ylococcus aureus using natural (−)-terreic acid of 1000 μg/mg activity as a standard. The unnatural isomer, (+)-terreic acid, was as active as the (−)-terreic acid used as a standard (Table II). The synthetic (−) isomer was slightly less active than the natural compound, which could be due to decomposition. There is only one other report of the unnatural isomer of an antibiotic possessing biological activity.[6] Cycloserine has been found to be active against *E. coli* B in the D (natural) and L forms; the racemate is more active than either isomer alone. The racemic form of terreic acid is more active than either optical antipode alone, suggesting some form of synergistic behavior.

Experimental Section

General. Melting points were determined on a Fisher-Johns hot-stage melting point apparatus. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Mrs. Nancy Alvord at MIT. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer; only significant maxima are listed. Nuclear magnetic resonance spectra were obtained on a Varian T-60 using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6. Optical rotations were measured at 546 and 578 nm on a Zeiss photoelectric precision polarimeter, and the values at 589 nm (sodium D line) were obtained by using the equations§

$$X = \alpha_{578}/(\alpha_{546} - \alpha_{578})$$

$$\alpha_D = X(\alpha_{546})/(X + 1.37)$$

Thin-layer chromatography was performed on Baker-flex silica gel 1B or 1B-F.

2-Methyl-3-methoxy-1,4-hydrobenzoquinone (1). The compound is available from *o*-toluidine by a five-step reaction sequence according to Winzor.[5] The following data were obtained: mp 118–119° (lit.[5] 117–118°); ir ($CHCl_3$) 3575, 3520, 3400–3300, 1480, 1075 cm^{-1}; nmr ($DCCl_3$) δ 6.74 (d, J = 9 Hz, 1 H), 6.48 (d, J = 9 Hz, 1 H), 4.65 (br, 2 H), 3.70 (s, 3 H), 2.20 ppm (s, 3 H); mass spectrum m/e 154 (100), 152 (46), 139 (78.7), 122 (18.7), 111 (33.7), 18 (31.3); metastable peaks at m/e 88 and 125.

2-Methyl-3-hydroxy-1,4-benzoquinone (3). Cold boron tribromide (1 ml, 15.25 mmol) was added by pipet to a suspension of 2-methyl-3-methoxy-1,4-hydrobenzoquinone (1, 1 g, 6.50 mmol) in methylene chloride (15 ml) at −80°. The resulting mixture was kept cold for 0.5 hr and then stirred overnight at room temperature. Complete solution was achieved by the end of the reaction. The excess boron tribromide and the solvent were removed at reduced pressure to give the boric acid ester as a glass. It was hydrolyzed by water (10 ml) for 1 hr at 0° and the resulting mixture extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, treated with activated charcoal, filtered, and evaporated to give 0.63 g of a brown syrup: R_f 0.47 (1:1 C_6H_6–EtOAc); ir (film) 3490, 3400–2500, 1495, 1250–1220, 1070 cm^{-1}; nmr (acetone-d_6) δ 6.68 (d, J = 9 Hz, 1 H), 6.36 (d, J = 9 Hz, 1 H), 3.30 (br, 3 H), 2.10 ppm (br, methyl proton signal mixed with acetone-d_6 peaks). This compound was used without further purification.

Silver oxide was prepared immediately before use according to Cason.[8]

2,3,6-Trihydroxytoluene (2, 0.63 g, 4.50 mmol) dissolved in anhydrous ether (50 ml) was added quickly to a suspension of silver oxide (about 10 g) and anhydrous sodium sulfate (5 g) in anhydrous ether (100 ml). The reaction mixture was swirled for 15 min and filtered. The solid was washed with portions of anhydrous ether. Evaporation of the ether solution at reduced pressure gave a brown-yellow solid which was purified by sublimation to give orange crystals: 0.57 g (64% from 1); mp 115–120° dec (lit. 134–135°,[4] 110–134° dec);[9] ir (CCl_4) 3400, 1665, 1650, 1070 cm^{-1}; nmr ($DCCl_3$) δ 6.93 (s, 1 H), 6.70 (s, 2 H), 1.95 ppm (s, 3 H). The spectroscopic data agree with that recorded in the literature.[4]

(±)-Terreic Acid (4). 2-Methyl-3-hydroxy-1,4-benzoquinone (3, 0.57 g, 4.13 mmol) in 95% ethanol (90 ml) was treated with a solution of sodium perborate[4] (3.20 g, 39.50 mmol) in water (250 ml). After standing for 18 min at room temperature, 1 N acetic acid (15 ml) was added to stop the reaction. The solution was extracted with benzene and the extract dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure leaving a pale yellow solid which was purified by sublimation to give pale yellow crystals: 101.7 mg (16%); mp 131.5–132° (lit.[4] 124–125°); ir (KBr) 3250, 1690, 1655, 1625, 1375, 1345, 1300, 1190 cm^{-1}; nmr ($DCCl_3$) δ 7.11 (s, 1 H), 4.06 (s, 2 H), 2.11 ppm (s, 3 H). Spectroscopic data for comparison are available in the literature.[3,4] *Anal.* Calcd for $C_7H_6O_3$ (138): C, 54.50; H, 3.90. Found: C, 54.65; H, 3.89.

Resolution of (±)-Terreic Acid (4) with (+)- and (−)-Ephedrine. (±)-Terreic acid (0.40 g, 2.94 mmol) was mixed with *l*-ephedrine (0.47 g, 2.85 mmol) in anhydrous ethyl ether (410 ml) and cooled in an acetone–Dry Ice bath. The deposited solid was redissolved in excess anhydrous ethyl ether. Partial evaporation of the solvent to the saturation point was carried out at reduced pressure. The saturated solution was cooled in the cold bath again. The salt was deposited in this manner ten times. Hydrochloric acid (1 N) was added to recover the resolved terreic acid from the last crop of deposited salt. The acidic solution was extracted with benzene and the extract was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave crude terreic acid which was then purified by sublimation to give 67 mg (17%) of pale yellow crystals. The terreic acid recovered from the salt formed with *l*-ephedrine was the (+) enantiomer: $[\alpha]^{25}D$ +26.5° (*c* 0.5, $CHCl_3$); mp 124.5–125°. The (−)-terreic acid could be obtained from the salt formed with *d*-ephedrine by the same method: $[\alpha]^{25}D$ −24.9° (c 1.8, $CHCl_3$); mp 124.5–125°. The authentic terreic acid had $[\alpha]^{25}D$ −26.1° (c 10.4, $CHCl_3$); mp 127–127.5°.

§Instruction Manual G50-381/I-e for the Zeiss photoelectric polarimeter. The equation is the first approximation of Drude's formula[7] for normal rotatory dispersion and includes an apparatus constant.

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Synthesis of 2,4-Diamino-5-[4-arylthiophenyl]- and 5-[4-Arylsulfonylphenyl]pyrimidines as Antimalarials

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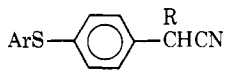
The value of 2,4-diaminopyrimidine antifols such as pyrimethamine[1,2] and trimethoprim[3] as antiparasitic agents has long been recognized.[4,5] Recently, a wide variety of 2,4-diaminoquinazoline antifols which are generally related by structure and mode of action to the 2,4-diaminopyrimidines has been reported to be potent antimalarials.[6-11] The exceptional activity observed for the 6-arylthio- and 6-arylsulfonyl-2,4-diaminoquinazolines[11] led us to prepare a limited series of 5-[4-arylthiophenyl]- and 5-[4-arylsulfonylphenyl]-2,4-diaminopyrimidines for evaluation as potential antimalarials.

Chemistry. The synthesis of the title compounds was achieved by an approach analogous to the reported synthesis of pyrimethamine.[1,2] The synthesis (Scheme I) begins with an arylthiotoluene (I) and the first step involves simple monobromination of the methyl group followed by bromide displacement with cyanide to form the arylthio-

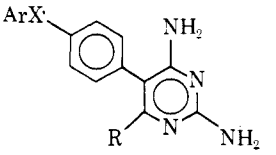
Table I. Arylacetonitriles



Compd	Ar	R	Mp, °C[a]	% yield	Recrystn solvent	Formula
1	β-Naphthyl	H	104–105	65	Pet. ether	$C_{18}H_{13}NS$
2	β-Naphthyl	COH	161–162	60	Pet. ether–Et_2O	$C_{19}H_{13}NOS$
3	4-Chlorophenyl	H	Oil			
4	4-Chlorophenyl	COH	133–134	33	Pet. ether–Et_2O	$C_{15}H_{10}ClNOS$
5	4-Chlorophenyl	COEt	75–77	50	Pet. ether	$C_{17}H_{14}ClNOS$

[a]All compounds, except **3**, were analyzed for C and H and the results were within 0.3% of theory.

Table II. 2,4-Diamino-5-arylpyrimidines



Compd	Ar	X	R	Mp, °C[a]	% yield	Recrystn solvent	Formula
6	β-Naphthyl	S	H	194–195	51	EtOH	$C_{20}H_{16}N_4S$
7[b]	β-Naphthyl	S	H	324–325	55	H_2O	$C_{20}H_{17}ClN_4S$
8	β-Naphthyl	SO_2	H	274–275	40	EtOH	$C_{20}H_{16}N_4O_2S$
9	*p*-Chlorophenyl	S	H	193–194	44	EtOH	$C_{16}H_{13}ClN_4S$
10[b]	*p*-Chlorophenyl	S	H	332–334	40	H_2O	$C_{16}H_{14}Cl_2N_4S$
11	*p*-Chlorophenyl	SO_2	H	244–245	60	EtOH	$C_{16}H_{13}ClN_4O_2S$
12	*p*-Chlorophenyl	S	Et	215–216	61	C_6H_6–EtOH	$C_{18}H_{17}ClN_4S$
13	*p*-Chlorophenyl	SO_2	Et	230–230.5	65	EtOH	$C_{18}H_{17}ClN_4O_2S$

[a]All compounds were analyzed for C, H, and N and the results were within 0.3% of theory. [b]Hydrochloride salt.

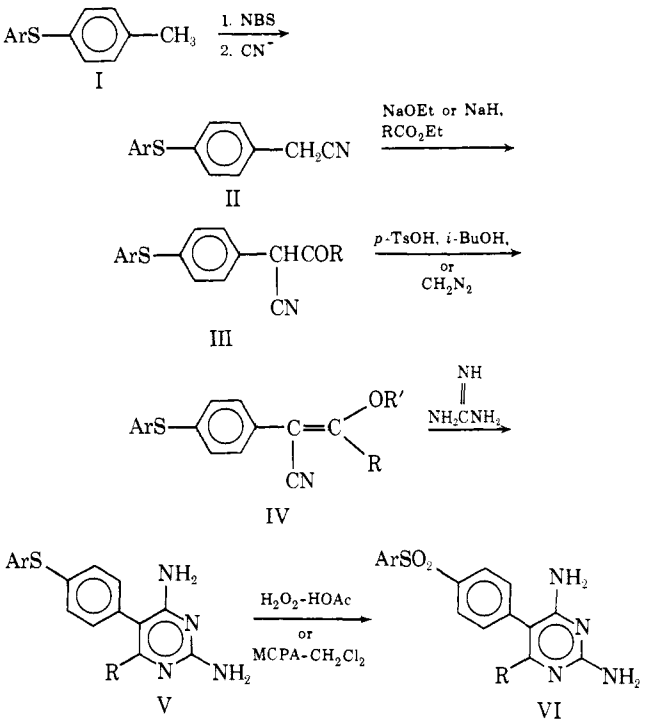
phenylacetonitrile (II). The NaOEt-catalyzed acylation of II with ethyl formate was readily accomplished. However, to prepare reasonable quantities of 1-cyano-1-[4-(*p*-chlorophenylthio)phenyl]butanone-2 (**5**) by condensation of II with ethyl propionate, it was necessary to employ aprotic conditions with NaH as the base. Conversion of the formylcyano compounds III to the enol ether IV was usually accomplished by the action of isobutyl alcohol and *p*-toluenesulfonic acid in refluxing toluene. This method failed with the cyano ketone **5** and even in refluxing xylene only low yields were obtained after 48 hr. Consequently, the *O*-methyl ether of the enol was prepared by the action of diazomethane. The enol ethers IV were converted smoothly with guanidine into the 2,4-diaminopyrimidines. Formation of isomeric benzyltriazines has been reported[1] on condensation of β-cyanocarbonyl compounds with guanidine and thus led to development of the enol sequence.[1,2] That the enol ethers formed the desired pyrimidines and not benzyltriazines in the reactions described here was demonstrated by the absence of the benzyl proton absorption in the nmr. Conversion of the 5-arylthiophenylpyrimidines V into their corresponding 5-arylsulfonylphenylpyrimidines VI was accomplished by oxidation either with H_2O_2–HOAc or *m*-chloroperbenzoic acid–CH_2Cl_2. The compounds prepared by these approaches are listed in Tables I and II.

Biological Activity. The compounds shown in Table II were screened against *Plasmodium berghei* by the method of Rane.[12] These compounds exhibit no useful activity. The only activity observed was for compounds 6 and 7 and they gave an increase in survival time at 640 mg/kg dosage level of 13.5 and 18.7 days, respectively. Compounds 11–13 are toxic at dosages of 160, 5, and 20 mg/kg, respectively.

Experimental Section

Melting points reported under 300° were taken on a Thomas-Hoover melting point apparatus; for those compounds melting above 300° the determinations were made on a Mel-Temp apparatus. All melting points are uncorrected. Ir spectra were recorded

Scheme I



on all new compounds with a Perkin-Elmer Model 337 spectrometer and nmr spectra were recorded on all the 2,4-diaminopyrimidines in TFA with a Varian A-60A instrument. All spectra were in accord with the structures assigned. Elemental analyses were performed by Atlantic Microlab, Atlanta, Ga.

Most of the 2,4-diaminopyrimidines reported herein, except as noted, were prepared *via* the same general reaction sequence, as typified by the following specific examples. The physical data on these compounds are included in Tables I and II.

4-Arylthiophenylacetonitriles (II). A solution of *p*-tolyl-2-naphthyl sulfide[13] (25 g, 0.1 mol) and 19 g (0.11 mol) of NBS in 300 ml of CCl_4 was irradiated with uv light for 4 hr at reflux. The mixture was cooled, the succinimide filtered, and the solvent removed under reduced pressure. The residual solid was crystal-

lized once from petroleum ether; 20 g (0.055 mol) of the semipure bromomethyl compound (*ca.* 90% by nmr) was dissolved in 500 ml of acetone and 10 g (0.15 mol) of KCN in 40 ml of H_2O was added to the solution. The reaction mixture was stirred and warmed at 50–60° for 12 hr. The solvent was removed under reduced pressure. The residue was extracted with Et_2O, washed (H_2O), and dried ($CaSO_4$), and the organic layer was evaporated under reduced pressure. The crude cyanomethyl compound **1** (14 g) was recrystallized from petroleum ether, mp 104–105°.

4-(*p*-chlorophenylthio)phenylacetonitrile was prepared in a similar manner from 4-chloro-4'-methyldiphenyl sulfide.[14] However, this acetonitrile was an oil which could not be recrystallized and was used as such in the next step.

α-Cyano-4-(2-naphthylthio)phenylacetaldehyde (2). The cyanomethyl compound 1 (16.5 g, 0.06 mol) was mixed with a NaOEt solution prepared from 1.5 g (0.065 mol) of Na and 100 ml of EtOH. Ethyl formate (45 g, 0.77 mol) was added to the solution and the mixture was refluxed for 2 hr. The solvent was removed, H_2O was added to the residue, and the aqueous mixture was acidified with HCl. The solution was extracted with Et_2O, washed (H_2O), dried ($CaSO_4$), and evaporated. A gummy solid remained, which on heating with petroleum ether turned into a solid (yield, 11 g). Recrystallization from petroleum ether–Et_2O gave a solid with mp 161–162°.

1-Cyano-1-[(4-chlorophenylthio)phenyl]butanone-2 (5). NaH Method. A solution of 30 g (0.065 mol) of the crude cyanomethyl compound (60% by nmr) in 100 ml of $PrCO_2Et$ was added dropwise to a suspension of 6.5 g (0.16 mol) of NaH (58% oil dispersion) in 50 ml of $PrCO_2Et$ at room temperature. After addition of about one-fourth of the cyanomethyl compound the reaction became exothermic and was placed in an ice bath. After the vigorous reaction subsided the remainder of the cyanomethyl compound was added to the mixture and stirring was continued overnight. The reaction was poured into ice-water and extracted with Et_2O, and the Et_2O layer was discarded. The clear aqueous layer was acidified with HCl and extracted with Et_2O, washed (H_2O), dried ($CaSO_4$), and evaporated to yield an oily substance which on standing overnight turned to a solid: yield, 10 g. Recrystallization was from petroleum ether, mp 75–77°.

NaOEt Method. Preparation of 5 was accomplished employing the procedure outlined for **2**; however, the yield was less than 10%. The material obtained for by the NaOEt method was identical with that obtained by the NaH method.

α-Cyano-β-isobutoxy-4-(2-naphthylthio)styrene (14). The formyl compound **2** (7.6 g, 0.025 mol) was dissolved in 150 ml of toluene to which was added 2.5 g of *i*-BuOH and 0.5 g of *p*-TsOH. The mixture was refluxed in a Dean-Stark apparatus for 10 hr. The solvent was removed under reduced pressure and the residue was extracted with Et_2O. The Et_2O layer was washed with $NaHCO_3$ and H_2O and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The oily residue was recrystallized from petroleum ether; the yield of 14 was 0.7 g, mp 109–110°. *Anal.* ($C_{23}H_{21}NOS$) C, H.

β-Isobutoxy-α-cyano-4-(*p*-chlorophenylthio)styrene (15) was prepared in a similar manner and recrystallized from petroleum ether, 99–100°. *Anal.* ($C_{19}H_{18}ClNOS$) C, H.

β-Isobutoxy-β-ethyl-α-cyano-4-(*p*-chlorophenylthio)styrene could not be prepared using the above conditions; however, refluxing the appropriate ketone in xylene for 48 hr produced about a 30% conversion to the enol ether as assessed by nmr. The crude mixture of enol ether gave the expected pyrimidine on treatment with guanidine (see below).

2,4-Diamino-5-[4-(2-naphthylthio)phenyl]pyrimidine (6). The isobutoxy ether 14 (4 g, 0.011 mol) was mixed with a suspension of 2 g (0.02 mol) of guanidine hydrochloride in a NaOEt solution prepared from 1 g (0.04 mol) of Na and 100 ml of EtOH. The mixture was refluxed for 2 hr and cooled, and the solid was filtered, washed with Et_2O, and crystallized from EtOH: yield, 2.0 g; mp 194–195°. The hydrochloride salt 7 was prepared by dissolving the base in Et_2O and adding concentrated HCl. The resulting solid was filtered and recrystallized from H_2O: mp 325–326°.

2,4-Diamino-5-[4-(*p*-chlorophenylthio)phenyl]-6-ethylpyrimidine (12). A solution of **5** (4.5 g, 0.014 mol) was allowed to react with CH_2N_2 in Et_2O, prepared from 8 g of *N*-nitrosomethylurea,[15] at 0° and allowed to warm to room temperature, with stirring, over a 5-hr period. The excess CH_2N_2 was decomposed with HOAc, the Et_2O was washed with H_2O, $NaHCO_3$, and again with H_2O, and dried ($CaSO_4$). The solvent was evaporated under reduced pressure and a liquid was obtained which failed to crystallize. The nmr of the oil was in accord with that expected of the *O*-methyl ether and the material was used directly. The *O*-methyl ether (3 g, 0.009 mol) was added to a solution of NaOEt (0.078 mol), prepared from 1.8 g of Na in 75 ml of EtOH, containing 4 g (0.04 mol) of guanidine hydrochloride and the mixture was refluxed for 2 hr. The EtOH was removed under reduced pressure and the residue was treated with H_2O and extracted with Et_2O. A white solid appeared at the interface and was removed by filtration and washed with H_2O and Et_2O. The solid was recrystallized from C_6H_6–EtOH, mp 215–216°.

2,4-Diamino-5-(2-naphthylsulfonyl)pyrimidine (8). H_2O_2 Method. The corresponding sulfide **6** (1 g, 0.003 mol) was dissolved in 20 ml of acetic acid and mixed with 10 ml of 30% H_2O_2, and the mixture was stirred 18 hr at room temperature. The mixture was poured into water, filtered, washed (H_2O), and crystallized from ethanol, mp 274–275°.

MCPA Method. The corresponding sulfide **6** (1.1 g, 0.0032 mol) was dissolved in 150 ml of CH_2Cl_2, 1.35 g (0.066 mol) of 85% MCPA was added, and the mixture was stirred at room temperature for 1 hr and at reflux for 15 min. The reaction mixture was treated with a dilute $NaHCO_3$ solution and a solid appeared at the interface which was separated by filtration. The solid was washed with H_2O, Et_2O, and finally with EtOH: yield, 0.25 g; mp 274–275°. A mixture melting point with a sample prepared by the above method showed no depression.

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Quinazolines and 1,4-Benzodiazepines. 64. Comparison of the Stereochemistry of Diazepam with That of Close Analogs with Marginal Biological Activity

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Numerous attempts have been made in recent years to correlate the biological activity of various anticonvulsants with their stereochemistry.[1] However, despite the pub-