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Quantitative Structure–Activity Relationships in 2,5-Bis(1-aziridinyl)-*p*-benzoquinone Derivatives against Leukemia L-1210

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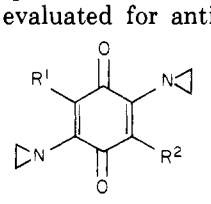
Antileukemic activities of more than 30 2,5-bis(1-aziridinyl)-*p*-benzoquinones (**4**) were correlated against well-defined physicochemical constants. These compounds were evaluated against lymphoid leukemia L-1210 in BDF_1 mice. The best equations obtained exhibited a linear dependence on the hydrophobic constant, π. Characteristic aspects of the equations are that the larger the relative hydrophilicity of the drugs the stronger the antileukemic activity will be and that the more hydrophilic compounds have a greater chemotherapeutic index. Steric and electronic effects were also determined to be important. Based on the correlations, three compounds (**11**, **15** and **19**) were designed, synthesized, and biologically evaluated.

Considerable progress has been shown by Hansch and others in quantitative structure–activity relationships (QSAR) in the area of antitumor agents.[1-4] Although a number of 2,5-bis(1-aziridinyl)-*p*-benzoquionones have been synthesized and evaluated against various tumors,[5-8] no QSAR has been established.

Our laboratory has been engaged for a number of years in the search for better drugs in this series. Syntheses of *p*-benzoquinone derivatives were proceeded[5-9] in modification of mitomycin C (**1**), and finally the more potent and less toxic agent carboquone, 2,5-bis(1-aziridinyl)-3-[2-(carbamoyloxy)-1-methoxyethyl]-6-methyl-*p*-benzoquinone (**2**), was chosen for the market under the trade name "Esquinon"[10] (Figure 1).

In the present study, antileukemic activities of 39 2,5-bis(1-aziridinyl)-*p*-benzoquinones were correlated against well-defined physicochemical constants.

Method. The prepared 2,5-bis(1-aziridinyl)-*p*-benzoquinones (**4**) were evaluated for antileukemic activity



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against lymphoid leukemia L-1210 in BDF_1 mice according to the method of CCNSC.[11,12] L-1210 cells (10^5) were intraperitoneally inoculated. The compounds were dissolved in dimethyl sulfoxide, and sterile physiological saline was added to make injectable solutions. Four kinds of biological data were obtained: minimum effective dose (MED) and optimal dose (OD) on a chronic treatment schedule (12 days, QD 1–12) and those in single injection (Q1D, day 1 only), where MED is the dose giving a 40% increase in life span (ILS) compared to the controls and OD the dose giving maximum ILS. If a dose exceeding the OD is administered, the ILS decreases. Therefore, OD/MED might be defined as a kind of chemotherapeutic index (CI). *C* in the correlation equations is the mol/kg description of MED and OD. Most of the biological data has been previously published.[5]

The substituent constants used in this work are from the compilation by Pomona College[13] or were calculated from these values. Hydrophobic constants π_1 for R^1 and π_2 for R^2 were employed. Many examples of the calculation of π values have been reported.[13b,14]

Based on the molecular refractivity constants[13a] (MR_1 for R^1 and MR_2 for R^2), R^1 and R^2 were assigned to the groups which satisfy the condition $MR_1 \leq MR_2$. We have scaled MR values by 0.1 to obtain equiscalar with π.

In this paper, terms in MR values are defined as those accounting for steric effects and not dispersion forces (in fact, molecular refractivity constants were proportional to molecular volume constants in the Lorenz–Lorenz equation[13a]) as a working hypothesis. Then, $\pi_{1,2}$ ($\pi_1 + \pi_2$) and $MR_{1,2}$ ($MR_1 + MR_2$) were used to estimate the total hydrophobicity and steric effects of R_1 and R_2.

Results and Discussion

Most of the effective compounds were substituted by alkyl functions at R^1 and R^2 (**4**). Since a compound with an acetyl group did not show potent activity, other de-

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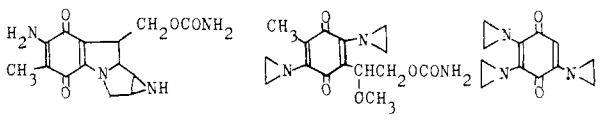


1 Mitomycin C 2 Carboquone 3 Trenimon

Cont. Inj.			
MED	0.90 mg/kg	0.13	0.082
OD	2.0	0.70	0.15
C.I.(^{OD}/MED)	2.2	5.4	1.8

Figure 1.

rivatives with strong electron-attracting functions were not prepared. Considering the biomedical mechanism of alkylating anticancer agents, hydrophobic effects might be evaluated to be related to the transport to the target organ and the binding force with the tumor cells. Steric as well as electronic effects were considered important in the electrophilic reactions with the nucleophilic functions of biomacromolecules, for example, DNA.

In the first estimation of the correlation, several compounds (**1**, **12**, **36**, and **38** in Table I) with strong electronic effects were eliminated. All combinations of six variables, $\pi_{1,2}$, $MR_{1,2}$, π_1, π_2, MR_1, and MR_2, were correlated to each series of antileukemic activities shown in Table I. Mathematically best equations among physicochemically meaningful correlations obtained are summarized in Table II. Statistically significant equations were obtained for the four test systems, showing a linear dependence on $\pi_{1,2}$ (eq 1, 3, 5, and 6; Table II). Addition of a term in MR further improved the equations for the chronic treatment (eq 2 and 4; Table II).

The most characteristic aspect of the former equations is that they suggested that drugs with greater relative hydrophilicity should have stronger antileukemic activity. In contrast to the finding of Hansch et al.[1-3] of a parabolic relationship correlating log P with the activity in a series of nitrosourea derivatives, we found a linear relationship between π and the activity in the present series of compounds. In a set of seven compounds of N-substituted 5-aziridino-2,4-dinitrobenzamide, Khan and Ross[15] found a linearity between log P and activity without mathematical treatment. Considering these results, one might suspect a possibility of the intrinsic difference between nitrosoureas and aziridinyl compounds, although both of them are biomedically defined as alkylating agents. Therefore, it remains to be demonstrated whether additional hydrophilic agents than the present compounds have more activity.

The next most characteristic aspect is the difference between the slopes of eq 1, 3, 5, and 6 (Table II) which imply the coefficients of $\pi_{1,2}$. The slopes of MED (eq 1 and 5; Table II) in each dose regimen are sharper than those of OD (eq 3 and 6; Table II). The ratio of MED to OD or the difference between them in logarithmic terms was defined as a chemotherapeutic index (CI, see Method). The CI of **1**, **2**, and trenimon (**3**) after chronic injection are 2.2, 5.6, and 1.8, respectively (see Figure 1). Now one might recognize the superiority of **2** to **1** and trenimon without doubt.

The four equations were exhibited graphically in Figure 2. The more hydrophilic compound has the larger chemotherapeutic index in the chronic as well as the single-injection regimens, therefore, the more active the larger chemotherapeutic index.

All compounds were then used in deriving equations, and electronic substituent constants, $\mathcal{F}$ and $\mathcal{R}$[13a] were

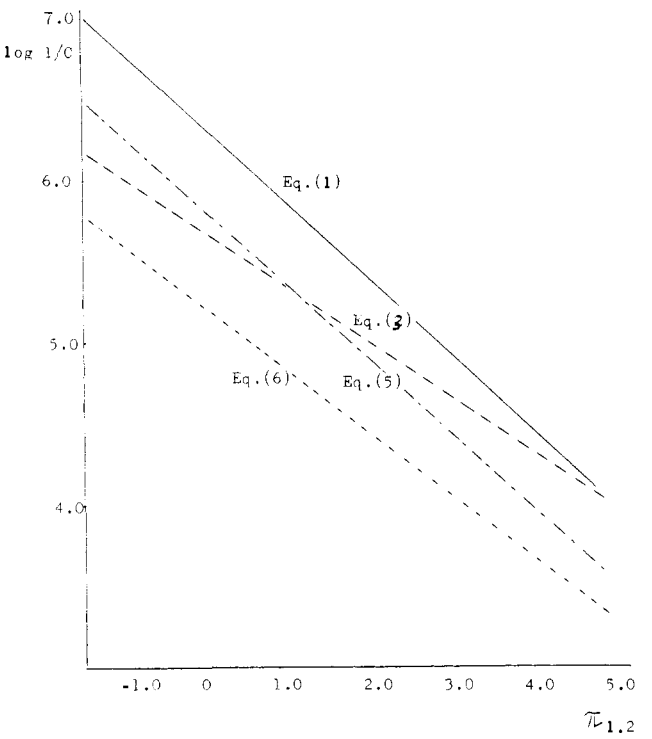


Figure 2. Graphical description of eq 1, 3, 5, and 6.

employed to account for the electronic effects of R^1 and R^2, where $\mathcal{F}$ and $\mathcal{R}$ were the sum of field effects and resonance effects. In this time, no compounds were eliminated from the correlation. A few compounds among 39 were not determined biologically in each set. Now, all combinations of eight variables were correlated to four sets of antileukemic activities shown in Table I. Equations obtained were summarized in Table III. In addition to the hydrophobic and steric effects, electronic effects were proved to be very significant. The positive $\mathcal{F}$ and $\mathcal{R}$ or the electron-attracting R^1 and R^2 were shown in mathematical form to make the compounds less active. Equations 8, 10, 12, and 14 (Table III) exhibited the best correlation in each set in view of lower standard deviations, greater correlation coefficients, and significant F statistics. These equations are superior to 2, 4, 5, and 6 both in terms of accounting for all data and because of the greater correlation coefficients.

In order to examine the relative characteristics of the variables of all 39 compounds used in deriving eq 7–14 (Table III), the squared correlation matrix was computed (Table IV). The correlations between MR values (MR_1, MR_2, and $MR_{1,2}$) and those between π values (π_1, π_2, and $\pi_{1,2}$) are somewhat high, but the relations between MR and π values are quite orthogonal, except for MR_1 and π_1, which was not so highly correlated. Although π and MR were highly collinear in regular congeners of organic compounds,[16] the collinearity was broken in the present set, and MR values accounting for steric effects were proved important independently from π values, especially in eq 2, 4, 8, and 10. On the other hand, the significance of π values was definitely confirmed in all equations.

Based on the equations which include only π terms, three more hydrophilic compounds were designed, synthesized, and biologically evaluated. Those are 2,5-bis(1-aziridinyl)-3,6-bis(2-hydroxy-1-methoxyethyl)-*p*-benzoquinone (**11**), 2,5-bis(1-aziridinyl)-3,6-bis[2-(carbamoyloxy)-1-methoxyethyl]-*p*-benzoquinone (**15**), and 2-(3,6-bis(1-aziridinyl)-5-methyl-*p*-benzoquinon-2-yl)-2-methoxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside

Table I. Constants Used for Deriving eq 1-14

			chron inj, log 1/C				sing. inj, log 1/C									
			MED		OD		MED		OD							
no.[e]	R^1	R^2	obsd	calcd[a]	obsd	calcd[b]	obsd	calcd[c]	obsd	calcd[d]	$MR_{1,2}$	$\pi_{1,2}$	π_2	MR_1	$\mathcal{F}$	R
1	CH_3	$COCH_3$					3.94	4.12	3.48	3.72	1.69	−0.05	−0.55	0.57	0.28	0.07
2	C_6H_5	C_6H_5	4.33	4.05	4.14	3.81			3.53	2.97	5.08	3.92	1.96	2.54	0.16	−0.16
3	CH_3	$(CH_2)_3C_6H_5$	4.47	4.61	4.21	4.57	3.93	4.23	3.60	3.99	4.50	3.66	3.16	0.57	−0.08	−0.26
4	C_5H_{11}	C_5H_{11}	4.63	4.31	4.52	4.27	4.07	3.58	3.62	3.50	4.86	5.00	2.50	2.43	−0.08	−0.26
5	$CH(CH_3)_2$	$CH(CH_3)_2$	4.77	5.26	4.59	4.96	4.36	4.74	4.14	4.38	3.00	2.60	1.30	1.50	−0.08	−0.26
6	CH_3	$CH_2C_6H_5$	4.85	5.18	4.69	4.92	4.74	4.77	4.26	4.37	3.57	2.51	2.01	0.57	−0.12	−0.14
7	C_3H_7	C_3H_7	4.92	5.15	4.44	4.89	4.32	4.55	4.14	4.23	3.00	3.00	1.50	1.50	−0.08	−0.26
8	CH_3	$CH_2OC_6H_5$	5.15	5.21	4.71	4.87	4.68	4.61	3.89	4.23	3.79	2.16	1.66	0.57	−0.04	−0.13
9	$(CH_2)_2OCON(CH_3)_2$	$(CH_2)_2OCON(CH_3)_2$	5.16	5.21	4.85	4.83			4.62	5.07	6.14	0.72	0.36	3.07	−0.08	−0.26
10	C_2H_5	C_2H_5	5.46	5.57	5.09	5.20	4.94	5.01	4.79	4.58	2.06	2.00	1.00	1.03	−0.08	−0.26
11	CH_3	$(CH_2)_2OCH_3$	5.57	5.98	5.42	5.50	5.19	5.51	5.12	4.95	2.28	1.03	0.53	0.57	−0.08	−0.26
12	OCH_3	OCH_3	5.59	5.74	5.17	5.27	4.81	4.79	4.32	4.45	1.58	−0.04	−0.02	0.79	0.52	−1.02
13	CH_3	$CH(CH_3)_2$	5.60	5.58	5.21	5.23	4.96	5.13	4.69	4.67	2.07	1.80	1.30	0.57	−0.08	−0.26
14	C_3H_7	$CH(OCH_3)CH_2OCONH_2$	5.63	6.03	5.07	5.37	5.01	5.18	4.64	4.66	4.24	0.98	−0.52	1.50	−0.04	−0.13
15	CH_3	$(CH_2)_2CON(CH_3)_2$					5.09	5.59	4.84	5.01	3.64	0.86	0.36	0.57	−0.08	−0.26
16	CH_3	CH_3	5.66	5.99	5.36	5.51	5.36	5.52	4.79	4.96	1.14	1.00	0.50	0.57	−0.08	−0.26
17	H	$CH(CH_3)_2$	5.68	5.56	5.37	5.13	5.16	5.02	4.59	4.54	1.60	1.30	1.30	0.10	−0.04	−0.13
18	CH_3	$CH(OCH_3)CH_2CH_3$	5.68	5.54	5.33	5.09	5.26	4.91	4.84	4.46	2.75	1.53	1.03	0.57	−0.04	−0.13
19	C_3H_7	$(CH_2)_2OCONH_2$	5.68	5.96	5.23	5.43	4.90	5.30	4.42	4.80	3.56	1.45	−0.05	1.50	−0.08	−0.26
20	$(CH_2)_2OCH_3$	$(CH_2)_2OCH_3$	5.69	5.59	5.31	5.17	5.18	5.51	4.71	4.95	3.42	1.03	0.53	1.71	−0.08	−0.26
21	C_2H_5	$CH(OC_2H_5)CH_2OCONH_2$	5.76	5.93	5.24	5.33	5.40	5.18	4.64	4.66	4.23	0.98	−0.02	1.03	−0.04	−0.13
22	CH_3	$(CH_2)_2OCOCH_3$	5.78	5.87	5.78	5.43					2.78	1.23	0.73	0.57	−0.08	−0.26
23	CH_3	$(CH_2)_3$ dimer	5.82	5.47	5.39	5.16					1.96	2.00	1.50	0.57	−0.08	−0.26
24	CH_3	C_2H_5	5.86	5.73	5.37	5.33	5.16	5.28	4.52	4.78	1.60	1.50	1.00	0.57	−0.08	−0.26
25	CH_3	$CH(OCH_2CH_2OCH_3)CH_2OCONH_2$	6.03	6.33	5.39	5.62	5.45	5.65	4.96	5.01	4.45	0.01	−0.49	0.57	−0.04	−0.13
26	CH_3	$CH_2CH(CH_3)OCONH_2$	6.14	6.12	5.79	5.60	5.86	5.64	5.18	5.05	3.09	0.75	0.25	0.57	−0.08	−0.26
27	C_2H_5	$CH(OCH_3)CH_2OCONH_2$	6.16	6.19	5.22	5.50	5.62	5.42	4.92	4.84	3.77	0.48	−0.52	1.03	−0.04	−0.13
28	CH_3	$CH(C_2H_5)CH_2OCONH_2$	6.18	5.86	5.66	5.42	6.03	5.40	5.20	4.87	3.55	1.25	0.75	0.57	−0.08	−0.26
29	CH_3	$CH(OC_2H_5)CH_2OCONH_2$	6.18	6.09	5.22	5.46	5.53	5.42	4.62	4.84	3.77	0.48	−0.02	0.57	−0.04	−0.13
30	CH_3	$(CH_2)_3OCONH_2$	6.18	6.02	5.93	5.53	5.55	5.55	5.48	4.98	3.09	0.95	0.45	0.57	−0.08	−0.26
31	CH_3	$(CH_2)_2OCONH_2$	6.21	6.28	5.75	5.70	5.83	5.79	5.46	5.16	2.63	0.45	−0.05	0.57	−0.08	−0.26
32	C_2H_5	$(CH_2)_2OCONH_2$	6.25	6.12	5.48	5.57	5.98	5.55	4.88	4.98	3.09	0.95	−0.05	1.03	−0.08	−0.26
33	CH_3	$(CH_2)_2OH$	6.39	6.34	5.79	5.74	5.89	5.84	5.25	5.20	1.78	0.34	−0.16	0.57	−0.08	−0.26
34	CH_3	$CH(CH_3)CH_2OCONH_2$	6.41	6.12	5.71	5.60	5.93	5.64	5.31	5.05	3.09	0.75	0.25	0.57	−0.08	−0.26
35	CH_3	$CH(OCH_3)CH_2OCONH_2$	6.41	6.35	5.66	5.64	5.81	5.67	5.03	5.03	3.31	−0.02	−0.52	0.57	−0.04	−0.13
36	H	$N(CH_2)_2$	6.45	6.54	6.19	6.16	6.02	6.19	5.74	5.60	1.66	0.18	0.18	0.10	0.10	−0.92
37	$(CH_2)_2OH$	$(CH_2)_2OH$	6.54	6.12	6.05	5.56	5.93	6.16	5.60	5.45	2.42	−0.32	−0.16	1.21	−0.08	−0.26
38	CH_3	$N(CH_2)_2$	6.77	6.56	6.21	6.25	6.54	6.30	5.69	5.72	2.13	0.68	0.18	0.57	0.06	−1.05
39	CH_3	$CH(OCH_3)CH_2OH$	6.90	6.40	5.75	5.67	6.05	5.72	5.27	5.07	2.47	−0.13	−0.63	0.57	−0.04	−0.13

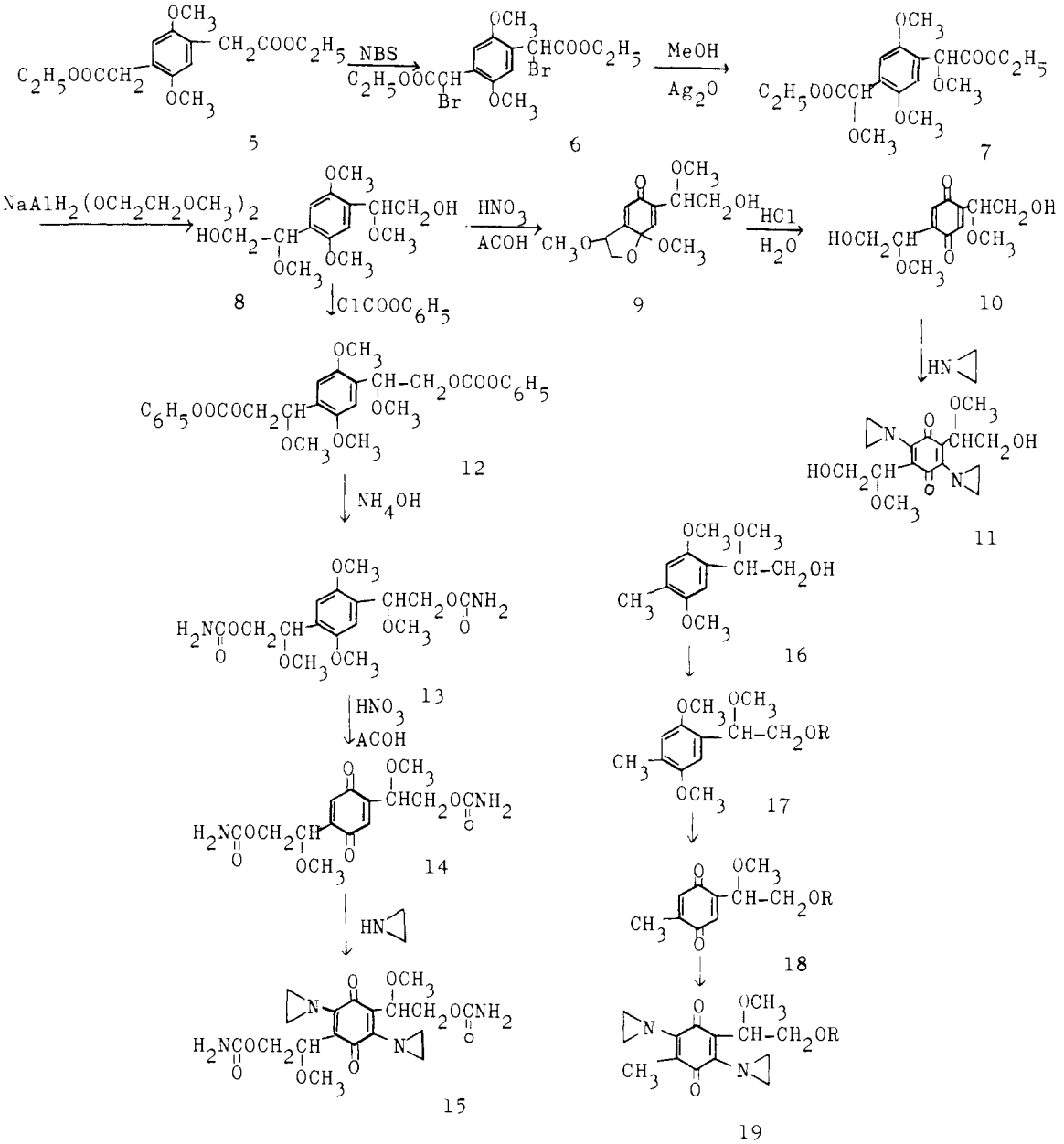
[a] Calculated using eq 8. [b] Calculated using eq 10. [c] Calculated using eq 12. [d] Calculated using eq 14. [e] The compound numbers in this table refer to structure 4 and not to other structures cited in the text.

Table II. Equations Obtained from the Data Excluding Several Compounds

anti-leukemic act.	equations	eq no.	n^a	r^b	s^c	F^d test
chron inj						
MED	$\log 1/C = -0.462(\pm 0.09)\pi_{1,2} + 6.354(\pm 0.16)$[e]	1	34	0.881	0.300	$F_{1,32} = 111.2$
	$\log 1/C = -0.551(\pm 0.10)\pi_2 - 0.371(\pm 0.15)MR_1 + 6.402(\pm 0.17)$	2	34	0.908	0.270	$F_{2,31} = 72.4$
OD	$\log 1/C = -0.338(\pm 0.08)\pi_{1,2} + 5.727(\pm 0.15)$	3	34	0.820	0.285	$F_{1,32} = 100.5$
	$\log 1/C = -0.304(\pm 0.08)\pi_{1,2} - 0.135(\pm 0.08)MR_{1,2} + 6.109(\pm 0.27)$	4	34	0.871	0.249	$F_{2,31} = 48.7$
sing. inj						
MED	$\log 1/C = -0.447(\pm 0.09)\pi_{1,2} + 5.486(\pm 0.16)$	5	31	0.876	0.288	$F_{1,29} = 95.2$
OD	$\log 1/C = -0.378(\pm 0.09)\pi_{1,2} + 5.247(\pm 0.15)$	6	31	0.849	0.276	$F_{1,29} = 74.0$

[a] Number of data. [b] Correlation coefficient. [c] Standard deviation. [d] $F_{1,30;\alpha=0.001} = 13.3$; $F_{2,30;\alpha=0.001} = 8.8$; $F_{1,29;\alpha=0.001} = 13.4$. [e] The figures in parentheses indicate 95% confidence intervals.

Scheme I



(19) prepared in the routes in Scheme I.

The activities of those hydrophilic compounds were determined, but only the diol 11 ($\pi_1 = \pi_2 = -0.63$; $MR_1 = MR_2 = 1.90$; $\mathcal{F} = \mathcal{R} = 0.00$) was as active as 2, and the others (15 and 19) were much less active than 2. The low activity of the dicarbamate 15 ($\pi_1 = \pi_2 = -0.52$; $MR_1 = MR_2 = 2.74$; $\mathcal{F} = \mathcal{R} = 0.00$) might be attributed to the very low solubility of it in any solvents (including water, DMF,

Table III. Equations Obtained from the All Data

antileukemic act.	equations	eq no.	n	r	s	F^a test
chron inj						
MED	$\log 1/C = -0.454(\pm0.10)\pi_{1,2} + 6.347(\pm0.17)$	7	37	0.849	0.340	$F_{1,35} = 90.1$
	$\log 1/C = -0.521(\pm0.10)\pi_2 - 0.344(\pm0.14)MR_1 - 1.784(\pm1.12)\mathcal{F} - 0.825(\pm0.54)\mathcal{R} + 6.092(\pm0.26)$	8	37	0.921	0.262	$F_{4,32} = 44.8$
OD	$\log 1/C = -0.344(\pm0.09)\pi_{1,2} + 5.753(\pm0.16)$	9	37	0.786	0.325	$F_{1,35} = 56.6$
	$\log 1/C = -0.352(\pm0.09)\pi_2 - 0.290(\pm0.13)MR_1 - 2.075(\pm1.05)\mathcal{F} - 1.165(\pm0.51)\mathcal{R} + 5.383(\pm0.25)$	10	37	0.894	0.247	$F_{4,32} = 31.7$
sing. inj						
MED	$\log 1/C = -0.381(\pm0.15)\pi_{1,2} + 5.719(\pm0.25)$	11	35	0.667	0.493	$F_{1,33} = 26.5$
	$\log 1/C = -0.487(\pm0.09)\pi_{1,2} - 3.954(\pm1.05)\mathcal{F} - 1.490(\pm0.49)\mathcal{R} + 5.305(\pm0.20)$	12	35	0.907	0.288	$F_{3,31} = 48.0$
OD	$\log 1/C = -0.338(\pm0.13)\pi_{1,2} + 5.142(\pm0.22)$	13	37	0.675	0.450	$F_{1,35} = 29.3$
	$\log 1/C = -0.366(\pm0.07)\pi_{1,2} - 3.253(\pm0.83)\mathcal{F} - 1.391(\pm0.43)\mathcal{R} + 4.707(\pm0.18)$	14	37	0.913	0.257	$F_{3,33} = 54.8$

[a] $F_{1,30,\alpha=0.001} = 13.3$; $F_{4,30;\alpha=0.001} = 6.1$; $F_{3,30;\alpha=0.001} = 7.1$.

Table IV. Squared Correlation Matrix of Variables Pertaining to Equation 7

	$\pi_{1,2}$	$MR_{1,2}$	π_1	π_2	MR_1	MR_2	$\mathcal{F}$	$\mathcal{R}$
$\pi_{1,2}$	1.00	0.12	0.46	0.80	0.18	0.02	0.02	0.04
$MR_{1,2}$		1.00	0.23	0.03	0.45	0.66	0.02	0.15
π_1			1.00	0.08	0.41	0.02	0.02	0.07
π_2				1.00	0.03	0.01	0.02	0.01
MR_1					1.00	0.01	0.00	0.02
MR_2						1.00	0.05	0.17
$\mathcal{F}$							1.00	0.44
$\mathcal{R}$								1.00

and Me_2SO), but the most expected compound, **19** (π_1 = 0.50, π_2 = 1.25; if acetyl groups are hydrolyzed, π_2 = −2.31, MR_1 = 0.57, MR_2 = 9.40, $\mathcal{F}$ = −0.04, $\mathcal{R}$ = −0.13), sees no reason for the marginal activity from the obtained eq 1, 3, 5, and 6. Steric effects (MR values) might play an important role in the low activity. Electronic effects of these three molecules are negligible. Generally speaking, it might be very difficult to find more active compounds than those (**31–39**) in Table I, and no increase in the activity of the more hydrophilic compounds suggests that the activity would be correlated to π in the parabola in the area of extended hydrophilicity.

Experimental Section

Melting points were taken on a Büchi apparatus and are uncorrected. The compounds were checked by IR on a Perkin-Elmer 221, by UV on a Hitachi 124, and by NMR on a Varian A-60 and/or HA-100 spectrometer. Where the analyses were represented by symbols only, the values were found in adequate accordance with theoretical values.

2,5-Bis[1-(ethoxycarbonyl)-1-bromomethyl]-1,4-dimethoxybenzene (6). A mixture of 2,5-bis(ethoxycarbonylmethyl)-1,4-dimethoxybenzene (5; 9.3 g, 30 mmol), *N*-bromosuccinimide (14 g, 78 mmol), CCl_4 (200 mL) and azobis(isobutylnitrile) (catalytic amount) was heated under reflux for 6 h. The precipitated succinimide was filtered off and the filtrate was evaporated under reduced pressure. The residue was crystallized from EtOH to give 6: 13.5 g (96%); mp 120–123 °C. Anal. ($C_{16}H_{20}O_6Br_2$) C, H, Br.

2,5-Bis[1-(ethoxycarbonyl)-1-methoxymethyl]-1,4-dimethoxybenzene (7). A mixture of 6 (7.0 g, 15 mmol), Ag_2O (13 g, 60 mmol), and MeOH (500 mL) was stirred at room temperature for 17 h. The solid was filtered off from the mixture and the filtrate was evaporated to dryness. An ether-soluble part of the residue was crystallized from Et_2O–*n*-hexane to give 7: 5.3 g (95%); mp 77–79 °C. Anal. ($C_{18}H_{26}O_8$) C, H.

2,5-Bis(2-hydroxy-1-methoxyethyl)-1,4-dimethoxybenzene (8). To a stirred mixture of 7 (4.95 g, 13.4 mmol) and THF (70 mL) was added dropwise Vitride [$NaAlH_2(OCH_2CH_2OCH_3)_2$, 70% solution in C_6H_6; 8.0 mL, 28 mmol] in THF (15 mL). After 2.5 h under reflux, the mixture was cooled and 20% H_2SO_4 (100 mL) was added. Filtration of the precipitated solid, washing with Et_2O, and drying in vacuo gave 8, 1.50 g. Extraction of the filtrate with EtOAc, drying, and the evaporation of the solvent gave a second crop of 8, 2.21 g. Combined yields were 3.71 g (93%). Recrystallization from EtOH: mp 189–192 °C. Anal. ($C_{14}H_{22}O_6$) C, H.

3,7a-Dimethoxy-6-(2-hydroxy-1-methoxyethyl)-2,3,5,7a-tetrahydrobenzofuran-5-one (9) **and 2,5-Bis(2-hydroxy-1-methoxyethyl)-*p*-benzoquionone** (10). To a cooled mixture of 8 (1.43 g, 5.00 mmol) and HOAc (10 mL) was added dropwise 60% HNO_3 (1.5 mL). The mixture was stirred at 10 °C for 2 h, poured into 100 mL of ice–water, and extracted with EtOAc. The combined extracts were washed with 5% $NaHCO_3$, dried, and evaporated to dryness. The residue was chromatographed over silica gel eluting with C_6H_6–EtOAc. The first eluate (C_6H_6–EtOAc, 5:1) yielded 9: 0.91 g (67%); MS *m/e*: 270 (M^+); IR ν (film) 3480 (OH), 1690 (C=O), 1650 cm^{-1} (C=C). The second eluate (C_6H_6–EtOAc, 2:1) gave 10: 0.23 g (16%): mp 134–136 °C. Anal. ($C_{12}H_{16}O_6$) C, H.

A mixture of 9 (0.60 g, 2.2 mmol), EtOH (7 mL), and 5% HCl (2 mL) was stirred at room temperature for 2 h. The precipitated yellow crystallines were collected on a filter and washed with Et_2O to give 10, 0.40 g (67%).

2,5-Bis(1-aziridinyl)-3,6-bis(2-hydroxy-1-methoxyethyl)-*p*-benzoquinone (11). To a cooled mixture of 10 (0.50 g, 1.9 mmol) and EtOH (20 mL) was added ethylenimine (0.3 mL). The mixture was left to stand at 0–5 °C for 3 h and evaporated to dryness. The residue was chromatographed over silica gel eluting with $CHCl_3$–MeOH. The eluate ($CHCl_3$–MeOH, 100:3) gave 11: 0.1 g (15.3%); mp 149–152 °C. Anal. ($C_{16}H_{22}N_2O_6$) C, H, N.

2,5-Bis[1-methoxy-2-(carbamoyloxy)ethyl]-1,4-dimethoxybenzene (13). To a mixture of 8 (2.0 g, 7.0 mmol) and pyridine (50 mL) was added dropwise phenyl chloroformate (2.35 g, 15.0 mmol). The mixture was stirred at room temperature for 2.5 h and poured into 500 mL of ice–water. The separated crystallines were collected on a filter and washed with EtOH to give 2,5-bis[1-methoxy-2-(phenoxycarboxy)ethyl]-1,4-dimethoxybenzene (12): 3.68 g (100%); unstable and not purified.

A mixture of 12 (1.05 g, 2.00 mmol), EtOH (30 mL), and 28% NH_4OH (15 mL) was heated under reflux for 1 h and concentrated. The residual solid was washed with 3% NaOH (10 mL), H_2O, and Et_2O. Recrystallization from 80% EtOH afforded 13: 0.65 g (88%); mp 222–224 °C. Anal. ($C_{16}H_{24}N_2O_8$) C, H, N.

2,5-Bis[2-(carbamoyloxy)-1-methoxyethyl]-*p*-benzoquinone (14). To a cooled mixture of 13 (0.74 g, 2.0 mmol) and HOAc (20 mL) was added 60% HNO_3 (0.5 mL). The mixture was stirred at 10 °C for 3 h and poured into 100 mL of ice–water. The precipitates were collected on a filter and recrystallized from EtOH–MeOH (2:1) to give yellow prisms: 0.23 g (34%); mp 214–216 °C. Anal. ($C_{14}H_{18}N_2O_8$) C, H, N.

2,5-Bis(1-aziridinyl)-3,6-bis[2-(carbamoyloxy)-1-methoxyethyl]-*p*-benzoquinone (15). A mixture of 14 (500 mg, 1.46

mmol), DMF (6 mL), and ethylenimine (0.5 mL) was stirred at room temperature for 3 h. The addition of MeOH (6 mL) to the mixture gave crystallines and recrystallization from DMF–MeOH (1:1) yielded orange prisms: 0.18 g (29%); mp 217 °C (dec); UV λ_{max} (50% EtOH) 317 nm (log ϵ 4.25), 336 (4.15); IR ν (Nujol) 3450–3210 (NH_2), 1730 (carbamate), 1650 cm^{-1} (quinone). Anal. ($C_{18}H_{24}O_8N_4$) C, H, N.

2-(2,5-Dimethoxy-4-methylphenyl)-2-methoxyethyl 2,3,-4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (17). A mixture of **16** (2.90 g, 12.8 mmol), Ag_2O (3.60 g, 15.3 mmol), anhydrous $CaSO_4$ (10 g), and $CHCl_3$ (25 mL) was stirred at room temperature for 0.5 h. After the addition of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (5.80 g, 14.1 mmol), the mixture was stirred for 30 h and filtered. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel eluting with C_6H_6–EtOAc. The eluate (C_6H_6–EtOAc, 3:1) gave **17** as a powder: 3.0 g (43%); IR ν (Nujol) 1755 cm^{-1} (C=O). Anal. ($C_{26}H_{36}O_{13}$) C, H.

2-Methoxy-2-(5-methyl-*p*-benzoquinon-2-yl)ethyl 2,3,-4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (18). To a cooled mixture of **17** (3.0 g, 5.4 mmol) and HOAc (15 mL) was added dropwise 60% HNO_3 (2.0 mL). The mixture was stirred at room temperature for 0.5 h, poured into 100 mL of ice–water, and extracted with Et_2O. The extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed over silica gel eluting with C_6H_6–EtOAc. The eluate (C_6H_6–EtOAc, 3:1) gave **18** as a powder: 1.12 g (39.5%); IR ν (Nujol) 1740–1780 (ester), 1655 (quinone), 1620 cm^{-1} (C=C). Anal. ($C_{24}H_{30}O_{13}$) C. H.

2-[3,6-Bis(1-aziridinyl)-5-methyl-*p*-benzoquinon-2-yl]-2-methoxyethyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (19). To a cooled mixture of **18** (1.24 g, 2.36 mmol), EtOH (9 mL), and EtOAc (1 mL) was added ethylenimine (1 mL). The mixture was stirred at room temperature for 2 h and evaporated to dryness. The residue was chromatographed over silica gel eluting with C_6H_6–EtOH. The eluate (C_6H_6–EtOH, 10:1) gave **19** as red crystallines: 0.10 g (7.0%); mp 60–63 °C; IR ν (Nujol) 1755 (ester), 1645 (quinone), 1580 cm^{-1} (C=C); UV λ_{max} (EtOH) 333 nm (log ϵ 4.15). Anal. ($C_{28}H_{36}N_2O_6$) C, H, N.

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Alkylating Nucleosides 1. Synthesis and Cytostatic Activity of *N*-Glycosyl(halomethyl)-1,2,3-triazoles. A New Type of Alkylating Agent

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1,3-Dipolar cycloaddition of benzyl azide or peracetylated glucopyranosyl azides to propargyl halides or 1.4-dihalobutynes yielded 1-benzyl- or 1-glycosyl(halomethyl)-1,2,3-triazoles. Alkylating chloromethyl- bromomethyl- and iodomethyl-1,2,3-triazoles were also obtained from the corresponding hydroxymethyl derivatives by treatment with $(C_6H_5)_3P/CCl_4$, $(C_6H_5O)_3P/Br_2$, and $(C_6H_5O)_3P/I_2$, respectively. 1-Benzyl-4-(fluoromethyl)-1,2,3-triazole was obtained from 1-benzyl-4-(bromomethyl)-1,2,3-triazole by treatment with KF and 18-crown-6. Chloromethyl-, bromomethyl-, and iodomethyl-1,2,3-triazole derivatives inhibited the "in vitro" growth of HeLa cells. Some of these compounds increased the life span of mice bearing tumors.

Alkylating agents have been extensively studied in connection with cancer chemotherapy.[1,2] One of the classical major disadvantages of such drugs is their low selectivity for neoplastic tissue.[1] However, recent studies have shown the effectiveness and specificity of some alkylating agents, such as cyclophosphamide or merophan in the treatment of Burkitt's lymphoma[3,4] or the specificity of 5-aziridino-2,4-dinitrobenzamide on Walker tumor cells.[5] These and other examples[2] should encourage the search for new and more selective alkylating agents as anticancer drugs.

Several theoretical approaches have been used in the design of alkylating drugs.[6] One of the most fruitful approaches involves the attachment of the alkylating agent to a carrier that is related to substances normally involved in cell growth. Carriers which have been employed are naturally occurring amino acids,[7,8] carbohydrates,[9,10] steroids,[11] nucleic acid components, bases,[12,13] nucleosides,[14-20] and nucleotides.[16] Some of the alkylating derivatives of nucleic acid components have been reported to show anticancer activity. Thus, 5-[bis(2-chloroethyl)amino]uracil and its 6-methyl derivative (Dopan) are effective against tumors of the hematopoietic system,[21,22] 9-alkyl- and 9-ribofuranosyl derivatives of 6-(1-aziridinyl)purines show activity against adenocarcinoma 755,[14] and 5-[[bis(2-chloroethyl)amino]methyl]uridine is active against leukemia.[15]

Several functional groups have been commonly used as the active moiety of alkylating agents. These are nitrogen mustards, sulfur mustards, aziridines, epoxides, alkanesulfonates, and nitrosoureas. There are, however, some other chemically efficient alkylating groups, such as allylic-

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