posited at once. The product was filtered, extracted with two 100-cc. portions of ethanol and the extracts were evaporated to dryness. The residue was extracted with 200 cc. of ether and the red solution was washed with alkali and an acidic solution of stannous chloride, hydrochloric acid and water. The product was regenerated from the light yellow solution after drying with sodium sulfate as a yellow solidifying oil, which was extracted with two 100-cc. portions of ligroin (b. p. 90–120°), decanting the extracts from an orange, insoluble oil. The extract deposited 3.25 g. (29.5%) of the dinitrile in the form of yellow blades, m. p. 134–137.5°. After sublimation *in vacuo* and two recrystallizations from ligroin (90–120°) an analytical sample was secured in the form of colorless needles, m. p. 136.4–137.3°.

Anal.[26] Calcd. for $C_{14}H_8N_2S$: C, 71.16; H, 3.41; N, 11.86. Found: C, 71.16; H, 3.41; N, 11.69.

***p,p'*-Dicyanodiphenyl Sulfoxide.**—A warm solution of 3 g. of dicyanodiphenyl sulfide in 25 cc. of glacial acetic acid, was cooled to room temperature, mixed with a solution of 1.27 g. of chromic anhydride in a little water and warmed on the steam-bath for fifteen minutes. The oxidation mixture was poured into 200 cc. of water from which 2.65 g. (83%) of crystalline, slightly yellow dicyanodiphenylsulfoxide was collected, m. p. 171–174°, when immersed at 166°, melted and resolidified. The product can be recrystallized from alcohol–water 2:1 or from much benzene. For analysis a sample was sublimed *in vacuo* and recrystallized three times from benzene; prisms melting at 177.6–179.3°.

When in an attempt to prepare the corresponding iminoether the dinitrile was treated with alcohol saturated with hydrogen chloride, ***p,p'*-dicarbethoxydiphenyl sulfoxide** resulted, which after purification from ligroin (b. p. 70–90°) formed colorless leaflets, m. p. 119.3–120.5°.

Anal.[26] Calcd. for $C_{14}H_8ON_2S$: C, 66.65; H, 3.19; N, 11.10. Found: C, 66.99; H, 2.95; N, 10.90. Calcd. for $C_{18}H_{18}O_5S$: C, 62.62; H, 5.23. Found: C, 62.41; H, 5.33.

Summary

A number of new derivatives of *p,p'*-diaminodiphenyl sulfone have been synthesized for trial as possible antimalarials. Their preparation and their properties are described.

p,p'-Bisformylaminodiphenyl sulfone and *p,p'*-bismethylaminodiphenyl sulfone showed promising activity, the N-alkyl derivative being less toxic than the formyl compound.

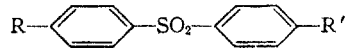
CAMBRIDGE, MASS. RECEIVED SEPTEMBER 1, 1945

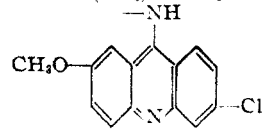
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Derivatives of *p,p'*-Diaminodiphenyl Sulfone. II[1]

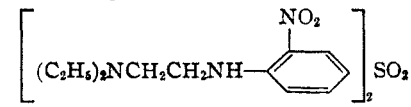
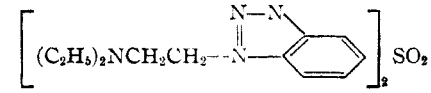
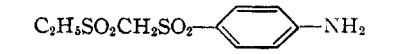
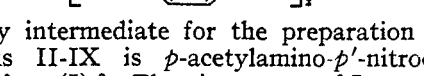
BY HANS HEYMANN AND CHARLES HEIDELBERGER

Since two derivatives of *p,p'*-diaminodiphenyl sulfone described in paper I[1] have shown some promise as possible antimalarials, further investigation of the series seemed desirable. These two compounds, the *p,p'*-bismethyl-[1] and the *p,p'*-bisformyl-amino[1] derivatives, are not very toxic and have considerable activity. Since the diacetyl derivative of the parent sulfone also showed encouraging antimalarial activity and low toxicity,[1a] we decided to prepare a number of derivatives with substitution in only one of the two amino groups or with different substituents in both of them. Coupling of the parent sulfone with the nucleus of atebrine also was investigated.



Compound number	R	R'
I	—NHCOCH$_3$	—NO$_2$
II	—NHCOCH$_3$	—NH$_2$
III	—NHCOCH$_3$	—NHCHO
IV	—NCHO	—NO$_2$
V	—NHCOCH$_3$	—NHSO$_2$C$_6$H$_5$
VI	—NHCOCH$_3$	—NHCH$_3$
VII	—NH$_2$	—NHCH$_3$
VIII	—NHCOCH$_3$	—N(CH$_3$)COCH$_3$
IX	—NHCOCH$_3$	

R = R'

X	—NHNH$_2$
XII	—CH$_2$NH$_2$.HCl
XIII	—NHCH$_2$CH$_2$OH
XIV	—NHC$_2$H$_5$
XV	
XVI	
XVII	
XVIII	

The key intermediate for the preparation of compounds II-IX is *p*-acetylamino-*p'*-nitrodiphenyl sulfone (I).[2] The nitro group of I was reduced by high pressure hydrogenation over copper chromite catalyst, and an 80% yield of *p*-acetylamino-*p'*-aminodiphenyl sulfone (II) was obtained. In our experience the method described is preferable to the use of stannous chloride,[3] iron and hydrochloric acid, and ammonium sulfide. The primary amino group of II was formylated by the action of strong formic acid, and III resulted in 83% yield. Compound III is mentioned in the patent literature,[4] but no

(1) First paper, Heymann and Fieser, THIS JOURNAL, **67**, 1979 (1945).

(1a) Coggeshall, Maier and Best, *J. Am. Med. Assoc.*, **117**, 1077 (1941).

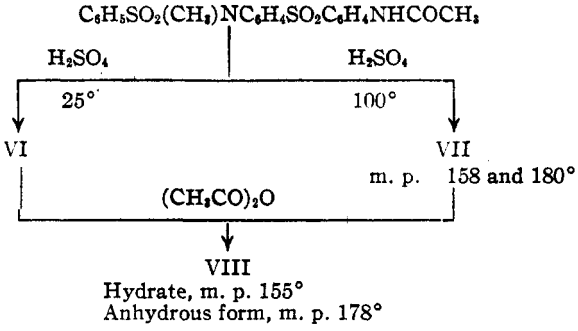
(2) "Organic Syntheses," **22**, 31 (1942).

(3) Raiziss, Clemence, Severac and Moetsch, THIS JOURNAL, **61**, 2763 (1939).

(4) Ellingworth and Rose, British Patent 517,421 (1940), *C. A.*, **35**, 6973 (1941).

analysis is given and the melting point reported is 20° lower than the value observed by us. We also prepared the *p*-nitro-*p'*-formylamino derivative IV; this substance has in the meantime been reported by Mingoja.[5] All attempts to obtain the desired *p*-amino-*p'*-formylamino derivative by reduction of the nitro group failed because the amide linkage was attacked under the conditions used.

p-Acetylamino-*p'*-methylaminodiphenyl sulfone (VI) was obtained by methylation of the Hinsberg derivative V and subsequent gentle hydrolysis. More drastic hydrolytic conditions led directly to the deacetylated base VII. Since compounds in this series tend to crystallize in a solvated form and often exist in polymorphic modifications, a more detailed study of the relation among VI, VII and VIII was made with the results summarized below.



The low melting form of VII has almost the same melting point as the hydrate of VIII, and the anhydrous form of VIII melts at about the same temperature as the high melting modification of VII, but pronounced depressions were noted on mixed melting point determinations.

According to the patented procedure for the manufacture of atebrine,[6] the acridine derivative IX was prepared by the condensation of II with the appropriate 9-chloroacridine in phenol solution at 125°. Under hydrolytic conditions the molecule suffers fission at the secondary amino group.

Compounds X-XVI are symmetrical derivatives, representing more drastic alterations of the parent sulfone. The hydrazine X resulted from the action of stannous chloride on the tetrazotized base.[7] Compound XII is the hydrochloride of a higher homolog of the parent sulfone; the free base is very unstable. The substance was obtained through the corresponding diacetyl derivative XI, which had been prepared by hydrogenation of the dinitrile[8] in acetic anhyride solution. Synthesis of XIII seemed desirable because of the biological activity of compounds containing hydroxylalkylamino side chains. The Hinsberg derivative of the parent sulfone,[1] in the form of the sodium salt, reacted with ethylene oxide in acetone solution under pressure. On hydrolysis of the benzenesulfonyl groups in a pressure reaction, XIII was obtained in poor yield. The substance was also prepared by direct action of ethylene oxide on the parent sulfone, and was isolated through the N-nitroso derivative.

In view of the metabolic dealkylation of *p,p'*-bismethylaminodiphenyl sulfone,[1] the behavior of a larger N-alkyl group was of interest, and the corresponding ethyl compound (XIV) was prepared by the method used to obtain the lower homolog.[1]

All attempts to prepare N,N'-alkylaminoalkyl derivatives failed. The parent sulfone or the Hinsberg derivative gave only intractable mixtures when brought together with the sensitive β-diethylaminoethyl chloride. The condensation of the parent sulfone with ω-diethylaminopropyl methyl ketone under reducing conditions yielded no isolable products. The chlorine atoms of *p,p'* dichlorodiphenyl sulfone are too inert to react with β-diethylaminoethylamine, but the corresponding *m,m'*-dinitro halide[9] reacted smoothly to give compound XV. The nitro groups of XV could not be eliminated by the conventional procedure because the secondary amino groups resisted all attempts at acetylation. However, XV could be reduced to a triamine, which reacted with nitrous acid to give the dibenzotriazolyl sulfone XVI.

The disulfonylmethanes XVII and XVIII were synthesized in the hope that there might be an increase of the density of negative charge around the sulfur atoms in the anions of these compounds. According to the theory of sulfa-drug action advanced by Bell and Roblin,[10] the bacteriostatic activity of a sulfanilamide derivative increases with the negativity of the sulfonyl group; these considerations appeared applicable to diaminodiphenyl sulfone, which is antagonized by *p*-aminobenzoic acid and thus possesses true sulfa-drug activity. The disulfones were obtained by oxidation of the appropriate N-acetyl methylene disulfides; the latter were prepared from *p*-acetylaminothiophenol and chloromethyl ethyl sulfide or methylene dibromide, respectively. Compound XVII is readily soluble in dilute alkali; the acid dissociation constant is approximately 10^{-10} to 10^{-11}.[11] Compound XVIII is so weak an acid that hot alkaline solutions on cooling deposit the free acid rather than the sodium salt.

The antimalarial activity of the compounds was tested against *P. gallinaceum* infections by Dr. J. Maier of the International Health Division of the Rockefeller Foundation, and the results will be

(5) Mingoja, *Arquiv. biol. (São Paulo)*, **27**, 4 (1943), *C. A.*, **38**, 4919 (1944).

(6) Mietzsch and Mauss, German Patent 553,072 (1930), *C. A.*, **26**, 4683 (1932).

(7) Meyer, *Ber.*, **16**, 976 (1883).

(8) Ashley, Barber, Ewins, Newberg and Self, *J. Chem. Soc.*, 103 (1942).

(9) Ullmann and Korselt, *Ber.*, **40**, 643 (1907).

(10) Bell and Roblin, THIS JOURNAL, **64**, 2905 (1942).

(11) Private communication from Dr. R. O. Roblin, American Cyanamid Company, Stamford, Conn.

published elsewhere. With the exception of compounds I, II, IV, V, VIII and XII all the substances listed were submitted, and none showed any encouraging antiplasmodial activity. Only VI and X had any demonstrable suppressive action. Surprisingly, the unsymmetrical sulfones IV, VI and VII were considerably more toxic than the corresponding symmetrical compounds.

The *in vitro* bacteriostatic power of XVII and XVIII has been tested in the laboratory of the American Cyanamid Company. The ethyl phenyl disulfonylmethane XVII was feebly active against *E. coli* in concentrations of 260 mg. %; the disulfone XVIII had no effect at a concentration of 4 mg. % against *E. coli, Staph. aureus, S. paradysenteria,* or a strain of T. B. 607. Higher concentrations of XVIII could not be tested because the compound is very sparingly soluble.[11] We are indebted to Dr. Roblin for his permission to report these results.

p,p'-Bismethylaminodiphenyl sulfone[1] was tested by Feldman[12] against experimental tuberculosis in guinea pigs. Although the drug is effective against the animal infection, clinical application is precluded because of the relatively high toxicity of the compound.

This investigation was supported by a grant from the International Health Division of the Rockefeller Foundation to Professor L. F. Fieser, who delegated to us the responsibility for conducting and reporting the present experiments.

We express our appreciation to Professor Fieser for his advice during the course of the investigation, and to Mrs. M. Fieser for aid in the preparation of the manuscript.

Experimental[13]

p-Acetylamino-p'-formylaminodiphenyl Sulfone (III).—The hydrogenation of I was carried out at 2000 lb./sq. in. and 240° over copper chromite catalyst (KAF 37). After eight hours the reaction was complete and II was isolated in 60–80% yield. After recrystallization from methanol the amine formed white needles, m. p. 242–243°.

A mixture of 13.5 g. of II and of 75 cc. of 87% formic acid was boiled for four hours. A white precipitate of III resulted when the solution was poured into 1.5 l. of ice water; it amounted to 12.2 g. (83% yield), m. p. 274–283°. The analytical sample, obtained by recrystallization from methanol, forms colorless needles melting at 289–290°.

Anal. Calcd. for $C_{13}H_{14}O_4N_2S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.38; H, 4.35; N, 8.51.

p-Formylamino-p'-nitrodiphenyl Sulfone (IV).—A mixture of 2.2 g. of *p*-amino-*p'*-nitrodiphenyl sulfone[14] and 10 cc. of 87% formic acid was boiled for two hours and poured into ice water. A yellow precipitate of 2.25 g. (93% yield) of IV separated; m. p. 231.5–233°. A slightly yellow analytical sample was obtained by recrystallization from ethanol; m. p. 234.5–235.5°.

Anal. Calcd. for $C_{13}H_{10}O_5N_2S$: C, 50.99; H, 3.30. Found: C, 51.16; H, 3.56.

p-Acetylamino-p'-benzenesulfonylaminodiphenyl Sulfone (V).—To a solution of 13.3 g. of II in 65 cc. of pyridine was added 8.8 g. of benzenesulfonyl chloride dissolved in 30 cc. of pyridine. The mixture stood for three hours and was heated on the steam-bath for one hour. When it was poured on 750 g. of an ice–hydrochloric acid mixture, 16 g. (81% yield) of V separated; m. p. 246–248°. Two recrystallizations from methanol gave colorless prisms; m. p. 249.5–250°.

Anal. Calcd. for $C_{20}H_{17}O_5N_2S_2$: C, 55.80; H, 4.21. Found: C, 55.52; H, 4.08.

p-Acetylamino-p'-methylaminodiphenyl Sulfone (VI).—A solution containing 13.0 g. of II, 4.5 cc. of methyl iodide, 1.27 g. of sodium hydroxide, 300 cc. of ethanol, and 200 cc. of water was boiled for three hours. After distillation of the alcohol a thick, brown sirup separated, which did not crystallize. When 5.0 g. of this sirup was allowed to stand with 5 cc. of concentrated sulfuric acid for two hours most of the oil dissolved. The solution was poured into 100 cc. of ice water and the liquid was made basic at once with sodium hydroxide. A brownish oil settled; it was taken up in dilute ethanol and clarified with Darco. The solution deposited 2.5 g. (73% yield) of VI; m. p. 202–205°. Recrystallization from dilute ethanol gave an analytical sample consisting of colorless needles; m. p. 205–205.5°.

Anal. Calcd. for $C_{13}H_{14}O_2N_2S$: C, 59.49; H, 5.38. Found: C, 59.77; H, 5.58.

p-Amino-p'-methylaminodiphenyl Sulfone (VII).—The sirup resulting from the methylation of 13.0 g. of V was heated on the steam-bath with 50 cc. of concentrated sulfuric acid for one-half hour. The clear solution was poured into 800 cc. of ice water, and the liquid was made alkaline. The resulting precipitate on recrystallization from 50% ethanol afforded 5.0 g. (65% yield) of VII, m. p. 176–177°. Two further recrystallizations gave colorless needles, m. p. 179.5–180°. In one run an isomorphic form of VII was obtained; m. p. 158°, m. p. 176.5–177° after resolidification. The melting point of the 180°-form was not depressed by admixture with the 158°-form. When 1.15 g. of VI was boiled for two hours with 30 cc. of concentrated hydrochloric acid and 10 cc. of water, compound VII also resulted. After recrystallization from 50% ethanol 0.65 g. (70% yield) of VII was obtained; m. p. 158°.

Anal. Calcd. for $C_{15}H_{16}O_3N_2S$: C, 59.19; H, 5.30. Found: C, 59.05; H, 5.20.

N,N'-Diacetyl-p-amino-p'-methylaminodiphenyl Sulfone (VIII).—A solution of 0.25 g. of VI in 3 cc. of glacial acetic acid and 3 cc. of acetic anhydride was boiled for two hours, poured into water, and neutralized exactly with sodium carbonate. The resulting sticky precipitate was recrystallized from dilute ethanol and 0.25 g. (90% yield) of crude VIII was obtained. After two additional recrystallizations from the same solvent, colorless prisms resulted; m. p. 155–155.5°. On sudden immersion into a bath at 140° the crystals gave off moisture. The compound gives the correct analytical values for a monohydrate. By crystallization from methanol anhydrous crystals were obtained, m. p. 177.5–178°; a pronounced depression was noted on admixture of VII. On acetylation of VII with acetic acid and acetic anhydride VIII was obtained in 81% yield.

Anal. Calcd. for $C_{17}H_{18}O_4N_2S \cdot H_2O$: C, 56.03; H, 5.53; H_2O, 4.95. Found: C, 56.16; H, 5.74; H_2O, 4.63. Calcd. for $C_{17}H_{16}O_4N_2S$: C, 58.93; H, 5.24. Found after drying at 120° in vacuum: C, 58.73; H, 5.36. Found (anhydrous form): C, 58.59; H, 5.41.

p-Acetylamino-p'-(2-methoxy-6-chloro-9-acridylamino)-diphenyl Sulfone (IX).—Commercial 2-methoxy-6,9-dichloroacridine (Merck) was recrystallized; the purified product melted at 64°. A mixture of 4 g. of the chloroacridine, 4.0 g. of II, and 16 g. of phenol was heated for four hours at 125°. The dark oil was poured dropwise into water containing excess sodium hydroxide, and the resulting yellow precipitate on recrystallization from ethanol afforded 4.36 g. (57% yield) of IX, m. p. 228–230°. The analytical sample forms yellow platelets and melts at 233–234°. The compound is insoluble in acid.

(12) Private communication from Dr. W. H. Feldman, The University of Minnesota, Rochester, Minn.

(13) All melting points are corrected. All analytical figures are based on microanalyses performed by Miss E. Werble unless otherwise stated.

(14) Buttle, Dewing, Foster, Gray, Smith and Stephenson, *Biochem. J.*, **32**, 1101 (1938).

Anal. Calcd. for $C_{28}H_{22}O_4N_2SCl$: C, 63.21; H, 4.17; N, 7.90. Found: C, 63.02; H, 4.27; N, 7.80.

p,p'-Dihydrazinodiphenyl Sulfone (X).—A solution of 15 g. of *p,p'*-diaminodiphenyl sulfone in 200 cc. of concentrated hydrochloric acid was cooled to 0°. The resulting suspension of the dihydrochloride was diazotized with 5 g. of sodium nitrite dissolved in 25 cc. of water. The solution was filtered from undissolved solid through a sintered glass funnel, and was added to a solution of 70 g. of stannous chloride in 100 cc. of concentrated hydrochloric acid. The mixture was stirred mechanically during the addition. Soon white platelets of the hydrochloride of X separated; the solid was dissolved in water, the solution was clarified and made basic, when X was precipitated. Since the substance is discolored by heating it was purified by repeated slow precipitation from acid solution. Thus 5.0 g. (30% yield) of white microcrystals was obtained, melting at 193–195° with decomposition. The compound gives colorless condensation products with acetophenone and benzaldehyde.

Anal. Calcd. for $C_{12}H_{14}O_2N_4S$: C, 51.78; H, 5.07; N, 20.13. Found: C, 52.12; H, 5.17; N, 19.98.

N,N'-Diacetyl-*p,p'*-bisaminomethyldiphenyl Sulfone (XI).—A solution of 3.0 g. of *p,p'*-dicyanodiphenyl sulfone in 7 cc. of acetic anhydride was hydrogenated over Adams catalyst at 150° and 2000 lb./sq. in. for eight hours. The solution was filtered and poured into 150 cc. of 7% sodium hydroxide. A brownish oil settled; it was dissolved in alcohol (Darco); the solution deposited 2.5 g. (62% yield) of colorless needles of XI, m. p. 224–225°. The analytical sample melts at 227–227.5°.

Anal. Calcd. for $C_{13}H_{20}O_4N_2S$: C, 60.00; H, 5.60. Found: C, 59.71; H, 5.51.

p,p'-Bisaminomethyldiphenyl Sulfone Dihydrochloride (XII).—A mixture of 2.4 g. of XI and 10 cc. of 6 *M* hydrochloric acid was boiled for two hours. On cooling the solution deposited 1.7 g. (73% yield) of colorless needles, which melt above 270°. After two recrystallizations from dilute ethanol, an analytical sample was obtained. The free amine is extremely unstable and could not be isolated. A solution of the hydrochloride immediately turns dark brown on being made basic.

Anal. Calcd. for $C_{14}H_{18}O_2N_2Cl_2S$: C, 48.24; H, 5.20; Cl, 20.29. Found: C, 48.07; H, 5.31. Cl, 20.06.

p,p'-Bis-(β-hydroxyethylamino)-diphenyl Sulfone (XIII).—(a) A mixture of 5.0 g. of the sodium salt of dibenzenesulfonamidodiphenyl sulfone[1] and 10 cc. of ethylene oxide was heated in a sealed tube for eight hours at 105°. The resulting oil did not crystallize. A solution of 1.0 g. of the oil in 5 cc. of pyridine was heated with 1.0 cc. of benzoyl chloride. The reaction mixture was worked up and 0.85 g. (64% yield) of the O,O'-dibenzoyl-N,N'-dibenzenesulfonyl derivative of XIII was isolated; m. p. 155–158°; after two recrystallizations from ethanol it formed long colorless needles, which disintegrated to a powder on drying; m. p. 159–160°.

Anal. Calcd. for $C_{42}H_{36}O_{10}N_2S_3$: C, 61.15; H, 4.40. Found: C, 61.27; H, 4.58.

The oil resulting from the pressure reaction (2.0 g.) was heated with 10 cc. of concentrated hydrochloric acid in a sealed tube for eight hours at 100°. The clear solution deposited an oil on neutralization; the material was dissolved in a small amount of warm methanol from which 0.43 g. (34% yield) of XIII crystallized; m. p. 175–180°. An analytical sample consisting of flat leaves was obtained by recrystallization from water; m. p. 187–188°.

Anal. Calcd. for $C_{16}H_{10}O_4N_2S$: C, 57.12; H, 5.99; N, 8.33. Found: C, 56.92; H, 5.77; N, 7.87.

(b) A mixture of 15 g. of *p,p'*-diaminodiphenyl sulfone, 25 cc. of acetone, 25 cc. of water and 15 cc. of ethylene oxide was heated in an autoclave for twelve hours at 80°. After removal of the acetone, a thick sirup was obtained, which was dissolved in 300 cc. of 2 *N* hydrochloric acid. To the ice-cold mixture a solution of sodium nitrite was added slowly until the starch iodide reaction became positive. The mixture was stirred mechanically during the addition. The resulting precipitate was recrystallized four times from ethanol; 2.5 g. (11% yield) of the N,N'-dinitroso derivative of XIII was obtained in the form of almost colorless platelets melting at 181–181.5°.

Anal. Calcd. for $C_{16}H_{18}O_6N_4S$: C, 48.72; H, 4.60; N, 14.21. Found: C, 48.75, 48.71; H, 4.15, 4.48; N, 13.97.

A suspension of 2.0 g. of the nitrosoamine in 80 cc. of 6 *N* hydrochloric acid was treated with 5 g. of mossy tin on the steam-bath for fifteen minutes. The clear solution was cooled and poured into excess sodium hydroxide solution. A crystalline precipitate resulted, which after recrystallization from water gave 1.1 g. (65% yield) of pure XIII.

N,N'-Dibenzenesulfonyl-*p,p'*-bisethylaminodiphenyl Sulfone.—A mixture of 10 g. of disodium *p,p'*-bisbenzenesulfonylaminodiphenyl sulfone,[1] 200 cc. of ethanol, 100 cc. of water, 16 cc. of ethyl iodide, and 16.8 g. of sodium bicarbonate was boiled on the steam-bath for about fifty hours. A portion of 5 cc. and of 6 cc. of ethyl iodide was added after twelve hours and after twenty-four hours, respectively. During the last twenty-four hours of the heating period, the *p*H of the solution changed from weakly basic to weakly acidic. The solution was neutralized and freed of ethanol in vacuum. The product appeared as a slowly solidifying gum, which was recrystallized from ethanol. The solution deposited 8.75 g. (85.6% yield) of glistening blades, m. p. 145–147°; the analytical sample melts at the same temperature. The substance may also crystallize in the form of slender needles, which contain one molecule of ethanol of crystallization and decompose at 66–68°. The use of ethyl bromide instead of the iodide is less satisfactory since the alkylation does not proceed to completion.

Anal. Calcd. for $C_{28}H_{28}O_6N_2S_3$: C, 57.51; H, 4.82; N, 4.79. Found: C, 57.61; H, 4.94; N, 4.60. Calcd. for $C_{28}H_{28}O_6N_2S_3 \cdot C_2H_5OH$: C, 57.12; H, 5.43. Found: C, 57.16; H, 5.38.

p,p'-Bisethylaminodiphenyl Sulfone (XIV).—A solution of 8.75 g. of the dibenzenesulfonyl derivative in 15 cc. of concentrated sulfuric acid was allowed to stand at room temperature for two hours. The slightly brown liquid was poured into a large volume of ice water, the solution was made basic with cooling, and the base was collected and recrystallized from 200 cc. of ethanol. In two crops 4.4 g. (97% yield) of rhombus-shaped plates was collected; m. p. 177–180°. The analytical sample melts at 178.5–180.5° when introduced into a bath at 177° and permitted to resolidify after previous sintering.

Anal. Calcd. for $C_{16}H_{20}O_2N_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.30; H, 6.93; N, 9.40.

p,p'-Bisdiethylaminoethylamino-*m,m'*-dinitrodiphenyl Sulfone (XV).—*p,p'*-Dichloro-*m,m'*-dinitrodiphenyl sulfone was prepared according to Ullman[9] and recrystallized until the melting point became constant at 203.2–204.4°. A solution of 20 g. of the chloronitrophenyl sulfone in 400 cc. of benzene was boiled with 20 g. of β-diethylaminoethylamine for fifteen hours. At the end of the heating period a yellow sirup had settled. The mixture was extracted exhaustively with 10% hydrochloric acid, from which the base was liberated with aqueous alkali. The solid was recrystallized from 3 liters of ethanol and 25.4 g. (89.5% yield) of long needles of XV was obtained, melting at 141.2–142°. A second crop of 1.55 g. raised the total yield to 95%. The purest sample obtained by recrystallization from ethanol melts at 141.1–142.3°.

Anal. Calcd. for $C_{24}H_{36}N_6O_6S$: C, 53.71; H, 6.76; N, 15.66. Found: C, 53.99; H, 6.67; N, 15.36.

Di-1-(β-diethylaminoethyl-1,2,3-benzotriazolyl-5) Sulfone (XVI).—A solution of 0.5 g. of XV in 15 cc. of absolute ethanol was shaken with Raney nickel and hydrogen at atmospheric pressure. The calculated amount of gas was consumed within one and one-half hour, the solvent was evaporated in vacuum, and the sirupy residue was dried in a vacuum desiccator over sulfuric acid. The material crystallized from benzene–hexane in the form of nicely shaped, brownish plates; yield 0.42 g. (96%); m. p. 65–

75° and remelting at 112–115° after resolidification. A nitrogen analysis gave the correct value for the hexamino compound containing one molecule of benzene.

Anal. Calcd. for $C_{24}H_{40}O_2N_6S \cdot C_6H_6$: N, 15.20. Found: N, 15.10.

For the preparation of the triazole the amine was not isolated. A solution of 16.7 g. of crude XV in 200 cc. of ethanol was hydrogenated over Raney nickel at 30 lb./sq. in. The calculated amount of gas was consumed in two hours. The red solution was filtered, and on addition of a small amount of stannous chloride in hydrochloric acid solution, the color turned to brown. The solution was made strongly acidic with hydrochloric acid, and 10 g. of sodium nitrite was added. The solvent and unchanged ethyl nitrite were removed in vacuum on the steam-bath, and on addition of alkali, XVI separated as a brown solid. After crystallization from benzene–hexane, 10.2 g. (65% yield) of tan needles was obtained; m. p. 147–149°. An analytical sample was obtained in the form of fine colorless needles by recrystallization from benzene–hexane (1:1); m. p. 152.5–153°.

Anal. Calcd. for $C_{24}H_{34}O_2N_6S$: C, 57.81; H, 6.87; N, 22.48. Found: C, 57.93; H, 6.83; N, 22.74.

p-Acetylaminophenyl Ethyl Thioformal.—To a solution of 4.15 g. of sodium in 200 cc. of absolute ethanol was added 30 g. of *p*-acetylaminothiophenol.[15] The mercaptan dissolved rapidly on slight warming. Then 20 g. (19 cc.) of chloromethyl ethyl sulfide[16] was added. Sodium chloride began to separate almost at once, and there was a slight evolution of heat. The mixture was boiled for one-half hour, diluted with ethanol to a volume of 400 cc., and filtered. To the filtrate was added an equal volume of water and on cooling the liquid deposited 35 g. of the thioformal, m. p. 109–113°. After one recrystallization from benzene (about 25 cc. per gram) 33 g. (76% yield) of product melting at 110–114.5° was obtained, suitable for the following oxidation.

An analytical sample was obtained by recrystallization from benzene and sublimation at 100–120° and 10^{-5} mm. of mercury. The substance forms colorless crystals melting at 114.2–115.8°.

Anal. Calcd. for $C_{11}H_{15}ONS_2$: C, 54.74; H, 6.26; N, 5.80; S, 26.57. Found: C, 54.89; H, 6.14; N, 5.85, 5.35; S, 26.57.

p-Acetylaminophenylsulfonylethylsulfonylmethane.—To a mixture of 20 cc. of glacial acetic acid and 20 cc. of acetic anhydride was added 6.1 g. of the thioformal. While the suspension was stirred mechanically and cooled in an ice-bath, 14 cc. of 30% hydrogen peroxide was added. After two hours all the solid had disappeared and the mixture was allowed to stand at 0–4° for forty hours. When a sample of the solution was boiled with water and hydrochloric acid, no odor of ethyl mercaptan was noticeable. The solution was diluted with water and neutralized with sodium bicarbonate; the resulting suspension was cooled in ice and the colorless solid was collected. The product was not completely soluble in alkali; therefore it was dissolved in 50 cc. of acetone and treated with finely powdered permanganate until the purple color persisted for five minutes. After decoloration with bisulfite and hydrochloric acid the solution was freed of acetone by distillation in vacuum, and the resulting white precipitate was collected; yield 5.4 g. (70%); m. p. 189.5–191°.

Attempts to conduct the oxidation at 15–25° failed because the reaction tends to become violent and to give yellow material in poor yield; oxidation of the thioformal with permanganate alone was likewise unsatisfactory. The procedure outlined has given yields varying from 54 to 79%.

By recrystallization from ethanol a constant-melting sample was obtained, consisting of glistening blades, which melt and resolidify at a temperature below 188° and then melt at 191–192°.

Anal. Calcd. for $C_{11}H_{15}O_5NS_2$: C, 43.26; H, 4.96; N, 4.58. Found: C, 43.46; H, 4.94; N, 4.34.

(15) Zincke and Jörg, *Ber.*, **42**, 3367 (1909).

(16) Böhme, *ibid.*, **69**, 1610 (1936).

p-Aminophenylsulfonylethylsulfonylmethane (XVII).—A suspension of 11.1 g. of the described acetyl derivative in 100 cc. of 10% hydrochloric acid was boiled for one hour. The solution was cooled and neutralized; the precipitated base was collected and recrystallized from ethanol. The yield was 8.45 g. (87.5%); m. p. 184–186.6°.

The analytical sample consists of colorless spear-like rods, which melt at 186–187°.

Anal. Calcd. for $C_9H_{13}O_4NS_2$: C, 41.05; H, 4.97; N, 5.32. Found: C, 40.85; H, 4.85; N, 5.21.

Di-(*p*-acetylaminophenyl) Thioformal.—To a hot solution of 1.17 g. of sodium in 500 cc. of absolute ethanol was added 8.5 g. of *p*-acetylaminothiophenol. The solid dissolved rapidly, and then 4.4 g. of methylene dibromide in 10 cc. of ethanol was added in one portion. The mixture was boiled for three hours, cooled and diluted with 500 cc. of water. The faintly yellow precipitate was collected and dried; yield 7.35 g. (84%); m. p. 212–215°. On repeated recrystallization from ethanol (charcoal) an analytical sample was obtained as dull leaflets melting at 213–214.8°.

Anal.[17] Calcd. for $C_{17}H_{18}O_2N_2S_2$: C, 58.93; H, 5.23; N, 8.08. Found: C, 58.90, 58.61; H, 5.62, 5.81; N, 8.04.

Di-(*p*-acetylaminophenylsulfonyl)-methane.—A mixture of 200 cc. of glacial acetic acid, 13 cc. of 30% hydrogen peroxide and 8.0 g. of crude thioformal was heated on the steam-bath for one and one-half hours. During this period the starting material dissolved, and the product crystallized from the brownish solution; 7.95 g. (83.6% yield) of tan crystals was collected. The substance is fairly soluble in dilute, warm alkali, but is quite insoluble in organic solvents; it is most satisfactorily recrystallized from approximately 0.1 *N* aqueous-alcoholic (50:50) sodium hydroxide, with clarification and acidification of the hot solution. When the liquid cools, creamy leaflets of the disulfone appear. The analytical sample melts at 320–325° with decomposition.

Anal.[17] Calcd. for $C_{17}H_{18}O_6N_2S_2$: C, 49.74; H, 4.42; N, 6.82. Found: C, 49.40, 49.46; H, 4.43, 4.62; N, 7.14.

Di-(*p*-aminophenylsulfonyl)methane (XVIII).—A suspension of 7.1 g. of the diacetyl disulfone in 80 cc. of 10% hydrochloric acid was boiled for one and one-quarter hours, when most of the solid had dissolved. Boiling was continued for an additional hour; then the solution was neutralized and cooled, and the resulting tan precipitate was collected; yield 5.5 g. (97%), m. p. 230–235°.

The compound is soluble in mineral acids, sparingly soluble in dilute alkali, and very sparingly soluble in organic solvents. The substance is diazotizable, and the diazonium salt couples with phenol with red color. The most satisfactory solvent for recrystallization of XVIII is 0.5 *N* sodium hydroxide or water. The disulfone is soluble in hot alkali, but as the solution cools the free acid rather than the sodium salt is deposited in long spear-like blades. The analytical sample was finally crystallized from ethanol; it melts at 239–240°.

Anal. Calcd. for $C_{13}H_{14}O_4N_2S_2$: C, 47.84; H, 4.32; N, 8.58. Found:[17] C, 47.89, 47.72; H, 4.65, 4.43; N, 8.90, 9.10. Found: C, 47.61; H, 4.09; N, 8.75.

Summary

A number of new derivatives of *p,p'*-diaminodiphenyl sulfone have been prepared and submitted for trial as antimalarials. Among the substances are several unsymmetrically substituted compounds, a higher homolog of the parent sulfone, a dihydrazino derivative, a hydroxyethyl derivative and two methylene disulfones.

None of the substances showed any promising biological activity.

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(17) Microanalysis by Dr. Carl Tiedcke.