removed after proper washing and drying and the crude ester (9.2 g, 71%) was collected, mp 135–136° (from EtOH). *Anal.* ($C_{17}H_{17}NO_3$) C, H.

Similar procedures carried out with the appropriate phenols gave the esters listed in Table III.

4-Phenoxyquinaldic Acid Hydrazide.—Crude 4-phenoxyquinaldate (7.5 g) in 50 ml of EtOH was refluxed with 4 ml of $H_2NNH_2 \cdot H_2O$ for 4 hr. After cooling, H_2O was added to complete the precipitation of the hydrazide (6.5 g, 91%), mp 182–184° (from EtOH). *Anal.* ($C_{16}H_{13}N_3O_2$) N.

Similar procedures were used to prepare the hydrazides listed in Table III.

2-Carbethoxyamido-4-phenoxyquinoline.—Crude 4-phenoxyquinaldic acid hydrazide (6.0 g) was dissolved in 50 ml of 1.5 *M* HCl. Insoluble gummy material was removed and the solution cooled to 10°. At approximately this temperature $NaNO_2$ (1.4 g) in a small amount of H_2O was added dropwise and with stirring. The solid which formed was collected (5.2 g), washed with H_2O, air-dried, and suspended in absolute EtOH. The mixture was refluxed for 3 hr until the evolution of N_2 ceased. On cooling 2.8 g was collected. An additional 1 g was obtained by concentrating the mother liquor. The analytical sample melted at 138–139° (from EtOH). *Anal.* ($C_{18}H_{16}N_2O_3$) N.

The carbamates listed in Table III were prepared essentially according to this method.

2-Amino-4-phenoxyquinoline.—A solution of 2.9 g of crude 2-carbethoxyamido-4-phenoxyquinoline and 2.0 g of KOH in 40 ml of EtOH was refluxed for 4 hr. Most of the solvent was removed and the residue diluted with H_2O and acidified with concentrated HCl. The mixture was boiled briefly, then cooled, and the crystalline material collected and dissolved in 100 ml of hot H_2O. The hot solution was filtered and made alkaline with 2.5 *M* NaOH. The precipitate was collected and recrystallized from C_6H_6–petroleum ether (bp 60–70°) (1.0 g, 45%), mp 135–136°. *Anal.* ($C_{15}H_{12}N_2O$) C, H, N.

Similar procedures were used to prepare the amines listed in Table III.

Acknowledgment.—The authors wish to thank Miss Jane A. Beach of Wells College for her valuable contributions to the synthetic work.

Antimalarials. 4,4′-Diaminodiphenyl Sulfone-Type Compounds

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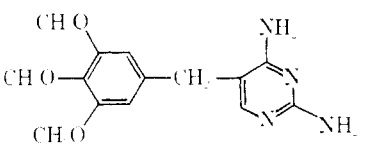
We have already reported[1,2] several derivatives of 4,4′-diaminodiphenyl sulfone (DDS) and their antimalarial activity. In view of the activity[3] of trimethoprim (I) against the resistant strains of malaria, greater interest was focussed on the structural features



I

of this drug. Compounds **3**, **8**, and **13** were prepared which incorporate the 3,4,5-trimethoxyphenyl group of trimethoprim on one side and the 4-aminophenyl group of DDS on the other. We had hoped to uncover a relationship of structure in folic acid inhibition to antimalarial activity.

Compounds **1**, **2**, **5**–**7**, and **9**–**12** were intermediates en route to the syntheses of **3**, **8**, and **13**. **4** was made as a derivative and **14** appeared as a by-product in the preparation of **1** and **5** through air oxidation of 3,4,5-trimethoxybenzenethiol.

Whereas it was easy to oxidize **1** with H_2O_2, the similar oxidation of **5** failed to give the sulfone. Some low melting substances were produced by fragmentation of the starting material, but further work was not pursued to characterize these materials. This difficulty was overcome by reducing **5** to **6** first, acetylating **6**, and then oxidizing with H_2O_2–AcOH.

The structure assigned to the triacetate **7** was rationalized on the consideration of steric hindrance prevailing at the 2 position which would therefore give only monoacetylation.

Biological Tests.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice by Dr. L. Rane according to the procedure already published.[4] None of them were found to be active.

Experimental Section[5]

4-Nitro-3′,4′,5′-trimethoxydiphenyl Sulfide (1).—A solution of 3,4,5-trimethoxyaniline (9.16 g, 0.05 mol) in 120 ml of H_2O and 20 ml of concentrated HCl was cooled to −5° and diazotized with 3.8 g of $NaNO_2$ in 20 ml of H_2O. Excess HCl was neutralized with 2.5 g of NaOAc maintaining the temperature at −5 to 0°. This solution was added, dropwise with vigorous stirring, to a hot (75–80°) solution of 16.0 g of ethyl potassium xanthate in 35 ml of H_2O. The mixture was then refluxed for 1 hr. After cooling to room temperature, it was extracted (Et_2O) and the extract dried (Na_2SO_4), filtered, and evaporated to leave a dark residue. This was mixed with 90% EtOH, 6.0 g of KOH, and 5 g of glucose and refluxed for 2 hr under N_2. Some solid separated at this stage which, on investigation, proved to be the disulfide **14**. This was removed by filtration and the filtrate evaporated to leave a dark brown residue which was mixed with some Zn dust and acidified, by cooling, with cold dilute H_2SO_4. The dark oil was extracted (Et_2O), dried (K_2CO_3), filtered, and concentrated to give 11.0 g of crude 3,4,5-trimethoxybenzenethiol. This was immediately mixed, under N_2, with 80 ml of MeOH, 20 ml of H_2O, 7.5 g of K_2CO_3, and *p*-fluoronitrobenzene (7.1 g, 0.05 mol), and the whole mixture refluxed for 2 hr. Solvent was removed under reduced pressure, the residue treated with H_2O, the solid removed by filtration and washed several times with cold MeOH.

4-Nitro-3′,4′,5′-trimethoxydiphenyl Sulfone (2).—A solution of **1** (9.64 g, 0.03 mol) in 140 ml of glacial AcOH and 60 ml of H_2O_2 was kept at 65° for 1.5 hr. On cooling to room temperature overnight 9.5 g of the product crystallized.

4-Amino-3′,4′,5′-trimethoxydiphenyl sulfone (3) was prepared by the reduction of **2** in 90% AcOH over Pt at room temperature and atmospheric pressure.

4-Diacetylamino-3′,4′,5′-trimethoxydiphenyl sulfone (4) was prepared by acetylating **3** in boiling Ac_2O.

2,4-Dinitro-3′,4′,5′-trimethoxydiphenyl sulfide (5) was prepared in the same way as **1**.

2,4-Diamino-3,4,5-trimethoxydiphenyl sulfide (6).—A mixture of **5** (18.32 g, 0.05 mol), $ZnCl_2 \cdot 2H_2O$ (78.75 g, 0.35 mol), 250 ml of concentrated HCl, and 1500 ml of EtOH was warmed on a steam bath to 80° till a clear solution was formed. EtOH was removed under reduced pressure and the residue was strongly basified with cold concentrated NaOH with cooling. The solid product was removed by filtration and washed free of alkali.

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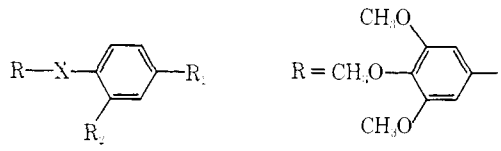
(5) See Table I for experimental data.

TABLE I



No.	X	R_1	R_2	Yield, %	Crystn solvent	Mp, °C,[a] or bp, °C (mm)	Formula[b]
1	S	NO_2	H	28.0	MeOH	123–124	$C_{15}H_{15}NO_4S$
2	SO_2	NO_2	H	90.0	AcOH–H_2O (80:20)	183–185	$C_{15}H_{15}NO_6S$
3	SO_2	NH_2	H	68.4	MeOH	218–220	$C_{15}H_{17}NO_5S$
4	SO_2	$N(COCH_3)_2$	H		MeOH	170–172	$C_{19}H_{21}NO_7S$
5	S	NO_2	NO_2	41.0	AcOH	203–205	$C_{15}H_{14}N_2O_7S$
6	S	NH_2	NH_2	91.4	MeOH	123–124.5	$C_{15}H_{18}N_2O_3S$
7	SO_2	$NH(COCH_3)$	$N(COCH_3)_2$		EtOH	243–245	$C_{21}H_{24}N_2O_8S$
8	SO_2	NH_2	NH_2	23.6	EtOH	191–192	$C_{15}H_{16}N_2O_5S$
9	C=NH	F	H·HCl	32.0	*i*-PrOH	197.5–199	$C_{16}H_{16}FNO_3$·HCl
10	CO	F	H	81.0	Cyclohexane	87–89	$C_{16}H_{15}FO_4$
11	CO	N_3	H	44.8	Cyclohexane	89–90	$C_{16}H_{15}N_3O_4$
12	CO	NH_2	H	81.0	C_6H_6	155–156	$C_{16}H_{17}NO_4$
13	CH_2	NH_2	H	40.0		155–160 (0.3)	$C_{16}H_{19}NO_3$
14	R———S———S———R				EtOH	141–143	$C_{18}H_{22}O_6S_2$

[a] All melting points are uncorrected. [b] Compounds **1–7**, **9**, **11–13** were analyzed for C, H, N; **8** was analyzed for N; and **10** and **13** were analyzed for C, H. All analyses were within ±0.4% of calculated values except **4**, C: calcd, 56.01; found, 56.43; and **11**, N: calcd, 13.41; found, 12.44; 12.48.

2-Acetylamino-4-diacetylamino-3′,4′,5′-trimethoxydiphenyl sulfone (**7**) was prepared by acetylating **6** in refluxing Ac_2O, removing Ac_2O under reduced pressure, and oxidizing the residue with H_2O_2 according to the procedure given for **2** except that the reaction mixture was evaporated to dryness under reduced pressure (bath temperature *ca.* 60°), the residue treated with H_2O, and the product removed by filtration and purified by crystallization.

2,4-Diamino-3′,4′,5′-trimethoxydiphenyl sulfone (**8**) was prepared by the hydrolysis of **7** with 6 *N* HCl.

4-Fluoro-3′,4′,5′-trimethoxybenzophenone Ketimine Hydrochloride (**9**).—The Grignard reagent of *p*-fluorobromobenzene (73.5 g, 0.42 mol) with 9.2 g (0.4 g-atom) of Mg was prepared in 300 ml of Et_2O. A solution of 3,4,5-trimethoxybenzonitrile (50.0 g, 0.26 mol) in 150 ml of dry THF was added to it slowly. The mixture was then brought to reflux and the solvent was replaced by an equivalent amount of PhMe and refluxed for 16 hr. It was cooled, gassed with NH_3 for 1 hr, and filtered hot, the filtrate concentrated to an oil, and the oil dissolved in Et_2O and converted into the HCl salt.

4-Fluoro-3′,4′,5′-trimethoxybenzophenone (**10**).—A mixture of **9** (40.0 g, 0.132 mol) and 350 ml of 6 *N* HCl was heated on a steam bath for 4 hr. The mixture was cooled and extracted with Et_2O to obtain the oily product which solidified on standing.

4-Azido-3′,4′,5′-trimethoxybenzophenone (**11**).—A mixture of **10** (5.8 g, 0.02 mol), NaN_3 (3.3 g, 0.05 mol), 60 ml of DMSO, and 15 ml of H_2O was heated with stirring at 100–110° for 16 hr. The mixture was cooled and diluted with H_2O, the product extracted with Et_2O, and the Et_2O extracts were worked up as usual.

4-Amino-3′,4′,5′-trimethoxybenzophenone (**12**).—A mixture of **11** (3.13 g, 0.01 mol), 0.4 g of 5% Pd–C, and 75 ml of Me_2CO was hydrogenated at room temperature and atmospheric pressure. After 3 hr the mixture was filtered and concentrated to give a solid product.

4-Amino-3′,4′,5′-trimethoxydiphenylmethane (**13**).—A mixture of **12**·HCl (5.0 g, 0.0155 mol), 0.4 g of 5% Pd–C, 100 ml of MeOH, and 10 ml of AcOH was hydrogenated at 5 kg/cm² for 5 hr at room temperature. The mixture was filtered and the filtrate was concentrated to a solid, treated with NaOH solution, and extracted with CH_2Cl_2. The CH_2Cl_2 extract, on the usual work-up, gave a syrup which was purified by distillation.

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Synthetic Trypanocides. I. Substituted 1,2,3,4-Tetrahydrocarbazoles[1]

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The high incidence of the Chagas–Mazza disease (South American trypanosomiasis) among blood donors in some places makes it difficult to reject infected blood.[2] Therefore it is necessary to add to the blood a trypanocidal substance that must be water soluble, compatible with the anticoagulant solution, and resistent to sterilization, and which prevents infection of the patient by the blood. So far only colorants[3] have been used for this purpose, but these have many disadvantages.[4]

Since some substituted 1,2,3,4-tetrahydrocarbazoles are active against *Trypanosoma cruzi*,[5] a series of related new compounds fulfilling the above requirements were prepared in order to test their trypanocidal activity (Table I).

Chemistry.—The 1,2,3,4-tetrahydrocarbazole (THC) and the 6-substituted THC (I) were prepared by the Fisher indole synthesis[6] with the modification described in the Experimental Section for 6-iodo-THC.

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