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# Structural Modification Study of Bis(substituted aminoalkylamino)anthraquinones. An Evaluation of the Relationship of the [2-[(2-Hydroxyethyl)amino]ethyl]amino Side Chain with Antineoplastic Activity

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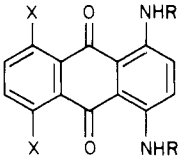
Several anthraquinones containing the [2-[(2-hydroxyethyl)amino]ethyl]amino, the [2-(dimethylamino)ethyl]amino, and the 2-(dimethylamino)ethoxy groups were prepared. Preparation of a lucanthone analogue, a 7-chloroquinoline derivative, and derivatives of naphthoquinones containing the [2-[(2-hydroxyethyl)amino]ethyl]amino side chain and related amino-substituted side chains was also conducted. It was found that the antineoplastic activity of anthraquinones containing the [2-[(2-hydroxyethyl)amino]ethyl]amino side chain is superior to those containing the tertiary amino side chain. However, the presence of the [2-[(2-hydroxyethyl)amino]ethyl]amino chain is an important, but not a sufficient, factor for good antineoplastic activity, as indicated by the lack of significant biological activity of other ring systems containing this side chain.

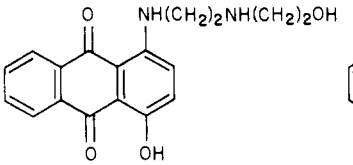
The outstanding antineoplastic activity displayed by a number of bis(substituted aminoalkylamino)anthraquinones,[2] particularly by 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione (**1a**) promoted a structural modification study in this



1a, X = OH; R = $(CH_2)_2NH(CH_2)_2OH$
b, X = H; R = $(CH_2)_2NH(CH_2)_2OH$
c, X = H; R = $(CH_2)_3NH(CH_2)_2OH$
d, X = H; R = $(CH_2)_2NH(CH_2)_2CH_3$
e, X = H; R = $(CH_2)_2NHCH_2CH_3$
f, X = H; R = $(CH_2)_2NHCH_3$
g, X = H; R = $(CH_2)_2NH_2$

laboratory. In order to further evaluate the relationship of the [2-[(2-hydroxyethyl)amino]ethyl]amino side chain with biological activity, synthesis of several additional anthraquinones with both side chains replaced by a similar side chain or one of the side chains replaced by other functional groups was conducted. In addition, several other biologically interesting ring systems containing this side chain or its analogues were also prepared for this investigation.

A structural comparison between the substituents of the aminoanthraquinones and those of the antineoplastic antibiotic adriamycin suggested the preparation of compound **2**, wherein one of the side chains is replaced by a



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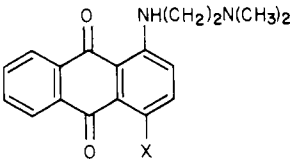
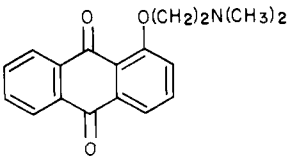


3a, X = $NH(CH_2)_2N(CH_3)_2$
b, X = OH



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hydroxyl group. To avoid the possibility of the formation of undesired cyclization products from the primary or the

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Table I. Comparison of Antineoplastic Activity of DHAQ, Other Amino-Substituted Anthraquinones, and Related Compounds[a]

| compd | test system[b] | dose,[c] mg/kg | survival | wt diff | T/C, % | cures |
|---|---|---|---|---|---|---|
| 1a | B1 | 2 | 50/50 | −2.0 | 231 | 13/50 |
| | | 1 | 50/50 | −1.4 | 342 | 19/50 |
| | | 0.5 | 50/50 | −1.1 | 299 | 10/50 |
| | | 0.25 | 50/50 | −0.7 | 186 | |
| | C6 | 1.08 | 10/10 | −2.3 | 353 | 4/10 |
| | | 0.69 | 10/10 | −1.9 | 305 | 4/10 |
| | | 0.39 | 10/10 | −1.5 | 259 | 2/10 |
| | LE | 18 | 8/8 | −6.2 | 308 | 5/8 |
| | | 10.8 | 8/8 | −5.5 | 261 | 1/8 |
| | | 4 | 10/10 | −3.8 | 256 | 4/10 |
| | | 2 | 10/10 | −2.9 | 198 | 2/10 |
| | | 1 | 10/10 | −1.9 | 163 | |
| | PS | 2 | 20/20 | −1.7 | 230 | 5/20 |
| | | 1 | 20/20 | −1.6 | 381 | 11/20 |
| | | 0.5 | 26/26 | −1.4 | 305 | 11/26 |
| | | 0.25 | 26/26 | −1.9 | 224 | 6/26 |
| | | 0.12 | 12/12 | −1.0 | 210 | |
| | | 0.06 | 12/12 | −1.0 | 192 | |
| 1b | B1 | 16 | 70/70 | −1.9 | 225 | 12/70 |
| | | 8 | 60/60 | −1.1 | 204 | 9/60 |
| | | 4 | 70/70 | −0.9 | 194 | 5/70 |
| | | 2 | 60/60 | −0.8 | 172 | 1/60 |
| | | 1 | 10/10 | −0.9 | 151 | |
| | C6 | 8 | 40/40 | −0.4 | 201 | 2/40 |
| | | 4 | 40/40 | −0.3 | 177 | 5/40 |
| | | 2 | 40/40 | −0.3 | 132 | 2/40 |
| | LE | 16 | 40/40 | −3.5 | 234 | 10/40 |
| | | 8 | 40/40 | −2.5 | 288 | 15/40 |
| | | 4 | 40/40 | −1.3 | 193 | 4/40 |
| | | 2 | 34/34 | −1.2 | 180 | 2/34 |
| | PS | 16 | 60/60 | −3.4 | 321 | 19/60 |
| | | 8 | 60/60 | −2.4 | 254 | 9/60 |
| | | 4 | 60/60 | −1.7 | 219 | 3/60 |
| | | 2 | 60/60 | −1.6 | 200 | |
| | | 1 | 34/34 | −1.1 | 155 | |
| 2 | B1 | 30 | 10/10 | −4.1 | 326 | 6/10 |
| | | 15 | 10/10 | −2.1 | 271 | 1/10 |
| | | 7.5 | 10/10 | −1.7 | 254 | 2/10 |
| | | 3.75 | 10/10 | −0.5 | 201 | 1/10 |
| | | 1.88 | 10/10 | 0.2 | 157 | |
| | C6 | 15 | 10/10 | −2.4 | 182 | 2/10 |
| | | 7.5 | 10/10 | −0.7 | 196 | 4/10 |
| | | 3.75 | 10/10 | −0.2 | 177 | 2/10 |
| | | 1.88 | 10/10 | −0.3 | 162 | |
| | LE | 15 | 6/6 | −4.4 | 151 | |
| | | 7.5 | 6/6 | −2.2 | 193 | 1/10 |
| | | 3.75 | 6/6 | −1.0 | 147 | |
| | | 1.88 | 6/6 | −1.8 | 136 | |
| | PS | 20 | 12/12 | −3.4 | 178 | 3/12 |
| | | 10 | 12/12 | −2.1 | 342 | 3/12 |
| | | 5 | 12/12 | −1.5 | 226 | |
| | | 2.5 | 6/6 | −1.1 | 216 | |
| 3a | B1 | 80 | 10/10 | −3.5 | 146 | |
| | | 40 | 10/10 | −1.1 | 148 | |
| | | 20 | 10/10 | −0.7 | 142 | |
| | | 10 | 10/10 | −1.0 | 125 | |
| | C6 | 20 | 10/10 | −0.9 | 113 | |
| | | 10 | 9/10 | −0.6 | 123 | |
| | LE | 30 | 5/6 | −0.7 | 150 | |
| | | 15 | 6/6 | −0.6 | 117 | |
| | PS | 40 | 6/6 | −2.3 | 202 | |
| | | 20 | 6/6 | −0.9 | 163 | |
| | | 10 | 6/6 | −1.4 | 149 | |
| | | 5 | 6/6 | −1.1 | 133 | |
| 3b | B1 | 200 | 10/10 | −2.5 | 156 | |
| | | 100 | 10/10 | −1.2 | 145 | |
| | | 50 | 10/10 | −1.0 | 110 | |
| | C6 | 80 | 10/10 | −1.4 | 115 | |
| | | 40 | 10/10 | −0.2 | 135 | |
| | | 20 | 10/10 | −0.3 | 104 | |

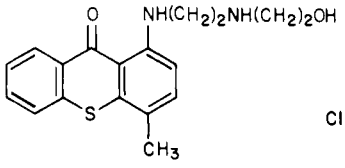
Table I (*Continued*)

| compd | test system[b] | dose,[c] mg/kg | survival | wt diff | T/C, % | cures |
|---|---|---|---|---|---|---|
| | LE | 160 | 10/10 | −4.2 | 139 | |
| | | 80 | 10/10 | −2.7 | 122 | |
| | | 40 | 10/10 | −0.6 | 107 | |
| | PS | 80 | 6/6 | −0.8 | 153 | |
| | | 40 | 6/6 | −0.9 | 124 | |
| | | 20 | 6/6 | −0.6 | 100 | |
| 4 | B1 | 100 | 10/10 | −0.7 | 104 | |
| | | 50 | 7/10 | −0.2 | 97 | |
| | | 25 | 10/10 | −1.2 | 93 | |
| | PS | 100 | 6/6 | −2.0 | 109 | |
| | | 50 | 6/6 | −1.0 | 107 | |
| 5 | PS | 30 | 6/6 | −4.3 | 136 | |
| | | 25 | 6/6 | −2.3 | 120 | |
| | | 15 | 6/6 | −3.2 | 123 | |
| | | 12.5 | 6/6 | −2.5 | 113 | |
| 6 | B1 | 100 | 10/10 | −1.5 | 110 | |
| | | 50 | 10/10 | −1.4 | 99 | |
| | LE | 25 | 6/6 | −0.3 | 111 | |
| | PS | 100 | 6/6 | −6.1 | 118 | |
| | | 50 | 6/6 | −3.3 | 116 | |
| 7a | PS | 100 | 9/12 | −2.5 | 93 | |
| | | 50 | 11/12 | −1.3 | 103 | |
| 7b | PS | 100 | 5/6 | −1.4 | 97 | |
| | | 50 | 6/6 | −1.8 | 100 | |
| 7c | PS | 12.5 | 6/6 | −3.6 | 97 | |
| | | 6.25 | 6/6 | −1.6 | 94 | |
| 7d | PS | 12.5 | 12/12 | −2.8 | 101 | |
| | | 6.25 | 6/6 | −1.0 | 96 | |

[a] All test results presented in this table were provided by the National Cancer Institute. For general screening procedure and data interpretation, cf. R. I. Geren, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, 3, 1 (1972); Instruction Booklet 14, "Screening Data Summary Interpretation and Outline of Current Screen", Drug Evaluation Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md., 1978. [b] B1 = B16 melanocarcinoma (homogenate tumor, ip, in $BDF_1$ mice); C6 = colon 26 (homogenate tumor, ip, in $CDF_1$ mice); LE = L-1210 lymphoid leukemia (ascite fluid, ip, in $CDF_1$ mice); PS = P388 lymphocytic leukemia (ascite fluid, ip, in $CDF_1$ mice). [c] Treatment schedule: QD 1-9.

secondary amino groups of the side chain during the preparation of compounds **1a** through **1g**,[2] a similar side chain containing a tertiary amino group, [2-(dimethylamino)ethyl]amine, was used to replace the original side chain. This resulted in the synthesis of compounds **3a** and **3b**. An oxygen analogue **4**, involving the replacement of a proximal amino linkage by an oxygen atom, was prepared to study the effect of biological activity by such a replacement.

The [2-[(2-hydroxyethyl)amino]ethyl]amino side chain was also introduced to a thioxanthone ring (compound **5**,

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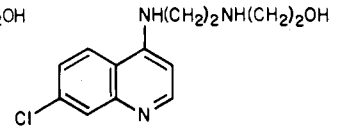


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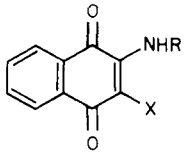


7a, X = H; R = $(CH_2)_2NH(CH_2)_2OH$
b, X = H; R = $(CH_2)_2N(CH_3)_2$
c, X = Cl; R = $(CH_2)_2N(CH_3)_2$
e, X = Cl; R = $(CH_2)_2N(C_2H_5)_2$

a lucanthone[3-5] analogue), to a quinoline ring (compound **6**, a chloroquine[6-9] analogue), and, together with other amino-substituted side chains, to a naphthoquinone ring (compounds **7a–d**). These ring systems were chosen since many compounds contained in such systems displayed antineoplastic activity.

**Chemistry.** Compounds **2** and **3b** were prepared by the treatment of quinizarin with 2-[(2-aminoethyl)amino]-ethanol and [2-(dimethylamino)ethyl]amine, respectively. Compound **3a** was obtained from leucoquinizarin (1,4,-9,10-tetrahydroxyanthracene) and [2-(dimethylamino)-ethyl]amine by the general procedure of Greenhalgh and Hughes.[10] The thioxanthone derivative **5** was prepared by heating a mixture of 2-[(2-aminoethyl)amino]ethanol and 1-chloro-4-methylthioxanthen-9-one. The latter was prepared by the condensation of 2-chlorobenzoic acid and 4-chloro-2-mercaptotoluene, followed by cyclization.[3,11] The chloroquine analogue **6** was prepared according to the procedure of Steck et al.[6] The naphthoquinone derivatives **7a** and **7b** were prepared by treatment of 1,4-naphthoquinone with 2-[(2-aminoethyl)amino]ethanol and [2-(dimethylamino)ethyl]amine, respectively. Compounds **7c** and **7d** were prepared in a similar manner from 2,3-dichloro-1,4-naphthoquinone and the appropriate amine.

**Biological Activity and Discussion.** Preliminary screening results of the aforementioned compounds are listed in Table I. For comparative purposes, accumulated screening data of **1a** and **1b** are also included. It is of interest to note that antineoplastic activity of compound **2**, which contains only one aminoalkylamino side chain, is comparable to that of **1b** and only slightly inferior than

that of **1a**, indicating that the bis(substituted aminoalkylamino) side chain is not necessary for activity (this is also substantiated by the activity of **3b**). Both compounds **2** and **1b** require approximately ten times the dosage of **1a** to achieve comparable activity. The oxygen analogue **4** was found to be inactive.

The significance of the [2-[(2-hydroxyethyl)amino]-ethyl]amino side chain, the most hydrophilic of this type employed, can be readily visualized by comparison of both the biological activity and dosage requirement of **3a** and **3b** with those of **1b** and **2**, respectively. Nevertheless, the presence of this side chain on other ring systems does not necessarily confer antineoplastic activity. Although the thioxanthone derivative **5** possesses a low activity against leukemia P388, other compounds, such as the chloroquine analogue **6** and the naphthoquinone derivative **7a**, are devoid of antileukemic activity.

## Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

**1-Hydroxy-4-[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione (2).** A solution of 8.5 g (0.08 mol) of 2-[(2-aminoethyl)amino]ethanol in 30 mL of BuOH was added to a stirred suspension of 15 g (0.06 mol) of quinizarin in 160 mL of BuOH. The resulting brick-red suspension was heated, with stirring, under $N_2$ in an oil bath at 150–155 °C, which gradually transformed the reaction mixture into a purple-colored solution. After 5 h, the reaction mixture was cooled and allowed to stand overnight. To the mixture was added 200 mL of petroleum ether (bp 35–60 °C). After stirring the mixture for 30 min, the solid product was collected by filtration, washed with petroleum ether (3 × 100 mL), and dried to give 20.5 g of the crude aminoanthracenedione, mp 136–138 °C. This was recrystallized from 400 mL of EtOH and 1000 mL of petroleum ether to give 17 g (85% yield) of pure **2**: mp 138–140 °C; UV $\lambda_{max}$ (EtOH) 252 nm (log $\epsilon$ 4.42), 276 (4.19), 545 (3.95), 578 (4.12), 635 (4.08). Anal. ($C_{18}H_{18}N_2O_4 \cdot H_2O$) C, H, N.

**1,4-Bis[[2-(dimethylamino)ethyl]amino]-9,10-anthracenedione (3a).** A mixture of 27 g (0.3 mol) of [2-(dimethylamino)ethyl]amine and 7.3 g (0.03 mol) of 1,4,9,10-tetrahydroxyanthracene was heated under $N_2$ with stirring at 55 ± 2 °C for 2 h. After cooling the mixture, 250 mL of EtOH was added. Dry air was bubbled through the mixture by means of a glass sparge tube while the temperature of the mixture was maintained at 60–65 °C for 3 h. The volume of the reaction mixture was reduced to about 100 mL in vacuo. To this was added, with stirring, 200 mL of petroleum ether (bp 35–60 °C). Stirring was continued for 30 min after the addition. The resulting solid was collected by filtration, washed with petroleum ether (3 × 30 mL), and dried to give 10 g (87% yield) of the bissubstituted aminoanthracenedione, mp 170–172 °C. An analytical sample was obtained by recrystallizing 1 g of the product from 50 mL of $CHCl_3$ and 120 mL of petroleum ether, yielding 0.6 g: mp 170–172 °C; UV $\lambda_{max}$ (EtOH) 255 nm (log $\epsilon$ 4.41), 273 (4.11), 310 (3.65), 594 (4.07), 630 (4.16). Anal. ($C_{22}H_{28}N_4O_2$) C, H, N.

**1-[[2-(Dimethylamino)ethyl]amino]-4-hydroxy-9,10-anthracenedione (3b).** This compound was prepared in a manner similar to that for the preparation of **2** from 15 g (0.06 mol) of quinizarin and 8 g (0.09 mol) of [2-(dimethylamino)-ethyl]amine in 150 mL of BuOH. The yield of the purple crystalline **3b** was 7 g (36%), mp 108–110 °C. Recrystallization from a mixture of 50 mL of EtOH and 150 mL of $H_2O$ afforded an analytical sample: mp 118–120 °C; UV $\lambda_{max}$ (EtOH) 248 nm (log $\epsilon$ 4.37), 548 (3.89), 591 nm (3.85). Anal. ($C_{18}H_{18}N_2O_3 \cdot 0.25H_2O$) C, H, N.

**1-[2-(Dimethylamino)ethoxy]-9,10-anthracenedione Hydrochloride (4).** To 54 g (0.6 mol) of 2-(dimethylamino)ethanol was added 2.4 g (0.06 g-atom) of metallic K. To the resulting solution was added 14.6 g (0.06 mol) of 1-chloroanthraquinone. The mixture was heated at 140 °C for 10 h, cooled, and poured into 500 mL of ice–water with stirring. After the mixture was left standing overnight, the solid was collected by filtration, washed with $H_2O$ (2 × 100 mL), and dried to give 34 g of crude product. This was stirred with 600 mL of 5% HCl. The aqueous solution was extracted with 3 × 150 mL of $Et_2O$. The aqueous layer was separated, filtered, and, with cooling, made basic with 20% of NaOH. The basic solution was extracted with $Et_2O$ (3 × 400 mL) and dried ($Na_2SO_4$). To the dried $Et_2O$ extract was added 30 mL of 20% HCl in EtOH with stirring. The resulting HCl salt was collected by filtration, washed with $Et_2O$ (2 × 50 mL), and dried to give 14 g of **4**. Further recrystallization from 1000 mL of EtOH gave 11.7 g (59% yield) of analytically pure **4** as a yellow powder: mp 274–275 °C; UV $\lambda_{max}$ (EtOH) 252 nm (log $\epsilon$ 4.52), 270 (4.15), 370 (3.63). Anal. ($C_{18}H_{17}NO_3 \cdot HCl$) C, H, N.

**1-[[2-[(2-Hydroxyethyl)amino]ethyl]amino]-4-methyl-9*H*-thioxanthen-9-one (5).** A mixture of 6.5 g (0.025 mol) of 1-chloro-4-methyl-9*H*-thioxanthen-9-one[2,11] and 30 g (0.29 mol) of 2-[(2-aminoethyl)amino]ethanol was heated, under $N_2$, at 140 °C for 12 h with stirring. It was cooled and triturated with 200 mL of $H_2O$, and the solid was collected by filtration. The crude product was stirred in 300 mL of dioxane–$CHCl_3$ (3:2) and filtered, and the filtrate was evaporated under reduced pressure to yield a crystalline solid. Since it still contained some starting chlorothioxanthone, it was dissolved in 150 mL of $CHCl_3$ and saturated with dry HCl. The mixture was evaporated to dryness, the solid was boiled with 400 mL of $H_2O$, and the solution was filtered while hot. The filtrate was cooled, made alkaline with $NH_4OH$, and allowed to stand overnight. The precipitate was collected by filtration, washed with $H_2O$, and dried at room temperature in vacuo to give 6.5 g (74.3% yield) of **5** as a yellow solid, mp 130–131 °C. Anal. ($C_{18}H_{20}N_2O_2S \cdot 1.25H_2O$) C, H, N.

**2-[[2-(7-Chloro-4-quinolylamino)ethyl]amino]ethanol (6).** This compound was prepared according to the procedure of Steck et al.[6] as a dihydrochloride, mp 239–241 °C (lit.[6] mp 239–239.5 °C).

**2-[[2-[(2-Hydroxyethyl)amino]ethyl]amino]-1,4-naphthalenedione (7a).** To 100 mL of absolute EtOH was added 8 g (0.05 mol) of 1,4-naphthoquinone followed by 10 g (0.1 mol) of 2-[(2-aminoethyl)amino]ethanol. The mixture was stirred for 2 days at room temperature. The resulting dark purple solution was refluxed for 1 h and allowed to cool to room temperature. Air was passed through the solution for 7 h, after which the solid was collected by filtration. Recrystallization from EtOH gave 7.02 g (54% yield) of **7a**, mp 149–150 °C. Anal. ($C_{14}H_{16}N_2O_3$) C, H, N.

**2-[[2-(Dimethylamino)ethyl]amino]-1,4-naphthalenedione (7b).** To a suspension of 15.8 g (0.1 mol) of 1,4-naphthoquinone in 200 mL of EtOH was added 17.6 g (0.2 mol) of 2-(dimethylamino)ethylamine. The purple reaction mixture was stirred overnight at room temperature and then under reflux for 2 h. After cooling, the reaction mixture was filtered to remove a slight amount of insoluble material. To the filtrate was added 500 mL of $H_2O$. The resulting solution was stirred for 1 h and then refrigerated overnight. The precipitate was collected by filtration to give 23 g (94% yield) of **7b** as a brown solid. An analytical sample was prepared by recrystallizing a portion of the product from a mixture of $H_2O$ and EtOH, mp 85–86 °C. Anal. ($C_{14}H_{16}N_2O_2$) C, H, N.

**2-Chloro-3-[[2-(dimethylamino)ethyl]amino]-1,4-naphthalenedione (7c).** To a suspension of 22.7 g (0.1 mol) of 2,3-dichloro-1,4-naphthoquinone in 200 mL of EtOH was added 8.8 g (0.1 mol) of 2-(dimethylamino)ethylamine. As the amine was added, a deep red color developed and a slight heat of reaction was noted. The reaction mixture was stirred at room temperature overnight (to yield a bright red solid) and then refluxed for 1 h. After cooling the mixture, the bright red precipitate was collected by filtration to give 29.8 g (95% yield) of crude product. Recrystallization of a portion of the product from MeOH gave analytically pure **7c** as a hydrochloride, mp 215–216 °C. Anal. ($C_{14}H_{15}ClN_2O_2 \cdot HCl$) C, H, N.

**2-Chloro-3-[[2-(diethylamino)ethyl]amino]-1,4-naphthalenedione (7d).** This compound was prepared in a manner similar to that used for the preparation of **7c**. Reaction of 11.3 g (0.05 mol) of 2,3-dichloro-1,4-naphthoquinone and 5.8 g (0.05 mol) of 2-(dimethylamino)ethylamine in 200 mL of EtOH gave 14.5 g (85% yield) of product. Recrystallization from

EtOH–$H_2O$ gave analytically pure **7d**·HCl, mp 242 °C dec. Anal. ($C_{16}H_{19}ClN_2O_2$·HCl) C, H, N.

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# Synthesis of 3,4-Dihydro-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylates, a New Series of Orally Active Antiallergy Agents

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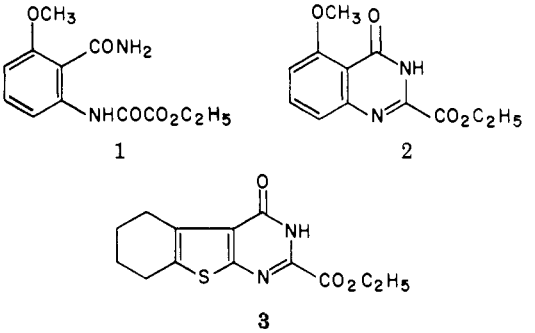
A series of novel 3,4-dihydro-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylic acid derivatives has been prepared and tested for antiallergenic activity. Members of the series, including both carboxylic acid salts and esters, have been found to exhibit oral activity in the rat passive cutaneous anaphylaxis (PCA) test. Activity is optimized by H or $CH_3$ substitution at the 5 position and lower alkyl groups at the 6 position. Ethyl 6-ethyl-3,4-dihydro-4-oxothieno-[2,3-*d*]pyrimidine-2-carboxylate and 3,4-dihydro-5-methyl-6-(2-methylpropyl)-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylic acid dipotassium salt were the most potent of the esters and salts, respectively. Such compounds have been shown to have a duration of action of up to 4 h in the PCA test and to inhibit both histamine release from rat peritoneal mast cells in vitro and allergen-induced bronchospasm in the rat lung.

The discovery of the mediator release inhibitor disodium cromoglycate (DSCG) has opened a new approach to the therapy of bronchial asthma in man.[1] The fact that the drug must be administered topically by insufflation has spurred considerable work toward developing similar agents with oral activity. For example, a recent paper[2] has shown that *N*-aryloxamic acid esters (**1**) and the corresponding quinazolinone derivatives (**2**) were orally effective antiallergy agents.

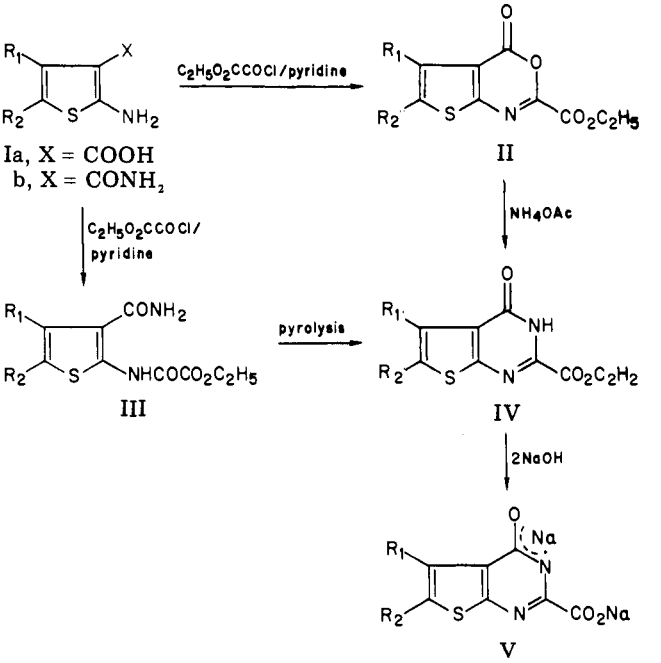


**1** **2** **3**

The observation that alkoxy substituents on **1** and **2** conferred maximal activity to those molecules prompted us to undertake the synthesis of related compounds in which the alkoxy-substituted benzo group of **2** was replaced by a $\pi$-rich thieno moiety. This provided compounds of type **3** whose lipophilicity could readily be modified via appropriate substitution of the thiophene ring. Our objective, therefore, was to prepare compounds of type **3** with maximal intrinsic activity, oral absorption, and duration of drug action.

Compound **3** was described in the literature as having been prepared by the condensation of diethyl oxalate with the corresponding 2-aminothiophene-3-carboxamide.[3]

Scheme I



We prepared thieno[2,3-*d*]pyrimidine **3** both by pyrolysis of the oxamate intermediate **5** and ammonolysis of the thieno[2,3-*d*]oxazine intermediate **14** (Table I), and it was found that compounds **3**, **5**, and **14** all showed weak oral PCA activity. The disodium salt of the corresponding carboxylic acid **16** showed an oral PCA $ED_{50}$ = 50 mg/kg.

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