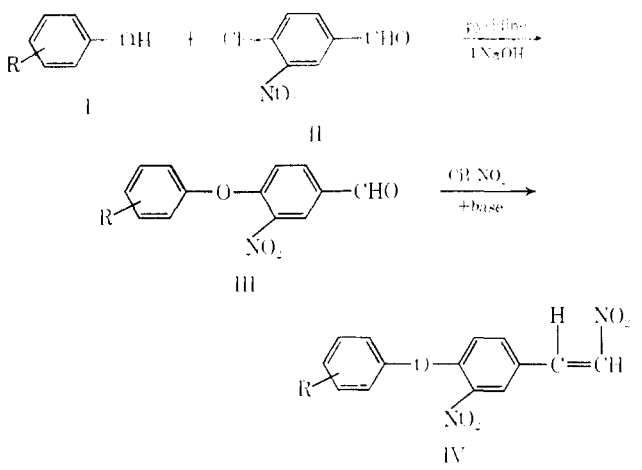
SCHEME I



hyde dissolved in 10 ml of CH_3NO_2 and 10 ml of EtOH was added 1.5 g of NH_4OAc and 2 ml of glacial HOAc. The mixture was heated with stirring for 45 min. Cooling gave a precipitate, which was recrystallized twice (Me_2CO–H_2O) to yield 0.1 g (10%) of the desired product, mp 196–198°. *Anal.* ($C_{14}H_5Br_5N_2O_5$) C, N.

Acknowledgment.—We wish to extend our sincere appreciation to Mrs. Carolyn A. Rogers, of the Northeastern Water Hygiene Laboratory, for her work in the testing program.

Antimalarials. 3,3′-Dinitro(or amino)-4,4′-di(substituted amino)diphenyl Sulfones

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Making use of the activated fluorine atoms in 4,4′-difluorodiphenyl sulfone, we have already[1] prepared a number of substituted aminodiphenyl sulfones. Some of these compounds showed promising antimalarial activity.

The reactions of 4,4′-difluorodiphenyl sulfone with various amines showed a broad pattern of reactivity in the replacement of the F atoms. Weak amines, such as aniline, did not react while others like piperidine, morpholine, and hydrazine reacted easily to replace both F atoms. NH_3 replaced only one F atom, even at 140°.

With a view to enhance the activity of the F atoms, it was considered logical to introduce another electron-withdrawing group at 3,3′ positions. Thus 4,4′-difluoro-3,3′-dinitrodiphenyl sulfone was selected as starting material for the preparation of many compounds. It was found to be much more reactive than 4,4′-difluorodiphenyl sulfone and presented no problem in reacting with aniline and other weak amines. The compounds and their constants are detailed in Table I on the following page.

Pharmacology.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice by Dr. L. Rane, University of Miami, Miami, Fla., according to the screening procedure previously described.[2] None of the compounds were found to be significantly active. The maximum increase in mean survival time of the treated mice was 1.6 days for **1**, 1.4 days for **3**, 1.0 day for **20**, and 0.8 day for **13**. The last one showed two toxic deaths. All others were nontoxic.

Experimental Section

4,4′-Di(substituted amino)-3,3′-dinitrodiphenyl Sulfones (16, 18, 19).—The starting material for these compounds was 4,4′-difluoro-3,3′-dinitrodiphenyl sulfone and the desired amines. DMSO was used as a solvent and the mixture was heated at various temperatures and for various periods of time as shown in the table. Two variations of the general procedure were employed. In one, the reacting amine was used in 3–5 *M* excess and this excess took care of the liberated HF. Where only molar proportions of the reacting amines were available, Et_3N was added as an acid acceptor. Two typical procedures are given below.

4,4′-Dibenzylamino-3,3′-dinitrodiphenyl Sulfone (4).—A mixture of 4,4′-difluoro-3,3′-dinitrodiphenyl sulfone (25.0 g, 0.073 mol), benzylamine (32.0 g, 0.30 mol), and 100 ml of DMSO was heated at 95° for 2 hr. The mixture was cooled to room temperature and diluted with 1500 ml of H_2O. The precipitated solid was removed by filtration and crystallized from CH_2Cl_2 to give 34.3 g (90.0%) of the product, mp 233–234°.

4,4′-Diadamantylamino-3,3′-dinitrodiphenyl Sulfone (9).—A mixture of 4,4′-difluoro-3,3′-dinitrodiphenyl sulfone (15.3 g, 0.026 mol), adamantylamine hydrochloride (10.0 g, 0.0532 mol), Et_3N (20.2 g, 0.2 mol), and 50 ml of DMSO was refluxed for 3 hr. The reaction mixture was cooled to room temperature, diluted with about 1 l. of H_2O and the precipitated solid was removed by filtration. It was crystallized from toluene to give 12.6 g (88.0%) of the product, mp 298–301°.

4,4′-Di(substituted amino)-3,3′-diaminodiphenyl Sulfones (20, 22–25).—The reduction of the corresponding 3,3′-dinitro derivatives was carried out with Fe and HCl in EtOH. Compounds **20**, **23–25** were isolated as free bases while **22** was characterized as an HCl. The general procedure is exemplified by the following reduction experiment.

A mixture of 4,4′-dipiperidino-3,3′-dinitrodiphenyl sulfone (10.0 g, 0.021 mol), Fe powder (39.0 g, 0.7 g-atom), and 2 l. of EtOH was heated on the steam bath and concentrated HCl (80 ml) was added to it in small portions over a period of about 0.25 hr. Heating was continued for another 2 hr. The hot mixture was filtered to remove excess Fe, made basic with 50% NaOH, and filtered and the filtrate was evaporated to dryness. The residue was crystallized from MeOH to give 7.0 g (80.0%) of the product, mp 196–198°.

4,4′-Di(N-isopropylidenehydrazino)-3,3′-dinitrodiphenyl Sulfone (17).—To a refluxing solution of 4,4′-dihydrazino-3,3′-dinitrodiphenyl sulfone (3.5 g, 0.0095 mol) in 25 ml of 2 *N* HCl and 300 ml of MeOH was added 100 ml of Me_2CO. A yellow precipitate was immediately formed, which was removed by filtration and twice crystallized from Me_2CO to give 3.0 g (70.5%) of the product as yellow-orange needles, mp 250–252°.

4,4′-Di(4-methylpiperazino)-3,3′-diacetamidodiphenyl Sulfone (21).—A solution of 4,4′-di(4-methylpiperazino)-3,3′-diaminodiphenyl sulfone (3.5 g) in 50 ml of Ac_2O was refluxed for 1 hr. Excess Ac_2O was removed under vacuum, the residue was taken up in Me_2CO and made basic with a saturated solution of $NaHCO_3$, and the precipitate was filtered. It was crystallized from a C_6H_6–xylene mixture to give 1.3 g (31.6%) of the product, mp 228–231°.

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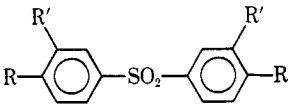
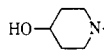
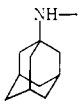
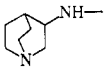
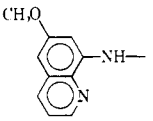
(1) H. Bader, J. F. Hoops, J. H. Biel, H. H. Koelling, R. G. Stein, and T. Singh, *J. Med. Chem.*, **12**, 709 (1969).

(2) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, **10**, 431 (1967).

TABLE I



No.	R	R'	Reaction Time, hr	Reaction Temp, °C	Yield, %	Crystn solvent	Mp, °C[a]	Formula[b]
1		NO_2	2	95	81.0	*i*-PrOH	201–203	$C_{22}H_{28}N_6O_6S$
2	*m*-OHC_6H_4NH	NO_2	3	130	28.0	EtOAc–toluene	220–222	$C_{24}H_{18}N_4O_8S$
3	*n*-$C_5H_{11}NH$	NO_2	2	95	95.0	CH_2Cl_2–heptane	141–142	$C_{22}H_{30}N_4O_6S$
4	$C_6H_5CH_2NH$	NO_2	2	95	90.0	CH_2Cl_2	233–234	$C_{26}H_{22}N_4O_6S$
5	$HOCH_2CH_2NH$	NO_2	2	95	80.0	EtOAc	211–213	$C_{16}H_{18}N_4O_8S$
6	$CH_3OOCC_2H_4NH$	NO_2			91.0	EtOAc–Me_2CO	170.5–172.5	$C_{20}H_{22}N_4O_{10}S$
7		NO_2	2	95	86.0	MeOH	154–156	$C_{22}H_{26}N_4O_8S$
8	CH_3OOCCH_2NH	NO_2	3	130	25.0	Me_2CO–heptane	204–208	$C_{18}H_{18}N_4O_{10}S$
9		NO_2	3	130	88.0	Toluene	298–301	$C_{32}H_{38}N_4O_6S$
10	Et_2N	NO_2	2	Reflux	92.0	C_6H_6–heptane	127–130	$C_{20}H_{26}N_4O_6S$
11		NO_2	2	95	99.8	CH_2Cl_2–MeOH	187–188	$C_{22}H_{26}N_4O_6S$
12		NO_2	2	95	99.0	CH_2Cl_2–EtOH	203–204	$C_{20}H_{22}N_4O_8S$
13		NO_2	3	130	76.6	EtOH	249–251	$C_{26}H_{32}N_4O_6S$
14		NO_2	3.5	125	93.0	CH_2Cl_2–MeOH	257	$C_{32}H_{24}N_6O_8S$
15	NH_2	NO_2	1.5[c]	140	83.6	Me_2CO–EtOH	287 dec	$C_{12}H_{10}N_4O_6S$
16	NH_2NH	NO_2	5 min	0	81.3	DMAC	284 (explodes)	$C_{12}H_{12}N_6O_6S$
17	$(CH_3)_2C{=}NNH$	NO_2			70.5	Me_2CO	250–252	$C_{18}H_{20}N_6O_6S$
18	$(HOCH_2CH_2)_2N \cdot 2HCl$	NO_2	3	130	24.4	MeOH–EtOAc	152–165	$C_{20}H_{28}Cl_2N_4O_{10}S$
19		NO_2	3	130	97.3	Xylene	254–256	$C_{24}H_{18}N_4O_6S$
20		NH_2			43.6	EtOH	232–235	$C_{22}H_{32}N_6O_2S$
21		$NHCOCH_3$			31.6	C_6H_6–xylene	228–231	$C_{26}H_{36}N_6O_4S$
22	*n*-$C_5H_{11}NH \cdot HCl$	$NH_2 \cdot HCl$			75.0		182–186	$C_{22}H_{38}Cl_4N_4O_2S$
23		NH_2			20.0	MeOH	121–125	$C_{22}H_{30}N_4O_4S$
24		NH_2			80.0	MeOH	196–198	$C_{22}H_{30}N_4O_2S$
25		NH_2			20.4	CH_2Cl_2–MeOH	248–250.5	$C_{20}H_{26}N_4O_4S$

[a] All melting points are uncorrected. [b] Compounds **1**, **2**, and **20** were analyzed for C, H, N; **3**–**19**, 21, **23**–**25** for C, H, N, S; **22** for C, H, N, Cl. All analyses were within ±0.4% except for **16** where N: calcd, 22.82; found, 22.30. [c] NH_3 gas was bubbled through the reaction mixture at 140° for 1.5 hr.