Lennox, U. S. Clearinghouse Fed. Sci. Tech. Inform., AD1969 No. 852897 (1969); Chem. Abstr., 75, 33401 (1971).
(11) H. L. Borison and S. C. Wang, Pharmacol. Rev., 5, 193 (1953).
(12) N. N. Mel'nikov and M. V. Prilutskaya, Zh. Obshch. Khim., 29, 3746 (1959); Chem. Abstr., 54, 19566 (1960).
(13) R. Tachikawa, Tetrahedron, 7, 118 (1959).
(14) F. D. Popp and W. E. McEwen, J. Amer. Chem. Soc., 79, 3773 (1957).
(15) A. Ferratini, Gazz. Chim. Ital., 23, 410 (1893); Beilstein, 20, 276.
(16) R. Pschorr, Ber., 37, 1926 (1904).
(17) R. H. F. Manske, "The Alkaloids," Vol. 4, Academic Press, New York, N. Y., 1954, p 120.

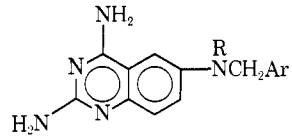
Synthesis of 5-Substituted Quinazolines as Potential Antimalarial Agents†

Wallace T. Ashton and John B. Hynes*

Department of Pharmaceutical Chemistry, College of Pharmacy, Medical University of South Carolina, Charleston, South Carolina 29401. *Received June 25, 1973*

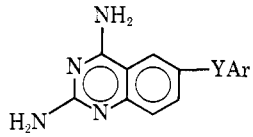
A series of 5-arylethyl-, 5-arylthio-, and 5-arylthiomethyl-2,4-diaminoquinazolines and related compounds was prepared and evaluated for antimalarial activity against *Plasmodium berghei* in mice. Surprisingly, none showed even marginal activity although several of the compounds were isomeric with highly potent 6-arylthioquinazolines. Each of the new quinazolines was also evaluated as an inhibitor of rat liver dihydrofolate reductase.

The discovery of the potent antiparasitic action of 2,4-diaminoquinazolines bearing an aromatic function attached by a suitable spacer at the 6 position has generated considerable excitement. In particular, compounds such as **1a–c** have been extensively investigated as potential antimalarial agents.[1-4] More recently, it was reported



1a, R = H; Ar = 3,4-$Cl_2C_6H_3$
b, R = NO; Ar = 3,4-$Cl_2C_6H_3$
c, R = $CH(CH_3)_2$; Ar = 4-ClC_6H_4

that numerous 6-arylthio- (**2a**), 6-arylsulfinyl- (**2b**), and 6-arylsulfonyl-2,4-diaminoquinazolines (**2c**) also possess potent antimalarial activity.[5] It was of interest, therefore, to synthesize analogs of **2a–c** in which the aryl function was attached at the 5 position of the quinazoline nucleus. The contention that this class of compounds would display useful chemotherapeutic effects was supported by earlier *in vitro* studies which showed that for small nonpolar substituents, antibacterial activity with respect to substitution position followed the order 5 > 6 > 7.[6] Furthermore, a recent study from this laboratory demonstrated that diaminoquinazolines bearing small nonpolar groups in the 5 position were more potent inhibitors of rat liver dihydrofolate reductase than their 6 isomers.[7]



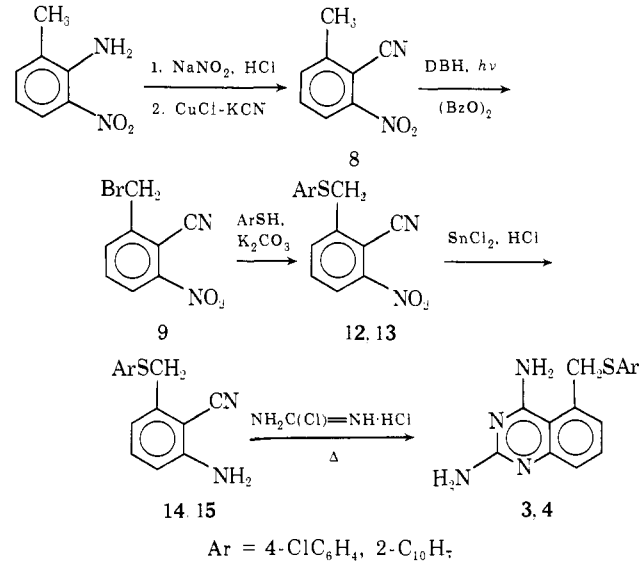
2a, Y = S
b, Y = SO
c, Y = SO_2

Consequently, a series of compounds was prepared in which a hydrophobic aryl moiety was bridged to the 5 position of the quinazoline nucleus by various one- or two-atom spacers. The synthetic routes to the new quinazolines (Table I) and their corresponding intermediates (Table II) are described below.

†This work was supported by U. S. Army Medical Research and Development Command Contract No. DADA 17-71-C-1066.

Chemistry. The 5-arylthiomethyl-2,4-diaminoquinazolines **3** and **4** were prepared according to Scheme I. 2-Methyl-6-nitrobenzonitrile (**8**) was obtained in good yield from 2-methyl-6-nitroaniline by employing improved procedures over those previously reported.[8] Photochemical bromination of **8** with 1,3-dibromo-5,5-dimethylhydantoin (DBH) yielded crude **9**, which was suitable for use without purification. The thioethers **12** and **13** were obtained by alkylation of the appropriate aryl thiol with **9** in the presence of K_2CO_3. Reduction of the nitro groups of **12** and **13** with $SnCl_2$ afforded the anthranilonitriles **14** and **15**. Cyclization with chloroformamidine hydrochloride[9] then proceeded to give the quinazolines **3** and **4**.

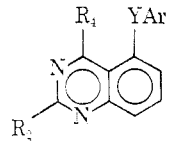
Scheme I



Ar = 4-ClC_6H_4, 2-$C_{10}H_7$

Scheme II outlines the synthesis of *cis*- and *trans*-5-[2-(2-naphthyl)vinyl]- and 5-[2-(2-naphthyl)ethyl]quinazolines **5a–c**. The phosphonium salt intermediate **10** for use in the Wittig reaction was obtained by reaction of the benzyl bromide **9** with triphenylphosphine. Generation of the ylide with DBN (1,5-diazabicyclo[4.3.0]non-5-ene) in the presence of 2-naphthaldehyde yielded a mixture of cis (**16a**) and trans (**16b**) olefins, which were separated by fractional crystallization. After isolation, the isomers were obtained in a cis:trans ratio of approximately 6:7. Each

Table I. Physical Properties of 5-Substituted Quinazolines

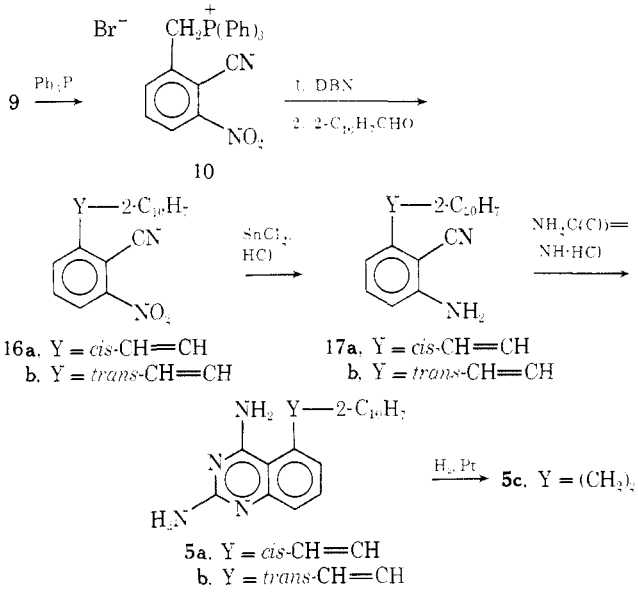


No.	R_2	R_4	ArY	Method[a]	Yield, %	Recrystn medium[b]	Mp, °C	Formula[c]
3	NH_2	NH_2	$4\text{-}ClC_6H_4SCH_2$	C	62	I[d]	202.5–205 dec[e]	$C_{15}H_{13}ClN_4S$
4	NH_2	NH_2	$2\text{-}C_{10}H_7SCH_2$	C	72	I[d]	196–197	$C_{19}H_{16}N_4S$
5a	NH_2	NH_2	$2\text{-}C_{10}H_7CH{=}CH$(cis)	C	69	I[d]	223–224	$C_{20}H_{16}N_4$
5b	NH_2	NH_2	$2\text{-}C_{10}H_7CH{=}CH$(trans)	C	72	II[d]	257–258 dec	$C_{20}H_{16}N_4$
5c	NH_2	NH_2	$2\text{-}C_{10}H_7CH_2CH_2$	E	82		227–229.5[e]	$C_{20}H_{18}N_4$
6a	NH_2	NH_2	$2\text{-}C_{10}H_7S$	C	65	I[d]	218–219.5	$C_{18}H_{14}N_4S$
6b	NH_2	NH_2	$3,4\text{-}Cl_2C_6H_3S$	C	67	I[d]	232–234	$C_{14}H_{10}Cl_2N_4S$
6c	NH_2	NH_2	$2\text{-}C_{10}H_7SO$	G	57	I[d,g]	217–219[e]	$C_{18}H_{14}N_4O_2S$
6d	NH_2	NH_2	$3,4\text{-}Cl_2C_6H_3SO$	G	54	I	215–217[h]	$C_{14}H_{10}Cl_2N_4OS \cdot H_2O$
6e	NH_2	NH_2	$2\text{-}C_{10}H_7SO_2$	H	68	II[g]	301–303 dec[e]	$C_{18}H_{14}N_4O_2S$
6f	NH_2	NH_2	$3,4\text{-}Cl_2C_6H_3SO_2$	H	70	II	268–270[e]	$C_{14}H_{10}Cl_2N_4O_2S$
6g	NH_2	OH	$2\text{-}C_{10}H_7S$	I	72	II[d]	354–356 dec	$C_{18}H_{13}N_3OS$
6h	NH_2	OH	$2\text{-}C_{10}H_7SO_2$	I	57	II[d]	333–335 dec	$C_{18}H_{13}N_3O_3S$
7	H	NH_2	$3,4\text{-}Cl_2C_6H_3S$	J	56	II	191–193	$C_{14}H_9Cl_2N_3S$

[a] See Experimental Section. [b] I, 2-methoxyethanol–H_2O; II, DMF–H_2O. [c] *Anal.* C, H, N. [d] Containing excess concentrated NH_4OH. [e] Preliminary softening. [f] Precipitated product collected by filtration before neutralization with NH_4OH. [g] Reprecipitation. [h] After initial melting at 130–140°, followed by resolidification.

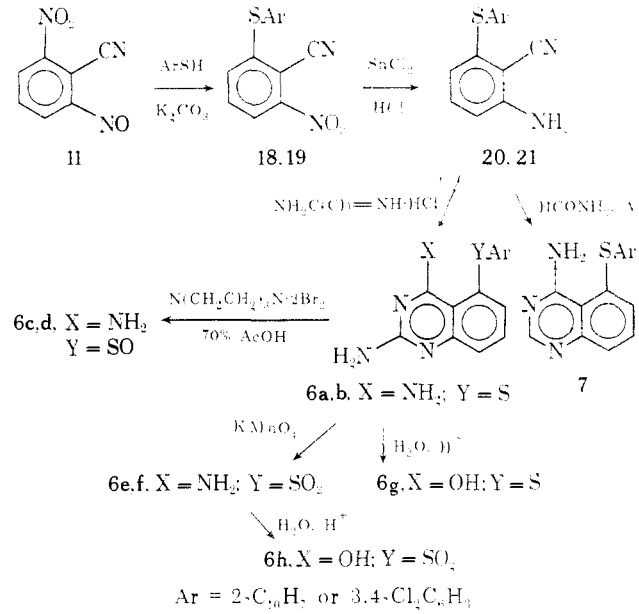
nitro isomer was reduced to the corresponding anthranilonitrile **17a,b** and subsequently cyclized to the quinazolines **5a,b** as described above. The more soluble *cis*-2-naphthylvinylquinazoline (**5a**) was then reduced to the saturated analog **5c** by hydrogenation in the presence of PtO_2 and $MeSO_3H$.

Scheme II



The facile displacement of one nitro group of 2,6-dinitrobenzonitrile (**11**)[10] by mercaptans in the presence of K_2CO_3 was the key step in the synthesis of 5-arylthioquinazolines and derivatives thereof (Scheme III). Reduction of the resulting 2-arylthio-6-nitrobenzonitriles **18** and **19** to the anthranilonitriles **20** and **21** and cyclization to the diaminoquinazolines **6a,b** were carried out in the standard manner. Treatment of **6a** or **6b** with excess triethylenediamine·$2Br_2$[11] in 70% AcOH gave the sulfoxide derivatives **6c,d**. Whereas 6-arylthio-2,4-diaminoquinazolines have been oxidized to sulfones with a mixture of 30% H_2O_2 and AcOH,[5] this treatment was not successful in this case. Either elevated temperature or a long reaction time was required for complete oxidation to the sulfone, and the

Scheme III

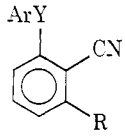


accompanying side reactions under these conditions were severe. However, **6e** and **6f** were obtained cleanly by treatment of **6a** and **6b** with excess permanganate in aqueous AcOH. Acid hydrolysis of **6a,e** yielded the 2-amino-4-hydroxyquinazolines **6g,h**, respectively. Condensation of the anthranilonitrile **21** with formamide resulted in cyclization to the 4-aminoquinazoline **7**.

Biological Results. Each of the quinazolines presented in Table I was tested for activity against *Plasmodium berghei* in mice.[12,‡] None showed activity in this system even at the highest dose levels employed (640 mg/kg). Several of the quinazolines, **3**, **4**, and **5c**, were found to be more potent as inhibitors of rat liver dihydrofolate reductase than pyrimethamine, having I_{50}'s comparable to that displayed by **1a** (*cf.* Table III). This implies that quinazolines bearing a bulky group at position 5 may not effectively cross the plasmodial membrane. It is noteworthy that

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

Table II. Physical Properties of Nitro and Amino Intermediates



No.	ArY	R	Method[a]	Yield, %	Recrystn medium[b]	Mp, °C	Formula[c]
12	4-$ClC_6H_4SCH_2$	NO_2	A	62	I	132–134	$C_{14}H_9ClN_2O_2S$[d]
13	2-$C_{10}H_7SCH_2$	NO_2	A	79	I	132–133	$C_{18}H_{12}N_2O_2S$
14	4-$ClC_6H_4SCH_2$	NH_2	B	75	II	102–103	$C_{14}H_{11}ClN_2S$
15	2-$C_{10}H_7SCH_2$	NH_2	B	71	II	116–119[e]	$C_{18}H_{14}N_2S$
16a	2-$C_{10}H_7CH{=}CH$(cis)	NO_2	D	30		180.5–182[f]	$C_{19}H_{12}N_2O_2$
16b	2-$C_{10}H_7CH{=}CH$(trans)	NO_2	D	35	65	257–258.5[g]	$C_{19}H_{12}N_2O_2$
17a	2-$C_{10}H_7CH{=}CH$(cis)	NH_2	B[h,i]	71	III	130–134[j]	
17b	2-$C_{10}H_7CH{=}CH$(trans)	NH_2	B[i,k,l]	72	III	192–194	$C_{19}H_{14}N_2$
18	2-$C_{10}H_7S$	NO_2	F	90		146–148[m]	$C_{17}H_{10}N_2O_2S$[d]
19	3,4-$Cl_2C_6H_3S$	NO_2	F	76	I	176–178	$C_{13}H_6N_2Cl_2O_2S$
20	2-$C_{10}H_7S$	NH_2	B[n,o]	82	II	104–105[p]	$C_{17}H_{12}N_2S$
21	3,4-$Cl_2C_6H_3S$	NH_2	B[h,q]	78	II	157–158	$C_{13}H_8N_2Cl_2S$

[a]See Experimental Section. [b]I, C_6H_6–hexane; II, MeOH–H_2O; III, 2-methoxyethanol–H_2O containing excess concentrated NH_4OH. [c]*Anal.* C, H, N where formula is given. [d]*Anal.* C, H, N, S. [e]Analytical sample recrystallized from MeOH–H_2O had mp 119–120°. [f]Analytical sample recrystallized from 2-methoxyethanol had mp 181–182°. [g]Analytical sample recrystallized from DMF–2-methoxyethanol had mp 257–259°. [h]DMF instead of diglyme used as reaction cosolvent. [i]Crude product extracted into EtOAc, precipitated as HCl salt, and neutralized during recrystallization. [j]Yield of material suitable for use without further purification; a similar preparation gave a 63% yield with mp 133–136°. [k]Dimethylacetamide instead of diglyme used as reaction cosolvent. [l]Large excess of $SnCl_2 \cdot 2H_2O$ required (18 mol/mol of amine). [m]Analytical sample recrystallized from C_6H_6–hexane had mp 148–149°. [n]Dioxane instead of diglyme used as reaction cosolvent. [o]Used 6 mol of $SnCl_2 \cdot 2H_2O$/mol of amine. [p]Analytical sample, prepared similarly, had mp 103–105°. [q]Used 9 mol of $SnCl_2 \cdot 2H_2O$/mol of amine.

Table III. Quinazolines Assayed as Inhibitors of Rat Liver Dihydrofolate Reductase

No.	I_{50},[a] μM	No.	I_{50},[a] μM
3	0.02	**6d**	55
4	0.01	**6e**	15
5a	0.30	**6f**	57
5b	5.2	**6g**	0.7
5c	0.02	**6h**	14
6a	0.12	**7**	>20[b]
6b	0.16	**1a**[c]	0.018
6c	45	Pyrimethamine[c]	0.070

[a]Assayed spectrophotometrically (340 mμ) with 9 μM dihydrofolate, 30 μM NADPH, and 0.15 M KCl in 0.05 M Tris buffer (pH 7.4). [b]No detectable inhibition at the limit of solubility. [c]Sample kindly provided by Division of Medicinal Chemistry, Walter Reed Army Institute of Research.

the 7 position isomer of **1a** as well as 8-benzylamino-2,4-diaminoquinazoline was also shown to be devoid of antimalarial activity.[3]

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 spectra (Beckman IR-8) in agreement with their assigned structures and appeared free of significant impurities by tlc (Gelman SAF). Representative examples are presented for each of the synthetic methods designated in Tables I and II.

2-Methyl-6-nitrobenzonitrile (8). The diazotization of 25.8 g (0.17 mol) of 2-methyl-6-nitroaniline was carried out according to the procedure of Morgan and Coulson.[8] The general method of Clarke and Read[13] for conversion of the diazonium salt to the nitrile was modified as follows. The solution of the diazonium salt was covered with 20 ml of toluene and cooled to *ca.* −23° in a CCl_4 slush. Neutralization was then accomplished by adding solid $NaHCO_3$ slowly with vigorous stirring. In a separate vessel, a solution of 72.8 g (1.12 mol) of KCN in 140 ml of H_2O was added to a stirred suspension of 43.2 g (0.41 mol) of 97% CuCl in 170 ml of H_2O. The resulting mixture was stirred in an ice bath for 1 hr and then covered with a layer of 300 ml of EtOAc. The neutralized diazonium salt was added as rapidly as practicable to this cold, vigorously stirred two-phase system. After gas evolution had nearly ceased, the mixture was heated to 70°, then cooled, and filtered to remove insoluble salts, which were washed with EtOAc. The organic solution was washed thoroughly with H_2O, 10% Na_2CO_3, and dilute HCl, then dried with $MgSO_4$, and partially decolorized with charcoal. After evaporation, the residue was recrystallized from MeOH (Dry Ice bath) to give 23.1 g (84%) of 2-methyl-6-nitrobenzonitrile, mp 108–109° (lit.[6] mp 107.5–108°) (tlc in C_6H_6).

In subsequent runs, 2-methyl-6-nitroaniline, CuCl, and KCN were used in a molar ratio of 1:2:8. The CuCl-KCN mixture then gave a complete solution due to formation of the soluble complex $K_3Cu(CN)_4$. However, this did not affect the yield of the nitrile. Commercial CuCN by itself was unsatisfactory, presumably because of its very low solubility in water.

2-Bromomethyl-6-nitrobenzonitrile (9). A stirred mixture of 20.0 g (0.124 mol) of 2-methyl-6-nitrobenzonitrile, 15.9 g (0.056 mol, 0.112 equiv) of 1,3-dibromo-5,5-dimethylhydantoin (DBH), 0.4 g of benzoyl peroxide, and 190 ml of CCl_4 was refluxed with protection from moisture under irradiation from a 275-W sun lamp. After 2 hr, when the solid had risen to the surface and the transient color due to Br_2 had disappeared, the mixture was filtered twice while hot. The product separated from the filtrate as an oil which solidified on scratching. This was collected on a filter and washed with a small amount of CCl_4 to give 19.5 g (65%) of cream-colored crystals, mp ~65–85°. This material showed only minor impurities on tlc (C_6H_6), gave a positive active halogen test with 4-(*p*-nitrobenzyl)pyridine, and was suitable for use without further purification. Somewhat less than the stoichiometric amount of DBH was inadvertently used here. Surprisingly, when this reaction was repeated using a stoichiometric amount of DBH, the yield was not as high. *Caution*: this material is a skin irritant.

Method A (12 and 13). A mixture of 7.6 g (0.0315 mol) of **9**, 5.03 g (0.0315 mol) of 2-naphthalenethiol, 4.35 g (0.315 mol) of K_2CO_3, and 35 ml of DMF was stirred in an ice bath with protection from moisture for 1.5 hr and then diluted with 35 ml of pyridine. The precipitated product obtained by gradual addition of 200 ml of H_2O was collected on a filter and washed successively with 100 ml of 10% pyridine, 100 ml of 0.5 N HCl, and 200 ml of H_2O. The partially dried material was stirred and washed with three 25-ml portions of MeOH. Recrystallization from C_6H_6–hexane gave 8.0 g (79%) of **13** as light yellow crystals, mp 132–133° (tlc in C_6H_6). *Anal.* ($C_{18}H_{12}N_2O_2S$) C, H, N.

Method B (14, 15, 17a,b, 20, and 21). To a solution of 5.2 g (0.017 mol) of 12 in 85 ml of diglyme was added slowly with cooling in a water bath a solution of 12.0 g (0.053 mol) of $SnCl_2 \cdot 2H_2O$ in 35 ml of concentrated HCl. The resulting solution was stirred at ambient temperature for 1.5 hr and then added to a vigorously stirred mixture of 100 g of 50% KOH and 200 g of ice. The product separated as an oil which solidified as stirring was continued. The solid was collected on a filter and washed first with 2 *N* NaOH and then with a large volume of H_2O. Upon recrystallization from MeOH-H_2O, 3.5 g (75%) of 14 as light yellow crystals, mp 102–103°, was obtained (tlc in C_6H_6). *Anal.* ($C_{14}H_{11}ClN_2S$) C, H, N.

Method C (3, 4, 5a,b, and 6a,b). A mixture of 3.8 g (0.0131 mol) of 15, 1.66 g (0.0144 mol) of chloroformamidine hydrochloride, and 6.5 ml of diglyme was heated in an oil bath at 130–140°. After 0.75 hr an exotherm occurred, resulting in a rise of the internal temperature to 150° accompanied by vigorous gas evolution and heavy precipitation. After 1.5 hr the mixture was diluted with dioxane. The product was collected on a filter, washed with dioxane, and recrystallized from 2-methoxyethanol containing excess concentrated NH_4OH to give 3.15 g (72%) of 4 as fine, cream-colored plates, mp 196–197° (tlc in DMF). *Anal.* ($C_{19}H_{16}N_4S$) C, H, N.

2-Cyano-3-nitrobenzyltriphenylphosphonium Bromide (10). 2-Bromomethyl-6-nitrobenzonitrile (9) was prepared as described above except that in this case, instead of crystallizing the product from CCl_4, the filtrate was simply evaporated and the residue used without purification. To a solution of 44.2 g (0.183 mol maximum) of crude 2-bromomethyl-6-nitrobenzonitrile in 400 ml of hot toluene was added slowly with stirring 47.9 g (0.183 mol) of triphenylphosphine. The product precipitated during addition. The mixture, which became too thick to stir, was refluxed for 0.75 hr and then filtered while hot. The dark brown solid was washed first with a large volume of EtOAc and then with several small portions of acetone, which removed much of the dark color. Further washing with EtOAc and hexane gave 45.4 g (49%) of light brown solid, mp 243–246° dec, suitable for use in the next reaction. For analysis, a portion of another batch (obtained similarly and in comparable purity) was recrystallized from MeCN-C_6H_6-hexane, giving light yellow crystals, mp 242–244° dec. *Anal.* ($C_{26}H_{20}BrN_2O_2P$) C, H, N.

Method D (16a,b). To a stirred mixture of 47.6 g (0.0945 mol) of 10, 14.8 g (0.0945 mol) of 2-naphthaldehyde, and 180 ml of DMF was added a solution of 11.7 g (0.0945 mol) of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in 50 ml of DMF. The addition was carried out with stirring over a period of 1 hr and under protection from moisture. After stirring for 21 hr at ambient temperature, by which time the violet color had disappeared and heavy precipitation had occurred, the mixture was diluted with 1000 ml of MeOH, swirled briefly, and then filtered at once. The solid on the filter was washed with *ca.* 600 ml of MeOH (added to filtrate) and then Me_2CO (not combined with original filtrate) and dried to give 10.0 g of the trans olefin **16b** as fine yellow-orange needles, mp 257–258.5° (too insoluble for effective tlc). The analytical sample (from a previous batch) was recrystallized from DMF-2-methoxyethanol and had mp 257–259°. *Anal.* ($C_{19}H_{12}N_2O_2$) C, H, N.

Crystallization from the DMF-MeOH filtrate began almost immediately after filtration. After standing for 2 days, this material was collected on a filter, washed with MeOH, and dried to give 8.5 g of the cis olefin 16a as fine yellow needles, mp 180.5–182° (tlc in C_6H_6). The analytical sample (from a previous batch) was recrystallized from 2-methoxyethanol and had mp 181–182°. *Anal.* ($C_{19}H_{12}N_2O_2$) C, H, N.

Each of the isomers obtained above was suitable for use without recrystallization, and the combined yield was 65%. Compound **16b** had a strong ir absorption at *ca.* 955 cm^{-1}, typical of a trans olefin. This band was retained in olefinic derivatives of 16b, namely **17b** and **5b**, and was absent in the case of **16a** and its olefinic derivatives 17a and **5a**. The assignment of the trans configuration to **16b** was also consistent with its considerably higher melting point and much lower solubility relative to 16a.

Method E (5c). A mixture of 3.6 g (0.0116 mol) of **5a**, 2.23 g (0.0232 mol) of $MeSO_3H$, 80 mg of PtO_2, and 100 ml of DMF was shaken with H_2 at 2–4 atm. Additional PtO_2 (6 × 100 mg) was added at intervals when uptake of H_2 ceased due to poisoning of the catalyst. After 5 hr, no net uptake of H_2 was observed upon addition of fresh catalyst and tlc (DMF) showed that the reaction was complete. To the filtered solution was added 50 ml of concentrated NH_4OH. Upon gradual addition of *ca.* 400 ml of H_2O, the product precipitated. The isolated solid was washed with H_2O and then acetone and dried to give 2.95 g (82%) of off-white crystals, mp 227–229.5° with preliminary softening (tlc in DMF). *Anal.* ($C_{20}H_{18}N_4$) C, H, N.

Method F (18 and 19). A mixture of 15.4 g (0.080 mol) of 2,6-dinitrobenzonitrile,[10] 12.8 g (0.080 mol) of 2-naphthalenethiol, 11.0 g (0.080 mol) of K_2CO_3, and 80 ml of DMF was stirred in an ice bath under protection from moisture. After 0.75 hr, the thick mixture was diluted with 150 ml of pyridine and the product precipitated by gradual addition of *ca.* 500 ml of H_2O. The solid was isolated and washed successively with 10% pyridine, H_2O, MeOH, and Et_2O to give (after drying) 22.1 g (90%) of 18 as light yellow crystals, mp 146–148° (tlc in C_6H_6). For analysis, a sample was recrystallized from C_6H_6-hexane (mp 148–149°). *Anal.* ($C_{17}H_{10}N_2O_2S$) C, H, N.

Under vigorous conditions (dimethylacetamide at reflux for 1 hr) the major product isolated was not 18 but rather a colorless crystalline solid, mp 201–202° (recrystallized from 2-methoxyethanol), which had the same R_f as 18 on tlc (C_6H_6). Analysis for C, H, N, and S was consistent with the formula $C_{34}H_{20}N_2OS_2$, while the mass spectrum showed that the highest *m/e* value was 536 (parent ion). This, together with the presence of CN and the absence of NO_2 bands in the ir, suggested that the structure was bis[2-cyano-3-(naphthylthio)phenyl] ether. Such a compound could result from displacement of the NO_2 group of 18 by the carbonate anion, followed by loss of CO_2 and then attack of the resulting phenoxide on another molecule of 18. When a mixture of 18 and K_2CO_3 in dimethylacetamide was heated at reflux, the same product was obtained.

Method G (6c,d). To a stirred suspension of 4.75 g (0.011 mol, 0.022 equiv) of $N(CH_2CH_2)_3N \cdot 2Br_2$[11] in 200 ml of 70% AcOH was added portionwise 3.37 g (0.01 mol) of 6b over 1 hr. The resulting mixture was stirred at ambient temperature for 20 hr. After neutralization with concentrated NH_4OH, the product was separated by filtration, washed with H_2O, and air-dried. Recrystallization from 2-methoxyethanol-H_2O (charcoal) produced a yellow solid which was isolated by filtration, washed with H_2O, and vacuum dried over P_2O_5. The product **6d** (1.9 g, 54%) melted at 130–140°, then resolidified, and melted again at 215–217° (tlc in 1:1 DMF-MeCN). *Anal.* ($C_{14}H_{10}Cl_2N_4OS \cdot H_2O$) C, H, N.

Method H (6e,f). To a stirred solution of 3.4 g (0.01 mol) of **6b** in 124 ml of AcOH (glacial) was added dropwise a solution of 3.16 g (0.02 mol) of $KMnO_4$ in 75 ml of H_2O over 1 hr. After standing at ambient temperature for 20 hr, the mixture was filtered (Celite) and the filtrate basified with concentrated NH_4OH. The resulting solid was separated by filtration and washed successively with H_2O, MeOH, and acetone. Next, it was extracted with 100 ml of hot DMF (charcoal). The remaining solid, which was separated by filtration, was washed with an additional 50 ml of hot DMF. The extracts were combined, reheated, and H_2O added to effect crystallization. The light yellow solid, which separated upon cooling, was isolated by filtration, washed with H_2O, and then vacuum dried over P_2O_5. There was obtained 2.6 g (70%) of 6f, mp 268–270° with preliminary softening (tlc in 1:1 DMF-MeCN). *Anal.* ($C_{14}H_{15}Cl_2N_4O_2S$) C, H, N.

Method I (6g,h). A solution of 2.55 g (0.008 mol) of 6a in 40 ml of 2 *N* HCl and 80 ml of diglyme was stirred under reflux for 6 hr, during which time precipitation of product occurred. The cooled mixture was neutralized with concentrated NH_4OH and then filtered. The solid product was washed with H_2O. Recrystallization from DMF-H_2O made weakly basic with NH_4OH yielded 1.85 g (72%) of **6g** as cream-colored crystals, mp 354–356° dec (tlc in 1:1 DMF-MeCN). *Anal.* ($C_{18}H_{13}N_3OS$) C, H, N.

Method J (7). A mixture of 2.95 g (0.01 mol) of 21 and 10 ml of formamide was heated at 185 ± 10° for 5 hr. After cooling, the reaction mixture was diluted with acetone and filtered and the solid washed with acetone. Recrystallization from DMF-H_2O (charcoal) and vacuum drying over P_2O_5 produced 1.3 g of 7 as white needles, mp 191–193°. The addition of H_2O to the original filtrate yielded 0.5 g of crystals, mp 192–193° (56% combined yield). Both crops were homogeneous on tlc in EtOAc. *Anal.* ($C_{14}H_9Cl_2N_3S$) C, H, N.

Acknowledgment. The authors wish to express their appreciation to Dr. E. A. Steck of the Walter Reed Army Institute of Research for assistance and encouragement during the course of this work. This is Contribution No. 1182 to the Army Research Program on Malaria.

References

(1) P. E. Thompson, A. Bayles, and B. Olszewski, *Exp. Parasitol.*, **25**, 32 (1969).
(2) P. E. Thompson, A. Bayles, and B. Olszewski, *Amer. J. Trop. Med. Hyg.*, **19**, 12 (1970).
(3) J. Davoll, A. M. Johnson, H. J. Davies, O. D. Bird, J. Clarke, and E. F. Elslager, *J. Med. Chem.*, **15**, 812 (1972).
(4) E. F. Elslager, O. D. Bird, J. Clarke, S. C. Perricone, D. F. Worth, and J. Davoll, *ibid.*, **15**, 1138 (1972).
(5) E. F. Elslager, Plenary Lecture at Fourth International Congress of Heterocyclic Chemistry, Salt Lake City, Utah, July 8–13, 1973.
(6) A. Rosowsky, J. L. Marini, M. E. Nadel, and E. J. Modest, *J. Med. Chem.*, **13**, 882 (1970).
(7) W. T. Ashton, F. C. Walker, III, and J. B. Hynes, *ibid.*, **16**, 694 (1973).
(8) G. T. Morgan and E. A. Coulson, *J. Chem. Soc.*, 2551 (1929).
(9) A. Hantzsch and A. Vagt, *Justus Liebigs Ann. Chem.*, **314**, 339 (1900).
(10) P. T. Haken, British Patent 861,898 (1961); *Chem. Abstr.*, **55**, 17582 (1961).
(11) S. Oae, Y. Ohmeshi, S. Kozuka, and W. Tagaki, *Bull. Chem. Soc. Jap.*, **39**, 364 (1966).
(12) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(13) H. T. Clarke and R. R. Read, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 514.

Synthesis and Antiinflammatory Activity of 1-Alkyl-4-aryl-2(1*H*)-quinazolinones and Quinazolinethiones

R. V. Coombs, R. P. Danna, M. Denzer, G. E. Hardtmann,* B. Huegi, G. Koletar, J. Koletar, H. Ott,

Medicinal Chemistry Department

E. Jukniewicz, J. W. Perrine, E. I. Takesue,* and J. H. Trapold

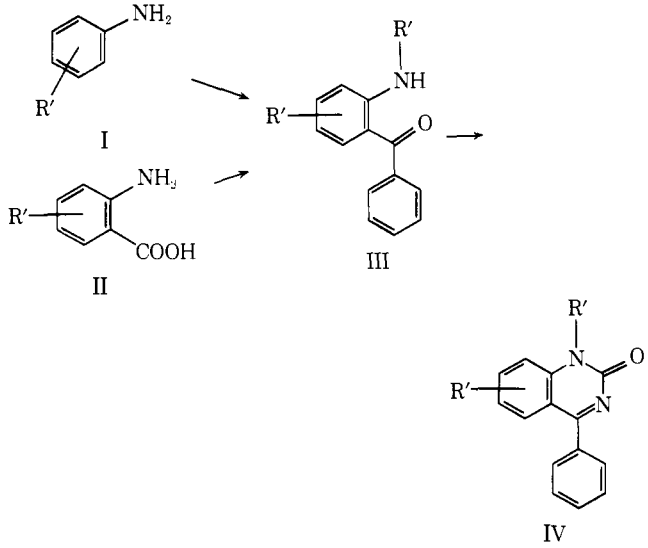
Biology Department, Sandoz-Wander, Inc., Research and Development Section, East Hanover, New Jersey 07936.

Received April 12, 1973

Several routes for the preparation of 1-alkyl-4-aryl-2(1*H*)-quinazolinones, a new class of potent antiinflammatory agents, are described. Two procedures for the synthesis of their sulfur analogs are discussed as is the antiinflammatory evaluation of these compounds.

In the course of our investigations into the chemistry and pharmacology of quinazoline derivatives we discovered a new reaction sequence leading to 1-alkyl-4-aryl-2(1*H*)-quinazolinones.[1] When these compounds were evaluated pharmacologically they were found to possess an interesting level of antiinflammatory activity and we therefore set out to undertake an intensive variation program in the hope of developing a compound of sufficient activity to warrant clinical investigation. This publication will describe only that fraction of the compounds prepared by us (approximately one-fourth) which we feel best illustrates our current thinking concerning the chemistry and structure–activity relationships in this series.

Chemistry. Apart from some early examples prepared by the sequence reported previously,[1] the majority of the quinazolinones IV was prepared by the ring closure of appropriately substituted *o*-aminobenzophenones III which were in turn prepared either from the corresponding anthranilic acids II or anilines I.



Scheme I shows the sequences employed to prepare the anthranilic acid derivatives and Scheme II those leading to the *o*-aminobenzophenones. Schemes III and IV continue the synthetic sequence and outline the preparation of the quinazolinones and their subsequent chemical modifications.

Many of the reactions are either described directly themselves in the literature or are very closely related to well-known procedures and therefore need no further discussion or amplification here, the particular sequence chosen in any one instance depending simply on the availabilities of the several possible starting materials. However, perhaps some synthetic aspects deserve brief comment, particularly the mono-N-alkylation of the various intermediates and end products.

For simple primary alkyl groups such as ethyl or propargyl, the most efficient method of introduction proved to be the alkylation of the sodio derivatives of the 1-unsubstituted quinazolinones (reaction CC, Scheme III). However, with alkyl halides of increasing chain length the yield of N-alkylated product dropped rapidly, much O-alkylation occurring, and secondary alkyl groups were also much less readily introduced in this way for a similar reason. Not unexpectedly, attempts with tertiary halides did not usefully lead to alkylated products.

It therefore became desirable to introduce these types of alkyl groups at an earlier stage of the synthesis. Preparation of the tosyl derivatives of the *o*-aminobenzophenones followed by alkylation was unexceptional with primary and secondary halides (reactions V and W, Scheme II). Subsequently it was found that *o*-aminobenzophenones and *o*-aminobenzonitriles could be alkylated directly with secondary halides, such as 2-iodopropane, to yield essentially monoalkyl derivatives, and this proved to be a general and efficient reaction (reactions G and Z, Schemes I and II).