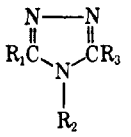
N^1,N^4-DISUBSTITUTED THIOSEMICARBAZIDES

$R_1CONHNHCSNHR_2$

No.	R_1	R_2	Yield, %	Mp, °C	Formula	Analyses
1	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	80	193	$C_{14}H_{11}Cl_2N_3OS$	N, S
2	$4\text{-}NH_2SO_2C_6H_4$	C_6H_5	80	218	$C_{14}H_{14}N_4O_3S_2$	N, S
3	$4\text{-}NH_2SO_2C_6H_4$	$4\text{-}ClC_6H_4$	89	202	$C_{14}H_{13}ClN_4O_3S_2$	N, S
4	$C_6H_5CH_2$	C_2H_5	83	147–148	$C_{11}H_{15}N_3OS$	S
5	$4\text{-}ClC_6H_4CH_2$	C_2H_5	59	178–180	$C_{11}H_{14}ClN_3OS$	S
6	H	C_2H_5	61	144–145	$C_4H_9N_3OS$	N, S
7	CH_3	C_2H_5	89	149–152	$C_5H_{11}N_3OS$	N, S
8	C_2H_5	C_2H_5	77	146–148	$C_6H_{13}N_3OS$	N, S
9	C_2H_5	$4\text{-}ClC_6H_4$	68	169–171	$C_{10}H_{12}ClN_3OS$	N, S

TABLE II

3,4,5-TRISUBSTITUTED 4*H*-1,2,4-TRIAZOLES



No.	R_1 (when $R_2 = C_2H_5$)	R_3 (when $R_2 = C_2H_5$)	Yield, %	Mp, °C	Formula	Analyses	Maximum blood sugar reduction[a] at a dose of 25 mg/kg in rats, % (hr)
10	$4\text{-}ClC_6H_4$	SCH_3	86	118	$C_{11}H_{12}ClN_3S$	C, H, N	19.8 (9)
11	$4\text{-}ClC_6H_4$	SC_2H_5	59	119–121	$C_{12}H_{14}ClN_3S$	C, H, N	31.4 (7), 30.0 (9), 18.9 (24)[b]
12	$4\text{-}ClC_6H_4$	$SC_3H_7(n)$	48	103–105	$C_{13}H_{16}ClN_3S$	N	(−)[c]
13	$4\text{-}ClC_6H_4$	$SC_4H_9(n)$	48	90–91	$C_{14}H_{18}ClN_3S$	C, H, N	10.3 (7)
14	$4\text{-}NH_2SO_2C_6H_4$	SCH_3	52	253–255	$C_{11}H_{14}N_4O_2S_2$	C, H, N	10.6 (7)
15	$4\text{-}NH_2SO_2C_6H_4$	SC_2H_5	61	229–231	$C_{12}H_{16}N_4O_2S_2$	C, H, N	18.3 (7)
16	$4\text{-}NH_2SO_2C_6H_4$	$SC_3H_7(n)$	58	199–201	$C_{13}H_{18}N_4O_2S_2$	N	(−)[c]
17	$4\text{-}ClC_6H_4$	SO_2CH_3	53	132–133	$C_{11}H_{12}ClN_3O_2S$	N	34.9 (9), 19.4 (24)[d]
18	$4\text{-}ClC_6H_4$	$SO_2C_2H_5$	43	101	$C_{12}H_{14}ClN_3O_2S$	N	(−)[c]
19	$4\text{-}ClC_6H_4$	$SO_2C_3H_7(n)$	62	89–90	$C_{13}H_{16}ClN_3O_2S$	C, H, N	(−)[c]
20	$4\text{-}ClC_6H_4$	$SO_2C_4H_9(n)$	49	102–103	$C_{14}H_{18}ClN_3O_2S$	C, H, N	(−)[c]
21	$4\text{-}NH_2SO_2C_6H_4$	SO_2CH_3	48	223	$C_{11}H_{14}N_4O_4S_2$	C, H, N	25.4 (7)[b]
22	$4\text{-}NH_2SO_2C_6H_4$	$SO_2C_2H_5$	39	198–200	$C_{12}H_{16}N_4O_4S_2$	C, H	15.1 (7)
23	$4\text{-}NH_2SO_2C_6H_4$	$SO_2C_3H_7(n)$	39	193–194	$C_{13}H_{18}N_4O_4S_2$	C, H, N	(−)[c]
24	$4\text{-}ClC_6H_4$	H	84	113–114	$C_{10}H_{10}ClN_3$	C, H, N	32.2 (9), 22.2 (24)[d]
25	$4\text{-}ClC_6H_4$	OH	56	199–200	$C_{10}H_{10}ClN_3O$	C, H, N	10.8 (7)
26	$4\text{-}ClC_6H_4$	SO_3H	79	289–291	$C_{10}H_{10}ClN_3O_3S$	C, H	(−)[c]
27	$4\text{-}NH_2SO_2C_6H_4$	H	42	220–222	$C_{10}H_{12}N_4O_2S \cdot HCl$	C, H	(−)[c]
28	$4\text{-}NH_2SO_2C_6H_4$	OH	35	265	$C_{10}H_{12}N_4O_3S$	C, H, N	20.7 (7)
29	$4\text{-}NH_2SO_2C_6H_4$	SO_3H	72	280	$C_{10}H_{12}N_4O_5S_2$	C, H	(−)[c]
30	$C_6H_5CH_2$	SH	68	158	$C_{11}H_{13}N_3S$	C, H, N	22.1 (7)
31	$4\text{-}ClC_6H_4CH_2$	SH	63	139–140	$C_{11}H_{12}ClN_3S$	C, H, N	22.2 (7)
	R_3 = SH						
	R_1	R_2					
32	H	C_2H_5	62	94–95	$C_4H_7N_3S$	C, H, N	18.5 (9), 14.3 (24)
33	CH_3	C_2H_5	75	133–134	$C_5H_9N_3S$	C, H, N	44.9 (7), 50.9 (24)[e]
34	C_2H_5	C_2H_5	77	147	$C_6H_{11}N_3S$	C, H, N	36.2 (9), 2.30 (24)[f]
35	C_2H_5	$4\text{-}ClC_6H_4$	80	187	$C_{10}H_{10}ClN_3S$	C, H, N	(−)[c]
36	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	85	244–245	$C_{14}H_9Cl_2N_3S$	C, H, N	25.4 (7), 6.4 (24)[g]
37	$4\text{-}NH_2SO_2C_6H_4$	C_6H_5	83	289	$C_{14}H_{12}N_4O_2S_2$	C, H, N	(−)[c]
38	$4\text{-}NH_2SO_2C_6H_4$	$4\text{-}ClC_6H_4$	58	251–253	$C_{14}H_{11}ClN_4O_2S_2$	C, H, N	16.3 (7), 3.0 (24)
39	$4\text{-}ClC_6H_4$	C_2H_5					53.7 (9), 34.1 (24)[h]
40	$4\text{-}H_2NSO_2C_6H_4$	C_2H_5					45.3 (9), 36.2 (24)[h]

[a] Figures indicate mean values of 6 rats. [b] 50% survival at 1 g/kg. [c] Inactive. [d] All mice died at 0.5 g/kg. [e] 30% survival at 0.25 g/kg. [f] All mice died at 0.25 g/kg. [g] All mice survived at 3 g/kg. [h] Reported by us.[1]

sition 3 by *S*-alkyl, SO_2-alkyl, H, or OH in order to ascertain its importance. Some other variations in positions 4 and 5 have also been studied.

Chemistry. The alkylthio derivatives of I and II were prepared by treating the Na salt of the mercaptotriazole with alkyl iodides as described by Hoggarth.[2] Conversion of *S*-alkyl derivatives into the corresponding alkylsulfonyl triazoles worked smoothly with $KMnO_4$ or H_2O_2.

Attempts to replace the SH group by OH with H_2O_2 resulted in the formation of 5-sulfonic acid derivatives. The desired OH derivatives were, however, finally obtained by refluxing 3-methylsulfonyl analogs with NaOMe in MeOH. The ir spectra of the resultant compounds showed the presence of a prominent peak at

(2) E. Hoggarth, *J. Chem. Soc.*, 1579 (1950).

1710 cm^{-1} indicating that the compounds were predominantly in the keto form.

The use of Raney Ni in alkaline medium for the replacement of SH by H gave the desired product with II, but with I simultaneous dechlorination also took place. This was confirmed by its identity with the desulfurization product of 4-ethyl-5-phenyl-4*H*-1,2,4-triazole-3-thiol. The use of 20% HNO_3 for desulfurization, however, gave the desired products with both I and II being obtained in better yields and purity.

N^1,N^4-disubstituted thiosemicarbazides (Table I) were prepared by literature methods and were cyclized to obtain the required triazoles (Table II).

Hypoglycemic Activity.—The majority of the compounds in the present series possessed hypoglycemic activity. The replacement of SH in I and II by H or OH either reduced or eliminated the activity. Their SEt derivatives (**11** and **15**) were fairly active while the other thioethers were much less active. Among the alkylsulfonyl analogs, Me derivatives (**17** and **21**) showed some activity, but the higher homologs were inactive. Interchange of the alkyl and aryl groups at positions 4 and 5 of II rendered it (**35**) completely inactive.

The replacement of *p*-chlorophenyl or *p*-sulfamoylphenyl groups by H considerably reduced the activity. However, when this replacement was with Me (**33**), the activity was pronounced and maintained for a long period (50.9% lowering at 24 hr), but the acute toxicity study of this compound and the other more active ones in this series (**11**, **17**, **24**, **33**, and **34**) revealed that they were toxic.

Experimental Section

Screening Method.—The hypoglycemic activity was tested in normal, fasting, albino rats weighing 180–200 g. The drug was administered orally as suspension in 2% gum acacia at a dose level of 25 mg/kg and blood sugar was determined at 1.5, 3, 5, 7, 9, and 24 hr by Somogyi's method[3] using Nelson's reagent.[4]

Chemistry.[5]—*p*-Chlorophenylacetic acid has been obtained in 43% yield from *p*-chloroacetophenone following a modified Wilgerodt reaction,[6] mp 104–105° (lit.[7] mp 103–105°). *Anal.* ($C_8H_7ClO_2$) C, H.

4-Ethyl-5-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole.—4-Ethyl-5-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole-3-thiol (1.42 g) dissolved in 3% $NaHCO_3$ was heated with activated Raney Ni (W-6, *ca.* 3 g) under reflux for 4 hr, cooled, neutralized (HCl), and extd (Et_2O). The product remaining after removal of the solvent was isolated as hydrochloride.

Action of Raney Ni on 5-*p*-Chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol.—5-*p*-Chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol (1.5 g) when treated with activated Raney Ni as above gave a cryst product (Et_2O–C_6H_{14}): yield 0.33 g (30%); mp 115–116°. This was identified as 4-ethyl-5-phenyl-4*H*-1,2,4-triazole, by mmp with an authentic sample prepd from 4-ethyl-5-phenyl-4*H*-1,2,4-triazole-3-thiol by desulfurization with Raney Ni. *Anal.* ($C_{11}H_{11}N_3$) C, H, N.

5-*p*-Chlorophenyl-4-ethyl-4*H*-1,2,4-triazole.—5-*p*-Chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol (1.5 g) was added in small batches to dil HNO_3 (40 ml of 20%) not allowing the temp to rise above 45°. The reaction mixt was maintained at 50° for a further 15 min, cooled, basified (NaOH), and extd (Et_2O). The combined exts were washed (H_2O) and dried (Na_2SO_4) and Et_2O was removed to obtain the title compound: crystd (Et_2O–C_6H_{14}); yield, 0.93 g.

4-Ethyl-5-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole was similarly prepared from 4-ethyl-5-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole-3-thiol in good yields.

5-*p*-Chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-sulfonic Acid.—5-*p*-Chlorophenyl-4-ethyl-4*H*-1,2,6-triazole-3-thiol (2.4 g) dissolved in 8% aq NaOH (25 ml) was treated with H_2O_2 (7.5 ml of 30%), maintaining the temp at 50–60° for 1 hr. It was then cooled and acidified with HCl (pH 4), and the solid was collected by filtration and crystd (H_2O).

5-*p*-Chlorophenyl-4-ethyl-3-methylthio-4*H*-1,2,4-triazole.—MeI (2 ml, 0.32 mole) was added to 5-*p*-chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol (5.9 g, 0.25 mole) dissolved in dil aq NaOH and stirred vigorously for 15 min during which turbidity developed and suddenly a white solid sepd. After allowing it to stand for 1 hr, the solid was collected by filtration, washed (H_2O), dried, and crystd (EtOH); yield 3.8 g.

5-*p*-Chlorophenyl-4-ethyl-3-methylsulfonyl-4*H*-1,2,4-triazole.—5-*p*-Chlorophenyl-4-ethyl-3-methylthio-4*H*-1,2,4-triazole (1.0 g) dissolved in AcOH (15 ml) was treated with H_2O_2 (3 ml of 30%) by heating on a steam bath for 90 min. Additional H_2O_2 (1 ml) was added and heated for a further 30 min. The mixt was then evapd to dryness under reduced pressure and the residue crystd (EtOH) to get white shining needles. Oxidation with $KMnO_4$ in AcOH gave the same product in 50% yield.

5-*p*-Chlorophenyl-4-ethyl-3-hydroxy-4*H*-1,2,4-triazole.—5-*p*-Chlorophenyl-4-ethyl-3-methylsulfonyl-4*H*-1,2,4-triazole (1.43 g) was refluxed with NaOMe in MeOH (0.28 g of Na in 25 ml of MeOH) for 8 hr. MeOH was distd off and the residue was dissolved in H_2O, neutralized with HCl (pH 7.5), and evapd to dryness. The residue was extd with EtOH and crystd (80% EtOH) to yield white needles; yield, 0.68 g.

Acknowledgments.—The authors wish to thank Mr. M. T. Jaokar and coworkers for the microanalyses and Dr. N. K. Dutta, Director, Haffkine Institute, for his interest in the work.

(3) M. Somogyi, *J. Biol. Chem.*, **160**, 69 (1945).

(4) N. Nelson, *ibid.*, **153**, 375 (1944).

(5) The melting points were taken in open capillary tubes with partial immersion thermometer and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within 0.4% of the theoretical values.

(6) E. Schwenk and E. Bloch, *J. Amer. Chem. Soc.*, **64**, 3051 (1942).

(7) (a) P. Petrenko-Kritschenko, *Ber.*, **25**, 2240 (1892); (b) F. von Straus, *Justus Liebigs Ann. Chem.*, **393**, 317 (1912).

Benzocycloalka[1,2-*c*]pyridazones

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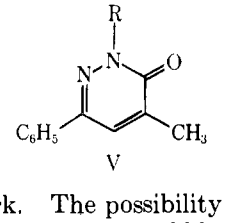
The varied pharmacological activities that have been reported by Laborit and coworkers[1] for the phenylpyridazone system V have prompted us to investigate the potential of this structural combination in a more con-



V

strained framework. The possibility then existed that the less flexible arrangement would lead to more specific and/or more potent activity.

Chemistry.—All the pyridazones listed in Table I were prepared by the synthetic route shown in Scheme I. The most efficient route to the N-substituted pyr-

(1) (a) H. Laborit, C. G. Wermuth, B. Weber, B. Delbane, C. Chekler, C. Baron, and H. Rosengarten, *Agressologie*, **6**, 415 (1965). (b) H. Laborit, B. Weber, C. Baron, B. Delbane, and H. Pavlovichova, *ibid.*, **6**, 463 (1965). (c) H. Laborit, B. Weber, B. Delbane, and C. Baron, *ibid.*, **6**, 483 (1965).