Bis-Basic-Substituted Polycyclic Aromatic Compounds. A New Class of Antiviral Agents.[1,2] 4. Bis-Basic Sulfonamides of Anthraquinone

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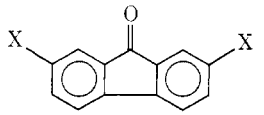
N,N[1]-Bis[3-(dibutylamino)propyl]-9,10-dihydro-9,10-dioxo-2,6-anthracenedisulfonamide dihydrochloride (**2**, RMI 9567 DA) was found to be a potent antiviral agent. A series of bis-basic sulfonamides of anthraquinone was prepared and evaluated *in vivo* for their ability to enhance survival against lethal infections by encephalomyocarditis (EMC) virus in mice. These compounds are related to bis-basic esters, ethers, and ketones of fluorenone, including tilorone hydrochloride, that induce interferon. The activity of **2** far surpassed that of other congeners in this series and even small deviations from its structure resulted in decrease or loss of activity. Bis-basic sulfonamides of fluorenone, fluorene, and 9,10-dihydroanthracene also showed antiviral activity but were less potent.

In the first paper of this series,[3] the discovery of antiviral activity of bis(3-dibutylaminopropyl) 9-oxofluorene-2,7-dicarboxylate dihydrochloride (I), which eventually led to the synthesis of tilorone hydrochloride (II),[4] was reported. These agents exhibit a broad spectrum of antiviral activity due to induction of interferon.[5-7] As part of an extensive program of structural modification, we synthesized the bis-basic sulfanamide III corresponding to I. This compound was found to also possess antiviral activity but to be less potent than I. We then synthesized a series of bis-basic sulfonamides of anthraquinone on which we wish to report here.



I, X = $-COO(CH_2)_3NBu_2$
II, X = $-O(CH_2)_2NEt_2$
III, X = $-SO_2NH(CH_2)_3NBu_2$

Chemistry. The bis-basic sulfonamides listed in Table I were prepared by reaction of the appropriate anthraquinonedisulfonyl chloride with an excess of the appropriate diamine in methylene chloride. Yields were generally good. Representative examples are given in the Experimental Section. In some instances the dihydrochloride salts were found to be hygroscopic or were for other reasons difficult to purify; it was then found advantageous to prepare the diacid maleate salts or the free bases. The anthraquinonedisulfonyl chlorides were obtained following the detailed description of Fierz-David,[8] who reworked this series to clarify the confusing reports in early dye patents of the 1880's. Fluorene-2,7-disulfonyl chloride and 9-oxofluorene-2,7-disulfonyl chloride were obtained following the procedure of Courtot and Geoffroy[9] and Courtot.[4,10] Disodium 9,10-dihydroanthracene-2,6-disulfonate was obtained directly by Zn-NH_4OH reduction of disodium anthraquinone-2,6-disulfonate as described in the Experimental Section and was converted to the disulfonyl chloride required for preparation of **35** and **36**. The monobasic and nonbasic sulfonamides were prepared by similar procedures.

Biological Evaluation and Structure-Activity Relationships. The bis-basic sulfonamides of anthraquinone prepared are listed in Table I. They were evaluated *in vivo* against encephalomyocarditis (EMC) virus infection in mice. Drug was administered subcutaneously in a dosage regimen consisting of several doses hours before and after inoculation with virus. The virus strength corresponded to approximately ten times the lethal dose. The antiviral activity was measured by determination of survival time ratio (STR), *i.e.*, the mean day of death of a treated group of ten mice divided by the mean day of death of a simultaneously infected, but untreated control group. An STR of 1.30 and above indicates high activity.[3,4]

The results differ from structure-activity relationships of earlier series, particularly those of compounds related to I,[3] in that high antiviral activity is confined to only a few compounds. Compound **2** stands out as the most active compound. Compounds **1**, **5**, **23**, and **24** also show high, but definitely less activity. Thus, while changes in the position of attachment of the two side chains (compounds **1–5**) influence but do not abolish activity, both the length of the side chains (compounds **6–15**) and the nature of the basic end groups (compounds **21–28**) are confined to narrow limits with the optimum defined by the structure of **2**. Of the tertiary sulfonamides only **16** and **20** show slight activity. Fel'dman reported preparation of compound **14**. Although it is implied that it was intended for evaluation as an anticancer agent, no results of such an evaluation are given.[11] We prepared this compound **14** and found it to possess no antiviral activity in our test system. It was also quite toxic. The "one-armed" analogs **29–34** (Table II) were inactive. The dihydroanthracene congener **36** showed good activity. The fluorenone congener **37** showed medium high activity, while the fluorene congener **38** showed only weak activity (Table II). Of a group of nonbasic mono- and bissulfonamides (Table III) none showed significant activity.

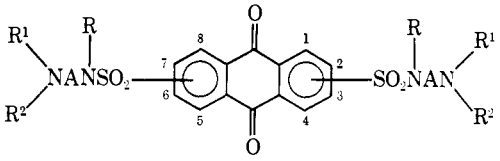
Compound **2** (RMI 9567 DA) also showed antiviral activity against another EMC strain, Mengo (STR 1.61). It was effective against other RNA viruses including the myxoviruses Influenza A_0 (Pr_8, STR 1.13), Influenza A/Equine-1 (STR 1.30), and the arbovirus Semliki Forest (STR 1.39). **2** was also effective against nonlethal doses of vaccinia IHD, a DNA virus, as indicated by decrease of severity (73%) of tail lesions. The compound was more effective subcutaneously than orally in these test systems. A comparison of antiviral and interferon responses of **2** with that of other bis-basic-substituted polycyclic aromatic compounds has been presented elsewhere.[7] Compound **2** also has been reported to protect mice against bacterial infection by *Staphylococcus aureus* and to stimulate the reticuloendothelial system.[12]

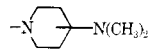
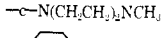
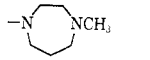
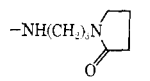
Experimental Section

Melting points were determined in open capillaries in a Thomas-Hoover apparatus and are corrected. Ir and uv spectra of all compounds were obtained and absorptions were as expected. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of theoretical values.

***N,N*[1]-Bis[4-(dibutylamino)butyl]-9,10-dihydro-9,10-dioxo-2,6-anthracenedisulfonamide Dihydrochloride (2).** To a suspension of 40.5 g (0.1 mol) of anthraquinone-2,6-disulfonyl chloride[8] in 500 ml of dry CH_2Cl_2 was added dropwise over 3 hr a solution of 46.6 g (0.25 mol) of 3-dibutylaminopropylamine in 250 ml of CH_2Cl_2 and the mixture was stirred overnight at room temperature. The resulting precipitate was collected, washed with

Table I. Bis-Basic Sulfonamides of Anthraquinone and Their Antiviral Activity



No.	Position	R | –NANR$_1$R$_2$	Mp, °C	Mol formula[a]	STR[b] *vs.* EMC virus in mice at mg/kg sc			
					250	50	10	2
1	2,7	–NH(CH$_2$)$_3$N(*n*-C$_4$H$_9$)$_2$	66–73	C$_{36}$H$_{56}$N$_4$O$_6$S$_2$·2C$_4$H$_4$O$_4$	0.87	1.57	1.60	1.45
2	2,6	–NH(CH$_2$)$_3$N(*n*-C$_4$H$_9$)$_2$	185–186	C$_{36}$H$_{56}$N$_4$O$_6$S$_2$·2HCl	1.95	2.33	2.09	1.31
3	1,5	–NH(CH$_2$)$_3$N(*n*-C$_4$H$_9$)$_2$	203–204 dec	C$_{36}$H$_{56}$N$_4$O$_6$S$_2$·2C$_4$H$_4$O$_4$	1.27	1.16	1.27	1.13
4	1,6	–NH(CH$_2$)$_3$N(*n*-C$_4$H$_9$)$_2$	57–60 dec	C$_{36}$H$_{56}$N$_4$O$_6$S$_2$·2C$_4$H$_4$O$_4$	Lethal	1.21	1.16	1.03
5	1,8	–NH(CH$_2$)$_3$N(*n*-C$_4$H$_9$)$_2$	176–178	C$_{36}$H$_{56}$N$_4$O$_6$S$_2$·2HCl	0.43	0.92	1.47	1.09
6	2,7	–NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	81–83 dec	C$_{26}$H$_{36}$N$_4$O$_6$S$_2$·2C$_4$H$_4$O$_4$	Lethal	0.67	0.98	
7	2,6	–NH(CH$_2$)$_2$N(*n*-C$_4$H$_9$)$_2$	165–166	C$_{34}$H$_{52}$N$_4$O$_6$S$_2$		1.00	1.20	1.09
8	2,6	–NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	185–188	C$_{26}$H$_{36}$N$_4$O$_6$S$_2$		1.02	1.14	1.05
9	2,7	–NH(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	136–138	C$_{28}$H$_{40}$N$_4$O$_6$S$_2$·2C$_4$H$_4$O$_4$	Lethal	Lethal	1.05	1.20
10	2,6	–NH(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	262–263 dec	C$_{28}$H$_{40}$N$_4$O$_6$S$_2$·2HCl	Lethal	Lethal	0.97	1.00
11	2,6	–NH(CH$_2$)$_4$N(*n*-C$_4$H$_9$)$_2$	155–156	C$_{38}$H$_{60}$N$_4$O$_6$S$_2$		1.29	1.13	1.00
12	2,6	–NH(CH$_2$)$_4$N(C$_2$H$_5$)$_2$	263–264	C$_{30}$H$_{44}$N$_4$O$_6$S$_2$·2HCl		Lethal	0.73	0.89
13	2,6	–NHCH(CH$_3$)(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	254–256 dec	C$_{32}$H$_{48}$N$_4$O$_6$S$_2$·2HCl		Lethal	Lethal	1.07
14[c]	1,5	–NHCH(CH$_3$)(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	229–230 dec	C$_{32}$H$_{48}$N$_4$O$_6$S$_2$·2HCl	Lethal	Lethal	Lethal	0.91[d]
15	2,6	–NH(CH$_2$)$_6$N(C$_2$H$_5$)$_2$	209–211	C$_{34}$H$_{52}$N$_4$O$_6$S$_2$·2HCl		Lethal	Lethal	1.00
16	2,7	–N(CH$_3$)(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	174–175 dec	C$_{28}$H$_{40}$N$_4$O$_6$S$_2$·2C$_4$H$_4$O$_4$	Lethal	0.90	1.19	
17	2,6	–N[(CH$_2$)$_2$N(C$_2$H$_5$)$_2$]$_2$	189–190	C$_{38}$H$_{62}$N$_6$O$_6$S$_2$·4C$_4$H$_4$O$_4$		1.07	1.07	1.00
18	2,6		311–312	C$_{28}$H$_{36}$N$_4$O$_6$S$_2$·2HCl		0.80	1.00	0.88
19	2,7		203–204 dec	C$_{24}$H$_{28}$N$_4$O$_6$S$_2$·2C$_4$H$_4$O$_4$		1.03	1.07	1.04
20	2,6		255–256 dec	C$_{26}$H$_{32}$N$_4$O$_6$S$_2$		1.27	1.02	0.96
21	2,6	–NH(CH$_2$)$_3$N(*n*-C$_3$H$_7$)$_2$	234–235	C$_{32}$H$_{48}$N$_4$O$_6$S$_2$·2HCl		0.72	1.09	1.13
22	2,6	–NH(CH$_2$)$_3$N(*n*-C$_5$H$_{11}$)$_2$	191–192	C$_{40}$H$_{64}$N$_4$O$_6$S$_2$·2HCl		1.16	1.14	1.07
23	2,6	–NH(CH$_2$)$_3$N(CH$_2$CH=CH$_2$)$_2$	147–149	C$_{32}$H$_{40}$N$_4$O$_6$S$_2$·2C$_4$H$_4$O$_4$		1.68	1.07	0.93
24	2,6	–NH(CH$_2$)$_3$N[CH$_2$CH$_2$CH(CH$_3$)$_2$]$_2$	199–200	C$_{40}$H$_{64}$N$_4$O$_6$S$_2$·2HCl	1.09	1.32	1.20	0.92
25	2,6	–NH(CH$_2$)$_3$-c-NC$_5$H$_{10}$	200–201 dec	C$_{30}$H$_{40}$N$_4$O$_6$S$_2$·2C$_4$H$_4$O$_4$		0.80	0.96	1.02
26	2,6	–NH(CH$_2$)$_3$-c-N(CH$_2$CH$_2$)$_2$NCH$_3$	296–297	C$_{30}$H$_{42}$N$_6$O$_6$S$_2$·4HCl	Lethal	0.72	0.98	0.98
27	2,6	–NH(CH$_2$)$_3$-c-N(CH$_2$CH$_2$)O	299–300	C$_{28}$H$_{36}$N$_4$O$_8$S$_2$·2HCl	1.11	1.11		
28	2,6		260–262	C$_{28}$H$_{32}$N$_4$O$_8$S$_2$		1.02	1.15	0.96
I, RMI 2557 DA[e]					1.66	1.50	1.16	1.05
II, tilorone hydrochloride[f]					Lethal	1.95	1.37	1.21

[a]All compounds were analyzed for C,H, and one other element usually S. Analytical results obtained for these elements were within ±0.4% of calculated values. [b]Survival time ratio as defined in ref 3. In those cases where several tests were run, average STR values are given. [c]See ref 8. [d]0.89 and 0.98 at 0.4 and 0.1 mg/kg, respectively. [e]See ref 3. [f]See ref 4.

CH_2Cl_2, and recrystallized twice from MeOH-MeCOEt to give 55.3 g (71%) of **2** (Table I).

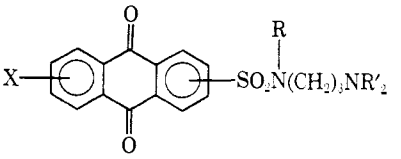
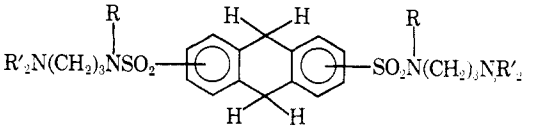
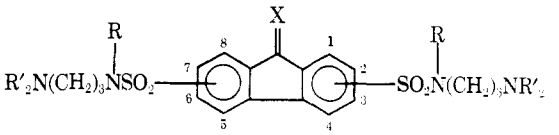
***N,N*^{1}-Bis[4-(dibutylamino)butyl]-9,10-dihydro-9,10-dioxo-2,6-anthracenedisulfonamide (11).** To a suspension of 20.2 g (0.05 mol) of anthraquinone-2,6-disulfonyl chloride[8] in 250 ml of dry CH_2Cl_2 was added a solution of 22.0 g (0.11 mol) of 4-dibutylaminobutylamine in 125 ml of CH_2Cl_2 and the mixture was stirred at room temperature overnight. The resulting solution was washed with H_2O, 2 *N* HCl, and saturated Na_2CO_3 solution and dried (Na_2SO_4), and the solvent was evaporated. The residue was recrystallized from *i*-PrOH to give 25.1 g (69%) of **11** (Table I).

***N*-[3-(Dibutylamino)propyl]-9,10-dihydro-*N,N*^{1}-dimethyl-9,10-dioxo-2,6-anthracenedisulfonamide Hydrochloride (33).** To a solution of 11.8 g (0.03 mol) of 2,6-bis(methylsulfamoyl)anthraquinone (**42**) in 50 ml of HCON $(CH_3)_2$ at 100° was added 6.0 g (0.076 mol) of 51% aqueous NaOH. A fine yellow precipitate resulted. To this suspension was added dropwise over 10 min 13.5 g (0.076 mol) of 3-dibutylaminopropyl chloride and the mixture was stirred at 100° for 5 hr. It was then poured into 1 l. of 1 *N* NaOH and the resulting precipitate was collected. It was dissolved in CH_2Cl_2, the solution was washed with 2 *N* NaOH and 2 *N* HCl and dried (Na_2SO_4), and the solvent was evaporated. The residue was crystallized and recrystallized from *i*-PrOH-H_2O to give 2.0 g (11%) of **33** (Table II).

***N*-(6-Diethylaminopropyl)-5-(3-diethylaminopropylsulfamoyl)-9,10-dihydro-9,10-dioxo-2-anthramide (34).** To 29.7 g (0.1 mol) of 5-nitro-9,10-dihydro-9,10-dioxo-2-anthroic acid[13] and 5.6 g of Na_2CO_3 in 400 ml of H_2O at 60–70° was added 37.8 g of Na_2SO_3 and the mixture was refluxed for 24 hr with stirring. The resulting homogeneous solution was acidified by addition of 27 ml of concentrated H_2SO_4 and allowed to cool and the precipitate that formed was collected and dried to give 46.3 g of crude 5-sulfo-9,10-dihydro-9,10-dioxo-2-anthroic acid disodium salt. To it was added 75.5 g of PCl_5 and the mixture was thoroughly mixed in a mortar, transferred to a reaction flask, and stirred with 50 ml of $POCl_3$ while heated in an oil bath maintained at 125°. After removing excess $POCl_3$ by distillation, the mixture was poured into H_2O and stirred, and the resulting precipitate was collected and dried in a desiccator over P_2O_5 to give 28.2 g of crude 5-chlorosulfo-9,10-dihydro-9,10-dioxo-2-anthroyl chloride. This material was treated with 3-diethylaminopropylamine in CH_2Cl_2 as described for **2** to give **34** (Table II).

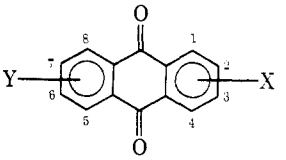
***N,N*^{1}-Bis[3-(dibutylamino)propyl]-9-oxo-9*H*-fluorene-2,7-disulfonamide (37).** To 11.3 g (0.03 mol) of fluorene-2,7-disulfonyl chloride[4,10] under 150 ml of CH_2Cl_2 was added dropwise over 4 hr a solution of 14.0 g (0.075 mol) of 3-dibutylaminopropylamine in 150 ml of CH_2Cl_2 and the mixture was stirred at room temperature for 24 hr. Since the dihydrochloride salt as well as the free

Table II. Related Basic Sulfonamides and Their Antiviral Activity

No.	Position	R	R′	X	Mp, °C	Mol formula[a]	STR[b] vs. EMC virus in mice at mg/kg sc 250	50	10	2
										
29	1	H	n-C_4H_9	H	126–128	$C_{25}H_{32}N_2O_4S \cdot HCl$		1.00	0.94	
30	2	H	n-C_4H_9	H	163–164	$C_{25}H_{32}N_2O_4S \cdot HCl$	0.88	0.94	0.96	
31	2	H	n-C_4H_9	5-NO_2	200–202	$C_{25}H_{31}N_3O_6S \cdot HCl$		1.06	1.00	1.00
32	2	H	n-C_4H_9	8-NO_2	138–140	$C_{25}H_{31}N_3O_6S \cdot HCl$			1.00	0.98
33	2	CH_3	n-C_4H_9	6-SO_2NHCH_3	222–224 dec	$C_{27}H_{37}N_3O_6S_2 \cdot HCl$	1.10	1.08	1.06	
34	1	H	C_2H_5	6-$CONH(CH_2)_3NEt_2$	100–103	$C_{29}H_{40}N_4O_3S$		0.88	0.92	1.12
										
35	2,6	H	C_2H_5		259–261 dec	$C_{28}H_{44}N_4O_4S_2 \cdot 2HCl$			0.96	1.00
36	2,6	H	n-C_4H_9		264–268 dec	$C_{36}H_{60}N_4O_4S_2 \cdot 2HCl$		1.57	1.15	1.02
										
37	2,7	H	n-C_4H_9	=O	186–187 dec	$C_{35}H_{56}N_4O_5S_2 \cdot 2C_4H_4O_4$	0.88	1.29	1.12	
38	2,7	H	n-C_4H_9	H, H	227–229	$C_{35}H_{58}N_4O_4S_2 \cdot 2HCl$	0.49	0.87	1.18	1.09

[a,b] See footnotes to Table I.

Table III. Nonbasic Sulfonamides of Anthraquinone



No.	X	Y	Mp, °C	Mol formula[a]	STR[b] vs. EMC virus in mice at mg/kg sc 250	50	10	2
39	2-SO_2NMe_2	7-SO_2NMe_2	298–300 dec	$C_{18}N_{18}N_2O_6S_2$	1.02	1.02		
40	2-SO_2NMe_2	6-SO_2NMe_2	>330	$C_{18}H_{18}N_2O_6S_2$[c]	1.04	1.00		
41	2-SO_2NH_2	6-SO_2NH_2	>360	$C_{14}H_{10}N_2O_6S_2$	0.98	1.20	0.96	1.10
42	2-SO_2NHMe	6-SO_2NHMe	307–308 dec	$C_{16}H_{14}N_2O_6S_2$	1.08	1.04	1.02	1.00
43	1-SO_2NMe_2	5-SO_2NMe_2	243–245 dec	$C_{18}H_{18}N_2O_6S_2$	0.84	1.10	1.02	1.00
44	1-SO_2NMe_2	6-SO_2NMe_2	234–235 dec	$C_{18}H_{18}N_2O_6S_2$		1.01	1.04	1.06
45	1-SO_2NMe_2	7-SO_2NMe_2	194–195	$C_{18}H_{18}N_2O_6S_2$		1.18	1.09	1.00
46	1-SO_2NMe_2	8-SO_2NMe_2	202–203	$C_{18}H_{18}N_2O_6S_2$	1.03	1.10		
47	2-SO_2NMe_2	H	210–212	$C_{16}H_{13}NO_4S$	1.05	1.07		
48	1-SO_2NMe_2	H	195–197	$C_{16}H_{13}NO_4S$	0.98	0.98		

[a,b] See footnotes to Table I. [c] *Anal.* Calcd: C, 51.17; H, 4.29; S, 15.18. Found: C, 51.33; H, 4.33; S, 14.69.

base failed to crystallize, the diacid maleate salt was prepared and recrystallized from CH_3OH to give 15.9 g (58%) of **37** (Table II).

9,10-Dihydroanthracene-2,6-disulfonyl Chloride. Zinc powder (100.0 g) was activated by allowing it to stand for 10 min in a solution of 0.5 g of $CuSO_4$ in 200 ml of H_2O, decanting, and washing it twice with H_2O.[14] It was added to 100.0 g of disodium 2,6-anthraquinonedisulfonate in 800 ml of H_2O and 250 ml of concentrated NH_4OH and the mixture was stirred at 70–80° for 7 hr. Another 100-g portion of activated zinc powder and 250 ml of concentrated NH_4OH was added and stirring was continued overnight at 100°. The solution completely decolorized. It was filtered hot through Celite to remove zinc and was saturated with NaCl (approximately 200 g), and 50 ml of concentrated HCl was added. The mixture was allowed to cool and the resulting precipitate was collected and dried for several days at 140° in a vacuum oven to give 96.8 g of 9,10-dihydroanthracene-2,6-disulfonic acid disodium salt.

The above salt (40.0 g) and 83.9 g of PCl_5 were thoroughly mixed in a mortar; the mixture was transferred to a reaction flask with 100 ml of $POCl_3$ and was stirred for 5 hr while heated in an oil bath maintained at 125°. After excess $POCl_3$ was removed by distillation, the mixture was poured into water and was thoroughly stirred for 1 hr to assure decomposition of the remaining $POCl_3$. The precipitate that formed was collected, washed with H_2O, and dried in a desiccator over P_2O_5 to give 31.4 g of 9,10-dihydroanthracene-2,6-disulfonyl chloride, mp 215° dec. A small sample was recrystallized twice from C_6H_6, mp 215° dec. *Anal.* ($C_{14}H_{10}Cl_2O_4S_2$) C, H, S.

Schüler[15] and Lampe[16] reported that Zn-NH_4OH reduction of 2,6-anthraquinonedisulfonic acid gives 2,6-anthracenedisulfonic acid, and Liebermann[17] reported that the latter is further reduced to 9,10-dihydroanthracene-2,6-disulfonic acid by treatment with refluxing 57% HI and red phosphorus. We found that 2,6-anthraquinonedisulfonic acid is reduced directly to 9,10-dihydroanthracene-2,6-disulfonic acid when activated Zn is used and

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.

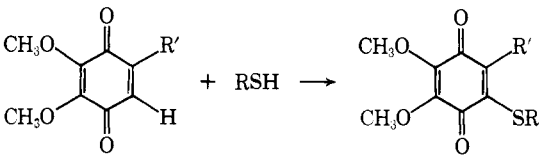
We now describe a new series of 2,3-dimethoxy-5-alkylmercapto-1,4-benzoquinones which have been synthesized in our continuing program[2-4] on lipoidal quinones as antimetabolites of coenzyme Q. In this study, optimum conditions for the addition of alkyl mercaptans to some substituted benzoquinones have 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