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Antileukemic Agents. II.[1] New 2,5-Bis(1-aziridinyl)-*p*-benzoquinone Derivatives

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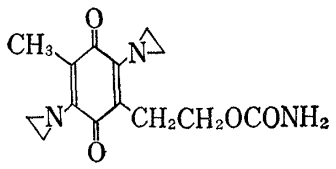
A series of 2,5-bis(1-aziridinyl)-*p*-benzoquinone derivatives were synthesized and evaluated as antileukemic agents. The most active compounds against lymphoid leukemia L-1210 in BDF_1 mice were 2,5-bis(1-aziridinyl)-3-(2-carbamoyloxyethyl-1-methoxy)-6-methyl-*p*-benzoquinone, carbazilquinone (**7**), and related compounds (**8**, **23** and **24**). Structure-activity relationships were discussed.

In the previous paper,[1] we reported syntheses of 2,5-disubstituted *p*-benzoquinones, one of which 2,5-bis(1-aziridinyl)-3-(2-carbamoyloxyethyl)-6-methyl-*p*-benzoquinone (**1**), exhibited a remarkable antitumor activity against lymphoid leukemia L-1210 in BDF_1 mice. Further efforts were carried out to find more active or less toxic compounds by the structural modification of **1**. The present paper describes the preparation of the title compounds and their antitumor activity.



1

From the results of previous report, it appears that presence of aziridinyl groups in **1** is necessary for antitumor activity. Therefore, structural modification of the methyl and 2-carbamoyloxyethyl groups in **1** was mainly carried out. Since 2,5-bis(1-aziridinyl)-*p*-benzoquinone and its 3,6-dibromo or dimethoxy derivatives were inactive or less active against L-1210, alkyl substituents at the 3 and 6 positions appeared more desiable. Such compounds have not been reported in the literature except 2,5-bis(1-aziridinyl)-3,6-dimethyl-*p*-benzoquinone (**10**) which showed only weak activity against ehrlich ascites cell in the literature.[3]

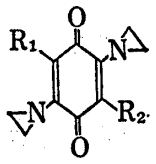
Thus, the 2,5-bis(1-aziridinyl)-3,6-disubstituted *p*-benzoquinones in Table I and II were prepared by the reaction of the corresponding *p*-benzoquinones with aziridine except 2,3,5-tris(1-aziridinyl)-6-methyl-*p*-benzoquinone (**22**) and 3,6-dibromo-2,5-bis(2-methyl-1-aziridinyl)-*p*-benzoquinone (**39**).

The former (**22**) was obtained by the reaction of 2-methoxy-5-methyl-*p*-benzoquinone[4] (**51**) and aziridine, and the latter (**39**) was prepared from bromanil and 2-methylaziridine. Most of 2,5-disubstituted *p*-benzoquinones (Table III) used in this work are new compounds. Except for 2,5-dipropyl-*p*-benzoquinone (**59**) prepared from 2,5-dipropylhydroquinone, they were synthesized by nitric acid oxidation of the corresponding hydroquinone dimethyl ethers (Table IV), which were obtained as follows (Chart 1 and 2).

β-Alkoxy-4-alkyl-2,5-dimethoxyphenethyl alcohol (**109**—**114**) were prepared by the previously reported procedure.[5] 4-Alkyl-2,5-dimethoxyphenethyl alcohol (**97** and **98**) were prepared from 4-alkyl-2,5-dimethoxyphenyl magnesium bromide and ethylene oxide by

1) H. Nakao and M. Arakawa, *Chem. Pharm. Bull.* (Tokyo), **20**, 1962 (1972).
2) Location: *Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.*
3) S. Hayashi, H. Ueki, H. Aoki, K. Tanaka, J. Fujimoto, K. Katsukawa and M. Mori, *Chem. Pharm. Bull.* (Tokyo), **11**, 948 (1963).
4) J.N. Ashley, *J. Chem. Soc.*, **1937**, 1471.
5) H. Nakao, M. Fukushima, and T. Torizuka, *Ann. Sankyo Res. Lab.*, **22**, 90 (1970).

TABLE I. 2,5-Bis(1-aziridinyl)-3,6-disubstituted-*p*-benzoquinone

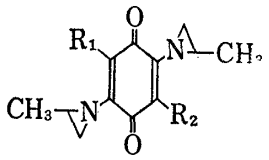


Compound	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
1	CH_3	$CH_2CH_2OCONH_2$	196 (decomp.)	$C_{14}H_{17}O_4N_3$	57.72	5.88	14.43	57.54	6.09	14.50
2	CH_3	$CH_2CH_2OCON(CH_3)_2$	120	$C_{16}H_{21}O_4N_3$	60.17	6.63	13.16	60.06	6.69	12.98
3	CH_3	$CH_2CH_2CH_2OCONH_2$	162	$C_{15}H_{19}O_4N_3$	59.00	6.27	13.76	58.92	6.60	13.73
4	CH_3	$CH(CH_3)CH_2OCONH_2$	135	$C_{15}H_{19}O_4N_3 \cdot C_3H_3$[a]	62.79	6.40	12.21	62.52	6.39	12.21
5	CH_3	$CH_2CH(CH_3)OCONH_2$	183	$C_{15}H_{19}O_4N_3$	59.00	6.27	13.76	58.97	6.34	13.74
6	CH_3	$CH(C_2H_5)CH_2OCONH_2$	177	$C_{16}H_{21}O_4N_3$	60.17	6.63	13.16	60.14	6.90	13.45
7	CH_3	$CH(OCH_3)CH_2OCONH_2$	203 (decomp.)	$C_{15}H_{19}O_5N_3$	56.06	5.96	13.08	55.94	6.15	13.11
8	CH_3	$CH(OC_2H_5)CH_2OCONH_2$	199 (decomp.)	$C_{16}H_{21}O_5N_3$	57.30	6.31	12.53	57.31	6.28	12.39
9	CH_3	$CH(OC_2H_4OCH_3)CH_2OCONH_2$	130	$C_{17}H_{23}O_6N_3$	55.88	6.35	11.50	55.85	6.60	11.73
10	CH_3	CH_3	208 (decomp.)	$C_{12}H_{14}O_2N_2$	66.03	6.47	12.84	66.19	6.61	12.87
11	CH_3	C_2H_5	156	$C_{13}H_{16}O_2N_2$	67.22	6.94	12.06	67.05	6.92	12.13
12	CH_3	$CH(CH_3)CH_3$	118 (decomp.)	$C_{14}H_{18}O_2N_2$	68.27	7.37	11.37	68.10	7.45	11.76
13	CH_3	$CH_2CH_2CH_2C_6H_5$	111	$C_{20}H_{22}O_2N_2$	74.51	6.88	8.69	74.21	7.07	8.63
14	CH_3	$CH_2C_6H_5$	187	$C_{18}H_{18}O_2N_2$	73.45	6.16	9.52	73.31	6.46	9.39
15	CH_3	CH_2CH_2OH	175	$C_{13}H_{16}O_3N_2$	62.89	6.50	11.28	62.69	6.70	11.38
16	CH_3	$CH_2CH_2OCH_3$	119	$C_{14}H_{18}O_3N_2$	64.10	6.92	10.68	64.19	7.14	10.93
17	CH_3	$CH_2CH_2OCOCH_3$	128	$C_{15}H_{18}O_4N_2$	62.05	6.25	9.65	61.73	6.32	9.48
18	CH_3	$CH(OCH_3)CH_2CH_3$	98	$C_{15}H_{20}O_3N_2$	65.19	7.30	10.14	65.05	7.53	9.89
19	CH_3	$CH_2OC_6H_5$	104	$C_{18}H_{18}O_3N_2$	69.66	5.85	9.03	69.72	6.00	9.40
20	CH_3	$COCH_3$	187 (decomp.)	$C_{13}H_{14}O_3N_2$	63.40	5.73	11.38	63.73	5.90	11.53
21	CH_3	Br	196 (decomp.)	$C_{11}H_{11}O_2N_2Br$	46.66	3.92	9.90	46.97	3.96	9.83
22	CH_3		173	$C_{13}H_{15}O_2N_3$	63.66	6.16	17.13	63.99	6.44	17.22
23	C_2H_5	$CH_2CH_2OCONH_2$	184	$C_{15}H_{19}O_4N_3$	59.00	6.27	13.76	59.44	6.61	13.67
24	C_2H_5	$CH(OCH_3)CH_2OCONH_2$	148	$C_{16}H_{21}O_5N_3$	57.30	6.31	12.53	57.10	6.39	12.52
25	C_2H_5	$CH(OC_2H_5)CH_2OCONH_2$	146	$C_{17}H_{23}O_5N_3$	58.44	6.64	12.03	58.55	6.82	11.99
26	C_3H_7	$CH(OCH_3)CH_2OCONH_2$	114	$C_{17}H_{23}O_5N_3$	58.44	6.64	12.03	58.76	6.82	12.35
27	C_3H_7	$CH_2CH_2OCONH_2$	176	$C_{16}H_{21}O_4N_3$	60.17	6.63	13.16	60.60	6.85	13.59
28	Br	$CH_2CH_2OCONH_2$	179 (decomp.)	$C_{13}H_{14}O_4N_3Br$	43.83	3.96	11.80	44.19	4.21	11.57
29	$CH_2CH_2OCONH_2$	$CH_2CH_2OCONH_2$	206 (decomp.)	$C_{16}H_{20}O_6N_4$	52.74	5.53	15.38	52.71	5.62	15.23
30	$CH_2CH_2OCON(CH_3)_2$	$CH_2CH_2OCON(CH_3)_2$	175	$C_{20}H_{28}O_6N_4$	57.13	6.71	13.33	56.89	6.75	13.48
31	CH_2CH_2OH	CH_2CH_2OH	185 (decomp.)	$C_{14}H_{18}O_4N_2$	60.42	6.52	10.07	60.57	6.79	10.19
32	$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$	144	$C_{16}H_{22}O_4N_2$	62.72	7.24	9.14	62.63	7.50	9.45
33	$CH_2CH_2OCOCH_3$	$CH_2CH_2OCOCH_3$	152	$C_{18}H_{22}O_6N_2$	59.66	6.12	7.73	59.93	6.13	7.68

Compound	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
34	C_2H_5	C_2H_5	179 (decomp.)	$C_{14}H_{18}O_2N_2$	68.27	7.37	11.37	68.15	7.57	11.70
35	n-C_3H_7	n-C_3H_7	119	$C_{16}H_{22}O_2N_2$	70.04	8.08	10.21	70.10	8.17	10.31
36	iso-C_3H_7	iso-C_3H_7	170	$C_{16}H_{22}O_2N_2$	70.04	8.08	10.21	69.70	8.19	10.16
37	n-C_5H_{11}	n-C_5H_{11}	117	$C_{20}H_{30}O_2N_2$	72.69	9.15	8.48	72.45	9.21	8.46
38	C_6H_5	C_6H_5	249 (decomp.)	$C_{22}H_{18}O_2N_2$	77.17	5.30	8.18	76.85	5.36	8.50

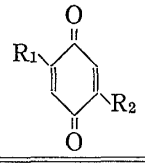
a) 1/2 solvent benzene

TABLE II. 2,5-Bis(2-methyl-1-aziridinyl)-3,6-disubstituted-*p*-benzoquinone



Compound	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
39	Br	Br	189 (decomp.)	$C_{12}H_{12}O_2N_2Br_2$	38.34	3.19	7.45	38.34	3.46	7.72
40	CH_3	CH_3	163	$C_{14}H_{18}O_2N_2$	68.27	7.37	11.37	68.25	7.39	11.18
41	CH_3	$CH_2CH_2OCONH_2$	175	$C_{16}H_{21}O_4N_3$	60.17	6.63	13.16	60.15	6.60	13.19
42	$CH_2CH_2OCON(CH_3)_2$	$CH_2CH_2OCON(CH_3)_2$	149	$C_{22}H_{32}O_6N_4$	58.91	7.19	—	58.64	7.15	—

TABLE III. 2,5-Disubstituted-*p*-benzoquinone

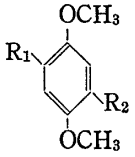


Compound	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
43	CH_3	$CH_2CH_2CH_2OCONH_2$	142	$C_{11}H_{13}O_4N$	59.18	5.87	6.28	59.11	5.88	6.31
44	CH_3	$CH(CH_3)CH_2OCONH_2$	124	$C_{11}H_{13}O_4N$	59.18	5.87	6.28	58.99	5.94	6.42
45	CH_3	$CH_2CH(CH_3)OCONH_2$	118	$C_{11}H_{13}O_4N$	59.18	5.87	6.28	59.10	5.83	6.13
46	CH_3	$CH(C_2H_5)CH_2OCONH_2$	116	$C_{12}H_{15}O_4N$	60.75	6.37	5.90	60.50	6.48	5.96
47	CH_3	$CH(OCH_3)CH_2OCONH_2$	142	$C_{11}H_{13}O_5N$	55.23	5.48	5.86	55.09	5.64	5.79
48	CH_3	$CH(OC_2H_5)CH_2OCONH_2$	100	$C_{12}H_{15}O_5N$	56.91	5.97	5.53	56.91	5.86	5.56
49	CH_3	$CH(OC_2H_4OCH_3)CH_2OCONH_2$	92	$C_{13}H_{17}O_6N$	55.12	6.05	4.95	55.45	5.98	4.89
50	CH_3	$CH_2CH_2CH_2C_6H_5$	80	$C_{16}H_{16}O_2$	79.97	6.71	—	79.75	6.64	—
51[a)]	CH_3	OCH_3	177	$C_8H_8O_3$	63.15	5.30	—	63.08	5.47	—
52	C_2H_5	$CH_2CH_2OCONH_2$	120	$C_{11}H_{13}O_4N$	59.18	5.87	6.28	59.18	5.80	6.25
53	C_2H_5	$CH(OCH_3)CH_2OCONH_2$	86	$C_{12}H_{15}O_5N$	56.91	5.97	5.53	56.80	5.96	5.50

Compound	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
54	C_2H_5	$CH(OC_2H_5)CH_2OCONH_2$	92	$C_{13}H_{17}O_5N$	58.42	6.41	5.24	58.66	6.50	5.28
55	C_3H_7	$CH_2CH_2OCONH_2$	118	$C_{12}H_{15}O_4N$	60.75	6.37	5.90	60.58	6.42	5.52
56	C_3H_7	$CH(OCH_3)CH_2OCONH_2$	87	$C_{13}H_{17}O_5N$	58.42	6.41	5.24	58.10	6.61	5.46
57	Br	$CH_2CH_2OCONH_2$	159	$C_9H_8O_4NBr$	39.44	2.94	5.11	39.29	2.93	4.86
58	$CH_2CH_2OCOCH_3$	$CH_2CH_2OCOCH_3$	90	$C_{14}H_{16}O_6$	59.99	5.75	—	59.94	5.69	—
59	C_3H_7	C_3H_7	100[b] (3 mm)	$C_{12}H_{16}O_2$	74.97	8.39	—	74.69	8.17	—
60	C_5H_{11}	C_5H_{11}	135[b] (0.05 mm)	$C_{16}H_{24}O_2$	77.37	9.74	—	77.16	9.62	—
61	CH_3	$CH_2C_6H_5$	compounds were used in the next reaction without purification							
62	CH_3	$CH_2CH_2OCH_3$								
63	CH_3	$CH(OCH_3)C_2H_5$								
64	C_2H_5	C_2H_5								
65	$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$								

a) lit.[4] mp 173° *b*) bp

TABLE IV. 2,5-Disubstituted-1,4-dimethoxybenzene



Compound	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
66	CH_3	$CH_2CH_2CH_2OCONH_2$	88	$C_{13}H_{19}O_4N$	61.64	7.56	5.53	61.68	7.64	5.53
67	CH_3	$CH(CH_3)CH_2OCONH_2$	99	$C_{13}H_{19}O_4N$	61.64	7.56	5.53	62.01	7.57	5.50
68	CH_3	$CH_2CH(CH_3)OCONH_2$	114	$C_{13}H_{19}O_4N$	61.64	7.56	5.53	61.61	7.64	5.61
69	CH_3	$CH(C_2H_5)CH_2OCONH_2$	110	$C_{14}H_{21}O_4N$	62.90	7.92	5.24	62.59	8.09	5.27
70	CH_3	$CH(OCH_3)CH_2OCONH_2$	117	$C_{13}H_{19}O_5N$	57.98	7.11	5.20	58.12	7.18	5.09
71	CH_3	$CH(OC_2H_5)CH_2OCONH_2$	113	$C_{14}H_{21}O_5N$	59.35	7.47	4.94	59.42	7.52	4.84
72	CH_3	$CH(OCH_4OCH_3)CH_2OCONH_2$	125	$C_{15}H_{23}O_6N$	57.49	7.40	4.47	57.49	7.53	4.40
73	CH_3	$CH_2CH_2CH_2C_6H_5$	155[a] (0.01 mm)	$C_{18}H_{22}O_2$	79.96	8.20	—	80.24	8.37	—
74	CH_3	$CH_2C_6H_5$	120[a] (0.04 mm)	$C_{16}H_{18}O_2$	78.72	7.27	—	79.11	7.49	—
75	CH_3	$CH_2CH_2OCH_3$	90[a] (0.4 mm)	$C_{12}H_{18}O_3$	68.54	8.63	—	68.75	8.58	—
76	CH_3	$CH(OCH_3)CH_2CH_3$	130[a] (0.08 mm)	$C_{13}H_{20}O_3$	69.61	8.99	—	69.27	8.74	—
77[b]	CH_3	Br	90	$C_9H_{11}O_2Br$	46.77	4.80	—	46.73	4.83	—
78	C_2H_5	$CH_2CH_2OCONH_2$	123	$C_{13}H_{19}O_4N$	61.64	7.56	5.53	61.44	7.57	5.48
79	C_2H_5	$CH(OCH_3)CH_2OCONH_2$	112	$C_{14}H_{21}O_5N$	59.35	7.47	4.94	59.64	7.41	5.03
80	C_2H_5	$CH(OC_2H_5)CH_2OCONH_2$	106	$C_{15}H_{23}O_5N$	60.59	7.80	4.71	60.38	7.83	4.71
81	C_3H_7	$CH_2CH_2OCONH_2$	127	$C_{14}H_{21}O_4N$	62.90	7.92	5.24	62.92	8.17	5.16

Compound	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
82	C_3H_7	$CH(OCH_3)$-CH_2OCONH_2	107	$C_{15}H_{23}O_5N$	60.59	7.80	4.71	60.45	7.84	4.80
83	Br	$CH_2CH_2OCONH_2$	144	$C_{11}H_{14}O_4N$	43.44	4.64	4.61	43.50	4.74	4.52
84	$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$	62	$C_{14}H_{22}O_4$	66.11	8.72	—	65.93	8.46	—
85	$CH_2CH_2OCOCH_3$	$CH_2CH_2OCOCH_3$	74	$C_{16}H_{22}O_6$	61.92	7.15	—	61.63	7.20	—
86	C_2H_5	C_2H_5	39	$C_{12}H_{18}O_2$	74.19	9.34	—	73.83	9.21	—
87	C_5H_{11}	C_5H_{11}	159[a] (5 mm)	$C_{18}H_{30}O_2$	77.65	10.86	—	77.29	10.99	—

a) bp *b*) lit.[6] mp 91°

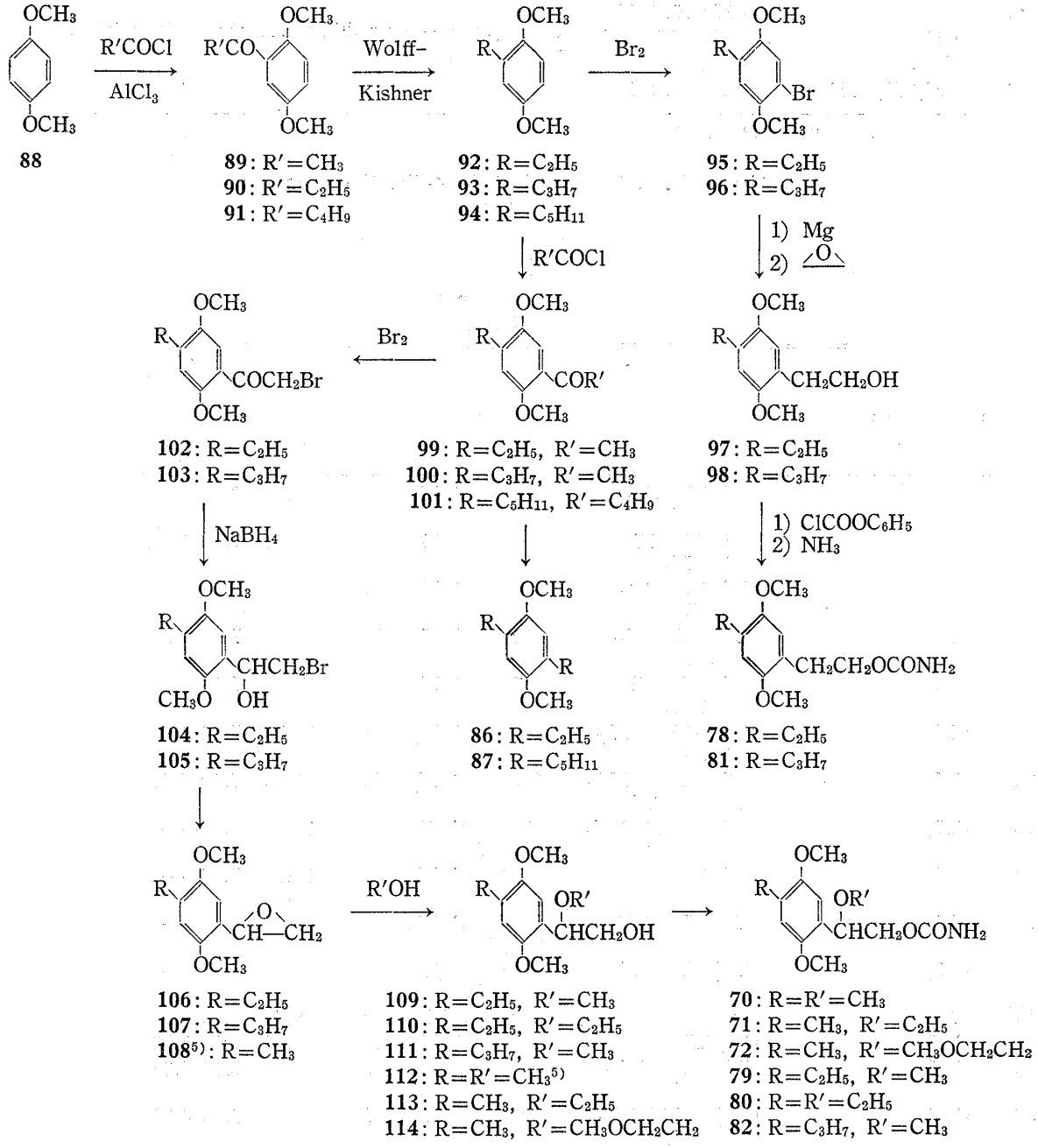


Chart 1

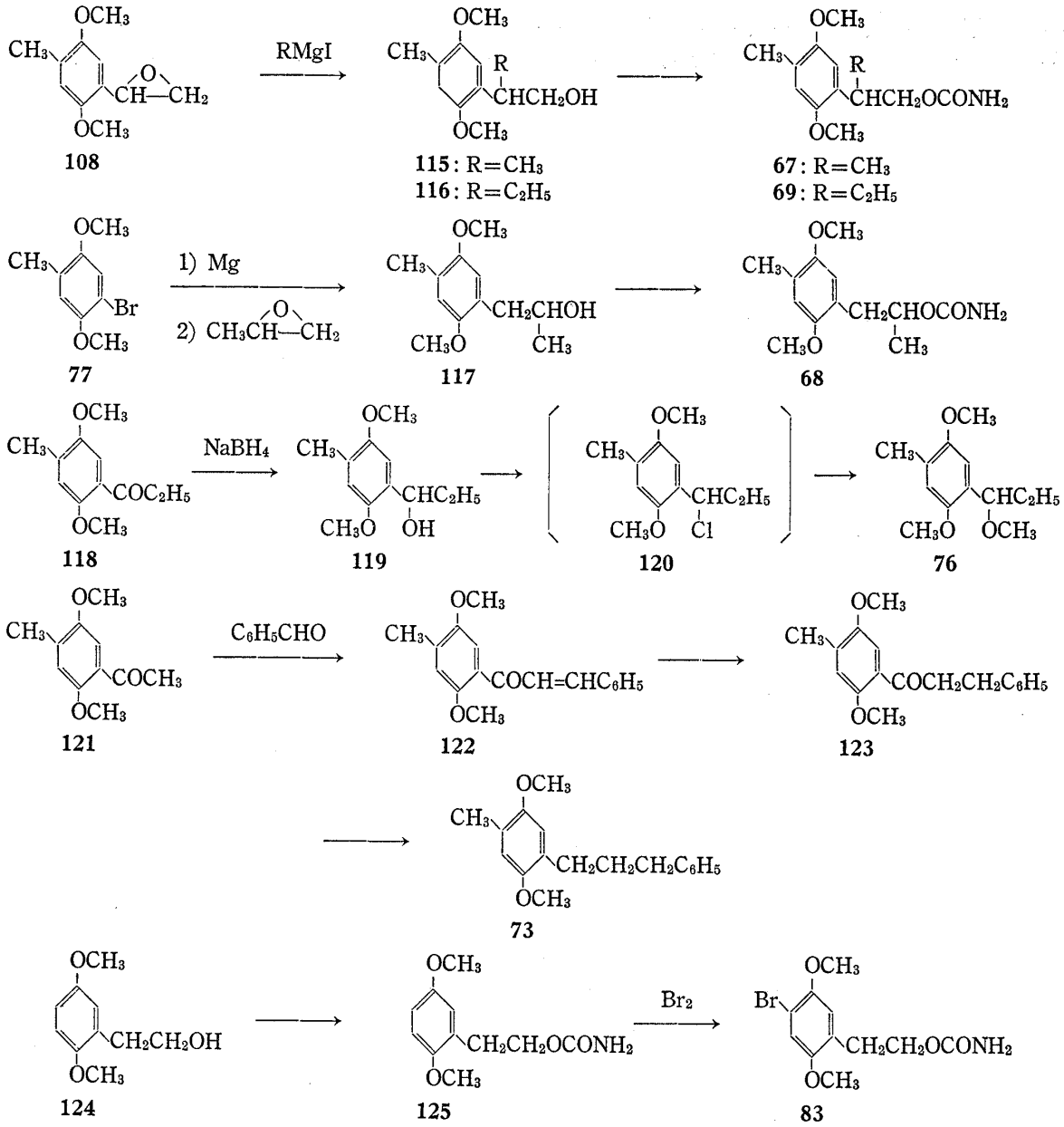


Chart 2

application of the D. MacHale's method.[6] Similarly, β-alkyl-2,5-dimethoxy-4-methylphenethyl alcohol (**115** and **116**) were synthesized from 2-epoxyethyl-1,4-dimethoxy-5-methylbenzene[5] (**108**) and alkyl magnesium iodide. The structures of these alcohols were supported by the fact that one of them, **115** was not identical with another possible isomer, 2,5-dimethoxy-α-ethyl-4-methylbenzyl alcohol (**119**) prepared from 2′,5′-dimethoxy-4′-methylpropiophenone (**118**).

In the reaction of 4-substituted 2,5-dimethoxytoluenes with nitric acid, wherein the 4-substituent contains an alkoxy group on the α-carbon, such a substituent has been reported[5] to be replaced by a nitro group to yield 2,5-dimethoxy-4-nitrotoluene (**127**). Actually, the reaction of 2,5-dimethoxy-4-(1-methoxypropyl)toluene (**76**) and nitric acid in acetic acid did yield **127**; however, the reaction of **76** and fuming nitric acid at −20° yielded the corresponding quinone (**63**) in low yield, which was converted into 2,5-bis(1-aziridinyl)-*p*-benzoquinone derivative (**18**). Interestingly, however, the reaction of β-alkoxy-2,5-

6) D. McHale, P. Mamalis, J. Green, and S. Marcinkiewicz, *J. Chem. Soc.*, **1958**, 1600.

dimethoxy-4-methylphenethyl carbamate, *e.g.* compound **70** with nitric acid in acetic acid gave the corresponding quinone (**47**) as main product and nitro compound (**127**) as byproduct (Chart 3).

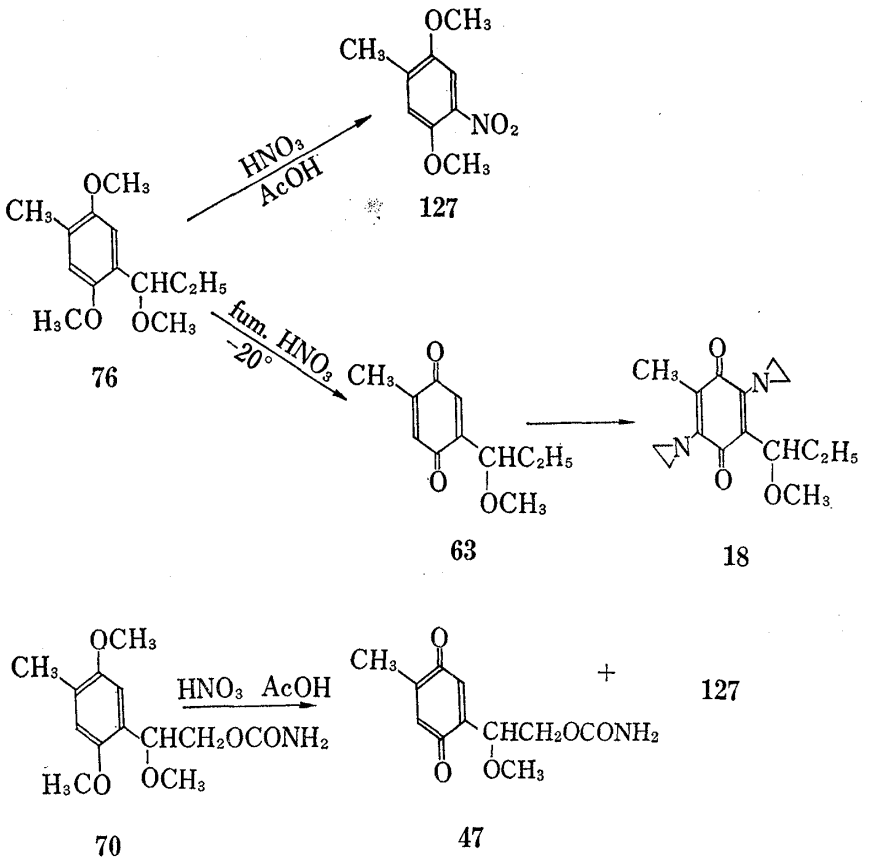


Chart 3

TABLE V. Antitumor Activity against Leukemia L-1210[a]

Compound	Continued injection[b]		Single injection[c]	
	Optimal dose[d] (mg/kg)	Effectiveness[e] (%)	Optimal dose (mg/kg)	Effectiveness (%)
1	0.5	140	1.0	77
2	—	—	4.0	63
3	0.36	52	1.0	55
4	0.6	126	1.5	>385
5	0.5	110	2.0	>350
6	0.7	103	2.0	>340
7	0.7	>433	3.0	>383
8	2.0	>222	8.0	>530
9	1.5	>325	4.0	84
10	0.96	107	3.5	69
11	1.0	98	7.0	>380
12	1.5	135	5.0	>119
13	20.0	65	80.0	80
14	6.0	60	16.0	>112
15	0.4	145	1.4	97
16	1.0	65	2.0	55
17	0.53	40	—	—
18	1.3	138	4.0	137
19	6.0	90	40.0	92
20	—	—	80.0	71

Compound	Continued injection[b]		Single injection[c]	
	Optimal dose[d] (mg/kg)	Effectiveness[e] (%)	Optimal dose (mg/kg)	Effectiveness (%)
21	inactive	—	—	—
22	0.15	139	0.5	140
23	1.0	>148	4.0	>290
24	2.0	>170	4.0	>490
25	2.0	144	8.0	>214
26	3.0	>516	8.0	105
27	1.9	106	12.0	>156
28	1.0	60	—	—
29	2.0	211	—	—
30	6.0	100	10.0	31
31	0.25	100	0.7	87
32	1.5	130	6.0	>350
33	inactive		—	—
34	2.0	94	4.0	62
35	10.0	145	20.0	62
36	7.0	143	20.0	83
37	10.0	53	80.0	97
38	25.0	90	—	—
39	inactive		—	—
40	10.0	40	40.0	68
41	3.5	63	10.0	61
42	27.0	52	160.0	98
MMC	2.0	85	4.0	54

a) L-1210 cells (10^5) were intraperitoneally inoculated.
b) Intraperitoneal therapy was begun 24 hr after implant and continued for 12 days except on sunday.
c) Intraperitoneal therapy was made 24 hr after implant.
d) Dose providing maximum increase in life span.
e) increase in life-span at optimal dose (T-C/C×100)

The above described 2,5-bis(1-aziridinyl)-*p*-benzoquinone derivatives were tested for antitumor activity against lymphoid leukemia L-1210 in BDF_1 mice. The results were summarized in Table V. Replacement of either or both methyl and carbamoyloxyethyl groups of compound (**1**) with bromine (**21** and **28**), acetyl (**20**) or phenyl (**38**) reduced the activity. On the contrary, the introduction of an alkoxy group such as methoxy (**7**), ethoxy (**8**) and 2-methoxyethyloxy (**9**) into position 1 of the 2-carbamoyloxyethyl group in compound (**1**) enhanced the activity. By the comparison of optimal dose (O.D.) of 2,5-bis(1-aziridinyl)-3,6-dialkyl-*p*-benzoquinones, the larger the alkyl group, the lower the toxicity appeared although the relationship between the toxicity and activity was not obvious.

In this series of compounds, **7**, **8**, **23**, and **24** were highly active both by single and continued administration. Among these substances, compound (**7**) under generic name of calbazilquinone is undergoing preclinical evaluation after further studies[7] as an antitumor agent.

Experimental

2,5-Bis(1-aziridinyl)-3,6-disubstituted-*p*-benzoquinones (Table I and II)——a) General Procedure: To a solution of a 2,5-disubstituted-*p*-benzoquinone in EtOH was added excess aziridine at room temperature. The resulting mixture was allowed to stand in refrigerator for 1—3 days. The separated crystals were collected, washed with EtOH and recrystallized from EtOH.

b) 3,6-Dibromo-2,5-bis(2-methyl-1-aziridinyl)-*p*-benzoquinone (**39**) was prepared according to the method of W. Gauss, *et al.*[8] To a stirred suspension of 8.6 g of bromanil in 100 ml of dry benzene was added

7) M. Arakawa, T. Aoki, and H. Nakao, *GANN*, **61**, 485 (1970).
8) Farbenfabriken Bayer Akt. Ges, (W. Gauss, S. Petersen, G. Domagk and C. Hackmann), *Ger.*, 967793 Dec., **12**, (1957), [*C.A.* **53**, P13173 fh (1959)].

dropwise a solution of 2.2 ml of 2-methylaziridine and 5.2 ml of triethylamine in 50 ml of dry benzene at 15°. After stirring at room temperature for 5 hr, the reaction mixture was filtered, washed with EtOH and then water. The dried crude product was recrystallized from benzene to give 1 g of red brown needles.

c) 2,3,5-Tris(1-aziridinyl)-6-methyl-*p*-benzoquinone (**22**): To a stirred suspension of 2.3 g of 2-methoxy-5-methyl-*p*-benzoquinone[4] (**51**) in 35 ml of MeOH was added 5 ml of aziridine at 0°. The resulting mixture was stirred at room temperature for 12 hr. After evaporation of solvent *in vacuo* the oily residue obtained was chromatographed on Al_2O_3. Elution with $CHCl_3$ and recrystallization of eluate from cyclohexane gave 100 mg of **22** as red purple needles.

2,5-Disubstituted-*p*-benzoquinones (Table III)——a) General Procedure: To a stirred solution of a 2,5-disubstituted-1,4-dimethoxybenzene in 5—10 parts of AcOH was added dropwise 60% HNO_3 (1.2—1.5 equivalent) at 15—20°. The resulting mixture was stirred for 1—3 hr at room temperature and then diluted with ice–water to separate products, which were recrystallized from EtOH. If product was liquid, it was extracted with ether and the ether extract was washed with aq. $NaHCO_3$ then water. After evaporation of solvent the oily residue obtained was distilled or used in the next reaction without further purification.

b) 2-(1-Methoxypropyl)-5-methyl-*p*-benzoquinone (**63**): To 80 ml of fuming nitric acid was added dropwise a solution of 10 g of 2,5-dimethoxy-4-(1-methoxypropyl)toluene (**76**) in 20 ml of AcOH at −20° with stirring. After stirring at −20° for 15 min, the resulting mixture was poured slowly onto 400 g of crushed ice and then extracted with ether. The extract was washed with aq. $NaHCO_3$, dried (Na_2SO_4) and evaporated to give oily residue, which was chromatographed on Al_2O_3 with benzene to yield 1.1 g of **63** as yellow oil. This product was used in the next reaction without further purification.

c) 2-(2-Carbamoyloxy-1-methoxyethyl)-5-methyl-*p*-benzoquinone (**47**): To a stirred solution of 1 g of **70** in 5 ml of AcOH was added dropwise 0.4 ml of 60% HNO_3 at 15°. After stirring at 10° for 1—2 hr the resulting mixture was poured into 50 ml of ice–water and the separated crystals were collected, washed with water, EtOH and then benzene. Recrystallization from EtOH–benzene (1:1) to give 0.4 g of **47** as yellow needles, mp 144°. UV λ_{max}^{EtOH} mμ (log ε): 251 (4.21), 257 (shoulder 4.19). IR ν_{max}^{Nujol} cm^{-1}: 3500, 3300, 1720, 1640 (quinone C=O). The benzene washings were evaporated to dryness and the residue was recrystallized from EtOH to give 0.1 g of yellow needles, mp 117°, not depressed on admixture with 2,5-dimethoxy-4-nitrotoluene[9] (**127**) possessing an identical infrared spectrum.

d) 2,5-Dipropyl-*p*-benzoquinone (**59**): A mixture of 2.4 g of 2,5-dipropylhydroquinone,[10] 7.2 g of Ag_2O, 1.2 g of Na_2SO_4 and 36 ml of dry tetrahydrofuran was stirred at room temperature for 1 hr. The resulting mixture was filtered and the filtrate was concentrated followed by distilled *in vacuo* to give 1.1 g of **59** as orange yellow liquid.

e) 2,5-Dimethyl,[11] 2-ethyl-5-methyl,[5] 2-isopropyl-5-methyl,[12] 2-(2-hydroxyethyl)-5-methyl,[5] 2-(2-acetoxyethyl)-5-methyl,[5] 2-methyl-5-phenoxymethyl,[5] 2-acetyl-5-methyl,[13] 2-bromo-5-methyl,[14] 2,5-bis-(2-hydroxyethyl),[15] 2,5-diisopropyl[16] and 2,5-diphenyl-*p*-benzoquinone[17] were prepared according to the methods in literature.

2′,5′-Dimethoxyvalerophenone[18] (91)——To an ice-chilled, stirred 30 g of *n*-valeryl chloride was added 30 g of powdered anhydrous $AlCl_3$. To the resulting mixture was added dropwise a solution of 28.5 g of 1,4-dimethoxybenzene in 57 ml of CS_2 at 20—25°, and the mixture was stirred for 2.5 hr at room temperature. After removal of upper CS_2 layer by decantation, the red brown viscous residue was poured into a mixture of 44 ml of conc. HCl and 290 ml of ice–water followed by extraction with ether. The ether extract was washed with water, dried (Na_2SO_4) and evaporated. The residue was distilled under reduced pressure to yield 32 g of **91** as pale yellow liquid, bp 142° (0.6 mmHg). *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.08; H, 8.35 IR. ν_{max}^{liquid} cm^{-1}: 1675 (C=O).

1,4-Dimethoxy-2-pentylbenzene[18] (94)——A mixture of 10 g of ketone (**91**), 20 ml of 80% $NH_2NH_2 \cdot H_2O$, 10.5 g of KOH and 40 ml of ethyleneglycol was refluxed for 1 hr with stirring. The resulting mixture was distilled until the temperature of the reaction mixture reached to 195°. The distillate was extracted with ether. The extract was washed with water, dried (Na_2SO_4) and distilled to give 4 g of **94**, bp 114° (5 mmHg). *Anal.* Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.47; H, 9.69.

9) P. Mamalis, J. Green, S. Marcinkiewicz and D. McHale, *J. Chem. Soc.*, **1959**, 3350.
10) K. Kitahonoki, *Chem. Pharm. Bull.* (Tokyo), **7**, 114 (1959).
11) D. Smith and A. Gilbert, *J. Chem. Soc.*, **1964**, 873.
12) E. Kremers, N. Wakeman, and R.M. Hixon, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New Yrok, N.Y. 1941, p. 511.
13) E. Kurosawa, *Bull. Chem. Soc. Japan*, **34**, 300 (1961).
14) L. Gattermann, *Chem. Ber.*, **27**, 1931 (1894).
15) G. Wegner, N. Nakabayashi, and H.G. Cassidy, *J. Org. Chem.*, **32**, 3155 (1967).
16) V.A. Bogolybskii, *Zh. Obshch. Khim.*, **32**, 869 (1962) [*C.A.*, **58**, 2391d (1963)].
17) J. Cason, "Org. Reaction," Vol. 4, ed. by John Wiley and Sons, Inc., New York, N.Y., 1948, p. 326.
18) T. Shoji, *Yakugaku Zasshi*, **79**, 1038 (1959).

2′,5′-Dimethoxy-4′-propylacetophenone (**100**)——138 g of 1,4-dimethoxy-2-propylbenzene[19] (**93**) was acetylated with 72 g (66 ml) of AcCl, 113 g of $AlCl_3$ and 280 ml of CS_2 in a similar manner to that for **91** to give 145 g of **100** as colorless liquid, bp 124° (0.4 mmHg). *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.23; H, 8.09. IR ν_{max}^{liquid} cm^{-1}: 1670 (C=O).

2′,5′-Dimethoxy-4′-pentylvalerophenone (**101**)——11.5 g of **94** was acetylated with 7.6 g of valeryl chloride, 7.7 g of $AlCl_3$ and 23 ml of CS_2 in a similar manner to that for **91** to give 11.5 g of **101** as colorless liquid, bp 155—160° (0.6 mmHg). *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.80; H, 9.96.

2,5-Diethyl-1,4-dimethoxybenzene (**86**)——A mixture of 4.4 g of 2′,5′-dimethoxy-4′-ethylacetophenone[20] (**99**), 4.6 g of KOH, 8.8 ml of 80% $NH_2NH_2 \cdot H_2O$ and 17.6 ml of ethyleneglycol was refluxed for 1 hr with stirring. The resulting mixture was distilled until the temperature of the reaction mixture reached to 195° and the residual mixture was refluxed for more 3 hr. After cooling, the mixture was poured into 100 ml of water and combined with the above distillate and then acidified with HCl followed by extraction with benzene. The extract was distilled to give 2.5 g of colorless liquid, which soon solidified. Recrystallization from MeOH–H_2O gave 1.5 g of colorless crystals, mp 39° (Table IV).

1,4-Dimethoxy-2,5-dipentylbenzene (**87**)——11.5 g of ketone (**101**) was reduced with 12.1 g of KOH, 23 ml of 80% $NH_2NH_2 \cdot H_2O$ and 46 ml of ethyleneglycol in a similar manner to that for **86** to give 5.4 g of **87** as colorless liquid (Table IV).

2-Bromo-5-ethyl-1,4-dimethoxybenzene (**95**)——To a solution of 16 g of 2-ethyl-1,4-dimethoxybenzene[21] in 40 ml of AcOH was added dropwidse a solution of 16 g of bromine in 10 ml of AcOH at 15—25° with stirring. After stirring for 2 hr at room temperature, the resulting mixture was diluted with ice–water to separate crystals, which were collected, washed with water and recrystallized from EtOH–H_2O to give 15 g of colorless prisms, mp 36°. *Anal.* Calcd. for $C_{10}H_{13}O_2Br$: C, 49.00; H, 5.34; Br, 32.60. Found: C, 49.02; H, 5.00; Br, 32.34.

2-Bromo-1,4-dimethoxy-5-propylbenzene (**96**)——18 g of **93** was brominated with 16 g of bromine in a similar manner to that for **95**. The resulting products were distilled to give 21 g of colorless liquid, bp 125° (5 mmHg). *Anal.* Calcd. for $C_{11}H_{15}O_2Br$: C, 50.99; H, 5.79; Br, 30.84. Found: C, 51.03; H, 5.81; Br, 30.61.

4-Ethyl-2,5-dimethoxy-phenethyl Alcohol (**97**)——15 g of **95** was hydroxyethylated in a similar manner to that for 2,5-dimethoxy-4-methylphenethyl alcohol[6] to give 6 g of **97** as colorless crystals, mp 65°. *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.32; H, 8.62.

2,5-Dimethoxy-4-propylphenethyl Alcohol (**98**)——15 g of **96** was similarly hydroxyethylated to give 7 g of **98** as colorless needles, mp 60°. *Anal.* Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.25; H, 9.00.

2-Bromo-4′-ethyl-2′,5′-dimethoxy-acetophenone (**102**)——To an ice-chilled stirred solution of 30 g of **99** in 120 ml of $CHCl_3$ was added dropwise a solution of 23 g of bromine in 40 ml of $CHCl_3$. The resulting mixture was stirred for 1.5 hr at room temperature and concentrated to dryness below 40°. To the residue was added cyclohexane and the product was collected and recrystallized from 80 ml of MeOH to give 16 g of **102** as colorless prisms, mp 85°. *Anal.* Calcd. for $C_{12}H_{15}O_3Br$: C, 50.19; H, 5.27. Found: C, 50.00; H, 5.42. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.15), 264 (3.89), 345 (3.71).

2-Bromo-2′,5′-dimethoxy-4′-propylacetophenone (**103**)——To a stirred solution of 10 g of ketone (**100**) in 40 ml of CCl_4 was added dropwise a solution of 7.2 g of bromine in 14 ml of CCl_4 at 10—15°. The resulting mixture was stirred for 1 hr at room temperature. During this time separated yellow crystals were dissolved and the solution blacked. After evaporation of the solvent *in vacuo* the residue was recrystallized from MeOH (40 ml) to give 5.4 g of **103**, mp 83°. *Anal.* Calcd. for $C_{13}H_{17}O_3Br$: C, 51.84; H, 5.69. Found: C, 51.36; H, 5.57.

α-(Bromomethyl)-4-ethyl-2,5-dimethoxy-benzyl Alcohol (**104**)——To a stirred solution of 26.4 g of bromoketone (**102**) in 240 ml of dioxane was added dropwise a solution of 2.4 g of $NaBH_4$ in 26 ml of water at 15—20°. After stirring at room temperature for 1.5 hr, to the mixture was added dropwise 26 ml of 10% H_2SO_4. The resulting mixture was poured into 1.3 liter of water and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and evaporated. The residue solidified was recrystallized from cyclohexane to give 20 g of colorless crystals, mp 71°. *Anal.* Calcd. for $C_{12}H_{17}O_3Br$: C, 49.84; H, 5.93. Found: C, 49.62; H, 5.88. IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH).

α-(Bromomethyl)-2,5-dimethoxy-4-propylbenzyl Alcohol (**105**)——40 g of bromoketone (**103**) was reduced with 5.4 g of $NaBH_4$ in a similar manner to that for **104** to give 35 g of **105** as colorless needles, mp 83°. *Anal.* Calcd. for $C_{13}H_{19}O_3Br$: C, 51.49; H, 6.32. Found: C, 51.52; H, 6.42.

4-Ethyl-β, 2,5-trimethoxyphenethyl Alcohol (**109**)——A mixture of 22 g of bromoalcohol (**104**), 260 ml of benzene, 10.5 g of KOH and 80 ml of water was vigorously stirred under reflux for 1.5 hr. After cooling,

19) T.B. Johnson and W.W. Hodge, *J. Am. Chem. Soc.*, **35**, 1014 (1913).
20) R. Royer, P. Demerseman, A.L. Teantet, J.F. Rassignol, and A. Cheutin, *Bull. Soc. Chim. France*, **1968**, 1026.
21) G.R. Ramage and C.V. Stead, *J. Chem. Soc.*, **1953**, 3602.

the benzene layer was washed with water, dried (Na_2SO_4) and then evaporated to give 13 g of crude 2-(1,2-epoxyethyl)-5-ethyl-1,4-dimethoxybenzene (**106**) as colorless liquid. To a stirred solution of 13 g of this compound in 96 ml of MeOH was added 3 drops of BF_3 ether solution at room temperature. The mixture was stirred for 1 hr at 40° and concentrated under reduced pressure to give crude product, which was recrystallized from petroleum benzin yielding 10.5 g of **109** as colorless crystals, mp 88°. *Anal.* Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.82; H, 8.36. IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 1205, 1040.

β-Ethoxy-4-ethyl-2,5-dimethoxyphenethyl Alcohol (110)——To a solution of 5 g of crude epoxyethyl compound (**106**) prepared by the above described procedure in 30 ml of EtOH was added 2 drops of BF_3 ether solution. The mixture was stirred for 1 hr at 40° and concentrated under reduced pressure. The resulting residual oil was dissolved in 60 ml of ether and washed with water, dried (Na_2SO_4) and concentrated to give a crude product as liquid, which was distilled to yield 4 g of **110** as colorless viscous oil, bp 135° (0.05 mmHg). *Anal.* Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.25; H, 8.37.

4-Propyl-β, 2,5-trimethoxyphenethyl Alcohol (111)——In a similar manner to that for **109**, 20 g of **105** was converted to 13 g of 1,4-dimethoxy-2-(1,2-epoxyethyl)-5-propylbenzene (**107**), which was reacted with MeOH to give 7.5 g of colorless crystals, mp 95°. *Anal.* Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.84; H, 8.72.

β-Ethoxy-2,5-dimethoxy-4-methylphenethyl Alcohol (113)——In a similar manner to that for **110** or **112**,[5] 10 g of 4-(1,2-epoxyethyl)-2,5-dimethoxy-toluene[5] (**108**) was reacted with EtOH to give 8 g of **113** as liquid, which was uded for next reaction without purification.

2,5-Dimethoxy-β-(2-methoxyethyloxy)-4-methylphenethyl Alcohol (114)——To a solution of 20 g of **108** in 100 ml of ethyleneglycol monoethyl ether was added 3 drops of BF_3 ether solution. After stirring at 40° for 1 hr, the resulting mixture was concentrated under reduced pressure below 50° and the residue was dissolved in 100 ml of ether and washed with water, dried (Na_2SO_4) and concentrated to give a crude product, uhich was distilled to yield 12 g of **114** as colorless liquid, bp 158° (0.6 mmHg). *Anal.* Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 61.97; H, 8.35.

2,5-Dimethoxy-β, 4-dimethylphenethyl Alcohol (115)——To an ice-chilled, stirred solution of CH_3MgI prepared from 2.2 g of Mg and 13.5 g of CH_3I in 60 ml of dry ether was added dropwise a solution of 15 g of **108**[5] in 150 ml of dry ether below 5°. The resulting mixture was refluxed for 1.5 hr with stirring and then allowed to stand overnight at room temperature. To the mixture was added 10 ml of ice–water and 70 ml of 10% H_2SO_4 and the ether layer was separated and the aqueous layer was extracted with ether. The combined ether layer was washed with water, dried (Na_2SO_4) and evaporated. The residue was distilled to give 8.3 g of **115**, bp 130° (3 mmHg), which soon solidified. Recrystallization from ligroin gave colorless needles, mp 79°. *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.67; H, 8.55.

β-Ethyl-2,5-dimethoxy-4-methylphenethyl Alcohol (116)——In a similar manner to that for **115**, 29 g of **108** was reacted with EtMgI prepared from 5.3 g of Mg and 32 g of EtI. The curde product was distilled to give 17.5 g of **116** as colorless liquid, bp 143° (3 mmHg). *Anal.* Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.24; H, 8.99.

2,5-Dimethoxy-α, 4-dimethylphenethyl Alcohol (117)——This compound was prepared by a similar procedure to that for 2,5-dimethoxy-4-methylphenethyl alcohol.[6]

To a stirred mixture of 8.2 g of Mg and 30 ml of dry ether was added dropwise a solution of 40 g of 4-bromo-2,5-dimethoxytoluene[6] (**77**) and 24 g of CH_3I in 240 ml of dry ether. The resulting mixture was refluxed for 2 hr with stirring. After cooling to −5°, to the mixture was added dropwise a solution of 40 g of propylene oxide in 50 ml of dry ether at 0°. The resulting mixture was refluxed for 2 hr and then allowed to stand overnight at room temperature. To the reaction mixture was added dropwise 95 ml of 25% H_2SO_4 and the ether layer was washed with water, dried (Na_2SO_4) and evaporated to give a crude product, which was distilled yielding 10 g of **117**, bp 110° (0.6 mmHg) soon solidified. Recrystallization from petroleum benzin gave 4.5 g of colorless crystals, mp 76°. *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.21; H, 8.38.

α-Ethyl-2,5-dimethoxy-4-methylbenzyl Alcohol (119)——To a stirred solution of 20 g of 2′,5′-dimethoxy-4′-methylpropiophenone[5] (**118**) was added dropwise a solution of 1.8 g of $NaBH_4$ in 20 ml of water at room temperature. After stirring for 1.5 hr, to the mixture was added dropwise 20 ml of 10% H_2SO_4 and then the mixture was poured into 1 liter of ice–water followed by extraction with ether. The extract was distilled to give 12 g of **119** as colorless liquid, bp 133° (1.5 mmHg). *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.90; H, 8.53.

2,5-Dimethoxy-4-(1-methoxypropyl)toluene (76)——To an ice-chilled, stirred solution of 5 g of **119** in 25 ml of dry benzene was added dropwise a solution of 3.4 g of $SOCl_2$ in 4 ml of dry benzene. The resulting mixture was stirred at room temperature for 2 hr and then concentrated below 40° to give 6 g of crude chloride (**120**) as liquid. This chloride was mixed with a solution of 0.75 g of Na in 30 ml of MeOH and refluxed for 2 hr. After removal of MeOH, the reaction mixture was diluted with water and then extracted with ether. The ether extract was dried (Na_2SO_4) and then distilled to give 2.5 g of **76** as colorless liquid (Table IV).

2′,5′-Dimethoxy-4′-methylchalcone (122)——To a mixture of 20 g of powdered 2′,5′-dimethoxy-4′-methylacetophenone[20] and 20 ml of benzaldehyde was added a solution of 0.56 g of Na in 10 ml of MeOH.

The resulting mixture was vigorously stirred for 10 min at room temperature and then allowed to stand in refrigerator overnight. The separated crystals were collected, washed with water and recrystallized from EtOH to give 20 g of orange-yellow crystals, mp 82°. *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.44; H, 6.34. IR ν_{max}^{Nujol} cm^{-1}: 1655 (C=O).

2′,5′-Dimethoxy-4′-methyl-3-phenylpropiophenone (123)——21.3 g of chalcone (**122**) was hydrogenated with 0.6 g of 10% Pd-C in 400 ml of EtOH. 1.8 liter of H_2 was absorbed. The reduction mixture was filtered followed by concentration to separate crystals, which were recrystallized from EtOH to give 13 g of **123** as colorless crystals, mp 95°. *Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.19; H, 7.12. IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O). UV λ_{max}^{EtOH} $m\mu$ (log ε): 225 (4.18), 259 (3.87), 332 (3.66).

2,5-Dimethoxy-4-(3-phenylpropyl)toluene (73)——A mixture of 14 g of **123**, 28 ml of 80% $NH_2NH_2 \cdot H_2O$, 15 g of KOH and 76 ml of ethylene glycol was refluxed for 2 hr, and then concentrated until the temperature of the reaction mixture reached to 185°. The resulting reaction mixture was stirred at 185° for 1 hr and then poured into 500 ml of water, acidified with HCl and extracted with benzene. The extract was dried (Na_2SO_4) and distilled to give 11 g of **73** as colorless liquid (Table IV).

2,5-Dimethoxyphenethyl Carbamate (125)——To an ice-chilled, stirred solution of 14 g of 2,5-dimethoxyphenethyl alcohol[22] (**124**) in 75 ml of pyridine was added dropwise 14.5 g of phenyl chloroformate. The resulting mixture was stirred at room temperature for 2.5 hr and then diluted with water to separate oily substance, which was extracted with ether. The extract was washed with water and evaporated to give 25 g of crude product (2,5-dimethoxyphenethyl phenyl carbonate) as pale yellow liquid. This compound (25 g) was heated with 120 ml of 28% aq. ammonia and 250 ml of EtOH under reflux for 3 hr. The resulting mixture was concentrated under reduced pressure to one-third the voluem. After cooling, to the mixture was added 100 ml of 5% aq. NaOH and the separated product was extracted with ether. The ether extract was dried (Na_2SO_4) and the solvent was evaporated. Recrystallization of the residue from EtOH–cyclohexane gave 8 g of **125** as colorless needles, mp 98°. *Anal.* Calcd. for $C_{11}H_{15}O_4N$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.21; H, 6.75; N, 5.93.

4-Bromo-2,5-dimethoxyphenethyl Carbamate (83)——To a stirred solution of 1.1 g of **125** in 8 ml of AcOH was added dropwise a solution of 0.8 g of bromine in 2 ml of AcOH at room temperatue. After stirring for 2 hr, the mixture was poured into 50 ml of ice–water to separate crystals, which were recrystallized from EtOH yielding 1 g of colorless leaflets (Table IV).

4-Benzyl-2,5-dimethoxytoluene (74)——In a similar manner to that for **86**, 8 g of 2,5-dimethoxy-4-methylbenzophenone[23] was reduced to 4 g of **74** (Table IV).

2,5-Dimethoxy-4-(2-methoxyethyl)toluene (75)——A mixture of 5 g of 2,5-dimethoxy-4-methylphenethyl alcohol, 8 ml of CH_3I and 9 g of Ag_2O was heated at 80—90° for 7 hr in a sealed tube. After adding 30 ml of benzene, the reaction mixture was filtered and the filtrate was concentrated. Distillation of the residue gave 2 g of **75** as colorless liquid (Table IV).

2,5-Bis(2-methoxyethyl)-1,4-dimethoxybenzene (84)——A mixture of 5 g of 2,5-dimethoxy-*p*-benzene diethanol,[1] 14 ml of CH_3I, 18 g of Ag_2O and 30 ml of benzene was heated at 80—90° in a sealed tube for 16 hr. The reaction mixture was filtered and the filtrate was concentrated to dryness and the residue was recrystallized from petroleum ether to give 2.2 g of colorless crystals (Table IV).

2,5-Dimethoxy-*p*-benzene Diethanol Diacetate (85)——A mixture of 5 g of 2,5-dimethoxy-*p*-benzene diethanol and 30 ml of acetic anhydride was refluxed for 1 hr. After cooling the reaction mixture was poured into 350 ml of water to separate crystals, which were recrystallized from EtOH yielding 3.5 g of colorless crystals (Table IV).

Preparation of Carbamate (66—72, 78—82)——General Procedure: Carbamates were prepared from the corresponding alcohols by the reaction with phenyl chloroformate followed by ammonolysis.

To an ice-chilled, stirred solution of 0.05 mole of a hydroxy compound in 60 ml of pyridine was added dropwise 0.06 mole of phenyl chloroformate. The resulting mixture was stirred at room temperature for 2.5 hr and then poured into 400 ml of ice–water to separate a crude reaction product (alkyl phenyl carbonate), which was extracted with ether. If a product was solid, it was collected by filtration. Evaporation of ether gave quantitatively a crude carbonate.

A mixture of the above crude carbonate, 150 ml of EtOH and 75 ml of 28% aq. ammonia was refluxed for 3 hr. The resulting mixture was concentrated to about one-third the volume and then to the residue was added 17 ml of 10% NaOH and 50 ml of ice–water. The separated crystals were collected, washed with water, dried and recrystallized from cyclohexane or benzene–cyclohexane to give a carbamate as colorless crystals. Yield, 50—80%. (Table IV).

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