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Synthesis of Analogs of 6-Arylthio-, 6-Arylsulfinyl-, and 6-Arylsulfonyl-2,4-diaminoquinazolines as Potential Antimalarial Agents†

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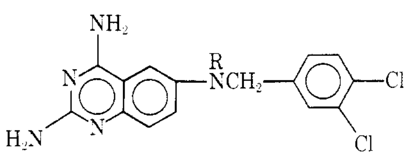
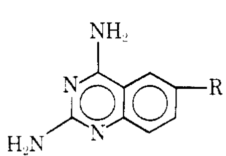
Numerous 6-arylthio-, 6-arylsulfinyl-, and 6-arylsulfonyl-2,4-diaminoquinazolines have been synthesized, many of which possess potent activity against both sensitive as well as drug-resistance strains of plasmodia. The present study describes the preparation of 23 analogs involving modifications of the substituents in the 2 and/or 4 positions of the quinazoline nucleus. Only one of the new compounds, 2-amino-4-hydroxy-6-(2-naphthylsulfonyl)quinazoline (**16a**), displayed curative activity against *Plasmodium berghei* in mice and was substantially less potent than its 4-amino counterpart **2a**.

The discovery of the antiprotozoan activity of 2,4-diaminoquinazolines as exemplified by **1a,b**[1,2] has led to the synthesis of a wide variety of compounds of this class.[3-5]



1a, R = H
b, R = NO

Of these, the most promising potential antimalarial agents are certain 6-arylthio-2,4-diaminoquinazolines and their sulfinyl and sulfonyl analogs. For example, **2a,b** are currently undergoing clinical trials since they have shown efficacy against drug-resistant strains of plasmodia.[6] Al-



2a, R = 2-$C_{10}H_7SO_2$-
b, R = 3-$(CF_3)C_6H_4S$-

though the mechanism of action of these compounds has not been fully elucidated, it is noteworthy that a variety of compounds of this type are effective inhibitors of dihydrofolate reductase isolated from either rat liver or *Streptococcus faecium* (*in vitro*).‡

In a recent communication, we described the preparation of a series of isomers and analogs of **2a,b** in which the aromatic moiety was attached to the 5 position of the quinazoline nucleus by a suitable spacer.[7] None of these displayed any significant activity against *Plasmodium berghei* in mice. However, several were found to be moderately potent inhibitors of rat liver dihydrofolate reductase.[7] The present study was initiated in order to determine the effect of altering the groups attached to the 2 and 4 positions of the quinazoline ring upon antimalarial activity. It was hoped that configurations such as 2-amino-4-hydroxy or 2-amino-4-mercapto would confer greater inhibitory action upon tetrahydrofolate-dependent enzymes such as thymidylate synthetase. Inhibitors of this type could prove to be of value when used in conjunction with 2,4-diaminoquinazolines such as **2a,b**. Physical data for the new compounds synthesized are summarized in Table I.

Chemistry. The 2-amino-4-hydroxyquinazolines **14a,b**, **15**, and **16a,b** were prepared by the standard acid-catalyzed hydrolysis of the corresponding 2,4-diamino compounds.[7,§] Two of the products **14a** and **16a** were subsequently reacted with P_2S_5 in pyridine to afford the corresponding 2-amino-4-mercapto analogs **7** and **8**. Acylation of **16a** with acetic anhydride or trichloroacetic anhydride in pyridine yielded the 2-acetamido derivatives **17** and **18**, respectively.

Synthetic routes to the remaining analogs of 6-arylthio-2,4-diaminoquinazolines are summarized in Scheme I. Standard cyclization procedures employing urea, thiourea, potassium ethyl xanthate, or formamide were employed to prepare compounds **13a,b**, **5**, **9**, and **19a,b**, respectively. The key 5-arylthioanthranilonitriles **3a,b** were prepared according to methods developed by Elslager and coworkers.[§,=] Similarly, the reaction of ethyl 2-amino-5-(2-naphthylthio)benzoate (**4**)[§,**] with thiourea and urea yielded **11** and **12**. Oxidation of the 4-aminoquinazolines **19a,b** with 30% H_2O_2 or triethylenediamine dibromide yielded the sulfoxides **20a,b**, while the corresponding sulfones **21a,b** were obtained with excess permanganate in aqueous AcOH.[7]

Alkylation of 4-amino-2-mercapto-6-(2-naphthylthio)quinazoline (**5**) with MeI in the presence of base afforded the 2-methylmercapto derivative **6**. The reaction of the 4-amino-2-hydroxyquinazoline **13a** with P_2S_5 was attempted as an alternate route to compound **5**. However, in this case the 4-amino group was preferentially displaced yielding **10**. Proof of this configuration was provid-

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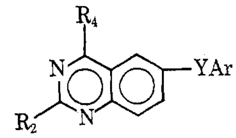
‡J. B. Hynes, W. T. Ashton, and J. H. Freisheim, unpublished results.
§Samples or synthetic procedures provided by the U. S. Army Program on Antimalarial Research.
=E. F. Elslager and coworkers, Parke, Davis and Co., unpublished results.
**F. W. Starks, Starks Associates, Inc., unpublished results.

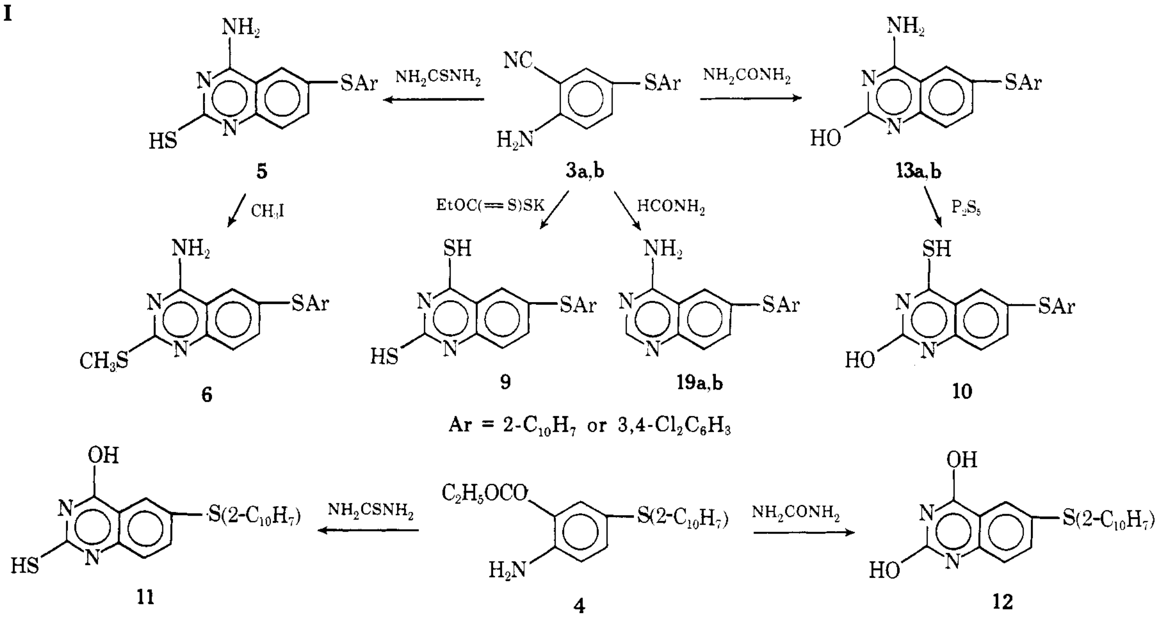
Table I. Properties of 6-Substituted Quinazolines Synthesized



No.	R_2	R_4	Y	Ar[a]	Mp, °C	Method[b]	Yield, %	Recrystn[c] medium	Formula[d]
5	SH	NH_2	S	A	298–299 dec	A	15	I	$C_{18}H_{13}N_3S_2$
6	CH_3S	NH_2	S	A	226–228	B	86		$C_{19}H_{15}N_3S_2$
7	NH_2	SH	S	A	260–261 dec	C	37		$C_{18}H_{13}N_3S_2 \cdot 0.5C_3H_7NO$[e]
8	NH_2	SH	SO_2	A	320 dec	C	56	III, IV	$C_{18}H_{13}N_3O_2S_2$[e]
8·HCl	NH_2	SH	SO_2	A	>275 dec		68		$C_{18}H_{13}N_3O_2S_2 \cdot HCl$
9	SH	SH	S	A	305–307 dec	D	84	V	$C_{18}H_{12}N_2S_3$
10	OH	SH	S	A	264–283 dec	C	57	VII	$C_{18}H_{12}N_2OS_2$[e]
11	SH	OH	S	A	287–288	A	29	III	$C_{18}H_{12}N_2OS_2$
12	OH	OH	S	A	318–320 dec	E	61	III	$C_{18}H_{12}N_2O_2S$
13a	OH	NH_2	S	A	380–382 dec	E	42	II	$C_{18}H_{13}N_3OS$[e]
13b	OH	NH_2	S	B	396–398 dec	E	27	II	$C_{14}H_9Cl_2N_3OS$[e]
14a	NH_2	OH	S	A	311–313 dec	F	73	III[f]	$C_{18}H_{13}N_3OS$[e]
14b	NH_2	OH	S	B	330–332	F	65	VIII	$C_{14}H_9Cl_2N_3OS$[e]
15	NH_2	OH	SO	A	347–350 dec	F	34	III	$C_{18}H_{13}N_3O_2S$
16a	NH_2	OH	SO_2	A	329–331.5 dec	F	73	III[f,g]	$C_{18}H_{13}N_3O_3S$
16b	NH_2	OH	SO_2	B	415–417 dec	F	46	V[h]	$C_{14}H_9Cl_2N_3O_3S \cdot HCl$
17	CH_3CONH	OH	SO_2	A	339–340 dec	G	89		$C_{20}H_{15}N_3O_4S$
18	CCl_3CONH	OH	SO_2	A	282–283 dec	G	77		$C_{20}H_{12}Cl_3N_3O_4S$
19a	H	NH_2	S	A	284–285	H	76	III	$C_{18}H_{13}N_3S$
19b	H	NH_2	S	B	264.5–266	H	67	III	$C_{14}H_9Cl_2N_3S$
20a	H	NH_2	SO	A	294–297	I	44	VI	$C_{18}H_{13}N_3OS$
20b	H	NH_2	SO	B	265–267	J	77	IX	$C_{14}H_9Cl_2N_3OS$
21a	H	NH_2	SO_2	A	297–299	K	65	III	$C_{18}H_{13}N_3O_2S$
21b	H	NH_2	SO_2	B	293–295	K	71	III	$C_{14}H_9Cl_2N_3O_2S$

[a]A = 2-$C_{10}H_7$; B = 3,4-$Cl_2C_6H_3$. [b]See Experimental Section. [c]I, pyridine; II, DMF; III, DMF–H_2O; IV, DMF–MeCN; V, DMF–AcOH; VI, 2-methoxyethanol; VII, 2-methoxyethanol–H_2O; VIII, DMAC, IX, EtOH. [d]*Anal.* C, H, N. [e]*Anal.* C, H, N, and S (solvated with DMF). [f]Reprecipitation. [g]Basified with NH_4OH. [h]In the presence of HCl.

Scheme I



ed by the synthesis of its isomer **11** which had different physical and spectroscopic properties.

Biological Results. Each of the compounds presented in Table I was tested against *P. berghei* in mice.[8,††] Data for compounds showing significant activity are summarized in Table II. 2-Amino-4-hydroxy-6-(2-naphthylsulfonyl)quinazoline (**16a**) was curative at dose levels of 160 mg/kg and above and is, therefore, significantly less potent than its 4-NH_2 counterpart **2a**.[6] The modest activity of the 2-trichloroacetyl derivative **18** may be due to slow *in vivo* hydrolysis to **16a** since the corresponding acetyl compound **17** was not active. Two other 2-amino-4-hydroxyquinazolines **14a** and **15** showed slight activity, while the 3,4-dichlorophenylthio **14b** and 3,4-dichlorophenylsulfonyl **16b** analogs were not effective. It is apparent from this work that as in the case of pyrimidines such as pyrimethamine, the 2,4-diamino configuration affords optimal antimalarial action for quinazolines bearing a large hydrophobic group in position 6.

††Testing of all compounds was carried out by Dr. L. Rane of the University of Miami.

Experimental Section

All analytical compounds gave combustion values for C, H, and N (and S, where noted) within ±0.4% of the theoretical values. Melting points were determined with a Fisher-Johns or a Mel-Temp apparatus and are uncorrected. All compounds had ir spec-

Table II. Antimalarial Testing Data (*P. berghei* in Mice)

Compd	Dose, mg/kg	Mean survival time, days[a]	Cures[b]
16a	20	3.7	
	40	6.3	
	80	11.3	
	160	15.9[c]	3/5
	320	13.9[c]	4/5
	640		5/5
14a	320	3.9	
	640	4.5	
15	320	3.1	
	640	3.9	
18	320	4.3	
	640	6.5	

[a]Mean survival time of controls, 6.1 days. [b]Mice surviving for 60 days are considered cured. [c]Data for uncured mice.

tra (Beckman IR-8) in agreement with their assigned structures and appeared free of significant impurities by tlc (Gelman SAF). Examples for each of the synthetic procedures designated in Table I are presented below with the exception of F, H, J, and K which have been described in detail in a recent paper.[7]

Method A. 5 and 11. A mixture of 5.53 g (0.02 mol) of 2-amino-5-(2-naphthylthio)benzonitrile (**3a**),‡ 4.57 g (0.06 mol) of thiourea, and 11 ml of tetramethylene sulfone was heated at *ca.* 200° for 1.5 hr. Precipitation of the product was effected by scratching and allowing the solution to stand at room temperature for 48 hr. The mixture was filtered after the addition of 5 ml of tetramethylene sulfone and the resulting solid was washed carefully with MeOH. Recrystallization from pyridine, washing the solid with MeOH, and vacuum drying at 100° afforded 1.0 g (15%) of **5** as a yellow solid, mp 298–299° dec (tlc in 1:4 DMF–MeCN).

Method B. 4-Amino-2-methylmercapto-6-(2-naphthylthio)-quinazoline (6). To a stirred mixture of 1.7 g (0.005 mol) of 5 and 0.57 g (0.01 mol) of KOH in 11 ml of H_2O was added 1.44 g (0.01 mol) of MeI. An immediate reaction ensued and after 1 hr the product was separated by filtration, washed with H_2O and MeOH, and then vacuum dried over P_2O_5. There was obtained 1.5 g (86%) of a white amorphous solid, mp 226–228° (tlc in 1:9 DMF–MeCN).

Mehod C. 7, 8, and 10. Each of these compounds was prepared by the reaction of excess P_2S_5 (purified by Soxhlet extraction with CS_2) with the appropriate quinazoline (**14a**, **16a**, and **13a**, respectively) in pyridine at 75–80°. In the case of **10**, however, a 19-hr reflux was employed while crude **7** was initially purified by formation of a phosphate salt with 85% H_3PO_4 in 2-methoxyethanol.

A mixture of 5.0 g (0.0143 mol) of **16a**, 7.5 g of P_2S_5, and 125 ml of pyridine was stirred at 75–80° under protection from moisture and a continuous N_2 purge for 23 hr. The tlc indicated incomplete reaction so 3.75 g of P_2S_5 was added and the heating continued for an additional 3 hr. The two-phase mixture was added gradually to 1250 ml of stirred, boiling H_2O. After boiling for 2 hr, the mixture was filtered while hot and the filter cake washed with H_2O. Two recrystallizations (*cf.* Table I) afforded 2.93 g (56%) of **8** as yellow crystals after vacuum drying at 100°, mp 320° dec (tlc in 1:12 DMF–EtOAc).

The hydrochloride salt was prepared by suspending 1.68 g (0.0046 mol) of **8** in 150 ml of 2-methoxyethanol and admitting HCl gas until complete dissolution had occurred. After cooling to 0°, the solution was saturated with HCl and the product precipitated by gradual addition of ice. The solid was collected on a filter, washed successively with H_2O, MeOH, and Me_2CO, and then vacuum dried over P_2O_5. There was obtained 1.25 g (68%) of orange solid, mp >275° dec (tlc in 1:12 DMF–MeCN).

Method D. 2,4-Dimercapto-6-(2-naphthylthio)quinazoline (9). The following is a modification of the general procedure of Kabbe.[9] A solution of 2.21 g (0.008 mol) of 2-amino-5-(2-naphthylthio)benzonitrile‡ (3a) and 2.56 g (0.016 mol) of potassium ethyl xanthate in 12 ml of DMF was stirred at reflux for 1 hr. Next, the mixture was diluted with *ca.* 30 ml of DMF, cooled, and acidified with glacial AcOH. The product was precipitated by gradual addition of H_2O and then isolated by filtration and washed with H_2O, MeOH, and Et_2O. Recrystallization gave 2.37 g (84%) of fine yellow crystals, mp 305–307° dec, with slight preliminary softening (tlc in EtOAc).

Method E. 12 and 13a,b. The fusion of ethyl 2-amino-5-(2-naphthylthio)benzoate** (4) with excess urea was conducted in tetramethylene sulfone at *ca.* 195° for 1.75 hr to yield **12**. Compounds **13a,b** were prepared similarly as exemplified below.

A mixture of 4.23 g (0.0143 mol) of 2-amino-5-[(3,4-dichlorophenyl)thio]benzonitrile‡ (**3b**) and 4.50 g (0.075 mol) of urea was heated at *ca.* 180° for 5 hr. The resulting solid was extracted twice with boiling H_2O, isolated by filtration, and vacuum dried over P_2O_5. Recrystallization produced 1.3 g (27%) of **13b** as a yellow crystalline solid, mp 396–398° dec, after vacuum drying at 100°.

Method F. 14a,b, 15, and 16a,b. This method involved refluxing the requisite 2,4-diaminoquinazoline in a 2:1 mixture of diglyme and 2 *N* HCl for 4–6 hr.[7]

Method G. 17 and 18. Compound **17** was prepared by heating **16a** with a large excess of Ac_2O in pyridine at reflux for 1 hr. Compound **18** was prepared at ambient temperature as follows. To a stirred suspension of 3.86 g (0.011 mol) of **16a** in 50 ml of acetone were added 2.08 g (0.0264 mol) of pyridine and 7.48 g (0.0242 mol) of $(CCl_3CO)_2O$. The resulting solution was stirred for 3.75 hr and then diluted with 150 ml of MeOH. The solid which separated was isolated by filtration and washed with MeOH and then Et_2O yielding 4.2 g (77%) of a white solid, mp 282–283°, with preliminary softening (tlc in EtOAc).

Method H. 19a,b. This procedure involves heating the requisite anthranilonitrile with excess formamide.[7]

Method I. 4-Amino-6-(2-naphthylsulfinyl)quinazoline (20a). To a stirred solution of 2.8 g (0.009 mol) of **19a** in 44 ml of glacial AcOH was added 29.4 ml (0.294 mol) of 30% H_2O_2. After 3.5 hr the reaction mixture was poured into 44 ml of 50% NaOH containing an equal amount of ice which resulted in precipitation of the product. The solid was separated by filtration, washed with H_2O, and then recrystallized from 2-methoxyethanol. After vacuum drying there was produced 1.3 g (44%) of yellow crystals, mp 294–297° (tlc in 1:1 DMF–MeCN).

Method J. 4-Amino-6-[(3,4-dichlorophenyl)thio]quinazoline (20b). This oxidation was conducted using $N(CH_2CH_2)_3N \cdot 2Br_2$[10] in 70% AcOH.[7]

Method K. 21a,b. Compounds **19a,b** were oxidized by the recently described procedure using $KMnO_4$.[7]

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