e. *2,6-Dichloroquinoxaline* (IX). A 200-mg. sample of recrystallized VIII was treated with 3 ml. of phosphorus oxychloride for 10 min. at 90°. The excess phosphorus oxychloride was removed by distillation. The oily residue was mixed with ice water and the precipitate thus formed was removed and recrystallized from ethanol. The white crystalline product weighed 100 mg., m.p. 153–155°.

Anal. Calcd. for $C_8H_4N_2Cl_2$: C, 48.2; H, 2.0; N, 14.1; Cl, 35.7. Found: C, 47.81; H, 1.87; N, 13.16; Cl, 35.28.

f. *2-Aminoquinoxaline.* A 2.75-g. sample of alloxazine was degraded in 75% sulfuric acid in the same manner as indicated for III above. In this case the amount of unchanged material was 1.18 g., giving a yield of 68% (0.68 g.). The yellow solid was recrystallized from benzene:ether, giving long, needleshaped crystals melting at 155–157°. In contrast to 2-amino-7-chloroquinoxaline, the 2-aminoquinoxaline is more soluble in benzene than ether.

Anal. Calcd. for $C_8H_7N_3$: C, 66.1; H, 4.83; N, 29.0. Found: C, 68.5; H, 5.1; N, 28.5.

Comparison of physical properties. 1. *Ultraviolet spectra.* Table III gives the ultraviolet spectral data of compounds III, X, IV, IX, V, XI, and VI.

These data indicate the similarity of the related compounds and the fact that the substitution of the chlorine does cause some alteration in the absorption spectra.

2. *Chromatographic behavior.* Table IV gives the R_f values of the compounds described here using circular paper chromatography and two solvent systems. By using two solvent systems, it is possible to determine some aspects of structure. Thus, in the case of IV and IX, Solvent B shows a distinct difference in R_f values whereas Solvent A did not. The change from VI to VII is evident in the R_f in each solvent solvent.

TABLE IV

CHROMATOGRAPHIC CHARACTERISTICS

Compound	No.	R_f[a] A[b]	R_f[a] B[c]	Ultraviolet Fluorescence
8-Chloroalloxazine	III	0.81	0.39	Yellow-gold
Alloxazine	X	0.74	0.26	Gold
2-OH-6-Cl-Quinoxaline-3-carboxyureide	IV	0.65	0.51	Green-yellow
2-OH-Quinoxaline-3-carboxyureide	IX	0.67	0.36	Gold
2-NH_2-7-Cl-quinoxaline	V	0.90	0.88	Light blue
2-NH_2-quinoxaline	XI	0.85	0.81	Light blue
2-OH-6-Cl-quinoxaline	VI	0.90	0.69	Light blue
2-6-dichloroquinoxaline	VII	—	0.97	Dark blue

[a] R_f values measured from spot of origin to center of band. Location of bands determined by fluorescence under ultraviolet lamp. Solvents: [b] A. *n*-Butyl alcohol, 6; pyridine, 4; water, 3 (v./v./v.). [c] B. *n*-Butyl alcohol, 50; piperidine, 1; water, 10 (v./v./v.).

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KALAMAZOO, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] LVII. Synthesis of Alkylating Agents Derived from 6-Amino-6-deoxy-D-glucose and 5-Amino-5-deoxy-D-ribose

ELMER J. REIST, ROLAND R. SPENCER, MARY E. WAIN, IRENE G. JUNGA, LEON GOODMAN, AND B. R. BAKER

Received December 27, 1960

The synthesis of a series of one-armed mustards of 6-amino-6-deoxy-D-glucose is described in order to investigate the effect of structure on the antitumor activity. The effect of change in the sugar on antitumor activity was also investigated by the synthesis of the two-armed and one-armed mustards of 5-amino-5-deoxy-D-ribose.

An earlier paper in this series[2] presented a rationale for the design of specific enzyme inhibitors. As part of the rationale, it was proposed that a nitrogen mustard, attached to a substrate as carrier, might operate as a specific, irreversible enzyme inhibitor. It was further suggested that a "one-armed" mustard could be as good as, or possibly even better than, the corresponding "two-armed" mustard as an alkylating agent. A later paper[3] described the synthesis for biological evaluation of a "one-armed" mustard, a "two-armed" mustard, and a "mono" mustard of 6-amino-6-deoxy-D-glucose, namely 6-[(2-chloroethyl)ethylamino]-6-deoxy-D-glucose hydrochloride (I), 6-[bis(2-chloroethyl)amino]-6-deoxy-D-glucose hydrochloride (II), and 6-(2-chloroethylamino)-6-deoxy-D-glucose hydrochloride (III), respectively.

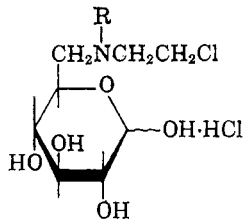
The one-armed mustard (I) and two-armed mustard (II) were both inactive against Sarcoma 180, and Adenocarcinoma 755.[4] The one-armed mustard (I) showed considerable activity against Leukemia

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, see L. O. Ross, W. W. Lee, M. G. M. Schelstraete, L. Goodman, and B. R. Baker, *J. Org. Chem.*, 26, 3021 (1961).

(2) H. F. Gram, C. W. Mosher, and B. R. Baker, *J. Am. Chem. Soc.*, 81, 3103 (1959).

(3) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, 82, 2025 (1960).

(4) We wish to thank Dr. Joseph Greenberg, and staff of this Institute for the test data, performed under contract with the Cancer Chemotherapy National Service Center.



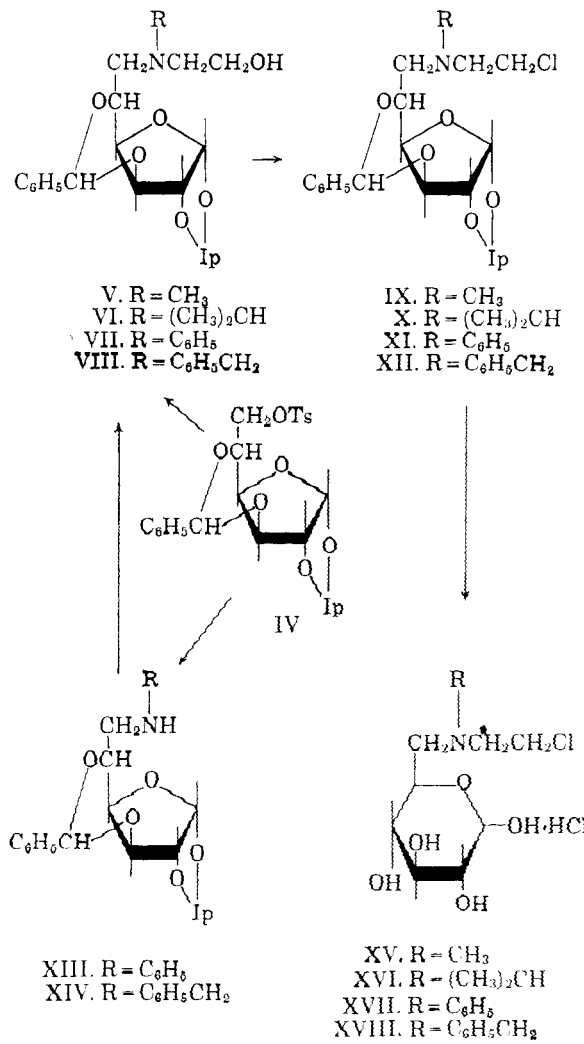
I. R = C_2H_5
II. R = CH_2CH_2Cl
III. R = H

L-1210 compared with the two-armed mustard (II), which had borderline activity on this tumor. The monochloroethyl derivative (III) was inactive on all three tumors.

There are few cases in which a comparison between a two-armed mustard and a one-armed mustard on the same carrier has been made. In two examples which have been reported, the one-armed mustard was either inactive,[5] as in the case of phenylalanine mustards, or its activity was borderline,[6] as in the benzimidazole mustards. In neither case was it possible to demonstrate any clear-cut selectivity of the one-armed mustard over the corresponding two-armed mustard. The pronounced activity of I against Leukemia L-1210 and its apparent superiority to the two-armed mustard (II) in this tumor made it desirable to prepare additional one-armed mustards of 6-amino-6-deoxy-D-glucose in order to investigate the structural limitations of such monofunctional alkylating agents.

The one-armed mustards chosen for this purpose were the methyl (XV), isopropyl (XVI), phenyl (XVII), and benzyl (XVIII) mustards. Their synthesis and biological activity is the subject of this paper. Also included is the synthesis and biological activity of the two-armed and ethyl one-armed mustards of 5-amino-5-deoxy-D-ribose in order to investigate the effect of a change in the sugar carrier on biological activity.

The synthesis of the various one-armed mustards of 6-amino-6-deoxy-D-glucose followed the same general route outlined in the previous paper on this subject.[3] Thus, the displacement of the tosylate group of 3,5-*O*-benzylidene-1,2-O-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (IV) with 2-methylaminoethanol gave an 82% yield of the crystalline 3,5-*O*-benzylidene-6-deoxy-6-[(2-hydroxyethyl)methylamino] - 1,2 - *O* - isopropylidene-α-D-glucofuranose (V). A 76% yield of crystalline 3,5-*O*-benzylidene-6-[(2-chloroethyl)methylamino]-6 - deoxy - 1,2 - *O* - isopropylidene - α - D - glucofuranose (IX) was obtained from the reaction of V with thionyl chloride in refluxing dichloromethane. Hydrolysis of the blocked mustard (IX) with 6*N* hydrochloric acid at about 100°, followed by



V. R = CH_3
VI. R = $(CH_3)_2CH$
VII. R = C_6H_5
VIII. R = $C_6H_5CH_2$

IX. R = CH_3
X. R = $(CH_3)_2CH$
XI. R = C_6H_5
XII. R = $C_6H_5CH_2$

XIII. R = C_6H_5
XIV. R = $C_6H_5CH_2$

XV. R = CH_3
XVI. R = $(CH_3)_2CH$
XVII. R = C_6H_5
XVIII. R = $C_6H_5CH_2$

lyophilization of the reaction mixture, gave a quantitative yield of 6-[(2-chloroethyl)methylamino]-6-deoxy-D-glucose hydrochloride (XV) as an amorphous foam which was homogeneous on paper chromatography[7] and was analytically pure.

Displacement of the tosylate of IV with 2-isopropylaminoethanol in the presence of potassium carbonate at 155° for three hours gave a 76% yield of crystalline 3,5-*O*-benzylidene-6-deoxy-6 - [(2 - hydroxyethyl)isopropylamino] - 1,2 - *O*-isopropylidene-α-D-glucofuranose (VI). The addition of potassium carbonate to this reaction resulted in much less darkening during the displacement and gave a product that was much easier to purify. Treatment of VI with thionyl chloride in refluxing dichloromethane gave a 79% yield of crystalline 3,5-*O*-benzylidene-6-[(2-chloroethyl)isopropylamino] - 6 - deoxy - 1,2 - *O* - isopropylidene-α-D-glucofuranose (X). Conventional hydrolysis[3]

(5) F. Bergel and J. A. Stock, *J. Chem. Soc.*, 90 (1959).
(6) W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *J. Org. Chem.*, 24, 1827 (1959).

(7) The paper chromatograms were run by the descending technique on Whatman No. 1 paper, with *n*-butyl alcohol–acetic acid–water (4:1:5). Spots were detected by an aniline citrate spray. Glucose was used as a standard and spot locations were expressed as R_g units with glucose at R_g 1.00.

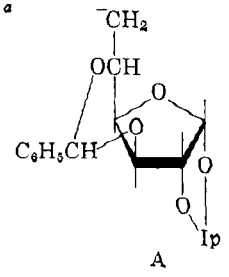
TABLE I

BLOCKED ω-(2-HYDROXYETHYL)AMINO SUGARS

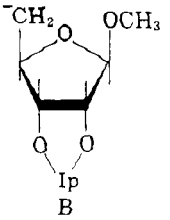
$$R{-}N(R')CH_2CH_2OH$$

No.	R	R'[a]	Method	M.P.	$[\alpha]_D^{27-33°}$	Yield, %	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
V	CH_3	A	I[b]	134–135°	19° (0.48% in chloroform)	82[c]	62.5	62.4	7.45	7.53	3.83	3.77
VI	$(CH_3)_2CH$	A	I[b,d]	105–106°	2.8° (1% in chloroform	76[e]	64.1	64.1	7.94	7.81	3.56	3.58
VII	C_6H_5	A	II[f]	112–113°	22° (0.27% in chloroform	65[c]	67.4	67.4	6.84	6.71	3.28	3.24
VIII	$C_6H_5CH_2$	A	II[g]	56–58°	33° (0.46% in chloroform	91[h]	68.0	67.6	7.08	7.32	3.17	3.32
XX	H	B	I[b]	—[i]	−58° (1% in ethanol)	57	53.4	53.3	8.56	8.54	5.66	5.54
XXI	C_2H_5	B	I[b]	[j]	−69° (1% in ethanol)	90	56.7	56.6	9.15	9.23	5.09	5.19
XXII	$HOCH_2CH_2$	B	I[b]	—[k]	−70° (1% in ethanol)	57	53.6	52.9	8.65	8.75	4.81	4.79

[a]



A



B

[b] Method I—procedure as described for the synthesis of 3,5-*O*-benzylidene-6-deoxy-6-[bis(2-hydroxyethyl)amino]-1,2-*O*-isopropylidene-α-D-glucofuranose.[3] [c] Recrystallized from absolute ethanol. [d] 1 mole of potassium carbonate was added to the reaction mixture. [e] Recrystallized from petroleum ether (b.p. 62–70°) containing a trace of absolute ethanol. [f] Method II—Procedure for the preparation of VII is described in experimental section. [g] Prepared from XIV and ethylene oxide in an autoclave at 150° for six hours by the procedure described for the preparation of VII. [h] Recrystallized from ether–petroleum ether.[9] [i] B.p. 114–120° (0.02 mm.). [j] B.p. 110–115° (0.06 mm.). [k] B.p. 170–174° (0.05 mm.), Vargha *et al.*,[8] reported b.p. 174–176° (0.02 mm.) $[\alpha]_D^{20}$ −71.2° (5% in methanol).

of X afforded 6-[(2-chloroethyl)isopropylamino]-6-deoxy-D-glucose hydrochloride (XVI) as a chromatographically homogeneous[7] and analytically pure foam.

The preparation of 3,5-*O*-benzylidene-6-deoxy-6-[*N*-(2-hydroxyethyl)anilino]-1,2-*O*-isopropylidene-α-D-glucofuranose (VII) by the displacement of the tosylate of IV by 2-anilinoethanol was unsuccessful. Although the infrared spectrum of the crude product suggested that the tosylate displacement had occurred at least in part, the removal of the last traces of 2-anilinoethanol was very difficult and no crystalline product could be obtained. The synthesis of VII from IV could be effected, however, in two steps *via* 6-anilino-3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (XIII). Thus, treatment of IV with aniline and potassium carbonate at 155° for three hours gave an 81% yield of crystalline XIII. The hydroxyethylation of XIII with ethylene oxide in benzene was unusually difficult and required a temperature of 190° for twenty-two hours to effect the conversion of XIII to crystalline VII in 65% yield. The over-all yield of the hydroxyethylanilino derivative (VII) from the tosylate (IV) was 52% by this 2-step sequence. Treatment of the hydroxyethylanilino derivative (VII) with thionyl chloride gave an oil which contained sulfur and was probably a chlorosulfite of VII. The use of phosphoryl chloride as the chlorinating agent was successful and a 45% yield of crystalline 3,5-*O*-benzylidene-6-[*N*-(2-chloroethyl)anilino]-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (XI) was obtained. Removal of the blocking groups with 6*N* hydrochloric acid gave the anilino mustard (XVII) as a sirup which analyzed well and was homogeneous on paper chromatography.

The synthesis of 6-[benzyl(2-chloroethyl)amino]-6-deoxy-D-glucose hydrochloride (XVIII) was accomplished by a sequence similar to that used for the synthesis of the anilino mustard (XVII). The displacement of the tosylate of IV by benzylamine proceeded in 74% yield to 6-benzylamino-3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopro-

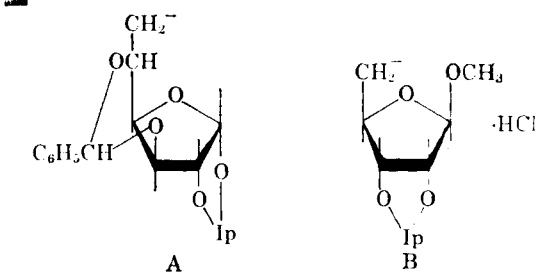
TABLE II

BLOCKED ω-AMINO SUGAR MUSTARDS

$$R{-}N{-}CH_2CH_2Cl$$
$$\quad\quad|$$
$$\quad\quad R'$$

No.	R	R'[a]	M.P.	$[\alpha]_D^{25-30°}$	Yield, %	Carbon		Hydrogen		Chlorine		Nitrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
IX[b]	CH_3	A	116–116.5°	0° (0.71% in chloroform)	76[c]	59.5	59.6	6.78	6.99	9.26	9.47	3.65	3.98
X[b]	$(CH_3)_2CH$	A	72–73°	0° (1% in chloroform)	79[c]	61.3	61.7	7.33	6.98	8.63	8.45	3.41	3.36
XI[d]	C_6H_5	A	130–131°	44° (1% in chloroform)	45[e]	64.6	64.7	6.29	6.51	7.98	7.86	3.15	3.22
XII[b]	$C_6H_4CH_3$	A	79–81°	−3.8° (1% in chloroform)	78[g]	65.7	65.2	6.53	6.63	7.72	7.72	3.05	3.17
XXIII[f]	H	B	165–166°	−23° (0.4% in methanol)	77[h]	43.7	43.6	6.95	7.00	23.5	23.6	4.64	5.04
XXIV[f]	C_2H_5	B	118–119°	−19° (0.5% in methanol)	64[h]	47.2	47.4	7.57	7.65	21.6	22.1	4.23	4.42
XXV[f]	$ClCH_2CH_2$	B	125–126°[i]	−24° (0.4% in methanol)	64[f]	42.8	42.8	6.60	6.75	29.1	29.2	3.85	3.86

[a]

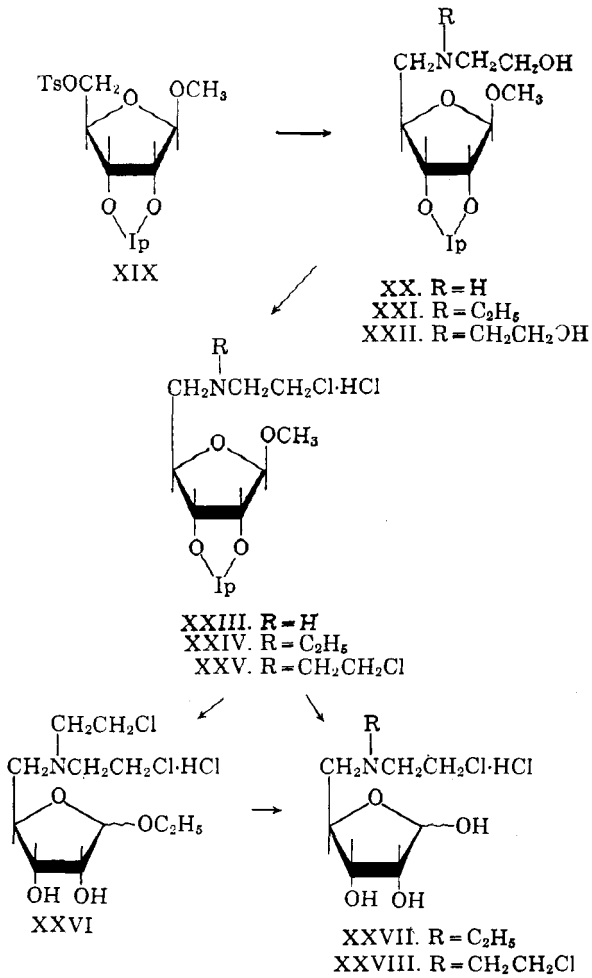


A

B

[b] Prepared from the corresponding 2-hydroxyethylamine and thionyl chloride by the procedure used for the preparation of 3,5-*O*-benzylidene-6-[(2-chloroethyl)ethylamino]-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose.[1] [c] Recrystallized from absolute ethanol. [d] Prepared from VII by the procedure used for the preparation of 3,5-*O*-benzylidene-6-[(2-chloroethyl)ethylamino]-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[3] with phosphoryl chloride substituted for thionyl chloride. [e] Recrystallized from petroleum ether-ethanol (33:1). [f] Prepared as the free base from the corresponding 2-hydroxyethylamine and thionyl chloride by the procedure used for the preparation of 3,5-*O*-benzylidene-6-[(2-chloroethyl)-ethylamino]-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose,[3] then purified and isolated as the hydrochloride. [g] Recrystallized from acetone. [h] Recrystallized from acetone-ether (1:3). [i] Vargha *et al.*[8] reported m.p. 127–128°, $[\alpha]_D^{20}$ −7.6° (1% in chloroform). [j] Recrystallized from acetone-ether (2:3).

pylidene-α-D-glucofuranose (XIV), which was hydroxyethylated in 91% yield to 6-[benzyl(2-hydroxyethyl)amino] - 3,5 - *O* - benzylidene - 6-deoxy - 1,2 - *O* - isopropylidene - α - D - glucofuranose (VIII). The difference in the ease of hydroxyethylation of the benzylamine (XIV) compared with the phenylamine (XIII) was noteworthy. Thus, while the phenylamine required a temperature of 190° for twenty-two hours for complete hydroxyethylation, hydroxyethylation of the benzylamine (XIV) was complete in six hours at 150°. The difference between these two series was also evidenced in the behavior of the 2-hydroxyethylamines (VII and VIII) toward thionyl chloride. Thus the *N*-(2-hydroxyethyl)phenylamine (VII) gave a chlorosulfite with thionyl chloride, but the *N*-(2-hydroxyethyl)benzylamine (VIII) gave the desired crystalline chloro derivative (XII) in 78% yield. Hydrochloric acid hydrolysis of XII gave the benzyl mustard (XVIII) as a chromatographically homogeneous[7] and analytically pure sirup.



The nitrogen mustards of 5-amino-5-deoxy-D-ribose were prepared by a similar set of transformations, starting with methyl 2,3-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-β-D-ribofuranoside (XIX). The displacement of the tosylate of XIX by 2-aminoethanol, 2-ethylaminoethanol, and 2,2′-iminodiethanol gave the corresponding 2-hydroxyethylamines (XX–XXII) in yields of 57%, 90%, and 57%, respectively. Reaction of the hydroxyethylamines (XX–XXII) with thionyl chloride in refluxing dichloromethane gave the blocked mustards, isolated as their crystalline hydrochlorides (XXIII–XXV), in yields of 77%, 64%, and 64% respectively.

The hydrolysis of the blocking groups of the monochloroethylamine (XXIII) was unsuccessful. The product obtained was largely insoluble in water and appeared to be polymeric from its behavior on paper chromatography. Hydrolysis of the blocking groups on the one-armed mustard (XXIV) and two-armed mustard (XXV) with 6*N* hydrochloric acid, using the conventional conditions,[3] proceeded satisfactorily to give the respective mustards (XXVII and XXVIII) as amorphous foams which were homogeneous on paper chromatography[7] and were analytically pure.

Vargha and co-workers[8] have reported the preparation of the blocked two-armed mustard (XXV) by the same sequence as described in this paper. They observed that hydrolysis of XXV with 5*N* hydrochloric acid afforded a sirup with a positive reducing sugar test, but did not otherwise identify the product. Treatment of this sirup with absolute ethanol in an effort to crystallize the mustard gave instead of XXVIII a crystalline ethyl glycoside (XXVI) of unspecified anomeric configuration. In the present work, the ethyl glycoside (XXVI) could also be prepared directly from the blocked mustard (XXV) by treatment with ethanolic hydrochloric acid. When prepared in this fashion, the ethyl glycoside (XXVI) was a more convenient precursor to the unblocked mustard (XXVIII) than was the blocked mustard (XXV). This was due primarily to the greater ease of purifying the ethyl glycoside (XXVI) by recrystallization as compared with the purification of XXV.

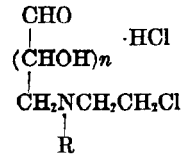
Biological results.[4] The six mustards were evaluated against Sarcoma 180, Adenocarcinoma 755, and Leukemia L-1210 and preliminary data are available. The methyl mustard (XV) had a response similar to that of the ethyl mustard (I) in that it was active against Leukemia L-1210. The isopropyl mustard (XVI), phenyl mustard (XVII), and benzyl mustard (XVIII) were toxic but inactive against all three tumors.

A similar spectrum was observed in the mustards containing D-ribose as the carrier. The bis-mustard (XXVIII) was active against Leukemia L-1210 and Adenocarcinoma 755. The one-armed ethyl mustard (XXVII) was active against Leukemia L-1210 but did not demonstrate any superiority to the bis-mustard (XXVIII) in this tumor.

(8) L. Vargha, Ö. Fehér, and S. Lendvai, *Acta. Chim. Hung.*, 19, 307 (1959).

TABLE III

ω-AMINO SUGAR MUSTARDS



No.[a]	n[b]	R	R_g[c]	Carbon		Hydrogen		Chlorine		Nitrogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
XV	4	CH_3	0.77	37.0	36.3	6.50	6.46	24.3	24.7	4.79	4.72
XVI	4	$(CH_3)_2CH$	1.5	41.3	41.5	7.20	7.26	22.2	22.2	4.37	4.30
XVII	4	C_6H_5	4.3	45.0[e]	45.0	6.17	6.44	19.1	19.1	3.76	3.61
XVIII	4	$C_6H_5CH_2$	2.9	48.9	48.5	6.25	6.75	19.3	19.3	3.80	3.86
XXVII	3	C_2H_5	1.14[d]	37.9[e]	38.2	6.70	6.75	27.7	28.0	4.91	5.17
XXVIII[f]	3	$ClCH_2CH_2$	1.14[d]	34.8	35.0	5.84	5.90	34.3	34.4	4.51	4.52

[a] The following mustards were prepared from the blocked mustards by the procedure described for the preparation of 6-[bis(2-chloroethyl)amino]-6-deoxy-D-glucose (II).[3] [b] When n = 4, the sugar has the glucose configuration. When n = 3, the sugar has the ribose configuration. [c] Calculated as monohydrate. [d] Ribose had R_g 1.32. [e] Calculated as 1¼ HCl. The amount of retained HCl over one mole depended on the drying efficiency. [f] Prepared by the hydrolysis of XXVI.

EXPERIMENTAL

6-Anilino-3,5-O-benzylidene-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (XIII) was prepared in 81% yield from 100 g. of tosylate (IV) and 100 g. of potassium carbonate in 1 l. of aniline by the procedure described for the preparation of 3,5,*O*-benzylidene-6-deoxy-6-[bis(2-hydroxyethyl)amino] 1,2,-*O*-isopropylidene-α-D-glucofuranose.[3]

Three recrystallizations from absolute ethanol gave the analytical sample, m.p. 184–185°, $[\alpha]_D^{24}$ 0° (1% in chloroform); λ_{max}^{Nujol} 2.95, 6.55 (NH), 13.34, 14.29 μ (monosubstituted phenyl); there was no tosyl band at 8.5 μ.

Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.9; H, 6.57; N, 3.65. Found: C, 69.1; H, 6.56; N, 3.72.

3,5-O-Benzylidene-6-deoxy-6-[N-(2-hydroxyethyl)anilino]-1,2-O-isopropylidene -α-D-glucofuranose (VII). A solution of 56 g. of 6-anilino-3,5-*O*-benzylidene-6-deoxy-1,2,-*O*-isopropylidene-α-D-glucofuranose (XIII) and 83 ml. of ethylene oxide in 83 ml. of dry benzene was heated in an autoclave at 190° for 22 hr. The reaction mixture was cooled to room temperature, then diluted with 380 ml. of benzene. The benzene solution was washed with three 140-ml. portions of water, then dried over magnesium sulfate, and evaporated to dryness *in vacuo* to leave a tan-colored solid. Two recrystallizations from absolute ethanol gave 39.5 g. (65%) of white crystals, m.p. 110–112°, which were suitable for use in the next step.

6-Benzylamino-3,5-O-benzylidene-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (XIV) was prepared from 81.5 g. of 3,5-*O*-benzylidene-1,2,-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose (IV) and 650 ml. of benzylamine in the manner described for the preparation of 3,5-*O*-benzylidene-6-deoxy-6-[bis-(2-hydroxyethyl)amino]-1,2,-*O*-isopropylidene-α-D-glucofuranose.[3] Recrystallization of the crude product from 200 ml. of absolute ethanol gave 52 g. (74%) of crystalline product, m.p. 107–108°, which was satisfactory for use in the next step.

A previous preparation gave the analytical sample, m.p. 107–108°; $[\alpha]_D^{28}$ 0° (1% in chloroform); λ_{max}^{Nujol} 3.01 (NH, weak), 6.55 (NH), 13.20, 14.30 μ (monosubstituted phenyl).

Anal. Calcd. for $C_{22}H_{27}NO_5$: C, 69.5; H, 6.85; N, 3.52. Found: C, 69.4; H, 7.06; N, 3.50.

Methyl 2,3-O-isopropylidene-5-O-(p-tolylsulfonyl)-β-D-ribofuranoside (XIX). The method of Levene and Stiller[11] was used with modifications for the preparation of methyl 2,3-*O*-isopropylidene-D-ribofuranoside. A mixture of 39.4 g. of D-ribose and 78.8 g. of anhydrous copper sulfate in 750 ml. of acetone and 40 ml. of methanol was cooled to 0°, then 2 ml. of 96% sulfuric acid was added dropwise with stirring while the temperature was maintained below 20°. The reaction mixture was stirred at 35–40° for 40 hr. protected from moisture. At the end of this time, the reaction mixture was filtered and the filtrate was neutralized to *p*H 7 with ammonium hydroxide. The resulting precipitate was filtered through a Celite pad and the filtrate was evaporated *in vacuo* to a dark sirup. The sirup was treated with 200 ml. of ether and the ether solution was filtered through a Celite pad, then evaporated to dryness. The last traces of acetone and methanol were removed by the addition and removal *in vacuo* of 20 ml. of benzene. The resulting pale yellow sirup, 61 g. (110%), was suitable for the next step; λ_{max}^{film} 2.90 (OH), 7.23 (CH_3), 9.10, 9.57 μ (C—O—C).

The method of Shunk *et al.*[12] was used with modifications for the preparation of XIX. A solution of 16.3 g. (0.08 mole) of crude methyl 2,3-*O*-isopropylidene-D-ribofuranoside in 25 ml. each of dry toluene and dry pyridine was cooled to 10° and 23.0 g. (0.12 mole) of *p*-tolylsulfonyl chloride was added in batches with stirring and continued cooling at a rate which kept the temperature below 10°. After the addition was complete, the reaction was left at room temperature overnight, then poured into 250 ml. of saturated aqueous sodium bicarbonate. The mixture was extracted with three 25-ml. portions of chloroform. The combined chloroform extracts were washed with 20 ml. of water, then dried over magnesium sulfate and evaporated *in vacuo* to give 30.2 g. of a tan sirup. Crystallization from 150 ml. of methanol gave 14.2 g. (57% from D-ribose) of XIX as white crystals, m.p. 84–85°; λ_{max}^{Nujol} 8.25 (CH_3), 8.48 μ (OSO_2); there was no OH band at 2.9 μ.

Shunk *et al.*[12] reported a m.p. of 83.5–84.5° for XIX obtained in a 31% yield from D-ribose

Ethyl 5-[bis(2-chloroethyl)amino]-5-deoxy-D-ribofuranoside hydrochloride (XXVI). A solution of 7.81 g. of methyl 5-[bis(2-chloroethyl)amino]-5-deoxy-2,3-*O*-isopropyli-

(9) The petroleum ether had a boiling range of 62–70°. It is supplied by the Special Products Division, Phillips Petroleum Co., Bartlesville, Okla.

(10) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured with a Standard Polarimeter model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solution.

(11) P. A. Levene and E. T. Stiller, *J. Biol. Chem.*, 104, 299 (1934).

(12) C. H. Shunk, J. B. Lavigne, and K. Folkers, *J. Am. Chem. Soc.*, 77, 2210 (1955).

dene - β - D - ribofuranoside hydrochloride (XXV) in 40 ml. of absolute ethanol containing 1 ml. of concd. aqueous hydrochloric acid was heated on a steam bath for 0.5 hr., then cooled at 0° overnight to give 4.2 g. (58%) of white crystals, m.p. 138–140°, $[\alpha]_D^{25}$ −25° (1% in methanol); λ_{max}^{Nujol} 2.98, 3.08 (OH), 3.98, 4.08 μ (NH^+).

Vargha *et al.*[8] reported m.p. 142–144°, $[\alpha]_D^{20}$ −14.2° (1% in methanol).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Potential Anticancer Agents. X. Nitrogen Mustards Derived from 4-Quinoline- and 1-Naphthalenemethanols[1,2]

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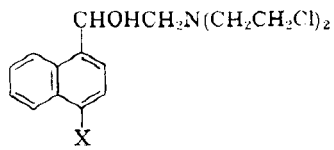
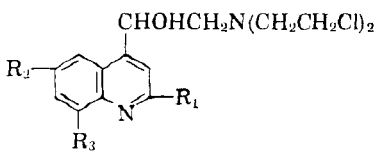
Synthesis of a series of nitrogen mustards derived from 4-quinoline- and 1-naphthalenemethanols is described.

In a preceding paper[3] the synthesis of a number of nitrogen mustards derived from standard antimalarial drugs (specifically the 8-aminoquinolines) has been described and the rationale underlying this approach to the management of neo-plastic disease has been indicated. Several of the substances described have shown high orders of activity against experimental animal tumors.[4] Paralleling this investigation we have investigated the synthesis of representative nitrogen mustards derived from 1-naphthalene- and 4-quinolinemethanols. (I–VII).



I. X = F
II. X = Cl



III $R_1 = C_6H_5$; $R_2 = R_3 = H$
IV $R_1 = R_3 = H$; $R_2 = OCH_3$
V $R_1 = C_6H_5$; $R_2 = H$; $R_3 = Cl$
VI $R_1 = C_6H_5$; $R_2 = R_3 = Cl$
VII $R = p\text{-}C_6H_4Cl$; $R_2 = R_3 = H$

Incentive for this study was provided by early reports of encouraginging activity against experimental tumors shown by alkylating agents derived from other types of antimalarials[5] as well as by the low order of activity reported for certain dialkylamino-4-naphthalenemethanols in which an alkylating function was absent.[6]

Choice of the methanol mustards to be prepared, particularly in the quinoline series, was based on pharmacological data accumulated with the analogous antimalarials.[7]

The reaction sequences employed in general paralleled those previously described for the preparation of aminomethanol derivatives of naphthalene and quinoline carrying alkyl groups on the amino nitrogen[8–11] with some modifications. In the naphthalene series these are represented by VIII–XI. Reduction of 4-fluoro-ω-bromo-1-acetonaphthone (VIII, X = F) with sodium borohydride proceeded smoothly to give α-bromomethyl-4-fluoro-1-naphthalenemethanol (IX, X = F) which could not be induced to crystallize and for which no other suitable method of purification could be found. Confirmation of the structure assigned to IX (X = F) was provided by its infrared spectrum, its chemical behavior and by the nature of the products prepared from it. The infrared spectrum showed a broad band at 3425 cm.$^{-1}$ (OH) but,

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(1) The work here reported was supported by a research grant (CY-2961) from the National Cancer Institute to the University of Michigan.

(2) For paper IX in this series see W. R. Vaughan, M. S. Habib, R. S. McElhinney, N. Takahashi and J. A. Waters, *J. Org. Chem.*, **26**, 2392 (1961).

(3) R. C. Elderfield and E. F. LeVon, *J. Org. Chem.*, **25**, 1576 (1960).

(4) Private communication from Dr. Ralph L. Jones, Jr., Jackson Memorial Hospital, University of Miami, Miami, Florida.

(5) For a summary of recent data see H. J. Creech, E. Breuninger, R. F. Hankowitz, Jr., G. Polsky and M. L. Wilson, *Cancer Research*, **20**, 471 (1960).

(6) Private communication from Dr. R. B. Ross, Cancer Chemotherapy National Service Center, Bethesda, Maryland.

(7) *Survey of Anti-malarial Drugs*, 1941–1945, F. Y. Wiselogle (editor), J. W. Edwards, Inc., Ann Arbor, Mich., 1946, Vol. 1, p. 142.

(8) R. E. Lutz *et al.*, *J. Am. Chem. Soc.*, **68**, 1813 (1946).

(9) S. Winstein *et al.*, *J. Am. Chem. Soc.*, **68**, 1831 (1946).

(10) S. Winstein *et al.*, *J. Org. Chem.*, **11**, 150 (1946).

(11) T. L. Jacobs *et al.*, *J. Org. Chem.*, **11**, 21 (1946).