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Folate Antagonists. 12. Antimalarial and Antibacterial Effects of 2,4-Diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines[1,2]

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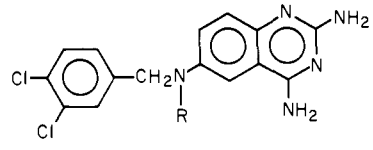
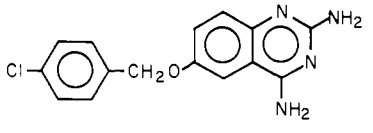
A series of 2,4-diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines was prepared via condensation of 5-chloro-2-nitrobenzonitrile or 5,6-dichloro-2-nitrobenzonitrile with the appropriate aralkyl or alicyclic thiopseudourea, reduction of the resulting 2-nitro-5-[(aralkyl or alicyclic)thio]benzonitrile with stannous chloride to the amine, and cyclization with chloroformamidine hydrochloride. Oxidation was effected with hydrogen peroxide or the bromine complex of 1,4-diazabicyclo[2.2.2]octane. These analogues when examined for suppressive activity against drug-sensitive lines of *Plasmodium berghei* in mice were not as active as 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (Ia).

Many 2,4-diaminoquinazoline antifolates have been demonstrated to possess strong antimalarial properties against sensitive and drug-resistant lines of *Plasmodium berghei* in mice, *P. gallinaceum* in chicks, and *P. cynomolgi* and *P. knowlesi* in rhesus monkeys.[3,4] Among the most potent are 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]-quinazoline (Ia), 2,4-diamino-6-[(3,4-dichlorobenzyl)-



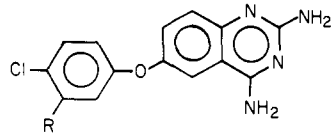
Ia, R = H
b, R = NO
c, R = CH_3

nitrosoamino]quinazoline (Ib), and 2,4-diamino-6-[(3,4-dichlorobenzyl)methylamino]quinazoline (Ic).[1,3-6] However, antimalarial activity of oxygen bioisosteres, exemplified by 2,4-diamino-6-[(*p*-chlorobenzyl)oxy]quinazoline (II), was greatly reduced.[7] Interestingly, extrusion of the



II

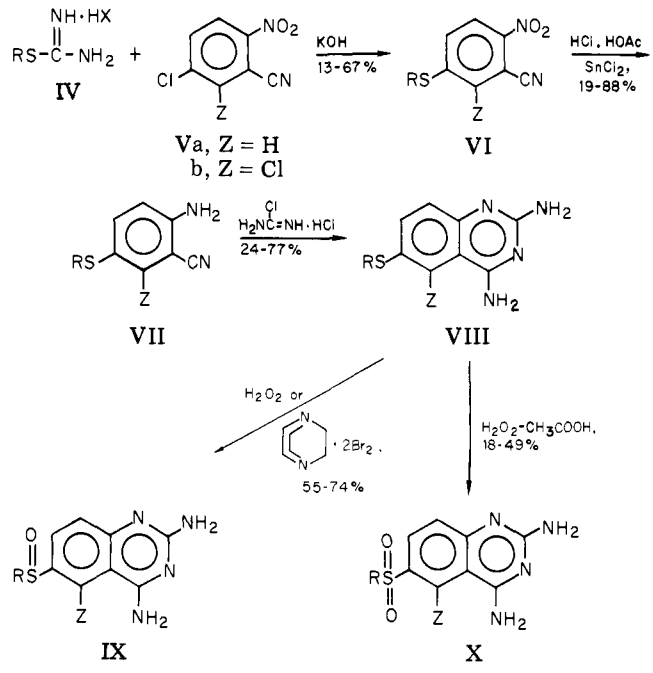
methylene bridge of II restored antimalarial activity. Thus 2,4-diamino-6-(*p*-chlorophenoxy)quinazoline (IIIa) and



IIIa, R = H
b, R = Cl

2,4-diamino-6-(3,4-dichlorophenoxy)quinazoline (IIIb) exhibited oral antimalarial effects against *P. berghei* in mice comparable with or superior to 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (Ia).[7] Comparison of the above diaminoquinazoline antifolates with representative thio bioisosteres would therefore be of interest, and we now describe the preparation and biological activities of some 2,4-diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines.

Scheme I



Results and Discussion

Chemistry. The 2,4-diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines were synthesized following the route depicted in Scheme I. Condensation of 5-chloro-2-nitrobenzonitrile (Va) or

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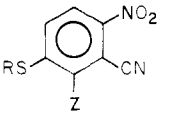
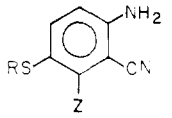
Table I. 2-Nitro-5-[(aralkyl and alicyclic)thio]benzonitriles



No.	R	Z	Mp, °C	Yield purified, %	Purifcn solvent	Procedure	Formula[a]
1	c-C_6H_{11}	H	84-85	38	C_6H_{12}	I	$C_{13}H_{14}N_2O_2S$
2	-CH_2-C_6H_5-*p*-Cl	Cl	145-146	27	EtOH	II	$C_{14}H_8Cl_2N_2O_2S$
3	-CH_2-C_6H_5	H	114-115.5	67	EtOH-H_2O	I	$C_{14}H_{10}N_2O_2S$
4	-$(CH_2)_2$-C_6H_5	H	77.5-80	58	2-PrOH	I	$C_{15}H_{12}N_2O_2S$
5		H	118-120	13	2-PrOH	I	$C_{17}H_{18}N_2O_2S$

[a] Analytical results for C, H, and N were within ±0.4% of theoretical values.

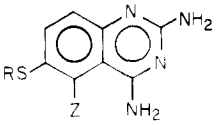
Table II. 2-Amino-5-[(aralkyl and alicyclic)thio]benzonitriles



No.	R	Z	Mp, °C	Yield purified, %	Purifcn solvent	Procedure	Formula[a]
6	c-C_6H_{11}	H	96-99	88	EtOH-H_2O	III	$C_{13}H_{16}N_2S$
7	-CH_2-C_6H_4-*p*-Cl	Cl	151-155	67	EtOH	III	$C_{14}H_{10}Cl_2N_2S$
8	-CH_2-C_6H_5	H	94-95	68	EtOH-H_2O	III	$C_{14}H_{12}N_2S$
9	-$CH(CH_3)$-C_6H_4-*p*-Cl	H	89-91	19	C_6H_6-cyclohexane	III	$C_{15}H_{13}ClN_2S$

[a] C (for 8): calcd, 69.97; found, 70.39. All other analytical values for C, H, and N were within ±0.4% of theoretical values.

Table III. 2,4-Diamino-6-[(aralkyl and alicyclic)thio]quinazolines

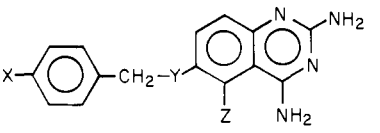


No.	R	Z	Mp, °C	Yield purified, %	Purifcn solvent	Procedure	Formula[c]
10	c-C_6H_{11}	H	190-192	71	EtOH-NH_4OH	IV	$C_{14}H_{18}N_4S$
11	-CH_2-C_6H_4-*p*-Cl	Cl	236-240	77	DMF-H_2O	V	$C_{15}H_{12}Cl_2N_4S$
12	-CH_2-C_6H_4-*p*-Cl	H	223-225	67	DMF-aq NaOH	IV	$C_{15}H_{13}ClN_4S$
13	-CH_2-C_6H_5	H	192-193.5	70	EtOH-H_2O	IV	$C_{15}H_{14}N_4S$
14	-$CH(CH_3)$-C_6H_4-*p*-Cl	H	235-236.5	45	EtOH	IV	$C_{16}H_{15}ClN_4S$
15	-$(CH_2)_2$-C_6H_5	H	156.5-159.5	24	EtOH	IV	$C_{16}H_{16}N_4S \cdot 0.33C_2H_6O \cdot 0.5H_2O$[a, b]
16		H	339-341 dec	38	DMF-H_2O	IV	$C_{18}H_{22}N_4S$

[a] The NMR spectrum confirmed the presence of ethanol. [b] H_2O: calcd, 2.80; found, 2.43. [c] N (for 13): calcd, 19.84; found, 20.26. C (for 16): calcd, 66.22; found, 65.80. All other analytical values were within ±0.4% of theoretical values.

5,6-dichloro-2-nitrobenzonitrile (Vb) with the appropriate aralkyl or alicyclic thiopseudourea hydrohalide IV in ethanol, using potassium hydroxide as an acid scavenger, produced the corresponding 2-nitro-5-[(aralkyl or alicyclic)thio]benzonitrile VI (**1–5**, Table I) in 13–67% yield (procedure I). Both the desired 2-chloro-3-[(*p*-chlorobenzyl)thio]-6-nitrobenzonitrile (**2**, Table I) (27% yield) and a by-product, 2,3-dichloro-6-[(*p*-chlorobenzyl)thio]-benzonitrile (13% yield), were obtained from the reaction of 5,6-dichloro-2-nitrobenzonitrile with 2-(*p*-chlorobenzyl)-2-thiopseudourea hydrochloride (procedure II). Reduction of the nitrobenzonitriles VI with stannous chloride–hydrochloric acid in glacial acetic acid (procedure III) afforded the 2-amino-5-[(aralkyl and alicyclic)thio]-benzonitriles VII (**6–9**, Table II) (19–88% yield). Cyclization of the aminobenzonitriles with chloroformamidine hydrochloride[8] in dry diglyme (procedure IV) or in dimethyl sulfone (procedure V) proceeded in 24–77% yield to give the desired 2,4-diamino-6-[(aralkyl and alicyclic)thio]quinazolines VIII (**10–16**, Table III). The 2,4-diamino-6-(benzylsulfinyl)quinazolines IX (**17** and **19**, Table IV) were obtained either by oxidation of the 2,4-diamino-6-(benzylthio)quinazolines VIII with 30% hydrogen peroxide in glacial acetic acid (procedure VI) or with the bromine complex of 1,4-diazabicyclo[2.2.2]octane[9] in 70% aqueous acetic acid (procedure VIII). Oxidation of 2,4-diamino-6-(benzylthio)quinazolines VIII with 30% hydrogen peroxide in glacial acetic acid gave the corre-

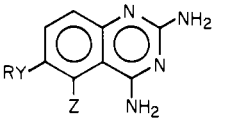
Table IV. 2,4-Diamino-6-[(benzyl)sulfinyl- and sulfonyl]quinazolines



No.	X	Y	Z	Mp, °C	Yield purified, %	Purifcn solvent	Procedure	Formula[b]
17	Cl	SO	Cl	256-258 dec	55	DMF-H_2O	VI	$C_{15}H_{12}Cl_2N_4OS$
18	Cl	SO_2	Cl	274-276	42	DMF-H_2O	VII	$C_{15}H_{12}Cl_2N_4O_2S$
19	Cl	SO	H	234-236	74	EtOH	VIII	$C_{15}H_{13}ClN_4OS$
20	Cl	SO_2	H	294-296	49	EtOH	VII	$C_{15}H_{13}ClN_4O_2S \cdot 0.9H_2O$[a]
21	H	SO_2	H	277-280 dec	18	EtOH-H_2O	VII	$C_{15}H_{14}N_4O_2S \cdot 1.8H_2O$

[a] H_2O: calcd, 4.44; found, 4.29. [b] Analytical values for C, H, and N are all within ±0.4% of theoretical values.

Table V. Parenteral Antimalarial Effects of 2,4-Diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines against *Plasmodium berghei* in Mice



No.	R	Y	Z	Δ MST, C or T[a] after single sc mg/kg dose 640	320	160	80	40	20
10	c-C_6H_{11}	S	H	C5	13.2; C2	9.3	5.7	2.5	0.7
					12.9; C2	9.1	6.1	2.7	0.7
11	-CH_2-C_6H_4-*p*-Cl	S	Cl	8.1	3.1	1.7	1.1	0.5	0.5
				7.9		1.9		0.7	
12	-CH_2-C_6H_4-*p*-Cl	S	H	25.5; C2	9.8	4.4	2.6	0.8	0.4
				17.3; C3		4.2		0.8	
13	-CH_2-C_6H_5	S	H	10.9	4.9	1.1	0.9	0.7	0.5
				10.7		1.3		0.5	
14	-$CH(CH_3)$-C_6H_4-*p*-Cl	S	H	C5	17.0; C2	10.9	9.7	5.7	3.7
					17.8; C2	11.2	9.6	6.0	4.0
15	-$(CH_2)_2$-C_6H_5	S	H		17.2; C2	4.5	0.9	0.5	0.5
16		S	H	2.9	1.1	0.3	0.3	0.3	0.1
17	-CH_2-C_6H_4-*p*-Cl	SO	Cl	0.3		0.3		0.1	
18	-CH_2-C_6H_4-*p*-Cl	SO_2	Cl	0.1		0.1		0.1	
19	-CH_2-C_6H_4-*p*-Cl	SO	H	5.9	2.9	0.9	0.7	0.5	0.3
20	-CH_2-C_6H_4-*p*-Cl	SO_2	H	5.9	0.9	0.3	0.3	0.1	0.1
Ia·HOAc				C5	C5	9.9; C3	12.9	7.1	2.5
					C5	9.9; C3	13.1	7.3	2.7
II				13.3; T3	11.2	7.7	3.7	1.7	1.3
					11.5	7.2	3.6	1.8	1.2
Cycloguanil hydrochloride				T5	C3; T2	C5	21.6; C2	13.4; C1	7.9
					C2; T3	C5	21.6; C2	13.4; C1	8.1

[a] Δ MST is the mean survival time (days) of treated mice (MSTT) minus the mean survival time (days) of control mice (MSTC). In the present study, the MSTC ranged from 6.1 to 6.2 days. T signifies the number of toxic deaths occurring on days 2-5 after infection which are attributed to drug action. C indicates the number of mice surviving at 60 days postinfection and termed "cured"; data to establish parasitological cure based on subinoculation are unavailable. Each entry at each dose level represents results with a five-animal group.

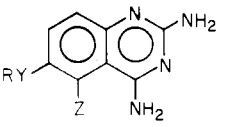
sponding 2,4-diamino-6-(benzylsulfonyl)quinazoline X (**18**, **20**, and **21**, Table IV) in 18–42% yield (procedure VII).

Biology. Suppressive Antimalarial Screening in Mice. The 2,4-diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines (**10–20**, Table V) were evaluated parenterally against a normal drug-sensitive strain of *P. berghei* in mice.[10,11] The drugs were dissolved or suspended in sesame or peanut oil and were administered in a single subcutaneous dose 72 h after infection. Antimalarial activity is assumed when the mean survival time of the treated mice is extended. The results, which are summarized in Table V, show that none of the compounds were as active as the acetate salt of 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (Ia).

However, it is interesting to note that certain of the thio compounds, notably **10**, **12**, **14**, and **15**, were less toxic and more active than the oxygen bioisostere 2,4-diamino-6-[(*p*-chlorobenzyl)oxy]quinazoline (II). The presence of a halogen in the 5 position of the quinazoline ring was detrimental to activity in the three cases examined, **11**, **17**, and **18**, in contrast to previous work with the nitrogen analogues related to I. In addition, further oxidation of the sulfur also decreased activity.

Antibacterial Activity. Most of the 2,4-diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]-quinazolines (**10**, **12**, **14**, and **16–20**) were tested in vitro against the following pathogenic bacteria: *Streptococcus faecalis* (MGH-2), normal (UC-76) and drug-resistant

Table VI. In Vitro Antibacterial Effects of 2,4-Diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines



No.	R	Y	Z	Min inhibitory concn, μg/mL: *S. faecalis* MGH-2	*S. aureus* UC-76	*S. aureus* S18713
10	c-C_6H_{11}	S	H	10	<0.25	10
12	-CH_2-C_6H_4-*p*-Cl	S	Cl	<0.25	<0.25	<0.25
14	-CH(CH_3)-C_6H_4-*p*-Cl	S	H	<0.25	<0.25	1
16		S	H	<0.25	<0.25	<0.25
17	-CH_2-C_6H_4-*p*-Cl	SO	Cl	<0.25	>25	>25
18	-CH_2-C_6H_4-*p*-Cl	SO_2	Cl	<0.25	5	10
19	-CH_2-C_6H_4-*p*-Cl	SO	H	>25	25	>25
20	-CH_2-C_6H_4-*p*-Cl	SO_2	H	>25	>25	>25
Trimethoprim				<0.25	<0.25	<0.25

(S18713), *Staphylococcus aureus*, *Pseudomonas aeruginosa* (28), *Escherichia coli* (Vogel), and *Shigella sonnei* (C-10). A modification of the gradient plate procedure of Szybalski[12] and Webb and Washington[13] was used. Although none of the compounds tested showed appreciable activity against *P. aeruginosa* (28), *E. coli* (Vogel), and *S. sonnei* (C-10), many were active against *S. faecalis* (MGH-2) and the *S. aureus* strains. The results of these activities are tabulated in Table VI. Two compounds, 2,4-diamino-6-[(*p*-chlorobenzyl)thio]quinazoline (**12**) and 6-(1-adamantylthio)-2,4-diaminoquinazoline (**16**), inhibited *S. faecalis* MGH-2, *S. aureus* UC-76, and *S. aureus* S18713 at concentrations of <0.25 μg/mL. Only 2,4-diamino-6-[(*p*-chlorobenzyl)sulfonyl]quinazoline (**20**) was completely inactive.

Conclusion

The thio bioisosteres of the 2,4-diamino-6-(aralkylamino)quinazoline antifolates Ia do not provide any advantage when examined for antimalarial activity. Interestingly, they are more active than the corresponding oxygen bioisosteres—an advantage which is lost if the oxidation state of the sulfur is raised to that of sulfoxide or sulfone.

Experimental Section

Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus.

The requisite precursor 5-chloro-2-nitrobenzonitrile (Va) is commercially available[14] and the preparation of 5,6-dichloro-2-nitrobenzonitrile (Vb) is described below. 2-(*p*-Chlorobenzyl)-2-thiopseudourea hydrobromide was obtained commercially.[15] Treatment[16] of 1-bromoadamantane[14] with thiourea and hydrobromic acid in acetic acid gave 2-(1-adamantyl)-2-thiopseudourea monohydrobromide. The remaining aralkyl and alicyclic thiopseudoureas were obtained by allowing the requisite halide to react with thiourea in acetone.[17]

5,6-Dichloro-2-nitrobenzonitrile (Vb). A mixture of 45.3 g (0.20 mol) of 1,2,3-trichloro-4-nitrobenzene[14] and 17.9 g (0.21 mol) of CuCN in 120 mL of *N*-methyl-2-pyrrolidinone was stirred and heated in an oil bath at 145–150 °C (external temperature) for 6 h. The reaction mixture was allowed to cool to room temperature and was stirred at room temperature for 18 h. The mixture was poured with stirring into 1.6 L of H_2O. Within 15 min, the precipitate had solidified and the crude brown-black solid was collected by filtration, washed thoroughly with H_2O, and air-dried. A second identical run was made, and the combined crude solids were stirred with 1.2 L of boiling EtOH for 45 min and filtered. The filtrate was treated with decolorizing charcoal, the charcoal was removed by filtration, and the filtrate was concentrated to dryness in vacuo. The residue was crystallized from 400 mL of EtOH to give 51.0 g (59%) of product, mp 75–92 °C, which was of satisfactory purity for use in successive reactions. A sample was recrystallized from EtOH to give an analytical sample, mp 90–93 °C. Anal. ($C_7H_2Cl_2N_2O_2$) C, H, Cl, N.

2-Nitro-5-[(aralkyl and alicyclic)thio]benzonitriles VI (1–5, Table I). Procedure I. To a stirred suspension of 6.0 g (0.0252 mol) of 2-(cyclohexyl)-2-thiopseudourea hydrobromide and 4.6 g (0.025 mol) of 5-chloro-2-nitrobenzonitrile in 70 mL of absolute ethanol was added dropwise a solution of 2.8 g (0.05 mol) of potassium hydroxide in 20 mL of absolute ethanol. The mixture was stirred at room temperature for 2.5 days and then filtered to collect the precipitate. The solid was washed well with water, dried, and recrystallized from cyclohexane to give 2.5 g (38%) of 5-(cyclohexylthio)-2-nitrobenzonitrile (1), mp 84–85 °C.

Procedure II. A solution of 7.2 g (0.13 mol) of potassium hydroxide pellets in 150 mL of ethanol was added dropwise to a stirred solution of 9.6 g (0.044 mol) of 5,6-dichloro-2-nitrobenzonitrile and 12.0 g (0.05 mol) of 2-(*p*-chlorobenzyl)-2-thiopseudourea hydrochloride in 150 mL of ethanol at 30–38 °C. The mixture was stirred 0.5 h and filtered. The filter cake was washed with water and recrystallized from ethanol to give 4.0 g (27%) of 2-chloro-3-[(*p*-chlorobenzyl)thio]-6-nitrobenzonitrile (**2**), mp 145–146 °C.

The filtrate of the reaction mixture afforded a second crop which was recrystallized from ethanol to give 1.8 g (13%) of the by-product 2,3-dichloro-6-[(*p*-chlorobenzyl)thio]benzonitrile, mp 106–108 °C. Anal. ($C_{14}H_8Cl_3NS$) C, H, N.

The other requisite 2-nitro-5-[(aralkyl and alicyclic)thio]-benzonitriles VI not listed in Table I were prepared in a similar manner. These intermediates were purified and then reduced directly to the corresponding 2-amino-5-[(aralkyl and alicyclic)thio]benzonitriles VII without microanalysis.

2-Amino-5-[(aralkyl and alicyclic)thio]benzonitriles VII (6–9, Table II). Procedure III. To a stirred solution of 9.0 g (0.04 mol) of stannous chloride dihydrate in a mixture of 30 mL of concentrated hydrochloric acid and 5 mL of glacial acetic acid was added slowly a warm solution of 3.2 g (0.012 mol) of 5-(cyclohexylthio)-2-nitrobenzonitrile (1) in 23 mL of glacial acetic acid. Before the addition was completed, a white solid began to precipitate. The suspension was stirred at room temperature for 18 h and poured into a stirred ice–water mixture containing 50 mL of 50% sodium hydroxide solution. The white solid which formed was collected and dried. The crude product was dissolved in hot ethanol, filtered to remove some insoluble solid, allowed to cool to room temperature, and poured into water. The solid that formed was collected and dried to give 2.5 g (88%) of 2-amino-5-(cyclohexylthio)benzonitrile (**6**), mp 96–99 °C.

The other intermediate 2-amino-5-[(aralkyl and alicyclic)-thio]benzonitriles VII were not analyzed but were used directly in the cyclization step following crystallization from aqueous ethanol.

2,4-Diamino-6-[(aralkyl and alicyclic)thio]quinazolines VIII (10–16, Table III). Procedure IV. A mixture of 2.3 g (0.01 mol) of 2-amino-5-(cyclohexylthio)benzonitrile (**6**) and 1.7 g (0.015 mol) of chloroformamidine hydrochloride[8] in 5 mL of dry diglyme was stirred and heated in an oil bath at 150 °C (bath temperature) for 0.5 h. During this time hydrogen chloride was evolved, a solution formed, and a new solid precipitated. The mixture was cooled and the solid was collected, washed with ether, and dried. It was recrystallized once from 90% aqueous ethanol containing an excess of ammonium hydroxide and then reprecipitated from 95% ethanol containing 0.5 mL of 2 N sodium hydroxide by addition of water. The pale yellow crystals were collected and dried to give 2.0 g (71%) of 2,4-diamino-6-(cyclohexylthio)-quinazoline (**10**), mp 190–192 °C with preliminary softening.

Procedure V. A mixture of 1.0 g (0.0032 mol) of 6-chloro-5-[(*p*-chlorobenzyl)thio]anthranilonitrile (**7**), 0.75 g (0.0065 mol) of chloroformamidine hydrochloride,[8] and 4.0 g of dimethyl sulfone was heated for 1 h in an oil bath that had been preheated to 160 °C. The dark solution was poured into water and the resulting cloudy solution was warmed on the steam bath and made basic with 50% sodium hydroxide. The precipitate that formed was collected, washed with water, and recrystallized from *N,N*-dimethylformamide–water to give 0.86 g (77%) of 2,4-diamino-5-chloro-6-[(*p*-chlorobenzyl)thio]quinazoline (**11**), mp 236–240 °C.

2,4-Diamino-6-[(benzyl)sulfinyl- and sulfonyl]quinazolines IX and X (17–21, Table IV). Procedure VI. A mixture of 0.64 g (0.0018 mol) of 2,4-diamino-5-chloro-6-[(*p*-chlorobenzyl)thio]quinazoline (**11**), 4.4 mL of 30% hydrogen peroxide, and 8 mL of glacial acetic acid was stirred at room temperature for 4 h, and the resulting solution was poured into a mixture of ice and 12 mL of 50% sodium hydroxide. The precipitate that formed was collected, washed with water, and recrystallized from *N,N*-dimethylformamide–water to give 0.37 g (55%) of 2,4-diamino-5-chloro-6-[(*p*-chlorobenzyl)sulfinyl]quinazoline (**17**), mp 256–258 °C dec.

Procedure VII. A mixture of 1.0 g (0.0028 mol) of 2,4-diamino-5-chloro-6-[(*p*-chlorobenzyl)thio]quinazoline (**11**), 8 mL of 30% hydrogen peroxide, and 15 mL of glacial acetic acid was stirred at room temperature for 48 h, and the resulting solution was poured into a mixture of ice and 23 mL of 50% aqueous sodium hydroxide. The precipitate that formed was collected, washed with water, and combined with 0.41 g of crude product which had been obtained in a similar manner from 0.5 g (0.0014 mol) of starting material. Recrystallization from *N,N*-dimethylformamide–H_2O and drying at 100 °C gave 0.86 g (42%) of 2,4-diamino-5-chloro-6-[(*p*-chlorobenzyl)sulfonyl]quinazoline (**18**), mp 274–276 °C.

Procedure VIII. A mixture of 3.2 g (0.01 mol) of 2,4-diamino-6-[(*p*-chlorobenzyl)thio]quinazoline (**12**) and 2.3 g (0.0053 mol) of the bromine complex of 1,4-diazabicyclo[2.2.2]octane[9] in 100 mL of 70% aqueous acetic acid was stirred at room temperature for 18 h. The mixture was poured into a stirred ice–water mixture containing 67 mL of 50% aqueous sodium hydroxide. The pale yellow solid which precipitated was collected and dried in vacuo. Recrystallization from ethanol followed by drying in vacuo (50 °C) yielded 2.5 g (74%) of 2,4-diamino-6-[(*p*-chlorobenzyl)sulfinyl]quinazoline (**19**), mp 234–236 °C. The infrared spectrum displayed sulfoxide absorption at 1040 cm^{-1}.

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References and Notes

(1) This is communication 40 of a series on antimalarial drugs. For paper 39, which is also the previous paper on folate antagonists, see L. M. Werbel, J. Johnson, E. F. Elslager, and D. F. Worth, *J. Med. Chem.*, **21**, 337 (1978).
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A New Class of Antimalarial Drugs: Derivatives of Benzothiopyrans[1]

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A series of substituted benzothiopyrans was synthesized and examined for antimalarial activity. Some were found to be active and curative at dose levels of 160–360 mg/kg against *Plasmodium berghei* in mice. A few observations concerning structure–activity relationships were made. The benzothiopyrans were prepared by treatment of either the *gem*-dichloro- or the thionothioflavone intermediate with various primary amines. The thionothioflavone intermediates were made from thioflavones. Condensation of thiophenols with benzoyl acetates gave the thioflavones.

We wish to report some derivatives of benzothiopyrans as a new class of antimalarial drugs[3] that are active in mice (against *Plasmodium berghei*) and chicks (against *Plasmodium gallinaceum*) in the Rane screen.[4] Some of these benzothiopyrans were curative at dose levels of 160–360 mg/kg in mice; a limited study of structure modification, however, did not result in compounds with any greater potency. In the same test, some of the most active known

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