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Benzimidazolediones. 1,4-Addition Reactions of 4,7-Benzimidazoledione (1)

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A number of 1,4-addition reactions of 4,7-benzimidazoledione with hydrogen halides, thiols and amines are described.

Thio-substituted 1,4-naphthoquinones are thought to possess enzyme-inhibiting activity (2) and 2-methylthio-1,4-naphthoquinone has been shown to possess antifungal properties (3). Certain 6-amino-5,8-quinolinequinones have been synthesized for the evaluation of their amebicidal activities (4) and some quinolinequinones containing halo and amino groups are reported to possess fungistatic activity (5). It was therefore thought that the addition of nucleophiles to the 4,7-benzimidazoledione system (6) might result in the formation of useful antimetabolites.

The reaction of concentrated aqueous hydrochloric acid with 4,7-benzimidazoledione gave 5-chloro-4,7-benzimidazolediol hydrochloride monohydrate (XXXV). The reaction with 48% aqueous hydrobromic acid was completely analogous and gave the corresponding bromo derivative (XXXVI). The reaction with 47% aqueous hydriodic acid did not result in 1,4-addition to the quinone but instead resulted in reduction to 4,7-benzimidazolediol hydroiodide. The 5-halo-4,7-benzimidazolediol hydrohalide monohydrates were oxidized to the corresponding 5-halo-4,7-benzimidazolediones (XI, XII) in aqueous ferric chloride solution.

The reaction of 4,7-benzimidazoledione with an excess of various thiols resulted in the formation of disubstituted quinones or hydroquinones exclusively. All reactions were carried out in methanol or, in one case, methanol-water solution and in the presence of air. The reactions of ethanethiol, 1-propanethiol, 1-butanethiol, 1-pentanethiol, 1-hexanethiol, and α-toluenethiol resulted in the isolation of disubstituted quinones only. However, the reactions with benzenethiol, *p*-toluenethiol, and 2-mercaptoethanol in each case formed air sensitive disubstituted hydroquinones which were stable as their hydrochloride salts. With the exception of 5,6-bis(*p*-tolylthio)-4,7-benzimidazolediol, the disubstituted hydroquinones were oxidized to the corresponding disubstituted quinones with silver oxide in methanol solution.

A sulfur mustard was prepared by the reaction of 5,6-bis[(2-hydroxyethyl)thio]-4,7-benzimidazolediol hydrochloride (XXXII) in refluxing thionyl chloride. Apparently, in addition to chlorination of the aliphatic hydroxyl groups, air oxidation occurred to give 5,6-bis[(2-chloroethyl)thio]-4,7-benzimidazoledione (IX). This compound showed some degree of antitumor activity against the Walker carcinosarcoma 256 (7).

The reactions of 5-chloro-4,7-benzimidazoledione (XI) with excess ethanethiol, α-toluenethiol and 1-propanethiol were carried out in methanol solution. Ethanethiol and α-toluenethiol yielded the disubstituted hydroquinone hydrochlorides as the major products and the disubstituted quinones as the minor products. In the reaction of 5-chloro-4,7-benzimidazoledione with 1-propanethiol, the disubstituted quinone was the only product which could be isolated. The dithio-substituted hydroquinone hydrochlorides were oxidized to the corresponding quinones with silver oxide in methanol solution. The structures of the various dithio-substituted benzimidazolediones and benzimidazolediols were established by infrared, ultraviolet, and, in some cases, n.m.r. spectroscopy.

The reaction of 4,7-benzimidazoledione with excess 1,2-ethanedithiol in methanol solution resulted in the formation of 4a,6,7,8a-tetrahydro-1*H*-*p*-dithiino[2,3-*f*]benzimidazole-4,9-dione (X). The infrared spectrum of this compound exhibited carbonyl frequencies at 1684 and 1674 cm^{-1}. The nmr spectrum of X was obtained in deuterated dimethylsulfoxide solution. A singlet with an integrated area of one was observed at δ 8.25 and was due to the proton at the 2-position. A singlet with an integrated

area of two was observed at δ 3.60 and was assigned to the protons in the 4a- and the 8a-positions. A singlet with an integrated area of four at δ 3.42 was due to the methylene protons. The mass spectrum exhibited an ion for the molecular weight of the compound at m/e 240.

The reaction of 4,7-benzimidazoledione with an excess of various primary and secondary amines in methanol solution in the presence of air resulted in the formation of 5-amino-substituted-4,7-benzimidazolediones (XIII-XXV). No substituted or unsubstituted hydroquinones were isolated possibly because these compounds are very air sensitive. The reactions of 5-chloro-4,7-benzimidazoledione

SCHEME I

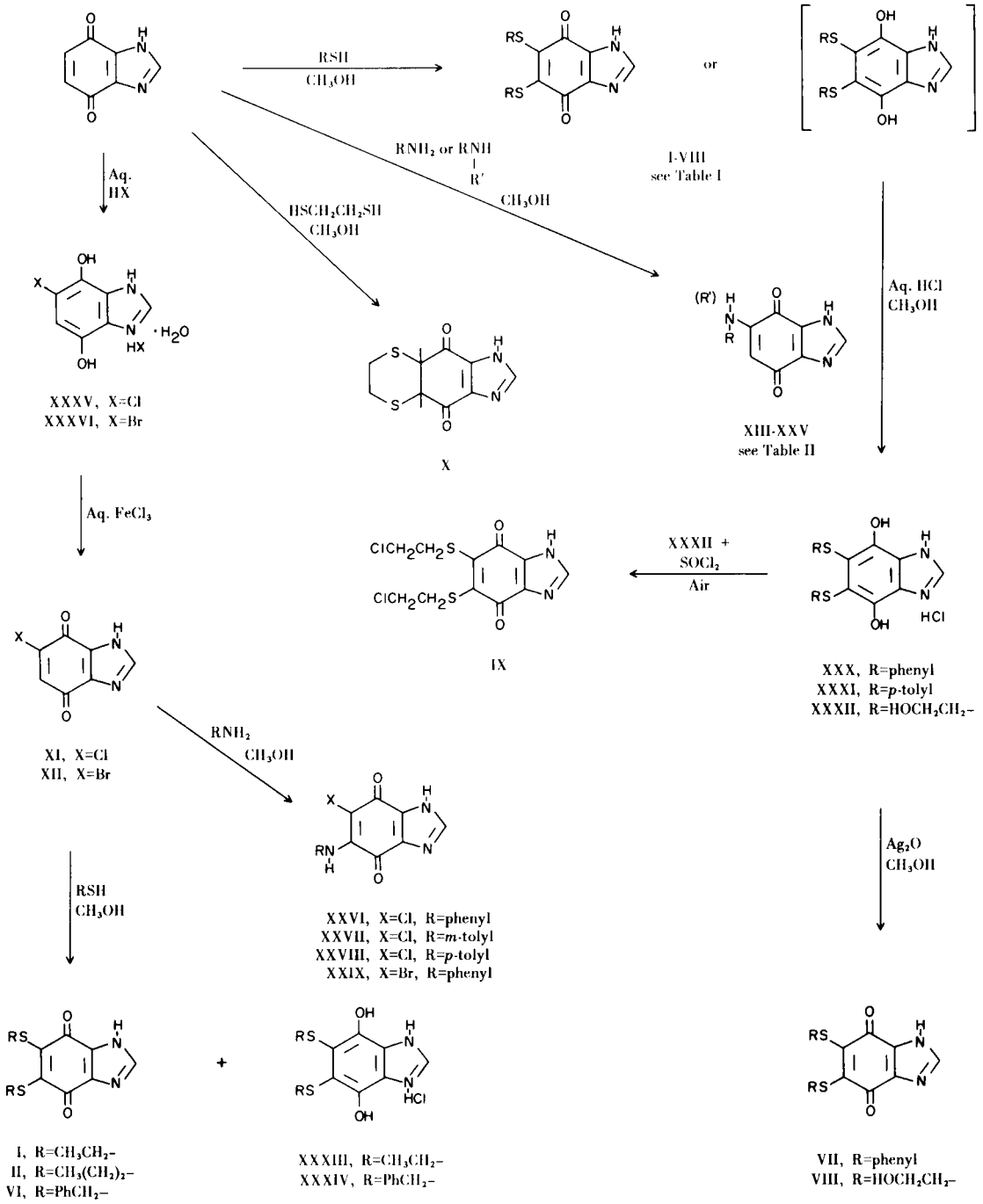
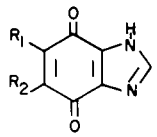


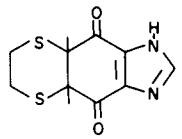
TABLE I

Thio-substituted 4,7-Benzimidazolediones



Compound No.	R_1, R_2	Yield %	M.p. °C	Formula	Calcd. % C	H	N	S	Found % C	H	N	S	ν C=O (KBr) cm^{-1}
I (a)	CH_3CH_2S-	39	256-259d	$C_{11}H_{12}N_2O_2S_2$	49.23	4.51	10.44	23.90	49.35	4.44	10.30	24.13	1679 1653
II	$CH_3(CH_2)_2S$-	48	223-226d	$C_{13}H_{16}N_2O_2S_2$	52.68	5.44	9.45	21.63	52.72	5.38	9.65	21.55	1675 1654
III	$CH_3(CH_2)_3S$-	39	189-193d	$C_{15}H_{20}N_2O_2S_2$	55.53	6.21	8.63	19.76	55.62	6.28	8.46	19.52	1653
IV	$CH_3(CH_2)_4S$-	37	183-187d	$C_{17}H_{24}N_2O_2S_2$	57.92	6.86	7.95	18.19	58.15	6.84	7.79	18.34	1654
V	$CH_3(CH_2)_5S$-	51	177-179d	$C_{19}H_{28}N_2O_2S_2$	59.96	7.42	7.36	16.85	60.03	7.39	7.18	17.05	1654
VI	$C_6H_5CH_2S$-	55	239-241d	$C_{21}H_{16}N_2O_2S_2$	64.26	4.11	7.14	16.34	64.40	4.29	7.06	16.40	1671 1653 1648
VII (b)	C_6H_5S-	32	241-243d	$C_{19}H_{12}N_2O_2S_2$	62.62	3.32	7.69	17.60	62.46	3.20	7.62	17.46	1656
VIII	$HOCH_2CH_2S$-	49	184-186d	$C_{11}H_{12}N_2O_4S_2$	43.99	4.03	9.33	21.35	43.98	4.13	9.24	21.22	1678 1648
IX (c)	$ClCH_2CH_2S$-	75	221-222d	$C_{11}H_{10}N_2O_2S_2Cl_2$ (d)	39.18	2.99	8.31	19.02	39.35	3.10	8.26	19.21	1675 1654

4a,6,7,8a-Tetrahydro-1*H*-*p*-dithiino[2,3-*f*]benzimidazole-4,9-dione

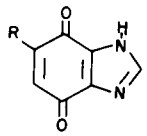


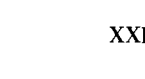
X		53	191-193d	$C_9H_8N_2O_2S_2$	44.98	3.36	11.66	26.68	45.07	3.29	11.63	26.44	1684 1674

(a) The n.m.r. spectrum in deuterated DMSO showed a singlet at δ 8.22 (1H), a quartet at δ 3.43, 3.32, 3.18 and 3.08 (4H), and a triplet at δ 1.38, 1.27 and 1.13 (6H). (b) The n.m.r. spectrum in deuterated DMSO showed a singlet at δ 8.22 (1H) and a singlet at δ 7.37 (10H). (c) The n.m.r. spectrum in deuterated DMSO showed a singlet at δ 8.15 (1H), a quintet with peaks at δ 3.98, 3.93, 3.88, 3.83 and 3.73 (4H) and a quintet with peaks at δ 3.58, 3.50, 3.44, 3.40 and 3.35 (4H). (d) % Cl, Calcd.: 21.01. Found: 20.93.

TABLE II

5-Amino and 5-Halo-substituted 4,7-Benzimidazolediones

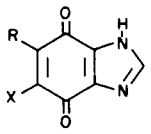


Compound No.	R	Yield %	M.p. °C	Formula	Calcd., % C	H	N	Cl, Br	Found, % C	H	N	Cl, Br	ν C=O (KBr) cm^{-1}
XI (a)	-Cl	70	>240d	$C_7H_3N_2O_2Cl$	46.05	1.66	15.34	19.42	46.08	1.82	15.49	19.29	1665
XII	-Br	51	>208d	$C_7H_3N_2O_2Br$	37.03	1.33	12.34	35.20	37.25	1.43	12.14	35.05	1665
XIII	C_6H_5NH-	55	307-310d	$C_{13}H_9N_3O_2$	65.27	3.79	17.56		65.17	3.90	17.45		1670
XIV	*p*-CH_3-C_6H_4-NH-	22	296-297d	$C_{14}H_{11}N_3O_2$	66.40	4.38	16.59		66.22	4.27	16.73		1672
XV	*m*-CH_3-C_6H_4-NH-	13	287-289d	$C_{14}H_{11}N_3O_2$	66.40	4.38	16.59		66.59	4.54	16.41		1679
XVI	*p*-Cl-C_6H_4-NH-	48	313-316d	$C_{13}H_8N_3O_2Cl$	57.05	2.95	15.35	12.96	56.91	3.12	15.55	12.95	1678
XVII (b)	*p*-Br-C_6H_4-NH-	59	319-320d	$C_{13}H_8N_3O_2Br$	49.08	2.53	13.21	25.12	48.95	2.60	12.92	25.02	16.85
XVIII	*p*-I-C_6H_4-NH-	47	317-320d	$C_{13}H_8N_3O_2F$	60.70	3.13	16.33	7.39	60.75	3.29	16.26	7.27	1672
XIX (c)	*p*-CH_3O-C_6H_4-NH-	58	303-307.5d	$C_{14}H_{11}N_3O_3$	62.45	4.12	15.61		62.32	4.29	15.47		1678
XX	*o*-CH_3O-C_6H_4-NH-	55	294-299d	$C_{14}H_{11}N_3O_3$	62.45	4.12	15.61		62.64	4.07	15.43		1685
XXI	2,5-$(CH_3O)_2$-C_6H_3-NH-	31	295-297d	$C_{15}H_{13}N_3O_4$	60.20	4.38	14.04		60.10	4.54	13.94		1680
XXII (d)	$C_6H_5CH_2NH$-	59	238-241d	$C_{14}H_{11}N_3O_2$	66.40	4.38	16.59		66.24	4.60	16.45		1687 1680
XXIII		41	246-248d	$C_{14}H_{11}N_3O_2$	66.40	4.38	16.59		66.36	4.53	16.48		16.72
XXIV		53	277d	$C_{11}H_{11}N_3O_3$	56.65	4.75	18.02		56.37	4.84	17.95		1677 1640
XXV (e)	$CH_3(CH_2)_4NH$-	21	239-241d	$C_{12}H_{15}N_3O_2$	61.79	6.48	18.01		61.67	6.55	17.90		1684 1678

(a) The nmr spectrum in DMSO-d_6 showed a singlet at δ 8.20 (1H) and a singlet at δ 7.08 (1H). (b) The nmr spectrum in DMSO-d_6 showed a singlet at δ 9.13 (1H), a singlet at δ 8.10 (1H), a doublet with peaks at δ 7.70 and δ 7.53 (2H), a doublet with peaks at δ 7.40 and δ 7.25 (2H), and a singlet at δ 5.72 (1H). (c) The nmr spectrum in DMSO-d_6 showed a singlet at δ 9.05 (1H), a singlet at δ 8.08 (1H), a doublet with peaks at δ 7.35 and δ 7.22 (2H), a doublet with peaks at δ 7.05 and δ 6.92 (2H), a singlet at δ 5.50 (1H), and a singlet at δ 3.75 (3H). (d) Recrystallized from methanol-low boiling petroleum ether. (e) Recrystallized from 1,2-dimethoxyethane. The nmr spectrum in DMSO-d_6 showed a singlet at δ 8.03 (1H), a singlet at δ 7.50 (1H), a singlet at δ 5.18 (1H), a multiplet at δ 3.18 (2H), a multiplet at δ 1.40 (6H), and a singlet at δ 0.88 (3H). A broad peak was observed at δ 13.58 (1H).

TABLE III

5-Arylamino-6-halo-4,7-benzimidazolediones

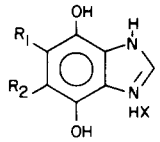


Compound No.	R	X	Yield %	M.p. °C	Formula	Calcd., % C	H	N	X	Found, % C	H	N	X	ν C=O (KBr) cm^{-1}
XXVI	C_6H_5NH-	Cl	53	319-320d	$C_{13}H_8N_3O_2Cl$	57.05	2.95	15.35	12.96	57.02	3.27	15.48	12,82	1685 1648
XXVII (a)	*p*-$CH_3C_6H_4$-NH-	Cl	67	310-311d	$C_{14}H_{10}N_3O_2Cl$	58.44	3.50	14.61	12.32	58.54	3.53	14.42	12.11	1682 1650
XXVIII	*m*-$CH_3C_6H_4$-NH-	Cl	79	319d	$C_{14}H_{10}N_3O_2Cl$	58.44	3.50	14.61	12.32	58.66	3.68	14.44	12.14	1693 1687 1642
XXIX	C_6H_5NH-	Br	58	265-267d	$C_{13}H_8N_3O_2Br$	49.08	2.53	13.21	25.12	49.19	2.59	13.13	25.04	1687 1640

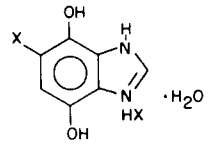
(a) The nmr spectrum in DMSO-d_6 showed a singlet at δ 9.08 (1H), a singlet at δ 8.18 (1H), a singlet at δ 7.08 (4H), and a singlet at δ 2.30 (3H).

TABLE IV

Substituted 4,7-Benzimidazolediol Hydrohalides



Compound No.	R_1, R_2	Yield %	M.p. °C	Formula	Calcd., % C	H	N	S	Cl, Br	Found, % C	H	N	S	Cl, Br
XXX	C_6H_5S-	70	255-256d	$C_{19}H_{15}N_2O_2S_2Cl$	56.64	3.75	6.95	15.91	8.80	56.50	3.81	6.89	15.83	8.55
XXXI	*p*-CH_3-C_6H_4-S-	64	251-254d	$C_{21}H_{19}N_2O_2S_2Cl$	58.53	4.44	6.50	14.88	8.23	58.55	4.53	6.34	14.73	8.00
XXXII	$HOCH_2CH_2S$-	84	196-197d	$C_{11}H_{15}N_2O_4S_2Cl$	38.99	4.46	8.27	18.93	10.46	39.12	4.40	8.10	18.76	10.32
XXXIII	CH_3CH_2S-	35	226-229d	$C_{11}H_{15}N_2O_2S_2Cl$	43.06	4.93	9.13	20.89	11.55	43.18	5.01	9.03	20.68	11.60
XXXIV	$C_6H_5CH_2S$-	73	223-225d	$C_{21}H_{19}N_2O_2S_2Cl$	58.53	4.44	6.50	14.88	8.23	58.54	4.67	6.53	14.75	8.19



	X													
XXXV	Cl	65	323-234d	$C_7H_8N_2O_3Cl_2$	35.17	3.37	11.72	---	29.66	35.34	3.50	11.65	---	29.42
XXXVI	Br	83	239-242d	$C_7H_8N_2O_3Br_2$	25.63	2.46	8.54	---	48.73	25.85	2.45	8.80	---	48.67

TABLE V

Ultraviolet Spectra of Thio-, Amino-, and Halo-substituted, 4,7-Benzimidazolediones

Compound No.	λ max (CH_3OH) mμ (log ε)			
I	213 (4.25),	245 (sh),	335 (3.90)	
II	213 (4.24),	238 (sh),	335 (3.87)	
III	213 (4.27),	241 (sh),	336 (3.90)	
IV	213 (4.26),	239 (sh),	335 (3.90)	
V	213 (4.26),	240 (sh),	337 (3.89)	
VI		252 (sh),	335 (3.86)	
VII	204 (4.55),	240 (sh),	343 (3.75)	
VIII	212 (4.23),	275 (3.85),	325 (3.59)	
IX	220 (4.23),	333 (3.90)		
X	211 (4.16),	230 (sh),	272 (3.83)	
XI	214 (4.25),	272 (4.19)		
XII	214 (4.30),	283 (4.16)		
XIII	202 (4.34),	251 (4.26),	321 (3.93)	
XIV	211 (3.70),	245 (4.08),	290 (3.80),	321 (3.70)
XV	211 (4.10),	245 (4.11),	282 (sh),	322 (3.79)
XVI	204 (4.35),	243 (sh),	263 (4.29),	322 (3.93)
XVII	208 (4.24),	240 (sh),	265 (4.29),	322 (3.87)
XVIII		244 (4.33),	282 (sh),	320 (3.98)
XIX	207 (4.37),	246 (4.35),	295 (4.10)	
XX	212 (4.40),	248 (4.22),	272 (4.12),	297 (sh)
XXI	229 (4.26),	246 (sh),	294 (4.08),	316 (sh)
XXII	209 (4.16),	238 (4.21),	309 (4.08)	
XXIII	209 (4.06),	248 (4.08),	322 (3.92)	
XXIV		232 (4.06),	323 (3.93)	
XXV	211 (4.18),	238 (4.24),	310 (4.14)	
XXVI	207 (4.25),	255 (4.29),	288 (3.98),	320 (sh)
XXVII	206 (4.35),	255 (4.31),	294 (4.02)	
XXVIII	206 (4.37),	255 (4.30),	293 (4.01)	
XXIX		251 (4.32),	295 (4.05)	

with an excess of aniline, *m*-toluidine and *p*-toluidine in methanol solution and in the presence of air resulted in the isolation of 5-anilino-6-chloro-, 6-chloro-5-*m*-toluidino-, and 6-chloro-5-*p*-toluidino-4,7-benzimidazoledione, respectively (XXVI-XXVIII). The reaction of 5-bromo-4,7-benzimidazoledione with aniline under similar conditions afforded 5-anilino-6-bromo-4,7-benzimidazoledione (XXIX).

EXPERIMENTAL (8)

The yields, melting points, and analytical data for the compounds prepared are shown in Tables I to V.

5-Chloro-4,7-benzimidazolediol Hydrochloride Monohydrate (XXXV).

4,7-Benzimidazoledione (2.94 g., 0.0199 mole) was placed in 295 ml. of concentrated hydrochloric acid. The mixture was refluxed on a steam bath with vigorous stirring until the solid was dissolved. The solution stood overnight and the white solid which separated was collected by filtration. Compound XXXV was recrystallized from methanol-diethyl ether using activated carbon. Compound XXXVI was prepared by the same method using 48% hydrobromic acid instead of concentrated hydrochloric acid.

5-Chloro-4,7-benzimidazoledione (XI).

5-Chloro-4,7-benzimidazolediol hydrochloride monohydrate (1.72 g., 0.0072 mole) was dissolved in 10 ml. of water. This solution was added to a solution of ferric chloride hexahydrate (5.85 g., 0.0216 mole) in 20 ml. of water with stirring. The yellow solid which formed was collected, washed with diethyl ether and dried. Analytical samples were recrystallized from acetone. Compound XII was prepared in an analogous manner.

5,6-Bis(ethylthio)-4,7-benzimidazoledione (I).

This procedure is typical for the preparation of compounds I-VI. 4,7-Benzimidazoledione (0.75 g., 0.00507 mole) was suspended in 500 ml. of methanol (620 ml. of methanol and 50 ml. of water were used to prepare compound VI). Ethanethiol (4.0 ml., 0.0542 mole) was added and the mixture was stirred for 19 hours. The solution was concentrated to a small volume on a steam bath using a rotary evaporator and reduced pressure. The dark red solid which separated was collected by filtration. Analytical samples were recrystallized from methanol.

Reaction of 5-Chloro-4,7-benzimidazoledione (XI) with α-Toluenethiol. The Formation of 5,6-Bis(benzylthio)-4,7-benzimidazolediol Hydrochloride (XXXIV) and 5,6-Bis(benzylthio)-4,7-benzimidasoledione (VI).

5-Chloro-4,7-benzimidazoledione (0.75 g., 0.00411 mole) was dissolved in 250 ml. of methanol. α-Toluenethiol (5.0 ml., 0.0426 mole) was added and the solution was stirred for 35 minutes after which it stood overnight. The red precipitate which formed was collected by filtration and recrystallized from methanol. The yield of VI was 0.054 g. (3.4%). After the dione was removed by filtration, the filtrate was evaporated to a small volume on a steam bath using a rotary evaporator and reduced pressure. Excess diethyl ether was added to the cooled solution and the white solid (XXXIV) which formed was collected by filtration. The reaction of ethanethiol with 5-chloro-4,7-benzimidazoledione followed the same course and the formation of compounds I and XXXIII was observed.

5,6-Bis[(2-hydroxyethyl)thio]-4,7-benzimidazoledione (VIII).

4,7-Benzimidazoledione (2.25 g., 0.0152 mole) was suspended in 500 ml. of methanol. 2-Mercaptoethanol (5.0 ml., 0.0715 mole) was added and the mixture was stirred for 15.5 hours. The solution was concentrated to a small volume on a steam bath using a rotary evaporator and reduced pressure. Excess diethyl ether was added and the crude white solid which separated was collected by filtration. This compound was air sensitive and was assumed to be 5,6-bis[(2-hydroxyethyl)thio]-4,7-benzimidazolediol. The yield was 3.71 g. (81%). The compound was oxidized without further purification by placing 1.15 g. (0.00381 mole) in 500 ml. of methanol. Silver oxide (3.0 g., 0.0129 mole) was added and the mixture was heated to reflux for ten minutes. The silver oxide was removed by filtration and the filtrate was concentrated to a small volume on a steam bath using a rotary evaporator and reduced pressure. The red-purple solid was collected from the cooled solution by filtration and recrystallized from methanol. A similar procedure was used in the preparation of VII.

5,6-Bis(2-hydroxyethyl)thio-4,7-benzimidazolediol Hydrochloride (XXXII).

A similar procedure was used in the preparation of XXX and XXXI. The white air sensitive compound which was assumed to be 5,6-bis(2-hydroxyethyl)thio-4,7-benzimidazolediol (3.71 g., 0.0123 mole) was dissolved in 200 ml. of methanol. Concentrated aqueous hydrochloric acid (10 ml.) was added and after treatment with activated carbon, the solution was concentrated on a steam bath using a rotary evaporator and reduced pressure until a light colored solid separated. Excess diethyl ether was added to the cooled solution and the solid was collected by filtration. This compound was recrystallized from methanol-diethyl ether.

5,6-Bis[(2-chloroethyl)thio]-4,7-benzimidazoledione (IX).

5,6-Bis[(2-hydroxyethyl)thio]-4.7-benzimidazolediol hydrochloride (1.50 g., 0.00444 mole) was placed in 75 ml. of thionyl chloride. The mixture was refluxed for 30 minutes and turned red. The solution stood for one day and the dark purple-red solid which formed was collected by filtration. The crude 5,6-bis[(2-chloroethyl)thio]-4,7-benzimidazoledione was recrystallized from acetone to give an orange-red compound.

4a,6,7,8a-Tetrahydro-1*H*-*p*-dithiino[2,3-*f*]benzimidazole-4,9-dione (X).

4,7-Benzimidazoledione (1.50 g., 0.0101 mole) was suspended in 500 ml. of methanol. 1,2-Ethanedithiol (4.0 ml., 0.0476 mole) was added and the mixture was stirred for 15 minutes and allowed to stand overnight. Colorless crystals formed along with an amorphous grey solid. The mixed solids were refluxed in 200 ml. of methanol until the crystalline solid was dissolved. The grey solid was removed by filtration and was not identified. The filtrate was concentrated to approximately 15 ml. on a steam bath using a rotary evaporator and reduced pressure. The pink solution was cooled and the white crystals which formed were collected by filtration. After removal of the above solids from the reaction mixture, addition of diethyl ether to the filtrate yielded additional product which was recrystallized from methanol. The compound turned pink in methanol solution which may indicate tautomerization to the hydroquinone followed by air oxidation to the quinone.

5-Anilino-4,7-benzimidazoledione (XIII).

A similar procedure was used for the preparation of compounds (XIV-XXV). 4,7-Benzimidazoledione (1.66 g., 0.112 mole) was suspended in 750 ml. of methanol and 5.0 ml. (0.0549 mole) of aniline was added. The mixture was refluxed for 45 minutes. The hot purple-red solution was filtered to remove any solid impurities and concentrated to approximately 50 ml. on a steam bath using a rotary evaporator and reduced pressure. The crystalline brown-red solid which formed in the cooled solution was collected by filtration and recrystallized from methanol.

5-Anilino-6-4,7-benzimidazoledione (XXVI).

5-Chloro-4,7-benzimidazoledione (0.85 g., 0.00466 mole) was dissolved in 300 ml. of methanol. Aniline (1.0 ml., 0.011 mole) was added and the solution was stirred for 4 hours at room temperature. After standing overnight, the purple solid which separated was collected by filtration and the filtrate was concentrated to a small volume on a steam bath using a rotary evaporator and reduced pressure. The additional product which formed was collected and the combined solids were recrystallized from methanol. A similar procedure was used to prepare compounds XXVII-XXIX.

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(7) Compounds were screened for antitumor activity by Dr. Harry B. Wood, Jr. and his group at the Cancer Chemotherapy National Service Center of the Department of Health, Education and Welfare, Bethesda, Maryland.

(8) Melting points were taken on Thomas-Hoover or Mel-Temp melting point apparatus. Infrared spectra were determined on a Perkin-Elmer 521 recording spectrophotometer as potassium bromide pellets. The ultraviolet spectra were obtained on a Cary Model 14 recording spectrophotometer. Microanalyses were carried out by Dr. A. Bernhardt, Max Planck Institute, 433 Mülheim (Ruhr), West Germany. The n.m.r. spectra were determined at 60 MHz on a Varian Associates Model HR-60 spectrometer and all values are reported in ppm (δ), relative to tetramethylsilane.

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