TABLE I

No.	Mp, C	Min inhib concn,[a] μg/ml S. a.[b]	S. s.	Ps. a.	P. v.	E. c.	C. a.	T. m.	F. b.	M. t.
IIIa	200–202	0.69	0.69	>50	18.7	4.2	>50	12.5		1.2
IIIb	232 dec	0.24	0.5	25.0	15.6	1.1	15.6	9.4	25.0	1.0
Va	231–233	9.4	0.12	37.5	>50	0.24	>50	>50	>50	2.3
Vb	290 dec	0.15	0.05	7.8	9.4	0.05	12.5	6.3	12.5	6.3

[a] The minimum inhibitory concentrations of each compound were determined by the twofold tube dilution assay using antibiotic assay broth (BBL). [b] S. a. = *Staphylococcus aureus*, S. s. = *Salmonella schottmuelleri*, Ps. a. = *Pseudomonas aeruginosa*, P. v. = *Proteus vulgaris*, E. c. = *Escherichia coli*, C. a. = *Candida albicans*, T. m. = *Trichophyton mentagrophytes*, F. b. = *Fusarium bulbigenum*, M. t. = *Mycobacterium tuberculosis*.

obtained by concentrating the filtrate. Crystallization from EtOH gave pure IIIa, mp 200–202°, in a yield of 7.2 g (88%). *Anal.* ($C_6H_4N_4O_4$) C, H, N.

5-Amino-3-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole (Vb).—A solution of 3.2 g of 3-[2-(5-nitro-2-furyl)vinyl]-5-trichloromethyl-1,2,4-oxadiazole in 35–40 ml of liquid NH_3 was prepared by adding small portions of the solid with continuous stirring. A dark solution and later a thick crystalline slurry resulted. The NH_3 was permitted to evaporate and the residue crystallized from dioxane; yield 2 g (90%), mp 290° dec. *Anal.* ($C_8H_6N_4O_4$) C, H, N.

3-(5-Nitro-2-furyl)-5-trichloromethyl-1,2,4-oxadiazole was prepared by treating 1 mole of 5-nitro-2-furanamidoxime[5] in dioxane with 2 moles of trichloroacetyl chloride in the presence of 2 moles of pyridine, evaporation of the solvent, treating the residue with H_2O, and filtering the crystals, yield 90%, mp 106–108° (*i*-PrOH). *Anal.* ($C_7H_2Cl_3N_3O_4$) C, H, N.

5-Amino-3-(5-nitro-2-furyl)-1,2,4-oxadiazole (Va).—3-(5-Nitro-2-furyl)-5-trichloromethyl-1,2,4-oxadiazole (10 g) was added portionwise with stirring to 100 ml of liquid NH_3. A dark solution was formed from which crystals separated. The NH_3 was allowed to evaporate, and the residue was treated with dilute HCl, yielding 6.3 g (95%) of product; recrystallization from Me_2CO provided pure material, mp 231–233°. *Anal.* ($C_6H_4N_4O_4$) C, H, N.

Acknowledgments.—The author is indebted to Dr. O. Wiedemann, Munich, Chairman of Chemische Fabrik von Heyden A.G., for his encouraging interest in this work, to Dr. R. Donovick and Dr. H. Gadebusch, The Squibb Institute for Medical Research, New Brunswick, New Jersey, for the microbiological testing data, and to E. Koller, Regensburg, for assistance in the preparation of these compounds.

(5) W. R. Sherman and A. Von Esch, *J. Med. Chem.*, **8**, 25 (1965).

Antimalarial Compounds Related to Diaminodiphenyl Sulfone

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The interest in preparing diaminodiphenyl sulfone derivatives was initiated in our laboratories from the work done on the nucleophilic displacement of activated fluorine in aromatic compounds.[1] The facile replacement of fluorine in 4,4′-difluorodiphenyl sulfone with one or two primary or secondary amines provided a versatile route for the preparation of many substituted derivatives which were not easily available by the methods previously used.[2–5]

Different amines showed different activity in replacing the fluorine atom. The replacement of the second fluorine atom was usually more difficult than the first. The dihydrazino derivative **6** served as a starting material for several compounds.

We had considerable difficulty in preparing 4-amino-4′-formamidodiphenyl sulfone. When prepared through the formylation of 4-amino-4′-nitrodiphenyl sulfone followed by catalytic reduction of the nitro to the amino group, the formyl group proved to be so labile that it was removed under the usual experimental conditions of purification. The same difficulty has been experienced by Heymann and Heidelberger.[4] An alternative route was tried to formylate diaminodiphenyl sulfone monohydrochloride in formic acid, because a monoprotonated diaminodiphenyl sulfone molecule left only one nucleophilic amino group to be formylated. In this way a product was obtained which was found to be 98% pure 4-amino-4′-formamidodiphenyl sulfone monohydrochloride as shown by its elemental analysis and acid–base titration. Its purity could not be enhanced by crystallization for fear of deformylation.

Compound **9** was prepared by refluxing 4,4′-dihydrazinodiphenyl sulfone with formic acid while **22** was the acetylation product of **15**.

Experimental Section

Symmetrically Substituted Diaminodiphenyl Sulfones from 4,4′-Difluorodiphenyl Sulfone (1–8).—In general 4,4′-difluorodiphenyl sulfone was heated with an excess (3 *M* or more) of the amine in DMSO at a temperature varying from 100 to 140° for a period of 3–10 hr. In some cases (**1–3, 5, 9**) a 2–3 *M* proportion of Et_3N was used as an acceptor for the liberated HF. After the heating period, the mixture was cooled to room temperature and diluted with H_2O whereby the product generally separated as a precipitate which could be removed by filtration or extracted with a solvent when it happened to be gummy, such as in **7**.

4,4′-Di(1,2-dihydro-1-keto-2-phthalazinyl)diphenyl Sulfone (10).—A mixture of 2-carboxybenzaldehyde (1.8 g, 0.012 mol), 4,4′-dihydrazinodiphenyl sulfone dihydrochloride (2.1 g, 0.006 mol), 250 ml of EtOH, and 150 ml of H_2O was refluxed for 15 min when a precipitate was formed. EtOH was allowed to boil off and the mixture was filtered to give 2.6 g of the product.

4-Fluoro-4′-substituted Aminodiphenyl Sulfones (11–14).—In preparing these compounds one molar proportion of 4,4′-difluorodiphenyl sulfone and the amine were heated together in DMSO in the presence of Et_3N. The reaction mixture was cooled to room temperature and diluted with H_2O whereby the product usually separated as a solid or as a gummy material, which was crystallized from an appropriate solvent. The hydrochlorides of

(1) H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **32**, 2319 (1966).

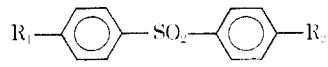
(2) E. Fromm and J. Whittmann, *Chem. Ber.*, **41**, 2269 (1908).

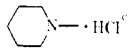
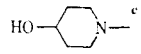
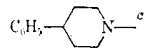
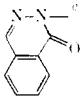
(3) H. Heymann and L. F. Fieser, *J. Amer. Chem. Soc.*, **67**, 1979 (1945).

(4) H. Heymann and C. Heidelberger, *ibid.*, **67**, 1986 (1945).

(5) W. H. Hartung, "Medicinal Chemistry," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1967, p 353.

TABLE I



Compd	R_1	R_2	Reaction Time, hr	Reaction Temp, °C	Yield, %	Crystn solvent	Mp,[a] °C	Formula[b]
1			6	100	92.0	*i*-PrOH–MeOH	222–224	$C_{22}H_{30}Cl_2N_2O_2S$
2			6	100	31.6	Me_2CO–EtOAc	217–221	$C_{22}H_{28}N_2O_4S$
3	$HOCH_2CH_2NH$[c]		10.5	95	91.9	CH_2Cl_2–MeOH	186–189	$C_{16}H_{20}N_2O_4S$
4			4.5	135	91.0	CH_2Cl_2–MeOH	289–293	$C_{20}H_{24}N_2O_4S$
5			5	125	61.6	Dichloroethane	297 dec	$C_{34}H_{32}N_2O_2S$
6	NH_2NH[c]		2.5	140	96.0	*d*	193–195	
7			4	140	11.8	EtOAc	131–134	$C_{36}H_{34}N_4O_4S$
8	$NH_2CH_2CH_2NH$[c]		6	Reflux	24.0	EtOH	163–164.5	$C_{16}H_{22}N_4O_2S$
9	$OCHNHNH$[c]		3.0	Reflux	34.0	MeOH	256–257	$C_{14}H_{14}N_4O_4S$
10			0.25	Reflux	85.6	CH_2Cl_2–EtOH	297–300	$C_{28}H_{18}N_4O_4S$
11	F		18	40	55.4	EtOH	165–168	$C_{16}H_{16}FNO_3S$
12	F	$N(CH_2CH_2OH)_2$	5	140	34.4	EtOAc	114–117	$C_{16}H_{18}FNO_4S$
13	F	$NHCH_2C{\equiv}CH$	6	Reflux	21.0	C_6H_6–petr ether	109.5–111.5	$C_{15}H_{12}FNO_2S$
14	F	$NHCH_2CONH_2$	6	Reflux	11.0	MeOH–CCl_4	210–212	$C_{14}H_{13}FN_2O_3S$
15	NH_2		4	135	88.6	EtOH	212–215	$C_{17}H_{21}N_3O_2S$
16	NH_2	$NHCH_2CH_2OH$	6	135	9.6	MeOH–H_2O	143–145[e]	
17	NH_2	$NHNH_2$	3	140	70.0	*i*-PrOH	159–161	$C_{12}H_{13}N_3O_2S$
18	CH_3NH		8	82	80.5	MeOH	134–140	$C_{18}H_{22}N_2O_2S$
19	$HOCH_2CH_2NH$		4	95	75.0	C_6H_6–heptane	147–148	$C_{19}H_{24}N_2O_3S$
20			5	130	98.4	*i*-PrOH	219–222	$C_{21}H_{26}N_2O_3S$
21	$C_5H_{11}NH$		4	130	51.0	Ether–CH_2Cl_2	102–104	$C_{21}H_{28}N_2O_3S$
22	CH_3CONH				26.8	MeOH	178–180	$C_{19}H_{23}N_3O_3S$
23	$C_6H_5CH_2NH$		5	100	72.0	Me_2CO	202–206	$C_{23}H_{24}N_2O_3S$
24	$HOCH_2CH_2NH$		5	100	44.0	Toluene	103–106	$C_{18}H_{22}N_2O_4S$

[a] All melting points are uncorrected. [b] Compounds **6** and **16** are reported in the literature and therefore were not analyzed. Compounds **5**, **7**, and 11 were analyzed for C, H, N. All others were analyzed for C, H, N, S. All analytical results were within ±0.4%. [c] $R_1 = R_2$. [d] The product separated from the reaction mixture by dilution was pure enough to correspond to that described by P. P. T. Sah, *Rec. Trav. Chim.*, **69**, 1025 (1950); *Chem. Abstr.*, **45**, 1532*g* (1951). [e] E. L. Jackson [*J. Amer. Chem. Soc.*, **70**, 680 (1948)] reported mp 143.5–144.5°.

11 and **12** were made but when crystallized from EtOH and EtOAc, respectively, the HCl was lost and free bases were obtained as the crystallized products. 4-Fluoro-4′-aminodiphenyl sulfone was prepared by a slightly modified method inasmuch as a current of NH_3 was passed through the solution of 4,4′-difluorodiphenyl sulfone in DMSO at 135°.

Unsymmetrically substituted diaminodiphenyl sulfones (15–21, 23, 24) were prepared from 4-fluoro-4-substituted amino- (or 4-amino-) diphenyl sulfones by treating them with the appropriate amine in excess of 1 *M* proportion in DMSO. The reaction time and temperatures are shown in Table I. NH_3 and $MeNH_2$ were bubbled through the reaction mixture. At the end the reaction mixture was cooled to room temperature and diluted (H_2O), and the product was worked up as usual.

Pharmacology.—The compounds were screened against *Plasmodium berghei* in mice by Dr. L. Rane of the University of Miami, Miami, Fla. The screening procedure has been described by T. S. Osdene, *et al.*[6] Results on the active compounds are given in Table II.

(6) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

TABLE II

Compd no.[a]	Activity[b] D	C	TD	MST	Remarks
3	40	0	0	7.4	
	160	0	0	9.2	
	640	0	0	12.6	Active
7	40	0	0	6.2	
	160	0	0	6.4	
	640	3	0	...	Curative
19	40	0	0	6.2	
	160	0	0	11.2	
	320	0	0	15.4	Active
	640	0	0	17.0	
21	40	0	0	8.8	
	160	1	0	...	Curative
	640	2	0	...	
24	40	0	0	6.8	
	160	0	0	7.2	
	320	0	0	12.4	
	640	2	0	...	Curative

[a] Numbers refer to the serial numbers in Table I. [b] D, dose in milligrams per kilogram; C, cures; TD, toxic deaths when the mice die within 5 days postinfection which is attributed to the drug toxicity; MST, mean survival time of the treated mice; mean survival time of the control mice varies from 6.0–6.3 days. A compound is active if the mean survival time of the treated mice exceeds two times the mean survival time of the control mice (*i.e.*, 6.3 days). A compound is curative if one or more of the animals live for 60 or more days postinfection.

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2-(ω-Aminoalkyl)-4-*t*-butyl-6-phenylphenols as Antimalarial Agents[1]

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The phenolic Mannich bases (*e.g.*, **1**) were one of the most intensively studied groups of antimalarial compounds during the World War II program. Burckhalter, *et al.*,[2,3] Coatney, *et al.*,[4] and Wiselogle[5] reported extensive animal testing data for compounds of this class, and several were evaluated in preliminary clinical studies.[6] Compound **1**, for example, showed a low order of therapeutic activity in man (*ca.* one-fifth the potency of quinine) but also elicited several undesirable side effects.[6]

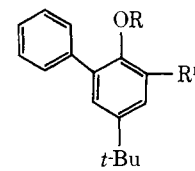
Because of the structural novelty of this class of compounds, we are reexamining it with regard to parameters not previously investigated. Thus, this paper reports the synthesis and biological evaluation of analogs of **1** and **2** having basic side chains longer than one carbon atom (*i.e.*, **3**–**5**). These compounds are no longer Mannich bases, of course, and more circuitous synthetic routes than the Mannich reaction had to be devised. The Experimental Section provides preparative details, and only a few salient features of the syntheses need be mentioned.

A Claisen rearrangement was the key step, and *o*-allylphenol derivative **7** was ultimately converted to all of the final products. The phenolic OH was protected by a benzyl group during most of the side-chain manipulations. Thus hydroboration followed by oxidation gave alcohol **8**, which provided **4** in several additional routine steps. Alcohol **8** similarly gave **5** through application of a standard cyanide chain-extension sequence. Isomerization of **7** in the presence of NaH gave the propenyl isomer (**9**), which was ozonized to aldehyde **10**. Reaction of **10** with nitromethane provided a suitably functionalized intermediate (**11**) for conversion to the Mannich base analog bearing the two-carbon side chain (**3**).

As can be seen in Table I, only the analog with the two-carbon side chain (**3**) possessed significant antimalarial activity,[7] and it was less potent and more toxic than the corresponding one-carbon Mannich base (**2**). Compound **6**, a demethyl precursor to **3**, was completely inactive, as were the three- and four-carbon side-chain members of the series (**4** and **5**). The one-carbon basic side chain is clearly preferred in this class of antimalarial agents. For comparison

TABLE I

2-PHENYL-4-*t*-BUTYLPHENOL DERIVATIVES



No.	R	R¹	Antimalarial act.[a] (toxicity deaths)
1	H	CH_2NEt_2[b]	7.5 (1/5)[c]
2	H	CH_2NMe_2[b]	9.4 (1/5)
3	H	$(CH_2)_2NMe_2$	5.9 (3/5)
4	H	$(CH_2)_3NEt_2$	1.6
5	H	$(CH_2)_4NEt_2$	1.6
6	H	$CH_2CH_2NH_2$	0.3
7	CH_2Ph	$CH_2CH{=}CH_2$	1.3[c]
8	CH_2Ph	$CH_2CH_2CH_2OH$	
9	CH_2Ph	$CH{=}CHCH_3$	
10	CH_2Ph	CHO	0.5
11	CH_2Ph	$CH{=}CHNO_2$	0.7
Quinine			6.5

[a] Results are expressed as increase in survival time (days) of treated mice (single subcutaneous dosages of 640 or 320 mg/kg) beyond that of treated controls. See F. S. Osdene, P. B. Russell, and L. Rane [*J. Med. Chem.*, **10**, 431 (1967)] for a complete description of the test. [b] Reported in ref 2 as the HCl salt. All compounds in this study were assayed as free bases. [c] Dosages of 320 mg/kg.

(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This is Contribution No. 529 from the Army Research Program on Malaria.

(2) J. Burckhalter, F. Tendick, E. Jones, W. Holcomb, and A. Rawlins, *J. Am. Chem. Soc.*, **68**, 1894 (1946).

(3) J. Burckhalter, F. Tendick, E. Jones, P. Jones, W. Holcomb, and A. Rawlins, *ibid.*, **70**, 1363 (1948).

(4) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, Washington, D. C., 1953, p 129.

(5) F. Y. Wiselogle, Ed., "Survey of Antimalarial Drugs, 1941–1945," Vol. II, Edwards Bros., Ann Arbor, Mich., 1946, p 375 ff.

(6) Reference 5, Vol. I, p 300.

(7) Bioassays were performed by Dr. Leo Rane of the University of Miami and the testing data were provided by Dr. David P. Jacobus of the Walter Reed Army Institute of Research.