25836). J.A.K. is a Camille and Henry Dreyfus Teacher-Scholar, and D.F.H. is a Procter and Gamble Fellow. Kurt W. Raack assisted in the preparation of diethylaminosulfur trifluoride (DAST). The binding affinity measurements to the uterine estrogen receptor were performed by Kathryn E. Carlson. The high-resolution mass spectrometry equipment used in this study was provided by a grant from the National Cancer Institute (CA 11388).

Aporphines. 31. Synthesis and Antitumor Activity of Aporphine Nitrogen Mustards[1a]

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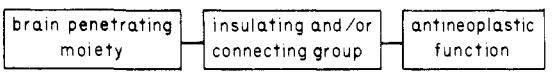
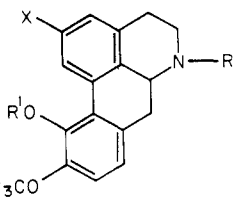
A series of aporphine nitrogen mustards and their congeners (**1b–g**) has been prepared. *N*-[[Bis(2-chloroethyl)-amino]acetyl]-2,11-dihyroxy-10-methoxynoraporphine (**1b**) and its mono- and diacetyl ester derivatives (**1c–d**) were prepared from *N*-(chloroacetyl)-2,11-diacetoxy-10-methoxynoraporphine (**2**). Reaction of **2** with diethanolamine under various conditions and different solvents resulted in the corresponding *N*-[[bis(2-hydroxyethyl)amino]acetyl] precursors, which were subsequently treated with $SOCl_2$ to yield the target compounds. *N*-(2-Choroethyl)norapocodeine (**1e**) was obtained from the chlorination of *N*-(2-hydroxyethyl)norapocodeine (**9**) with $SOCl_2$. Prolonging such treatment was found to result in the formation of *N*-[2-(chloroethoxy)ethyl]norapocodeine (**1f**) at the expense of **1e**. *N*-[[[*N'*-(2-Chloroethyl)carbamyl]oxy]ethyl]norapocodeine (**1g**) and its 11-(2-chloroethyl)carbamyl derivative (**1h**) were also prepared. All the double-armed aporphine amide nitrogen mustards (**1b–d**) were found to have antitumor activity. The single-armed aporphine nitrogen mustard (**1e**) was also active in P388 but the activity was less than that observed with **1b–d**. The lead compound **1a** was inactive in the LE1210 and P388 systems at the doses tested. Similarly, the two aporphine mustard congeners (**1f,g**) were also inactive in the P388 system. All the activity was observed in the intraperitoneally innoculated tumor systems.

In a continuing effort to design central nervous system (CNS) penetrating antitumor agents, our approach was the development of multiple-component drugs containing both CNS-penetrating moieties and antineoplastic functions. Thus, the overall drug structure may be viewed as a three-component compound incorporating the following structural features:



This approach has been used successfully by Driscoll[2] et al. who utilized the concept of attaching alkylating functions to such CNS-penetrating agents as the hydantoins,[2a] phenothiazines,[2b] and benzoquinones.[2c,d] When we utilized the CNS-penetrating 3-amino-4-(*p*-aryl and alkyl)isoquinolines as the brain-penetrating moiety, incorporating a nitrogen mustard as the antineoplastic function,[3] or when a bis(2-chloroethyl)aminoethyl moiety was attached directly to the nitrogen atom in 2,10,11-trimethoxynoraporphine[4] (**1a**), inactive antitumor compounds resulted. We attributed such inactivity to the apparent high lipophilic character of these compounds. Consequently, derivatives **1b–g** were synthesized in an effort to increase the hydrophilicity of the molecule without sacrificing its potential CNS-penetrating properties. The structural modifications featuring (a) replacements of the 2- and 11-methoxy groups with H and OH or metabolically labile acetoxy groups, (b) attachment of the nitrogen mustard moiety to the aporphine nitrogen atom via an amide bond as opposed to the hydrocarbon chain existing in **1a**, or (c) direct attachment of the chloroethyl group to the aporphine nitrogen atom led to antitumor activity of these compounds in one or several tumor systems.



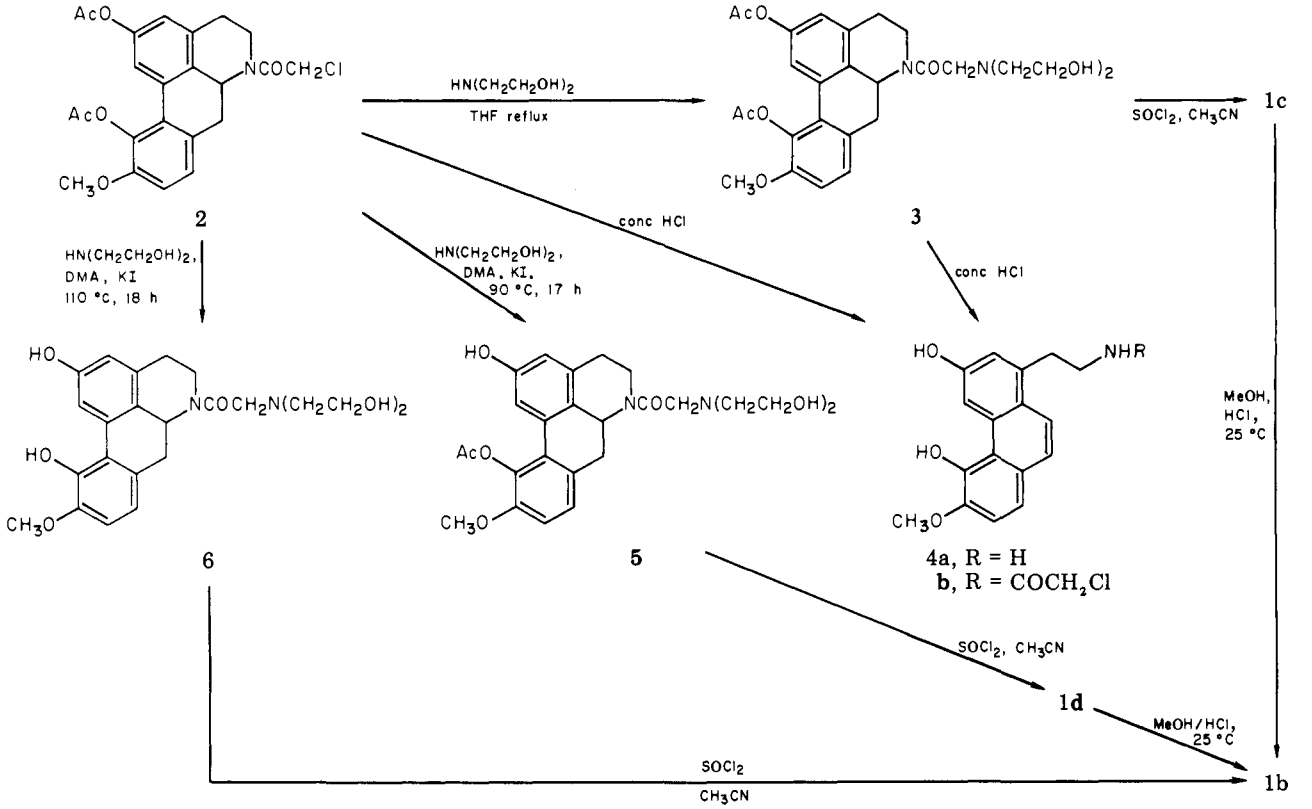
1a (NSC 278462), X = OCH_3; R^1 = CH_3; R = $CH_2CH_2N(CH_2CH_2Cl)_2$
b (NSC 311484), X = OH; R^1 = H; R = $COCH_2N(CH_2CH_2Cl)_2$
c (NSC 294134), X = $OCOCH_3$; R^1 = $COCH_3$; R = $COCH_2N(CH_2CH_2Cl)_2$
d (NSC 279847), X = OH; R^1 = $COCH_3$; R = $COCH_2N(CH_2CH_2Cl)_2$
e (NSC 304688), X = H; R^1 = H; R = CH_2CH_2Cl
f (NSC 311483), X = H; R^1 = H; R = $CH_2CH_2OCH_2CH_2Cl$
g (NSC 316161), X = H; R^1 = H; R = $CH_2CH_2OCONHCH_2CH_2Cl$
h (NSC 322369), X = H; R^1 = $CONHCH_2CH_2Cl$; R = $CH_2CH_2OCONHCH_2CH_2Cl$

We wish to report the synthesis of the active antitumor agents **1b–d** as well as the antitumor activity of the single-armed mustard, **1e**. The synthesis of **1e** has been

(1) (a) Presented at the 179th National Meeting of the American Chemical Society; see "Abstracts of Papers", 179th Meeting of the American Chemical Society, Houston, Texas, Mar 23–28, 1980, American Chemical Society, Washington, D.C., 1980, Abstr MEDI 63. (b) New England Nuclear Corp. (c) College of Pharmacy, Ohio State University. (d) Collaborative Research Corp.
(2) (a) G. W. Peng, V. E. Marquez, and J. S. Driscoll, *J. Med. Chem.*, 18, 846 (1975); (b) T. Hirata and J. S. Driscoll, *J. Pharm. Sci.*, **65**, 1699 (1976); (c) F. Chou, A. H. Khan, and J. S. Driscoll, *J. Med. Chem.*, **19**, 1302 (1976); (d) A. H. Khan and J. S. Driscoll, *ibid.*, 19, 313 (1976).
(3) C. N. Filer, F. E. Granchelli, A. H. Soloway, and J. L. Neumeyer, *J. Med. Chem.*, **20**, 1504 (1977).
(4) F. E. Granchelli, A. H. Soloway, J. L. Neumeyer, and C. N. Filer, *J. Org. Chem.*, 42, 2014 (1977).

0022-2623/80/1823-1008$01.00/0

Scheme I

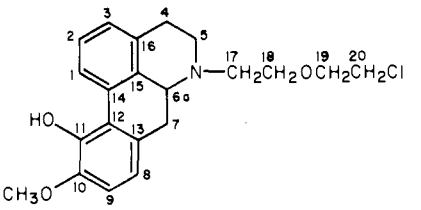


presented elsewhere.[5] Additionally, the derivatives **1f–g** arising from the substitution of the chloroethyl side chain of **1e** with chloroethoxyethyl or chloroethylcarbamylethyl moieties failed to demonstrate antitumor activity.

Chemistry. Careful treatment of the previously described[4] *N*-(chloroacetyl) derivative **2** with diethanolamine in refluxing THF provided the diol **3** (Scheme I). Further treatment with $SOCl_2$ yielded the desired mustard **1c**, which can rapidly give rise to **1b** in the presence of methanol and HCl. It is noteworthy that refluxing the diacetoxy diol **3** in concentrated hydrochloric acid for several hours causes ring scission with concomitant deamidation and deacetylation resulting in near quantitative formation of the phenanthrene **4a**. A similar scission of the nitrogen ring to give the phenanthrene analogue **4b** was observed when **2** was treated with concentrated HCl.[5] The preparation of **1d** requires treating **2** with a twofold excess of diethanolamine at 90 °C to give the partial deacetylated intermediate **5**. On steric grounds and on the basis of NMR interpretations it is postulated that deacetylation occurred at position 2 in preference to position 11. Treatment of **5**, with $SOCl_2$ afforded **1d**, which as in the deacylation of **1c** will give rise to **1b** in the presence of MeOH and HCl. Alternatively, **1b** can be obtained from **6** by its reaction with thionyl chloride in acetonitrile. This latter structure is derived by treating **2** with a large excess of diethanolamine at 110 °C.

Alkylation of norcodeine (**7**) with bromoethanol yielded *N*-(hydroxyethyl)norcodeine (**8**). Acid-catalyzed rearrangement with neat methanesulfonic acid led to *N*-(hydroxyethyl)norapocodeine (**9**),[5] which was converted to the mustard **1e** by standard procedures. However, if stirring of **9** with $SOCl_2$ was prolonged overnight, **1f** was generated as a side product at the expense of **1e**. Compound **1g** can be obtained by treating **9** with excess chloroethyl isocyanate in refluxing THF. A side product, the dicarbamate **1h**, was also generated (Scheme II). The structure of **1f** was confirmed by high-resolution mass spectrometic data and by ^1H and ^{13}C NMR spectral analysis (Table I). The

Table I. ^{13}C NMR Spectrum of 1f[a]

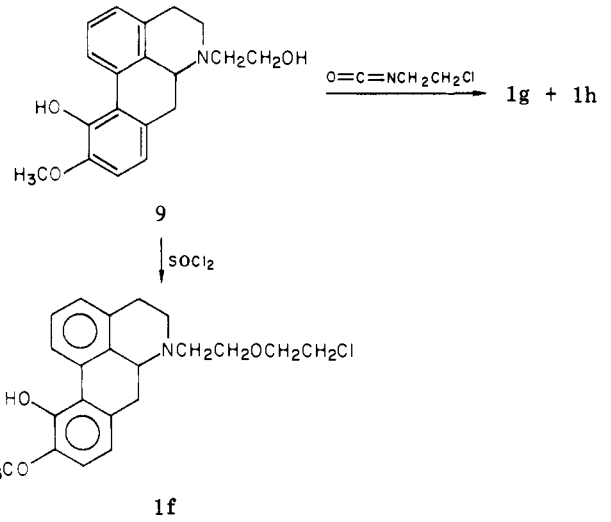


carbon assignment	chemical shift[a] (multiplicity)
1	128.41[b]
2	129.04[b]
3	129.24[b]
4	27.27 (t)
5	51.49 (t)
6a	63.48 (d)
7	32.78 (t)
8	119.89 (d)
9	111.88 (d)
10	149.20 (s)
11	146.00 (s)
12	119.75 (s)
13	127.00 (s)
14	129.66[b]
15	130.70[b]
16	134.06[b]
17	43.97 (t)
18	55.20 (t)
19	65.94 (t)
20	72.63 (t)
21	65.94 (q)

[a] Chemical-shift values are expressed in parts per million downfield from internal $(CH_3)_4Si$: s = singlet; d = doublet; t = triplet; q = quartet. [b] The aromatic resonances could not be rigorously assigned.

(5) F. E. Granchelli, C. N. Filer, A. H. Soloway, and J. L. Neumeyer, *J. Org. Chem.*, 45, 2275 (1980).

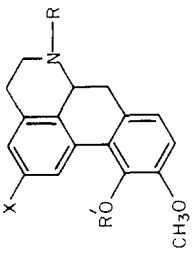
Scheme II



mass spectrum of **1f** showed a molecular peak of m/e 373 and a P + 2 peak of one-third intensity, supporting a combination of $C_{21}H_{24}NO_3Cl$ which is the empirical formula of **1f**. Major fragments shown in the mass spectrum of **1f** are shown in Scheme III. The elemental composition of the molecular ion and all fragment ions in the mass spectrum of **1f** have been confirmed by HRMS ($M/\Delta M$ = 30 000). Similar fragmentation patterns giving rise to m/e 280 and a retro-Diels–Alder type of fragmentation giving rise to m/e 238 have been encountered in several other aporphine derivatives [e.g., **1e** and *N*-(hydroxyethyl)norapomorphine[6]]. Physical and chemical data for all intermediates and target compounds are listed in Table II.

Antitumor Activity. Table III lists the antitumor activity of the aporphine derivatives evaluated in one or several tumor systems implanted intraperitoneally (ip) and intracerebrally (ic). The 2,10,11-trimethoxy derivative (**1a**, NSC 278462) was inactive in the LE1210 lymphoid leukemia (LE), ependymoblastoma (EM), and P388 lymphocytic leukemia (P388) assay systems using standard NCI protocols.[7,8] The 2,11-dihydroxy-10-methoxyaporphine amide nitrogen mustard (**1b**, NSC 311484) had confirmatory activity[9] in the ip inoculated P388 tumor system. Further studies in other tumor systems are still underway. The 2,11-diacetoxy-10-methoxyaporphine amide nitrogen mustard (**1c**, NSC 294134) showed activity in both P388 and B16 melanocarcinoma (B16) assays with reproducible activity down to the dose of 12.5 mg/kg in B16 and possibly lower in P388. The 2-hydroxy-11-acetoxy-10-methoxyaporphine amide nitrogen mustard (**1d**, NSC 279847), likewise, was found to be active in both ip inoculated P388 and B16 assays but failed to show confirmatory activity in LE1210 and ic inoculated EM and B16 tumor systems. The single-armed aporphine nitrogen mustard (**1e**, NSC 304688) showed only marginal but confirmatory activity in the P388 assay at a dose of 4.0 mg/kg. The derivatives of **1e**, **1f** (NSC 311483) and **1g**

Table II. Physical and Chemical Data



compd	NSC no.	X	R′	R	% yield[a]	mp, °C	formula	anal.
1b	311484	OH	H	$COCH_2N(CH_2CH_2Cl)_2$	10[b]	165–170	$C_{23}H_{26}Cl_2N_2O_4 \cdot HCl \cdot 2H_2O$	C, H, N
1c	294134	$OCOCH_3$	$COCH_3$	$COCH_2N(CH_2CH_2Cl)_2$	54	145–155	$C_{27}H_{28}Cl_2N_2O_6 \cdot HCl \cdot H_2O$	C, H, Cl, N
1d	279847	OH	$COCH_3$	$COCH_2N(CH_2CH_2Cl)_2$	50	115–119	$C_{25}H_{28}Cl_2N_2O_5$	C, H, Cl, N
1e	304688	H	H	CH_2CH_2Cl	32	212–215	$C_{19}H_{20}ClNO_2 \cdot HCl$	C, H, N
1f	311483	H	H	$CH_2CH_2OCH_2CH_2Cl$	40	202–205	$C_{21}H_{24}ClNO_3 \cdot HCl \cdot 0.5H_2O$	C, H, N
1g	316161	H	H	$CH_2CH_2OCONHCH_2CH_2Cl$	23	185–188	$C_{22}H_{25}ClN_2O_4 \cdot HCl \cdot 1.5H_2O$	C, H, N
1h	322369	H	$CONHCH_2CH_2Cl$	$CH_2CH_2OCONHCH_2CH_2Cl$	22	178–182	$C_{25}H_{29}Cl_2N_3O_5 \cdot HCl \cdot 1.5H_2O$	C, H, N
3		$OCOCH_3$	$COCH_3$	$COCH_2N(CH_2CH_2OH)_2$	47	160–170	$C_{27}H_{32}N_2O_8 \cdot HCl$	C, H, Cl, N
2	272339	$OCOCH_3$	$COCH_3$	$COCH_2Cl$	43	110–115	$C_{23}H_{22}ClNO_6$	C, H, Cl, N
5	282453	OH	$COCH_3$	$COCH_2N(CH_2CH_2OH)_2$	90	105–115	$C_{25}H_{30}N_2O_7 \cdot 0.5H_2O$	C, H, N

[a] Yield of last step. [b] Overall yield from the starting *N*-(chloroacetyl)-2,11-diacetoxy-10-methoxynoraporphine (**2**) was not optimized.

(6) J. L. Neumeyer, S.-J. Law, R. J. Baldessarini, and N. S. Kula, *J. Med. Chem.*, **23**, 594 (1980).
(7) "Instruction 14, Screening Data Summary Interpretation and Outlines of Current Screen", Drug Evaluation Branch, Drug Research and Development Division of Cancer Treatment, National Cancer Institute (NCI), Bethesda, MD.
(8) P. C. Merker, I. Wodinsky, and R. I. Geran, *Cancer Chemother. Rep.*, **59**, 729 (1975).
(9) Compounds are considered active in vivo in this system if they exhibit activity (T/C) values equal to or greater than 125%.

Scheme III

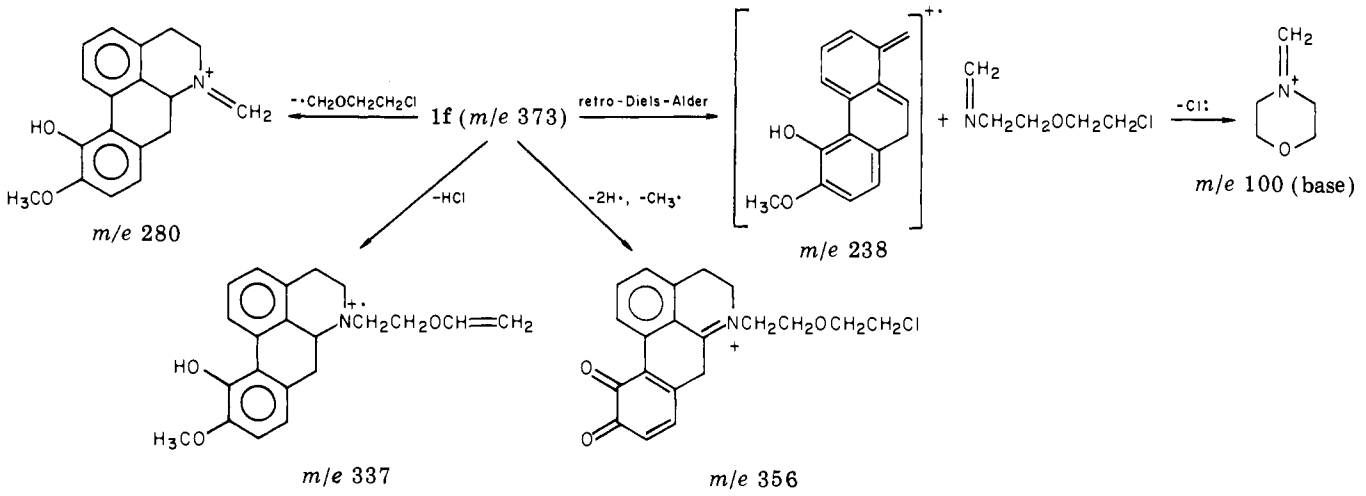


Table III. Antitumor Activity[a]

compd	NSC no.	schedule	dose, mg/kg	T/C[b]	compd	NSC no.	schedule	dose, mg/kg	T/C[b]
1a	278462	LE (ip)[c]	100	87	1e	304688	P388 (ip)	16	128
			50	101				8	114
			25	101				4	151
			12.5	98					
			6.25	101			P388 (ic)	16	107
								8	96
		EM (ic)[c]	16	108					
			8	104			B16 (ip)	16	97
			4	108				8	97
								4	91
		P388 (ip)	16	113					
			8	127			B16 (ic)	32	103
			4	106				16	106
								8	102
1b	311484	P388 (ip)	25	114				4	106
			12.5	158				2	100
			6.25	149					
			3.13	130			C6[d] (ip)	32	124
								16	108
1c	294134	P388 (ip)	50	95				8	119
			25	185				4	107
			12.5	170					
			6.25	150			EM (ic)	4	104
			3.13	138				2	99
								1	96
		B16	50	170				0.5	100
			25	150				0.25	105
			12.5	150					
			6.25	159	1f	311483	P388 (ip)	100	104
			3.13	120				50	101
			1.56	120				25	107
								12.5	99
1d	279847	LE (ip)	100	88					
			50	127	1g	316161	P388 (ip)	300	105
			25	136				105	99
								75	99
		P388 (ip)	50	130				37.5	97
			25	168				18.75	99
			12.5	174				9.38	101
			6.25	143					
		B16	50	170					
			25	135					
			12.5	134					
		EM (ic)	50	86					
			25	99					
			12.5	94					
		B16 (ic)	16	102					
			8	111					

[a] Biological evaluations were performed by independent screeners under the auspices of the National Cancer Institute.[7] [b] Activity is defined as a T/C value of ≥125 and was confirmed by two or more screeners. The results of one screener or average values are presented. [c] ip or ic in parentheses denotes intraperitoneally or intracerebrally implanted tumor. [d] Colon 26 tumor.

(NSC 316161) were inactive in the P388 assay at the doses tested (Table III).

Discussion

The antitumor activity exhibited by the aporphine mustards **1b–e** suggests that structural modifications which increase hydrophilic character will increase antitumor activity. Although none of the active compounds displayed the same effectiveness when tested with ic implanted tumors, it does not necessarily follow that these compounds failed to penetrate into the CNS. We have obtained evidence from closely related structures which indicate that such agents do indeed effectively penetrate the CNS.[6,10]

The fact that both the mono- and diacetoxyaporphine mustards (**1d** and **1c**) have the same order of activity as the phenolic derivative (**1b**) could reflect a fast in vivo hydrolysis of the acetates to their phenolic counterpart **1b**. Both the HCl salt and the free base of **1c** and **1d**, respectively, have been found to undergo autohydrolysis on prolonged storage as monitored by TLC.[11] Baldessarini et al.[12] have made similar observations with *O,O'*-diacetylapomorphine.

The indispensability of the functional nitrogen mustard side chain in the aporphine series must be emphasized. Changes of activity are observed in replacing the double-armed aporphine mustards with a single-armed derivative such as **1e** to the inactive congeners **1f** and **1g**. If the bulk of the antitumor activity of the two-armed mustards (**1b–d**) is due to lethal DNA cross-linking, then the effectiveness exhibited by the "one-armed" mustard **1e** must be due to nonspecific toxicity. The lack of activity of **1g** and **1h** is thus expected, based on the fact that bioactivation would produce 2-chloroethylamine, a known inactive antitumor agent.

Previous studies have shown that the optimum log *P* value for CNS antitumor activity is about 2.[2a] Log *P* values in the octanol–H_2O system were calculated from the experimentally measured log *P* value for nonmustard precursors, and the estimated lipophilic or hydrophilic contribution of other functional groups was either added or substracted.[13] Thus, compound **1a** was calculated to have a log *P* value of 5.74, whereas the active mustards **1d** and **1e** were calculated to have values of 4.11 and 3.29, respectively.[14] These values would indicate that **1d** and **1e** would penetrate the CNS, whereas a log *P* value of 5.74 for **1a** supports our conclusions that this compound is too lipophilic for CNS activity.

Experimental Section

General Methods. All melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Thin-layer chromatography (TLC) was performed on precoated silica gel 13179, polyethylene terephthalate foils (Eastman Kodak, Rochester, N.Y.). Column chromatography was performed on silica gel (Baker, 5-3405, 60–200 mesh). The IR spectra were obtained with a Perkin-Elmer Model 700 or Beckman IR10 spectrophotometer. The NMR spectra were measured in $CDCl_3$ or CD_3SOCD_3 or CD_3OD on a Varian T-60 spectrometer, and chemical shifts are reported in parts per million (δ) downfield from $(CH_3)_4Si$ as internal standard. Mass spectra were determined on a 12-90-G Nuclide mass spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter (Model 141).

6-[2-[Bis(2-hydroxyethyl)amino]acetyl]-2,11-diacetoxy-10-methoxynoraporphine (3). A mixture of 222 mg (0.5 mmol) of the *N*-(chloroacetyl) intermediate (**2**) prepared by the procedure of Granchelli et al.[5] and 140 mg (1.33 mmol) of diethanolamine in 15 mL of dry THF was allowed to reflux overnight. The THF solution was decanted from a small amount of insoluble oil and evaporated to dryness. The residue was dissolved in 40 mL of $CHCl_3$, shaken with 3 × 30 mL of aqueous brine, dried, and evaporated to dryness to give 470 mg of product. The crude residue was dissolved in 20 mL of a mixture of Et_2O and CH_3OH (2:1), filtered through Celite, and acidified with ethereal HCl, yielding a near colorless precipitate. The product was filtered, washed with Et_2O, and dried, giving 130 mg (47%) of the diol **3**·HCl: mp 160–170 °C; NMR ($CDCl_3$) δ 7.6 (d, 1 H, C_1 H), 6.75 (d, 1 H, C_3H), 6.95 (q, 2 H, C_8 H and C_9 H), 3.8 (s, 3 H, OCH_3), 2.7–3.8 (m, 17 H), 2.25 (d, 6 H, $C(=O)CH_3$); UV max (EtOH) 302 nm (log ϵ 3.83), 269 (4.19); IR ($CHCl_3$) 3375 (br), 1760 (s), 1640 (s) cm^{-1}. Anal. ($C_{27}H_{32}N_2O_8$·HCl) C, H, Cl, N.

6-[2-[Bis(2-Chloroethyl)amino]acetyl]-2,11-diacetoxy-10-methoxynoraporphine Hydrochloride Monohydrate (1c). A solution of 1.2 g (2.3 mmol) of the diol (**3**) in 60 mL of dry CH_3CN was treated with 1.4 mL (2.4 g, 0.019 mol) of $SOCl_2$ and stirred at room temperature for 3 h. The solution was evaporated to dryness and fresh CH_3CN was distilled from the residue several times under vacuum. The residue was dissolved in a mixture of 20 mL of Et_2O and 10 mL of CH_3CN and acidified with ethereal HCl. The product crystallized out on addition of Et_2O and was filtered, washed with Et_2O, and dried to give 730 mg (54%) of 1c, mp 145–155 °C dec. Anal. ($C_{27}H_{32}Cl_2N_2O_7$·H_2O·HCl) C, H, Cl, N.

11-Acetoxy-6-[2-[bis(2-hydroxyethyl)amino]acetyl]-2-hydroxy-10-methoxyaporphine Hemihydrate (5). A mixture of 1.51 g (14 mmol) of diethanolamine, 2.66 g (6 mmol) of the chloroacetylaporphine (**2**), 120 mL of dimethylacetamide, and 3.6 g (22 mmol) of pulverized KI was heated at 90 °C for 17 h. The solution was evaporated under reduced pressure, and the residue was stirred with 200 mL of H_2O at room temperature for 1 h, giving a gummy precipitate. The water phase was decanted and saved. The gum was dissolved in $CHCl_3$, and the $CHCl_3$ solution was washed with 5 × 75 mL of H_2O and 2 × 30 mL of brine. After drying, the solvent was removed under reduced pressure to give 0.87 g of a light tan solid, mp 105–115 °C. Anal. ($C_{25}H_{30}N_2O_7$·$0.5H_2O$) C, H, N.

The decanted H_2O phase above was also extracted with $CHCl_3$, and the extract was washed with H_2O and brine. After drying, the solvent was removed under reduced pressure to give 2.2 g of additional product containing a small amount of dimethylacetamide: total yield 90%.

11-Acetoxy-6-[2-[bis(2-chloroethyl)amino]acetyl]-2-hydroxy-10-methoxyaporphine Hemihydrate (1d). A solution of 2 g (3.9 mmol) of the diol (**5**) in 100 mL of dry CH_3CN was treated with 2 mL (3.3 g, 28 mmol) of $SOCl_2$ and stirred for 3 h at room temperature under N_2. The solution was evaporated under reduced pressure and $CHCl_3$ was distilled from the residue several times to remove traces of $SOCl_2$. The residue was crystallized from a mixture of 10 mL of 95% ethanol and 50 mL of ether. The crude product was then dissolved in a mixture of 50 mL of $CHCl_3$ and 50 mL of CH_3CN, and the organic solution was shaken with 10 mL of water. The dark aqueous phase was discarded, and the organic layer was dried (Na_2SO_4) and evaporated to give a residue which crystallized when triturated with ether. The product was filtered, washed with Et_2O, and dried, yielding 1.0 g (50%) of **1d**, mp 115–119 °C dec. Anal. ($C_{25}H_{28}Cl_2N_2O_5$) C, H, Cl, N.

***N*-[[Bis(2-chloroethyl)amino]acetyl]-2,11-dihydroxy-10-methoxynoraporphine Hydrochloride Dihydrate (1b). Method A.** A mixture of **2** (13.3 g, 0.030 mol), diethanolamine (35.0 g, 0.33 mol), and KI (24.0 g, 0.145 mol) in 200 mL of DMA was heated at 110 °C for 24 h and then distilled under vacuum to remove most of the DMA. The pot residue was added with a mixture of 300 mL of H_2O and 200 mL of $CHCl_3$, stirred at room temperature for 1 h. While the aqueous layer was discarded, the organic layer and the solid precipitate were dried, evaporated,

(10) B. Costall, D. H. Fortune, S.-J. Law, R. J. Naylor, J. L. Neumeyer, and V. Nohria, *Nature (London)*, **285**, 571 (1980).
(11) Compounds **1b–d** gave R_f values of 0.32, 0.57, and 0.41, respectively, in the solvent system $CHCl_3$–Et_2O (2:1).
(12) R. J. Baldessarini, N. S. Kula, K. G. Walton, and R. J. Borgman, *Biochem. Pharmacol.*, **26**, 1749 (1977).
(13) C. Hansch and A. Leo in "Substituent Constants for Correlation Analysis in Chemistry and Biology", Wiley, New York, 1979.
(14) Personal communication from Professor C. Hansch and Dr. A. J. Leo.

and combined to give a brown solid (6; 10.5 g). The crude product was added with 200 mL of CH_3CN and treated with $SOCl_2$ (15.0 mL). The resulting mixture was stirred at room temperature for 4 h and evaporated to dryness. The residue was added with 100 mL of H_2O basified with NH_4OH and extracted with 10% MeOH in $CHCl_3$ (4 × 75 mL). The combined extracts were dried and evaporated to give a dark oil (3.0 g). The oily residue was chromatographed on a silica gel column packed and eluted with Et_2O–$CHCl_3$–MeOH (80:20:3) to give 1.2 g of pure compound **1b**. The free base thus obtained was dissolved in a minimal amount of CH_3OH and diluted with anhydrous Et_2O up to the point when the solution started to cloud. A few drops of CH_3OH was then added to clear the solution. An excess of ethereal HCl was added to the solution until no further precipitation occurred. Filtration of the mixture gave 1.1 g (10%) of light pink solid: mp 165–170 °C; UV max (EtOH) 305 nm (log ε 3.87), 279 (4.09), 270 (4.08); $[\alpha]^{28}_{546}$ −266° (*c* 0.05, EtOH). Anal. ($C_{23}H_{26}N_2O_4Cl_2$·HCl·$2H_2O$) C, H.

Method B. A solution of **1d** (1.7 g, 0.0034 mol) in 80 mL of CH_3OH and 48 mL of concentrated HCl was allowed to stand at room temperature for 16 h. The mixture was diluted with 150 mL of $CHCl_3$ and neutralized with aqueous $NaHCO_3$. The organic layer was separated and the aqueous phase extracted with another 50 mL of $CHCl_3$. The combined $CHCl_3$ solutions were dried and evaporated to dryness to give about 1.4 g of product. The product was dissolved in a mixture of 10 mL of CH_3OH and 30 mL of ether and acidified with ethereal HCl to give a gummy precipitate. Trituration with fresh ether gave a crystalline solid weighing 1.24 g (74%), mp 165–170 °C, and has the identical R_f as **1b** obtained through method A.

***N*-(2-Chloroethyl)norapocodeine Hydrochloride (1e).** A mixture of **9**[5] (13.24 g, 0.0425 mol) in 350 mL of CH_3CN was treated with $SOCl_2$ (20.0 g, 0.168 mol), and the reaction mixture was worked up in the same manner as previously described[5] to give the free base of **1e** (4.55 g, 32%) after column chromatography. The HCl salt was prepared in the usual manner, mp 212–215 °C. Anal. ($C_{19}H_{20}NClO_2$·HCl) C, H, N.

***N*-[2-(2-Chloroethoxy)ethyl]norapocodeine Hydrochloride Hemihydrate (1f).** A solution of **9** (0.90 g, 2.9 mmol) and $SOCl_2$ (2.0 g, 16.8 mmol) in 25 mL of CH_3CN was stirred at room temperature for 20 h. The reaction mixture was evaporated to a residue, which was then added to 20 mL of H_2O, basified with $NaHCO_3$, and extracted with Et_2O (3 × 40 mL). The combined extracts were dried (Na_2SO_4) and evaporated to an oily residue. The residue was chromatographed on a silica gel column packed and eluted with Et_2O–petroleum ether (1:3) to give sequentially (a) compound **1e** (0.15 g, 16%) and (b) compound **1f** (0.45 g, 40%): NMR ($CDCl_3$) δ 2.40–4.0 [m, 19, H at C-4, C-5, C-6a, C-7, OCH_3, $NCH_2CH_2OCH_2CH_2Cl$, OH], 6.63–7.27 (m, 4, aromatic), 8.03–8.27 (dd, 1, aromatic); MS *m/e* 373 (M^+), 100 (base); UV max (EtOH) 310 nm (log ε 3.81), 276 (4.38); $[\alpha]^{28}_{546}$ −40° (*c* 0.05, EtOH); for ^{13}C NMR, see Table I. The HCl salt was prepared in the usual manner, mp 202–205 °C. Anal. ($C_{21}H_{24}ClNO_3$·HCl·$0.5H_2O$) C, H, N.

***N*-[[[*N'*-(2-Chloroethyl)carbamyl]oxy]ethyl]norapocodeine (1g) and *N*-[[[*N'*-(2-Chloroethyl)carbamyl]oxy]ethyl]-10-methoxy-11-[(chloroethyl)carbamyl]aporphine (1h).** A solution of **9** (1.01 g, 3.2 mmol) in 50 mL of THF was added dropwise via syringe to chloroethyl isocyanate (3.75 g, 35.5 mmol). The solution was further diluted with 25 mL of THF and allowed to reflux for 24 h. The reaction mixture was cooled and filtered to obtain a white solid (0.13 g, 13%), which was identified as the unreacted *N*-(hydroxyethyl)norapocodeine. The filtrate was evaporated to a residue, dissolved with 25 mL of 10% HCl, and washed with Et_2O (2 × 25 mL). The acidic aqueous layer was neutralized with NH_4OH and extracted with $CHCl_3$ (3 × 50 mL). The combined extracts were dried and evaporated to give a dark oil, which was chromatographed on a silica gel column packed and eluted with Et_2O–$CHCl_3$–MeOH (85:13.5:1.5) to give three fractions (I–III). Fraction I (**1g**; 0.27 g, 23%): UV max (EtOH) 300 nm (log ε 3.70), 275 (4.71); MS *m/e* 416 (M^+), 266 (base); $[\alpha]^{28}_{546}$ −25° (*c* 0.06, EtOH). The HCl salt was prepared in the normal manner, mp 185–188 °C. Anal. ($C_{22}H_{25}ClN_2O_4$·HCl·$1.5H_2O$) C, H, N. Fractions II and III were also identified. Fraction II contained a mixture of **1g** and **1h** (0.35 g) and fraction III contained pure **1h** (0.33 g, 22%); MS *m/e* 436 (M^+), 266 (base); UV max (EtOH) 300 nm (log ε 3.46), 268 (4.15); $[\alpha]^{28}_{546}$ −9.7°. The HCl salt was prepared in the normal manner, mp 178–182 °C (softened at 80 °C). Anal. ($C_{25}H_{29}Cl_2N_3O_5$·HCl·$1.5H_2O$) C, H, N.

1-(Aminoethyl)-3,5-dihydroxy-6-methoxyphenanthrene Hydrochloride (4a). A solution of **3** (0.150 g, 0.31 mmol) in 3 mL of concentrated HCl was heated at 110–120 °C under N_2 for 20 min. The reaction mixture was cooled and filtered to give a pink solid, which was washed with cold concentrated HCl and Et_2O and dried in a dessicator at 40–50 °C, giving 50 mg (50%) of **4a**·HCl: mp 240 °C dec; NMR ($CDCl_3$–Me_2SO-d_6) δ 2.75–370 (br signal, 4, CH_2CH_2N), 3.93 (s, 3, OCH_3), 7.0–7.90 (m, 7, aromatic H and phenolic OH), 8.10–8.90 (br signal, 3, NH_3^+), 9.20 (d, 1, aromatic H at C-4); UV max (EtOH) 321 nm (log ε 4.19), 298 (4.17), 257 (4.70), 240 (4.55).

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Retinoic Acid Analogues. Synthesis and Potential as Cancer Chemopreventive Agents

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Analogues of retinoic acid have been synthesized as potential chemopreventive agents against epithelial cancer. Ethyl (*E*)-9-(2-norbornenyl)-3,7-dimethylnona-2,4,6,8-tetraenoate (**9**), (*E*)-3,7-dimethyl-9-(2-ethyl-6,6-dimethyl-1-cyclohexen-1-yl)nona-2,4,6,8-tetraenoic acid (**25**), and 2-(2′-methoxyethoxy)ethyl retinoate (**26**) displayed good activity in the inhibition of tumor promoter-induced mouse epidermal ornithine decarboxylase assay. (*E*)-1-(3-Acetoxyphenyl)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)hexa-1,3,5-triene (**34**) had low activity. (*E*)-5-[2,6-Dimethyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)octa-1,3,5,7-tetraen-1-yl]tetrazole (**40**) was inactive.

The progressive loss of the regulation of cellular differentiation by epithelial cells can result in cancer. Retinoic acid (**1**) and some of its analogues (retinoids) prevent the expression of these unfavorable cellular changes at a fundamental level. The mechanism by which chemoprevention of carcinogenesis occurs has not yet been estab-

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