that the product remains unchanged by treatment with refluxing HI/P.

9,10-Dihydro-*N,N'*-dimethyl-9,10-dioxo-2,6-anthracenedisulfonamide (42). To a suspension of 40.5 g of anthraquinone-2,6-disulfonyl chloride[8] in 750 ml of Me_2CO was added 250 ml of 40% aqueous $MeNH_2$. The mixture was stirred overnight and acidified with 3 *N* HCl. The resulting precipitate was collected and recrystallized from $HCONMe_2$-H_2O (5:1) to give 35.2 g (90%) of 42 (Table III).

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Synthesis and Bioassays of New Dimethoxyalkylmercapto-1,4-benzoquinones†

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A new series of 5-alkylmercapto derivatives of 2,3-dimethoxy-1,4-benzoquinones has been synthesized as potential antimetabolites of coenzyme Q. Within the series of 2,3-dimethoxy-5-*n*-octadecylmercapto-1,4-benzoquinones, several 6-substituents (chloro, amino, *n*-octadecylmercapto, and methyl) provided potentially significant variation in oxidation-reduction potential of the new quinones. For the series of 6-substituted 2,3-dimethoxy-5-methyl-1,4-benzoquinones, lengthening the 6-alkylmercapto side chain from *n*-dodecylmercapto to *n*-octadecylmercapto furnished coenzyme Q analogs with increasing lipoidal character, which is important for an antimetabolite of coenzyme Q. Two of the seven new analogs inhibited succinoxidase, and one inhibited NADH-oxidase. These inhibitions permitted determinations of antimetabolite CoQ indices.

The reactions of 1,4-benzoquinones with alkyl mercaptans were examined in 1939[1] and became widely studied. In most cases 1,4 addition of the mercaptan to the quinone occurred readily, and the alkylmercaptohydroquinone could be isolated. However, if 2 equiv of the quinone were present in the reaction mixture, the initial adduct was oxidized by the excess quinone, and the alkylmercaptobenzoquinone was the predominant product. In the majority of examples reported, a bis(alkylmercapto)-1,4-benzoquinone was also formed, and this diadduct was the major product when equimolar or excess alkyl mercaptan was used. Porter, *et al.*,[2] described a new series of alkylmercapto-5,8-quinolinequinones which were synthesized by 1,4 addition of the appropriate *n*-alkyl mercaptan to 6-hydroxy-5,8-quinolinequinone and which exhibited significant curative antimalarial activity in mice.

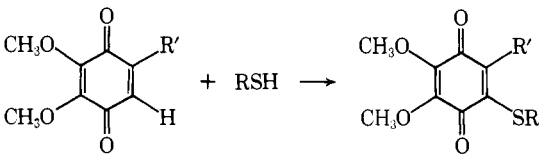
We now describe a new series of 2,3-dimethoxy-5-alkylmercapto-1,4-benzoquinones which have been synthesized in our continuing program[2-4] on lipoidal quinones as antimetabolites of coenzyme Q. In this study, optimum conditions for the addition of alkyl mercaptans to some substituted benzoquinones have been determined. This series of alkylmercapto-1,4-benzoquinones provided variation in alkyl chain length. Within the series of 2,3-dimethoxy-5-*n*-octadecylmercapto-1,4-benzoquinones, the 6-substituents provided significant variation in oxidation potential of the new quinones. For the 6-substituted 2,3-dimethoxy-5-methyl-1,4-benzoquinones, lengthening the 6-alkylmercapto side chain from C_{12} to C_{18} furnished coenzyme Q analogs with increasing lipoidal character.

†Coenzyme Q. 167. Antimetabolites of Coenzyme Q. 19.

Results and Discussion

The desired 2,3-dimethoxy-5-alkylmercapto-1,4-benzoquinones **1-3** were prepared by treating 2 equiv of 2,3-dimethoxy-1,4-benzoquinone in ethanol with a hexane solution of 1 equiv of the alkyl or isoprenyl mercaptan (Scheme I). The *n*-octadecylmercaptoquinone **1**, which precipitated from the reaction mixture in high yield, was collected and recrystallized. The filtrate containing mainly 2,3-dimethoxyhydroquinone was concentrated and oxidized with either $Na_2Cr_2O_7$ or Ag_2O. Recoveries of 45% of

Scheme I

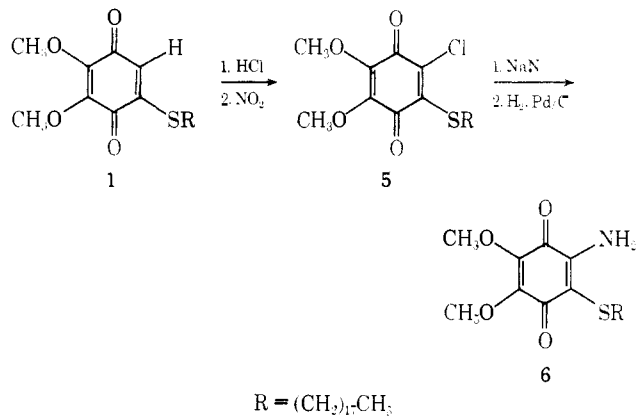


1, R = $(CH_2)_{17}CH_3$; R' = H
2, R = $(CH_2)_{11}CH_3$; R' = H
3, R = phytyl; R' = H
8, R = $(CH_2)_{17}CH_3$; R' = CH_3
9, R = $(CH_2)_{13}CH_3$; R' = CH_3
10, R = $(CH_2)_{11}CH_3$; R' = CH_3

the starting quinone were obtained, and three reactions through this cycle gave overall yields of 70–75% based on the quinone. When the 2,3-dimethoxy-5-alkylmercapto-1,4-benzoquinone was soluble in the reaction mixture, concentration of the solution followed by column chromatography gave good yields. The diadduct 4 was obtained from the reaction of equimolar amounts of 2,3-dimethoxy-1,4-benzoquinone and *n*-octadecyl mercaptan. This compound was also prepared by an alternate route (*vide infra*).

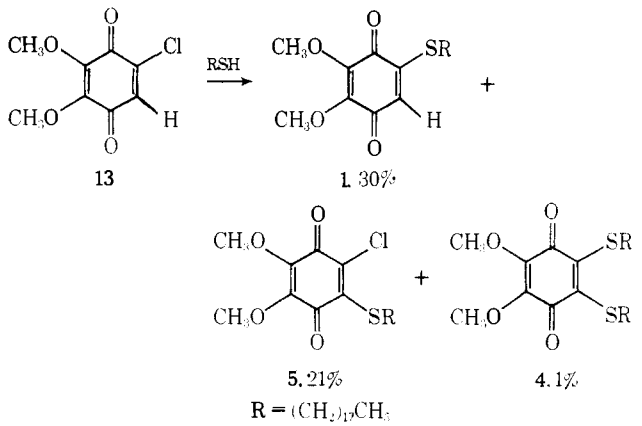
An additional substituted alkylmercapto-1,4-benzoquinone, 2,3-dimethoxy-5-*n*-octadecylmercapto-6-chloro-1,4-benzoquinone (**5**), was prepared by bubbling HCl into an ethanolic solution of 1 followed by isolation of the intermediate chlorohydroquinone and subsequent oxidation with nitrogen dioxide (Scheme II). Replacement of the chloro group by an azido moiety was smoothly accomplished[5] to give the azidoquinone which was reduced catalytically to yield the aminoquinone **6**.

Scheme II



In an attempt to prepare **5** by addition of *n*-octadecyl mercaptan to 5-chloro-2,3-dimethoxy-1,4-benzoquinone (**13**), a readily separable mixture of **5** (21%), the chloro replacement product, **1** (30%), the bis(octadecylmercapto) product **4** (1%), and recovered **13** (42%) was isolated (Scheme III).

Scheme III



Reductive acetylation[6] of 5-*n*-dodecylmercapto-2,3-dimethoxy-1,4-benzoquinone with zinc dust, acetic anhydride, and pyridine yielded 5-*n*-dodecylmercapto-2,3-dimethoxy-1,4-diacetoxybenzene (**7**).

Treatment of 2,3,5-trimethoxy-1,4-benzoquinone[7] with *n*-alkyl mercaptan (≃10% molar excess) gave the desired 2,3,5-trimethoxy-6-alkylmercapto-1,4-benzoquinone as an impure red oil after column chromatography. Attempts at crystallization failed. Reductive acetylation[6] of the crude quinones gave good yields of the crystalline diacetoxy derivatives **11** and **12**.

An additional series of potential CoQ antimetabolites was prepared by adding on an equimolar basis alkyl mercaptans to 2,3-dimethoxy-5-methyl-1,4-benzoquinone (**14**, CoQ_0) giving the analogs, 2,3-dimethoxy-5-methyl-6-alkylmercapto-1,4-benzoquinones **8–10** (Scheme I).

The ω-cyclohexylhexyl and phytyl mercaptans, new compounds, were prepared by hydrolysis of the appropriate alkylisothiourea hydrobromide, which was obtained by refluxing the corresponding alkyl bromides and thiourea in alcohol. Extended reaction times (48–72 hr) were necessary for complete reaction of the alkyl bromide. The "phytyl" bromide used was actually a mixture of phytyl bromide (90% by nmr) and isophytyl bromide, which was obtained from the reaction of commercial phytol with PBr_3. A previous result[8] indicated that both primary and tertiary allylic bromides yield the primary allylic mercaptan in the reaction with thiourea followed by hydrolysis. Thus, the crude mixture of bromides from the reaction of phytol and PBr_3 was used directly to produce phytyl mercaptan as the only detectable (nmr) isomer.

Respiratory Inhibition in Mitochondria by Certain Analogs. Effects of the CoQ analogs on the activity of succinoxidase and NADH-oxidase were studied. The assays were conducted in Gilson differential respirometer using beef heart mitochondria prepared as described.[9] The test compounds were each dissolved in absolute EtOH. The background for the assay has been described.[10] Each flask contained 1.6 ml of 0.1 *M* Tris–HCl buffer pH 7.5, 0.5 ml of 1 *M* sucrose, 0.05 ml of asolectin (20 mg/ml), 0.1 ml of CoQ analogs in ethyl alcohol, 0.05 ml of 0.2% cytochrome c, mitochondrial enzyme (0.684 mg of protein), and 0.2 ml of 0.75 *M* succinate or 0.07 *M* NADH in a total volume of 2.8 ml.

The results are summarized in Table I. In succinoxidase 6-*n*-octadecylmercapto-5-amino-2,3-dimethoxy-1,4-benzoquinone (**6**, 42% inhibition at 400 nmol) and 6-*n*-octadecylmercapto-5-chloro-2,3-dimethoxy-1,4-benzoquinone (**5**, 54% inhibition at 400 nmol) demonstrated the greatest inhibitory activity. In NADH-oxidase 6-*n*-dodecylmercapto-2,3,5-trimethoxy-1,4-diacetoxybenzene (**11**, 51% inhibition at 400 nmol) demonstrated the strongest inhibition.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the staffs of Chemalytics Inc., Tempe, Ariz., and of Spang Microanalytical Laboratory, Ann Arbor, Mich. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

2,3-Dimethoxy-5-*n*-octadecylmercapto-1,4-benzoquinone (1). To a stirred solution of 2,3-dimethoxy-1,4-benzoquinone (5.0 g, 30 mmol) in EtOH (100 ml) was added a solution of *n*-octadecyl mercaptan (4.3 g, 15 mmol) in petroleum ether (35 ml). After 1 hr, an orange precipitate was collected and washed with EtOH. The filtrate yielded three additional crops (6.5 g, 95%) over a 3-hr period. The concentrated filtrate treated with $Na_2Cr_2O_7$ or Ag_2O gave starting quinone. To the solution of crude 2,3-dimethoxy-1,4-benzoquinone in EtOH was added *n*-octadecyl mercaptan (7.5 mmol) as previously described, and product (2.7 g, 80%) was collected in three portions over a 3-hr period. After three cycles, 2,3-dimethoxy-5-*n*-octadecylmercapto-1,4-benzoquinone (9.8 g, 72% based on starting quinone) was obtained. The orange crystals from EtOH had mp 78–79°. *Anal.* ($C_{26}H_{44}O_4S$) C, H, S.

2,3-Dimethoxy-5-*n*-dodecylmercapto-1,4-benzoquinone (2). A procedure similar to that employed for the synthesis of 1 was used

Table I. Effect of CoQ Analogs on Succinoxidase and NADH-Oxidase Activities in Beef Heart Mitochondria

No.	Compound	Succinoxidase Concn, nmol	Succinoxidase Rel enzyme act.	Succinoxidase Antimetabolite CoQ index[a]	NADH-oxidase Concn, nmol	NADH-oxidase Rel enzyme act.	NADH-oxidase Antimetabolite CoQ index[a]
			100			100	
	6-ω-Cyclohexylpentyl-5-hydroxy-2,3-dimethoxy-1,4-benzoquinone (standard)	16	46	5	40	40	17
2	5-*n*-Dodecylmercapto-2,3-dimethoxy-1,4-benzoquinone	40	91		40	106	
		400	124		400	128	
1	5-*n*-Octadecylmercapto-2,3-dimethoxy-1,4-benzoquinone	40	92		40	94	
		400	94		400	75	
3	5-Phytylmercapto-2,3-dimethoxy-1,4-benzoquinone	40	80		40	100	
		400	73		400	84	
6	6-*n*-Octadecylmercapto-5-amino-2,3-dimethoxy-1,4-benzoquinone	20	72		40	97	
		40	66	121	400	93	
		400	42				
5	6-*n*-Octadecylmercapto-5-chloro-2,3-dimethoxy-1,4-benzoquinone	40	85		40	95	
		200	69	192	400	87	
		400	54				
11	6-*n*-Dodecylmercapto-2,3,5-trimethoxy-1,4-diacetoxybenzene	200	87		200	57	173
		400	79		400	51	
12	6-*n*-Octadecylmercapto-2,3,5-trimethoxy-1,4-diacetoxybenzene	40	104		40	87	
		400	91		400	82	

[a]Antimetabolite CoQ index is defined as the ratio of nanomoles of inhibitor to approximate nanomoles of CoQ_{10} in the mitochondria preparation which causes approximately 50% inhibition of enzyme activity. 50% inhibition is sometimes estimated by extrapolation.

except the reaction mixture was stirred at room temperature for 29 hr; there was no recycling. Equimolar amounts of reactants were used: mp 54–55°. *Anal.* ($C_{20}H_{32}O_4S$) C, H.

2,3-Dimethoxy-5-phytylmercapto-1,4-benzoquinone (3). To a stirred solution of 2,3-dimethoxy-1,4-benzoquinone (1.7 g, 10 mmol) in EtOH (40 ml) was added a solution of phytyl mercaptan (1.56 g, 5 mmol) in hexane (20 ml). The reaction mixture after being stirred overnight was concentrated to a dark red oil, which was treated with Ag_2O (2.5 mmol). The mixture was filtered, and the pad was washed with CH_2Cl_2. The concentrated filtrate was first chromatographed on silica gel and eluted with hexane–ether (3:1). The purest fraction was rechromatographed on deactivated silica gel using the dry column technique.[11] Other fractions were combined and also rechromatographed by the dry column technique:[11] yield, 1.29 g (54%). *Anal.* ($C_{28}H_{46}O_4S$) C, H, S.

2,3-Dimethoxy-5,6-di-*n*-octadecylmercapto-1,4-benzoquinone (4). When equimolar amounts of 2,3-dimethoxy-1,4-benzoquinone and *n*-octadecyl mercaptan were allowed to react as described above, a significant amount of the diadduct was obtained in the later crops. This material was purified by recrystallization from EtOH and hexane. The analytical sample was obtained from chromatography on deactivated silica gel using the dry column technique[11] and eluting with petroleum ether–ether (4:1): dull brick-red crystals; mp 61–64°. *Anal.* ($C_{44}H_{80}O_4S_2$) C, H, S.

2,3-Dimethoxy-6-*n*-octadecylmercapto-5-chloro-1,4-benzoquinone (5). HCl was bubbled through a suspension of 5.0 g of 1 in EtOH (200 ml) for 1.5 hr with stirring continued for another hr. A white precipitate was collected and dissolved in $CHCl_3$ (150 ml). Na_2SO_4 was added, and the mixture was cooled in ice while NO_2 was added dropwise. The color of the mixture turned dark red immediately. When no further reaction was noted, the mixture was allowed to warm to room temperature, and N_2 was bubbled through the mixture for 1 hr. The mixture was filtered, and the solvent was removed *in vacuo* leaving a red oil which solidified upon standing. Recrystallization from EtOH gave red crystals (2.8 g): mp 59–60°. The filtrate from the removal of the hydroquinone was evaporated to dryness. The residue in $CHCl_3$ was treated with NO_2 as described above yielding the chloroquinone **5** (0.7 g): total yield, 65%. *Anal.* ($C_{26}H_{43}ClO_4S$) C, H; S: calcd, 6.58; found, 7.01.

5-Amino-2,3-dimethoxy-6-*n*-octadecylmercapto-1,4-benzoquinone (6). To a solution of 1.4 g (2.9 mmol) of **5** in 100 ml of Me_2CO cooled to 0° was added a solution of NaN_3 (0.2 g, 3.1 mmol) in *ca.* 2 ml of H_2O with stirring. After 5 min, the mixture was warmed to room temperature for 30 min and was cooled overnight in the freezer. The grayish purple azidoquinone was collected, and the filtrate was evaporated to dryness *in vacuo* with the temperature kept under 30°. The residue and the filtered solid were dissolved in cyclohexane (*ca.* 200 ml). Pd/C (0.5 g) was added, and the mixture was shaken under 30 psi of H_2 for 2 hr at room temperature. The mixture was filtered, and the solvent was removed leaving a purple solid. Recrystallization from MeOH gave 1.2 g (90%) of the aminoquinone **6**: mp 64–65°. *Anal.* ($C_{26}H_{45}NO_4S$) C, H, N; S: calcd, 6.86; found, 7.58.

Reaction of 5-Chloro-2,3-dimethoxy-1,4-benzoquinone (13) with *n*-Octadecyl Mercaptan. To a solution of 5-chloro-2,3-dimethoxy-1,4-benzoquinone (2.0 g, 9.9 mmol) in EtOH (20 ml) was added a solution of *n*-octadecyl mercaptan (1.44 g, 5 mmol) in hexane (10 ml). After 15 min, an orange precipitate was collected and was washed with EtOH. This first crop (0.88 g) after recrystallization from hexane was identical (melting point, tlc, nmr) with 2,3-dimethoxy-5-*n*-octadecylmercapto-1,4-benzoquinone (1) prepared as described above. The stirred filtrate deposited a second crop after *ca.* 15 min. This precipitate was collected and washed with EtOH. After recrystallization from EtOH, red crystalline material (0.5 g) was obtained which was identical with 2,3-dimethoxy-6-*n*-octadecylmercapto-5-chloro-1,4-benzoquinone (**5**) prepared by the alternate route above. A third crop was obtained which was a mixture of the substitution and addition-oxidation products. Chromatography on silica gel (dry column) and elution with petroleum ether–ether (4:1) gave 0.37 g of 1 and 0.22 g of **5** along with 0.1 g of the diadduct, **4**. Concentrating the reaction mixture gave a fourth crop, which was chromatographed giving 0.13 g of 1 and 0.30 g of **5**. The remaining dried filtrate in ether was treated with Ag_2O (Na_2SO_4). Filtration and evaporation of solvent gave 5-chloro-2,3-dimethoxy-1,4-benzoquinone (0.85 g). The combined yields of 1 (30%), **5** (21%), **4** (1%), and recovered starting material (42%) account for 95% of the 5-chloro-2,3-dimethoxy-1,4-benzoquinone.

5-*n*-Dodecylmercapto-2,3-dimethoxy-1,4-diacetoxybenzene (7). 5-*n*-Dodecylmercapto-2,3-dimethoxy-1,4-benzoquinone (**2**, 200 mg) was treated with an excess of acetic anhydride and zinc dust followed by a few drops of pyridine in a manner similar to that described by Fieser and Gates.[6] After standing at room temperature for 1 hr, the reaction mixture was quenched with cold water and extracted with $CHCl_3$. The dried (anhydrous Na_2SO_4) extract was evaporated and codistilled with MeOH. MeOH was added to the residue, and the solution was seeded with few crystals from another batch. The product was recrystallized from MeOH–H_2O and then twice from MeOH–H_2O–Et_2O: yield ≅220 mg; mp 45–46°. *Anal.* ($C_{24}H_{38}O_6S$) C, H, S.

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.