2,3-Dimethoxy-5-methyl-6-*n*-octadecylmercapto-1,4-benzoquinone (8). A mixture of 2,3-dimethoxy-5-methyl-1,4-benzoquinone (3.0 g, 16.5 mmol) (CoQ_0) and *n*-octadecyl mercaptan (4.7 g, 16.5 mmol) in EtOH (90 ml) was stirred at room temperature (48 hr) and then at 60° (8 hr). Solvent was removed, and the residue was placed on a silica gel column and eluted with hexane-Et_2O. Repeated recrystallization from hexane yielded 800 mg: mp 75–77°. *Anal.* ($C_{27}H_{46}O_4S$) C, H.

2,3-Dimethoxy-5-methyl-6-*n*-tetradecylmercapto-1,4-benzoquinone (9). A procedure similar to that employed for the synthesis of **8** was used except the reaction mixture was stirred at room temperature for 24 hr under N_2, and the eluent from column chromatography was treated with Ag_2O and Na_2SO_4 for 2 hr: yield, 2.1 g from 3.0 g of CoQ_0; mp 69–70°. *Anal.* ($C_{23}H_{38}O_4S$) C, H.

2,3-Dimethoxy-5-methyl-6-*n*-dodecylmercapto-1,4-benzoquinone (10). A procedure similar to that employed for the synthesis of **9** was used. The products from two reaction mixtures, one stirring for 24 hr in Et_2O–EtOH and the other stirring for 48 hr under N_2 in EtOH, were pooled. The initial reaction mixtures contained 1.0 g of CoQ_0 and 0.77 ml of *n*-dodecyl mercaptan; and 2.5 g of CoQ_0 and 2.0 g of *n*-dodecyl mercaptan, respectively. The eluent from column chromatography was treated with Ag_2O and Na_2SO_4: yield, 3.8 g total from both reaction; mp 64–65°. *Anal.* ($C_{21}H_{34}O_4S$) C, H.

2,3,5-Trimethoxy-6-*n*-dodecylmercapto-1,4-diacetoxybenzene (11). A mixture of 2,3,5-trimethoxy-1,4-benzoquinone[7] (1.0 g, 5.1 mmol) and *n*-dodecyl mercaptan (1.0 g, 4.9 mmol) in 95% EtOH (25 ml) was stirred at room temperature for 5 days. The mixture was evaporated *in vacuo;* addition of Et_2O yielded a light yellow precipitate which was collected. The residue from the concentrated filtrate was placed on a silica gel column and eluted with ether. The red-banded fraction was collected and evaporated to yield a red syrup (1.1 g) contaminated with impurities (tlc). Nmr indicated this syrup was primarily 2,3,5-trimethoxy-6-*n*-dodecylmercapto-1,4-benzoquinone. This red syrup (≅620 mg) was treated with an excess of zinc dust and acetic anhydride and with a few drops of pyridine.[6] The quenched (H_2O) reaction mixture was extracted with ether. Evaporation of ether gave a yellow oil, which crystallized from cold EtOH–H_2O after seeding with a product from an earlier exploratory reaction to yield ≅53 mg of colorless crystals: mp 51–53°. The analytical sample was recrystallized from acetone–H_2O, acetone, and then twice from MeOH: mp 56.5–57.5°. *Anal.* ($C_{25}H_{40}O_7S$) C, H, S.

2,3,5-Trimethoxy-6-*n*-octadecylmercapto-1,4-diacetoxybenzene (12). A procedure similar to that employed for the synthesis of **11** was used for the preparation of 2,3,5-trimethoxy-6-*n*-octadecylmercapto-1,4-diacetoxybenzene except the reaction mixture of 2,3,5-trimethoxy-1,4-benzoquinone[7] (1.5 g, 7.6 mmol) with *n*-octadecyl mercaptan (2.0 g, 9.9 mmol) was stirred for 4 days at ≅50–60°: yield of red waxy semisolid ≅1.5 g. Nmr indicated this red wax was primarily 2,3,5-trimethoxy-6-*n*-octadecylmercapto-1,4-benzoquinone. Reductive acetylation of this red wax (1.25 g) yielded 650 mg of **11**: mp 71.5–73°, after recrystallization from MeOH, 95% EtOH, MeOH–hexane, MeOH–Et_2O–hexane, and hexane twice. *Anal.* ($C_{31}H_{52}O_7S$) C, H, S.

ω-Cyclohexylhexyl Mercaptan (15). ω-Cyclohexylcaproic acid was converted to ω-cyclohexylhexyl bromide as reported by Fieser, *et al.*[12] A mixture of ω-cyclohexylhexyl bromide (21.8 g, 89 mmol) and thiourea (6.76 g, 89 mmol) in EtOH (200 ml) was refluxed (72 hr). To the cooled mixture, a solution of NaOH (5.4 g) was added, and the mixture was refluxed (1 hr). A yellowish oil separated, and the alcohol layer was extracted with hexane. The dried (Na_2SO_4) hexane was concentrated to an oil, which was combined with the previously separated material and distilled. The colorless liquid, bp 98–101° (0.5 mm), weighed 16.3 g (82%): nmr (neat) δ 2.47 ppm (t, J = 6 Hz); mass spectrum, M^+ at *m/e* 200. *Anal.* ($C_{12}H_{24}S$) C, H, S.

Phytyl Mercaptan (4,8,12,16-Tetramethylheptadec-3-ene-1-thiol, 16). Phytyl bromide was prepared from commercial (Sigma) phytol by the method of Karrer, *et al.*[13] Nmr analysis indicated the product to be composed of approximately 90 and 10% of the primary and tertiary allylic bromides, respectively. A mixture of crude bromide (7.2 g, 20 mmol) and thiourea (1.6 g, 21 mmol) was refluxed in EtOH (100 ml) for 72 hr. To the cooled mixture was added a solution of NaOH (1.2 g, 30 mmol) in H_2O (5 ml). The mixture was refluxed (2 hr) and extracted with hexane. The dried (Na_2SO_4) hexane extract was concentrated to a yellow oil. Nmr analysis indicated no evidence of the tertiary allylic mercaptan but did indicate some bromide impurity.

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Notes

Antineoplastic Agents. 36. Acetylenic Carrier Groups[1]

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The development of experimentally facile routes to *N*-bis(2-chloroethyl)amines with multifunctional carrier groups was an initial objective of our efforts to design site specific[2] (*e.g.*, central nervous system) cancer chemotherapeutic agents. Methods were eventually uncovered for utilizing *N*-bis(2-chloroethyl)amine in Mannich reactions with, for example, ketones and imides (for leading references see ref 3 and 4). Of the common active hydrogen type compounds generally employed in Mannich reactions the acetylenic carbinols **1** proved most resistant to reaction with *N*-bis(2-chloroethyl)amine. However, an appropriate copper-catalyzed† procedure was eventually found and acetylenic Mannich bases **2a–d** were prepared.[3] Subsequent biological evaluation of these substances under

†More recently some related copper-catalyzed Mannich reactions have been described; see ref 5.

Table I. Antineoplastic Activity of Alkyne Nitrogen Mustard Hydrochlorides

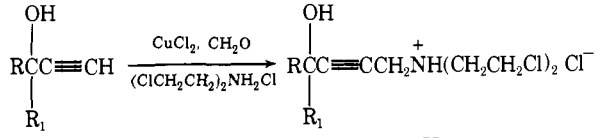
Alkyne	T/C, mg/kg[a,b] PS[c]	LE[d]	WM[e]
2a	272 (2)	151 (1.7)	3 (0.2)
2b	204 (3)		10 (1.2)
2c		141 (25)	12 (4.5)
2d		136 (5)	2 (10)
2e		142 (20)	
2f		123 (30)	
3		123 (300)	
4		180 (150)	
5		100 (200, inactive)	
6		121 (300)	

[a]Optimal value from available data. [b]Detailed summaries of the screening systems and criteria for activity have been described in ref 6. [c]P-388 lymphocytic leukemia. [d]Lymphoid leukemia L1210. [e]Walker carcinosarcoma 256 (intramuscular).

the direction of the National Cancer Institute led to the results shown in Table I.[6] Because of the promising inhibition shown by the acetylenic Mannich base **2a** against murine P-388 lymphocytic leukemia, the present study was undertaken to explore this structural lead and further scope of the copper-catalyzed reaction with *N*-bis(2-chloroethyl)amine.

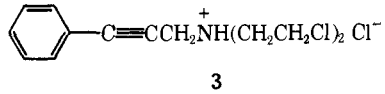
With slight modifications in our earlier general procedure[3] the tertiary acetylenic carbinols **2e,f** and acetylene derivatives **3–6** were prepared in 20–60% yields. The most satisfactory reaction conditions found involved first heating equimolar amounts of the acetylene and copper(II) chloride dihydrate in refluxing *tert*-butyl alcohol for 1 hr. The change in reaction mixture color from dark green to light yellow suggested possible formation of a copper complex and/or reduction of copper(II) to copper(I). Addition of 0.5 molar equiv each of *N*-bis(2-chloroethyl)amine hydrochloride and 37% formaldehyde solution followed by heating led to the required Mannich bases. Thus, this reaction of *N*-bis(2-chloroethyl)amine seems fairly general in scope and proved useful for obtaining other multifunctional nitrogen mustards such as the testosterone derivative **6.** Unfortunately, the androstane system did not prove to be a useful carrier group in the L1210 bioassay.

Presently, the antineoplastic activity of bis-acetylene **4** (Table I) as well as alcohol **2a** appears most interesting and suggests that the acetylenic carrier group bears further investigation.



1

2a, $R = R_1 = H$
b, $R = R_1 = CH_3$
c, $R = CH_3CH_2$; $R_1 = CH_3$
d, $R = R_1 = -CH_2(CH_2)_3CH_2-$
e, $R = CH_3CH_2CH_2$; $R_1 = H$
f, $R = R_1 = -CH_2(CH_2)_2CH_2-$



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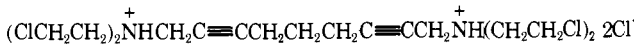

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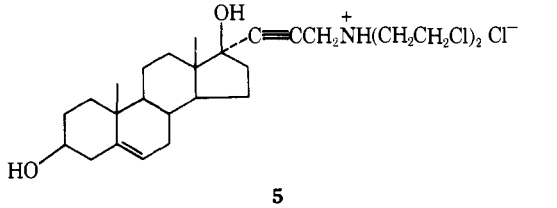
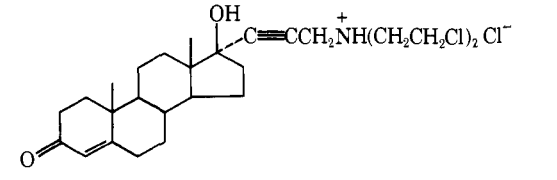


5



6

Experimental Section

Introduction to the experimental section of our prior report[3] in this area provides a summary of general chromatography (analytical specimens were colorless and exhibited one spot upon thin-layer chromatography) and physical measurements (by Miss K. Reimer). The infrared and proton magnetic resonance[3] spectra of each new substance were totally consistent with the assigned structure. For a proton magnetic resonance study of *N*-bis(2-haloethyl)amine hydrohalide salts in deuterium oxide, see ref 7.

All melting points were determined employing a Kofler melting point apparatus and are uncorrected. Microanalyses were performed by the laboratory of Dr. A. Bernhardt, West Germany.

General Procedure. The following synthesis of **3β,17β-dihydroxy-23-bis(2′-chloroethyl)amino-21,24-bisnorchol-5-en-20,22-yne hydrochloride (5)** outlines the method used to obtain each of the acetylenic nitrogen mustards. Copper(II) chloride dihydrate (6.8 g, 0.04 mol) was added to a solution of 3β,17β-dihydroxy-17α-ethynylandrost-5-ene (12.3 g, 0.04 mol) in *tert*-butyl alcohol (500 ml) and the mixture was heated at reflux 1 hr. Generally the reaction mixture color changed from dark green to straw color but in this case became dark brown. The mixture was cooled and *fresh* 37% formalin (10 ml) and *N*-bis(2-chloroethyl)amine hydrochloride (3.6 g, 0.02 mol) were added and heating at reflux was resumed for 1 hr. Solvent was removed *in vacuo* and the residue was cooled and treated with concentrated ammonium hydroxide (240 ml). The solution was extracted with diethyl ether (5 × 200 ml) and the combined extract was washed with water and dried (anhydrous sodium sulfate). Hydrogen chloride was passed through the ethereal solution and after remaining 5 days at refrigerator temperature 4.6 g (47%) of the hydrochloride separated and was collected. Five recrystallizations from methanol-diethyl ether afforded 2.4 g of alcohol **5** as needles melting at 177.5–180°. Elemental (C, H, Cl, and N) analyses for this substance and each described below were all within acceptable limits.

7-[Bis(2′-chloroethyl)amino]-5-heptyn-4-ol Hydrochloride (2e). The crude hydrochloride obtained from 12.7 g of 1-hexyn-3-ol weighed 7.7 g (42%). Three recrystallizations from acetone gave an analytical specimen melting at 108–109°.

1-(1′-Hydroxycyclopentane)-3-bis(2′-chloroethyl)amino-1-propyne Hydrochloride (2f). After five recrystallizations from ethyl acetate the hydrochloride **2f** from 11 g of 1-ethynyl-1-cyclopentanol amounted to 4.7 g (needles), mp 111.5–113.4°.

1-Phenyl-3-bis(2′-chloroethyl)amino-1-propyne Hydrochloride (3). Phenylacetylene (37.2 g) was converted to 30 g (59% yield after five recrystallizations from methanol-diethyl ether) of hydrochloride **3** as crystals melting at 136–138.5°.

1,9-Bis(2′-chloroethyl)amino-2,8-nonadiyne Hydrochloride (4). Conversion of 1,6-heptadiyne (9.2 g) to diyne **4** was realized in 26% yield (4.9 g). Five recrystallizations from acetone gave a pure sample as crystals melting at 125.5–127.5°.

3-Oxo-17β-hydroxy-23-bis(2′-chloroethyl)amino-21,24-bisnorchol-4-en-20,22-yne Hydrochloride (6). Five recrystallizations from ethyl acetate-methanol-diethyl ether of the hydrochloride derived from 31.2 g of 17α-ethynyltestosterone led to 6.9 g (22%) of ketone **6** as crystals melting at 161–163.5°.

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A Quantitative Reexamination of Structure–Activity Relationships in the Δ^6-6-Substituted Progesterone Series

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In a recent article Teutsch, *et al.*,[1] attempted to relate the steric and electronic characteristics of C(6) substituents in 6-substituted 16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate derivatives to the effect of such substituents on progestational (Clauberg) activity. These authors derived steric indexes based on bond lengths and van der Waals radii and used broad estimates of electronic features to reach their conclusions. Their treatment was qualitative and did not consider the partition coefficient of the molecules.

By contrast, in our own quantitative structure–activity relationship (QSAR) study of 9α-substituted cortisol derivatives,[2] we showed, for the first time, that the multiparameter regression technique (for a review, see ref 3) can be applied to steroids. In the present report we describe the application of this method to the foregoing progesterone derivatives (Table I) and the obtainment of a quantitative relationship differing from the conclusions drawn by Teutsch, *et al.*[1]

Instead of selecting and deriving new estimates of physical properties, we used the stochastic method utilizing known physicochemical parameters for the hydrophobic bonding power π,[4] the inductive and resonance effects $\mathcal{F}$ and $\mathcal{R}$,[5] and the size of the substituent (molar refraction, MR). As has been pointed out,[6] these parameters have been determined for a wide variety of substituents, an important consideration in using the relationship in predicting new candidates for synthesis. Although some of these parameters have been derived from aromatic systems, they are suitable for the present study in which the substituent is attached to a conjugated unsaturated carbon. From the data in Table I we derived eq 1–10 by the method of least squares. In these equations, n represents the number of data points used in the regression, r is the correlation coefficient, and s is the standard deviation. Of the 15 compounds in the series, two (R = CH_3 and R = C=NOMe) could not be included in the regression analysis, for reasons to be discussed later.

In the single parameter equations (1–3) the one with π gives the best result, accounting for over 50% of the variance in the data. It is noteworthy that eq 1 and 3, involving the steric and electronic parameters, each account for less than 20% of the variance. These were the features considered to be *most* important by Teutsch, *et al.*[1] Again, these authors considered resonance to be an important component of the electronic effect, but eq 4 indicates that this factor ($\mathcal{R}$) has no influence on activity.

Looking at the two parameter equations (5–8) it is seen that only the ones involving π (eq 5, 7, 8) have high r values. Equation 7, embodying π and the electronic term $\mathcal{F}$, gives the best two term result, accounting for 69% of the variance.

The three parameter equations (9 and 10) both give high correlations. Both equations satisfy the F test[7] at the 0.005 level, having F values of 11.6 and 11.4, respectively. In these equations, the π^2 and MR (steric) terms have a similar effect, and it is not possible to say which equation represents the data more accurately with the information at hand. We are inclined to favor eq 10 since π^2 must ultimately have importance in any series involving π itself. The use of all four parameters does not improve the situation. Both equations indicate that activity is promoted by electron-withdrawing groups and by lipophilic groups. However, eq 10 predicts that activity reaches a maximum with the group having π values of 0.50, whereas eq 9, hav-

	n	s	r^2	r	
$\log A = 1.45\ (\pm 1.15) - 0.09\ (\pm 0.12)$ MR	13	0.875	0.198	0.444	(1)
$\log A = 0.60\ (\pm 0.40) + 1.14\ (\pm 0.66)\ \pi$	13	0.645	0.564	0.751	(2)
$\log A = -0.29\ (\pm 1.55) + 2.94\ (\pm 4.39)\ \mathcal{F}$	13	0.892	0.165	0.406	(3)
$\log A = -0.41\ (\pm 1.74) + 3.15\ (\pm 4.72)\ \mathcal{F} - 0.52\ (\pm 2.54)\ \mathcal{R}$	13	0.926	0.182	0.427	(4)
$\log A = -1.11\ (\pm 0.84) - 0.06\ (\pm 0.09)$ MR $+ 1.04\ (\pm 0.65)\ \pi$	13	0.611	0.644	0.803	(5)
$\log A = 0.43\ (\pm 1.61) - 0.10\ (\pm 0.11)$ MR $+ 3.31\ (\pm 3.95)\ \mathcal{F}$	13	0.790	0.405	0.636	(6)
$\log A = -0.24\ (\pm 1.01) + 1.10\ (\pm 0.60)\ \pi + 2.54\ (\pm 2.86)\ \mathcal{F}$	13	0.574	0.686	0.828	(7)
$\log A = 0.79\ (\pm 0.63) + 1.13\ (\pm 0.68)\ \pi - 0.53\ (\pm 1.35)\ \pi^2$	13	0.652	0.595	0.771	(8)
$\log A = 0.26\ (\pm 1.01) - 0.07\ (\pm 0.07)$ MR $+ 0.97\ (\pm 0.53)\ \pi + 2.84\ (\pm 2.50)\ \mathcal{F}$	13	0.489	0.795	0.892	(9)
$\log A = -0.17\ (\pm 0.88) + 1.06\ (\pm 0.52)\ \pi + 3.46\ (\pm 2.68)\ \mathcal{F} - 1.05\ (\pm 1.11)\ \pi^2$	13	0.492	0.792	0.890	(10)