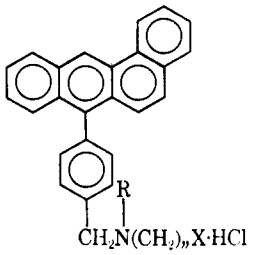
anthracene and have them screened for possible antitumor activity.

Of the several possible approaches, it appeared, based on our experience with benz[a]anthracene derivatives,[6] that the best approach would be to attach the mustard after the polycyclic system had been built. Therefore 7-(4-methylphenyl)benz[a]anthracene[7] was photochemically converted into 7-(4-bromomethylphenyl)benz[a]anthracene. This was treated with an amino alcohol leading to the polycyclic amino alcohols shown in Table I which were isolated as hydrochlorides. These were converted into the corresponding mustards.

TABLE I
ALCOHOLS AND MUSTARDS DERIVED FROM 4-BENZ[a]ANTHRACEN-7-YLBENZYLAMINE



R	X	n	Yield, %	Mp, °C	Formula[a]
CH_3	OH	2	80	202–203	$C_{28}H_{25}NO \cdot HCl$
C_2H_5	OH	2	80	227–228	$C_{29}H_{27}NO \cdot HCl$[b]
CH_2CH_2OH	OH	2	80	184–185	$C_{29}H_{27}NO_2 \cdot HCl$[c]
H	OH	3	80	218–219	$C_{28}H_{26}NO \cdot HCl$
CH_3	Cl	2	75	209–210	$C_{28}H_{24}ClN \cdot HCl$
C_2H_5	Cl	2	75	220–221	$C_{29}H_{26}ClN \cdot HCl$
CH_2CH_2Cl	Cl	2	70	203–204	$C_{29}H_{25}Cl_2N \cdot HCl$[d]
H	Cl	3	90	244–245	$C_{28}H_{24}ClN \cdot HCl$[e]

[a] All compds were analyzed for C, H, Cl, N. [b] C: calcd, 78.8; found, 78.3. [c] C: calcd, 76.0; found, 75.5. [d] C: calcd, 70.4; found, 70.9. [e] C: calcd, 75.3; found 74.8.

Experimental Section[8]

7-(4-Bromomethylphenyl)benz[a]anthracene.—To a soln of 64 g (0.20 mole) of 7-(4-methylphenyl)benz[a]anthracene[7] in 800 ml of CCl_4 heated under reflux, there was added 3 g of benzoyl peroxide followed by 36 g of NBS (excess), added in small portions. The soln, while being irradiated with two 200-W lamps, was refluxed for 90 min after all the NBS had been added, then cooled, and filtered. The filtrate was concd to 200 ml and filtered, and the filtrate was taken to dryness. The yellow solid was crystd from heptane and gave 64g (80%) of white rhombic crystals, mp 158–159°. *Anal.* ($C_{25}H_{17}Br$) C, H, Br.

***p*-Benz[a]anthracen-7-yl-*N*-(2-hydroxyethyl)-*N*-methylbenzylamine·HCl.**—To a soln of 10 g (0.025 mole) of 7-(4-bromomethylphenyl)benz[a]anthracene in 200 ml of C_6H_6 there was added 2 ml of *N*-methylethanolamine and the mixture was refluxed for 4 hr. The soln was cooled, washed (H_2O) 3 times, and dried ($MgSO_4$). When ethereal HCl was added, the product pptd and was recrystd from dry EtOH.

***p*-Benz[a]anthracen-7-yl-*N*-(2-chloroethyl)-*N*-methylbenzylamine·HCl.**—The above amino alcohol (10 g, 0.023 mole) was added to 500 ml of $CHCl_3$ and heated under reflux. Excess pure SO_2Cl_2 was then added slowly and the mixture was refluxed for 90 min. Removal of the solvent and excess SO_2Cl_2 left a solid which was crystd from dry EtOH.

***p*-Benz[a]anthracen-7-yl-*N*-{2-[(2-chloroethyl)thio]ethyl}-*N*-methylbenzylamine·HCl.**—To a hot soln of the above mustard (10 g, 0.022 mole) in $CHCl_3$ was added 5.0 g (0.064 mole) of 2-mercaptoethanol dissolved in NaOEt and 4 g of Na in 100 ml of EtOH. The soln was refluxed for 2 hr and then cooled and poured into H_2O. The product was extd with Et_2O, dried ($MgSO_4$), ethereal HCl was added, and the mixture was cooled overnight (refrigerator). The solid was filtered and dissolved in 200 ml of $CHCl_3$, excess SO_2Cl_2 was added, and the mixture was refluxed for 2 hr. The solvent and excess SO_2Cl_2 were distd, and the residue was recrystd 3 times from EtOH, yielding 7.2 g (65%), mp 182–183.[9] *Anal.* ($C_{30}H_{28}ClNS \cdot HCl$), C,[10] H, Cl, N, S.

***p*-Benz[a]anthracen-7-ylbenzyl 2-Chloroethyl Sulfide.**—To a soln of 10 g (0.025 mole) of 7-(4-bromomethylphenyl)benz[a]anthracene in EtOH was added 5.0 g (0.065 mole) of 2-mercaptoethanol dissolved in NaOEt. The soln was refluxed for 2 hr, cooled, and poured into H_2O. The product was extd with Et_2O, the soln dried, and the solvent distd, leaving an oil which was crystd from EtOH giving the alcohol as bright yellow plates, mp 116–117°, 8.4 g (85%). *Anal.* ($C_{27}H_{22}OS$) C, H, S. This alcohol was dissolved in $CHCl_3$ and excess SO_2Cl_2 was added. The soln was refluxed for 10 min and then taken to dryness under reduced pressure. The resulting oil was crystd from EtOH and gave 7.0 g (80%) of product, mp 108–109°. *Anal.* ($C_{27}H_{21}ClS$) C, H, Cl, S.[11]

Biological Testing.—All the mustards were tested by CCNSC against L-1210 lymphoid leukemia and none was found to be active.

(6) F. A. Vingiello, L. Ojakaar, and R. Kelsey, *J. Med. Chem.*, **8**, 144 (1955).

(7) F. A. Vingiello, A. Borkovec, and J. Shulman, *J. Amer. Chem. Soc.*, **77**, 2320 (1955).

(8) All melting points were taken on a Fisher-Johns melting apparatus 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.

(9) Two additional mixed N and S mustards were prepared: *p*-benz[a]anthracen-7-yl-*N*-{2[(2-chloroethyl)thio]ethyl}-*N*-ethylbenzylamine·HCl, ($C_{31}H_{30}ClNS \cdot HCl$) C, H, Cl, N, S, mp 153–154° (70%); *p*-benz[a]anthracen-7-yl-*N*-{3-[(2-chloroethyl)thio]propyl}benzylamine·HCl, ($C_{30}H_{28}ClNS$) C: calcd, 71.1; found, 68.0. Although a satisfactory C analysis could not be obtained, this compound was included in the antitumor screen. Anal. was satisfactory for H, Cl, N, S, mp 211–212° (60%).

(10) C: calcd, 71.1; found, 65.7. Although a satisfactory C anal. could not be obtained, this compd was included in the antitumor screen.

(11) Cl: calcd, 8.6; found, 8.1. S: calcd, 7.8; found, 7.3.

Synthesis and Anticancer Activity of Cytosine Arabinoside 3-*N*-Oxide (Ara-C 3-*N*-Oxide)[1]

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Cytosine arabinoside[3] has been shown to undergo a rapid enzymatic deamination in man to form arabinofuranosyluracil, an inactive metabolite.[4–7] The inhibition of pyrimidine nucleoside deaminase, the enzyme which causes this process, has been the subject of much study. Tetrahydrouridine (THU, H_4-U, 3,4,5,6-tetrahydrouridine) has been shown to be an effective inhib-

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(2) The recipient of a University of Utah Research Committee Fellowship, 1968–1970.

(3) Synonyms for cytosine arabinoside are: Ara-C, cytarabine, and 1-β-D-arabinofuranosylcytosine.

(4) G. W. Camiener and C. G. Smith, *Biochem. Pharmacol.*, **14**, 1405 (1965).

(5) R. V. Loo, M. J. Brennan, and R. W. Talley, *Proc. Amer. Ass. Cancer Res.*, **6**, 41 (1965).

(6) R. J. Papac, W. A. Creasy, P. Calabresi, and A. D. Welch, *ibid.*, **6**, 50 (1965).

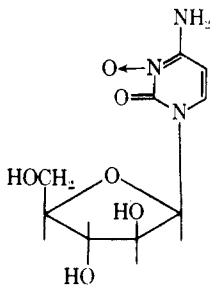
(7) W. A. Creasey, R. J. Papac, M. E. Markiuo, P. Calabresi, and A. D. Welch, *Biochem. Pharmacol.*, **15**, 1417 (1966).

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.

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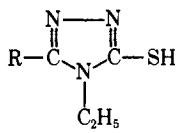
Earlier we reported[1] that 4-ethyl-5-*p*-sulfamoylphenyl-4*H*-1,2,4-triazole-3-thiol (I) and 5-*p*-chlorophenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol (II) possess potent and prolonged hypoglycemic activity. Further variations in these compounds revealed that the Et group at position 4 favored this property.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

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