layer gave 8.1 g. of oil, from which 3 g. of *p*-methylacetophenone was obtained by fractional distillation at 50 mm. (b. p. 138–150°). The semicarbazone of this ketone melted at 206.5–207.5°, and showed no depression when mixed with an authentic sample.

From the water layer there was obtained 3 g. (54%) of crude, sirupy acetate. This was deacetylated as usual, taken up in water, and purified by filtration through Norit and Celite. The filtrate yielded 0.67 g. of α-1-*p*-tolyl-β-1-phenyl-1-desoxyglucitol hydrate, m. p. 163.5–166.5°. After three recrystallizations from water the compound melted at 167–170°, $[\alpha]^{25}D$ 58.8° (*c*, 0.400; dioxane). A mixed melting point of this product with the anomeric α-1-phenyl-β-1-*p*-tolyl-1-desoxyglucitol hydrate showed a marked depression, 120–134°.

Anal. Calcd. for $C_{19}H_{24}O_5 \cdot H_2O$: C, 65.20; H, 7.48. Found: C, 65.37; H, 7.37.

Oxidation.—The oxidation was carried out as previously described for the anomeric product. The *p*-benzoylbenzoic acid obtained was less pure, m. p. 190–192°, but showed no mixed melting point depression (193–194°) with the previously obtained sample.

Tetraacetyl-α-D-glucosylbenzene and Toluene.—Sirupy tetraacetyl-α-D-glucosylbenzene (2.26 g., obtained from the mother liquors of the Grignard preparation of the anomer[3]), aluminum chloride (7.5 g.), and toluene (85 g.) were stirred together for five hours at 80°. After the customary treatment, from the water layer was obtained 0.75 g. of an amber, sirupy acetate. This was deacetylated to produce a small quantity of crystalline material, m. p. 152.5–161° from water. This substance showed melting point depressions with both α-1-phenyl-β-1-*p*-tolyl-1-desoxy-D-glucitol hydrate and α-1-*p*-tolyl-β-1-phenyl-1-desoxy-D-glucitol hydrate. When equal portions of these two compounds were recrystallized together from water, a product was obtained which melted at 145–146°. A mixed melting point of this recrystallized mixture with the product obtained above showed no depression, but melted in the intermediate range of 152–157°.

Summary

Polyacetylglycosylbenzenes have been shown to react with benzene in the presence of aluminum chloride to yield the same 1,1-diphenyl-1-desoxyalditols as are obtained directly by the glycosylation of benzene with sugar acetates or acetylated glycosyl halides. This confirms the hypothesis that in these latter glycosylations the 1,1-diphenyl-1-desoxyalditols arise from an intermediate glycosylbenzene.

Several members of a new class of mixed 1,1-disubstituted 1-desoxy-alditols have been prepared.

EVANSTON, ILLINOIS RECEIVED SEPTEMBER 4, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Derivatives of p,p'-Diaminodiphenyl Sulfone[1a]

BY HANS HEYMANN AND LOUIS F. FIESER

The studies of Coggeshall and Maier[1b] of the action of sulfanilamide and related drugs on malarial infections showed that cures with complete eradication of parasites could be effected in certain cases of experimental avian and monkey malaria. Trials with humans suffering from naturally acquired or therapeutic malaria were somewhat inconclusive but encouraging. Maier and Riley also showed that the action of sulfa drugs on plasmodia is susceptible to inhibition by *p*-aminobenzoic acid,[2] whereas with quinine and atebrine there is no inhibition. Therefore the sulfa drugs must act on the plasmodia in a different manner than the older antimalarials, and it may be hoped that a sulfa compound suitable for malaria therapy can be found superior to the drugs in use.

This investigation of the synthesis of additional members of the series for trial as antimalarials by the International Health Division of the Rockefeller Foundation was undertaken at the suggestion of Dr. L. T. Coggeshall and Dr. John Maier, and was supported by a grant from the Rockefeller Foundation. The present paper reports the preparation of several new derivatives of p,p'-diaminodiphenyl sulfone (I). This compound was introduced into chemotherapy in 1937 by Buttle and his associates[3] and by Fourneau and his collaborators,[4] and numerous derivatives and related substances have since been reported in patents and papers.[5] A brief review of methods for preparing I is given in "Organic Syntheses."[6]

In investigating the preparation of I by patented procedures for the ammonolysis of p,p'-dichlorodiphenyl sulfone we tried the claimed reaction[7] with alcoholic ammonia in the presence of copper without success but obtained the desired compound in 78% yield according to a patent of the I. G. Farbenindustrie,[8] in which the chloro compound is treated with aqueous ammonia and a catalyst at 200° under pressure. Shaking the reaction mixture was found to be necessary, although agitation is not mentioned in the patent procedure. One run resulted in a mixture, from which *p*-chloro-*p'*-aminodiphenyl sulfone (Ia) could be isolated with ease. The structure of Ia was proved by conversion of the substance to

(1a) This manuscript was originally received on October 27, 1942, but its publication has been withheld at the request of the National Research Council.—*The Editor.*

(1b) Coggeshall, Maier and Best, *J. Am. Med. Assoc.*, **117**, 1077 (1941); see also earlier references.

(2) Maier and Riley, *Proc. Soc. Exptl. Biol. Med.*, **50**, 152 (1942).

(3) Buttle, Smith, Dewing and Foster, *Lancet*, **232**, 1331 (1937).

(4) Fourneau, Nitti, Tréfouël, Tréfouël and Bovet, *Compt. rend.* **204**, 1763 (1937).

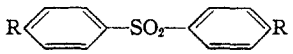
(5) For references see Roblin, Williams and Anderson, THIS JOURNAL, **63**, 1930 (1941).

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

(7) Laboratoires Français de Chimiothérapie and A. Girard French Patent 844,220 (1939).

(8) I. G. Farbenindustrie A. G., French Patent 829,926 (1938), British Patent 506,227 (1939).

TABLE I



	Substituent (R)
I	—NH_2; Ia, *p*-$ClC_6H_4SO_2C_6H_4NH_2(p)$; Ib, *p*-$ClC_6H_4SO_2H_4NHAc(p)$
II	—$NHCOCH_2CH_2COOH$
III	—NCO
IV	—$NHCONH_2$
V	—$NHCOOC_2H_5$
VI	—$NHCONHCH_2COOH$
VII	—$NHCONHCH_2CH_2N(C_2H_5)_2$
VIII	—$NHCOC_{17}H_{35}$
IX	—$NHCO(CH_2)_{12}$
X	—NHCHO
XI	—$[NSO_2C_6H_5]^-Na^+$
XII	—$NHCH_3$
XIII	—$N(CH_3)COCH_3$
XIV	—$[N(CH_3)_3]^+I^-$
XV	—$N(CH_3)_2$

p,p'-dichlorodiphenyl sulfone by means of the Sandmeyer reaction.

The necessary dichlorodiphenyl sulfone was obtained by treating sulfuric acid at 200° with chlorobenzene vapors in a suitable apparatus.[9] Although we were unable to realize a yield better than 40% of the theoretical amount, based on sulfuric acid, the method permits the preparation of as much as 100 g. of chloro compound in one run. If suitable facilities for the ammonolysis are available, a satisfactory product is easily prepared in two steps.

The derivatives investigated are shown. Compound II, *p,p'*-bis-succinoylaminodiphenyl sulfone,[10] was obtained in 77% yield on boiling I in dioxane solution with the calculated amount of succinic anhydride. The acid was converted into the half sodium salt which, however, was not water soluble but disproportionated to the free acid and the neutral salt.

When a solution of I in dioxane was treated with phosgene, a solution resulted which apparently contained the corresponding bis-carbamyl chloride, because when the solution was concentrated, diluted with benzene, and boiled, hydrogen chloride was evolved and diphenyl sulfone-*p,p'*-bis-isocyanate[11] (III) crystallized in good yield on cooling. The isocyanate is quite stable to moisture at room temperature but deteriorates rapidly when warmed in moist solvents. By interaction of III with ammonia, ethanol, glycine and β-diethylaminoethylamine compounds IV, V, VI and VII resulted. The yields in these reactions were satisfactory; the stability of III made it possible to carry out the condensation with glycine in an aqueous solution of the sodium salt.[12]

Two derivatives of higher fatty acids were prepared in the hope that the lipophilic residue might enable the drug to pass the stomach without hydrolysis and yet to be resorbed in the intestine. These substances were obtained by the action of the corresponding acid chlorides on I in the presence of pyridine, *p,p'*-bis-stearylaminodiphenyl sulfone (VIII) in 60% yield and *p,p'*-bischaulmoogrylaminodiphenyl sulfone (IX) in 40–50% yield, based on the free acids as starting material. The compounds are colorless solids which can be crystallized from alcohol or chloroform.

A description of the chemistry of *p,p'*-bisformylaminodiphenyl sulfone (X) could not be found in the literature although Nitti and his co-workers[13] and Digonnet[13] have used the substance in biological tests. Compound X was prepared in 93% yield by heating I with 98% formic acid.

Benzenesulfonyl chloride reacts with I in the presence of pyridine to give *p,p'*-bisbenzenesulfonylaminodiphenyl sulfone, but only the sodium salt (XI) could be obtained as a crystalline solid in about 85% yield. This reaction does not proceed satisfactorily in aqueous alkaline solution. Compound XI was methylated with methyl iodide and N,N'-dibenzenesulfonyl-*p,p'*-bismethylaminodiphenyl sulfone resulted in 81.5% yield. The sulfonic acid radical could be hydrolyzed with concentrated sulfuric acid at room temperature with the production of *p,p'*-bismethylaminodiphenyl sulfone (XII). Treatment of dichlorodiphenyl sulfone with methylamine and a catalyst also yields XII,[8] but extensive purification of the crude product was necessary, and the substance itself as well as the diacetyl derivative melted consistently lower than samples prepared by the first method. Acetylation of XII yielded N,N'-diacetyl-*p,p'*-bismethylaminodiphenyl sulfone (XIII) in 93% yield; the amine was further characterized by conversion to the dinitrosamine, from which the disecondary base can be regenerated by reduction with tin and hydrochloric acid.

In order to obtain a water-soluble N-alkyl derivative *p,p'*-bisdimethylaminodiphenyl sulfone dimethiodide (XIV) was prepared from I and methyl iodide in 47% yield by heating the reagents in a closed vessel. The salt decomposes in the melting point bath and the residue has the same melting point as *p,p'*-bisdimethylaminodiphenyl sulfone (XV)[8] which was prepared by thermal decomposition of XIV. The structure of XV was confirmed by reconverting it to the bisquaternary ammonium salt XIV.

Compound XV reacts with nitrous acid although it is a bistertiary amine. The action of nitrous acid on tertiary araliphatic amines bearing substituents in the *p*-position has recently been investigated by Crowley, *et al.*,[14] who showed that the reagent causes nuclear nitration and N-

(9) Meyer, *Ann.*, **433**, 339 (1923).

(10) *Cf.* The Wellcome Foundation, Ltd., British Patent 531,571 (1941); Kharasch and Reinmuth, U. S. Patent 2,268,754 (1942).

(11) Paul Pöhls and Fritz Mietzsch, U. S. Patent 2,218,030 (Oct. 15, 1940); *C. A.*, **35**, 1071 (1941).

(12) Paal, *Ber.*, **27**, 975 (1894).

(13) Nitti, Bovet, Tréfouël and Tréfouël, *Ann. inst. Pasteur*, **61**, 811 (1938); Digonnet, *Comp. rend. soc. biol.*, **130**, 543 (1939).

(14) Crowley, Milton, Reade and Todd, *J. Chem. Soc.*, 1286 (1940); see also earlier references.

nitrosation with elimination of an N-alkyl group. Hodgson and Crook[15] pointed out that the polarity of the substituent in the *p*-position to the amino group governs the ratio nitration/nitrosation, a potent electron-attracting group suppressing nitration in favor of nitrosation. Thus, only the mono- and the di-N-nitroso derivatives were obtained from the action of nitrous acid on Michler ketone.[16] When XV was treated with nitrous acid in strong hydrochloric acid, a yellow precipitate resulted from which *p,p'*-bismethylaminodiphenyl sulfone dinitrosamine was isolated. The compound has no characteristic melting point but decomposes at 207–212° to an orange-colored liquid, so that a direct comparison with the product of the nitrosation of XII was impossible. However, on reduction with tin and hydrochloric acid the substance yielded XII, identified by melting point and mixed melting point.

All these compounds have a tendency to crystallize in a solvated state; their solubilities are often influenced by the fact that the solvated form is taken up readily by a solvent, whereas the non-solvated modification is quite insoluble. Some of the compounds are remarkable inasmuch as they are insoluble in water and in alcohol but very soluble in a mixture of the solvents. Nearly all of the substances which do not decompose on melting have a double melting point, and in some cases it was possible to obtain the higher and the lower melting form separately.

Several preparations were attempted without success. We were unable to synthesize *p,p'*-dicyanodiphenyl sulfone from I by the Sandmeyer reaction but obtained the dinitrile by dehydration of the corresponding diamide.[9,17] Similar results have already been published by Ewins and his associates.[17] We wish to thank Dr. Ewins for his friendly advice concerning this preparation. We also investigated the possibility of obtaining the dinitrile by the preparation of *p,p'*-dicyanodiphenyl sulfide[17] from thioaniline and oxidation to the sulfone. Dicyanodiphenyl sulfide was obtained in 29% yield, but attempted oxidation of this compound with chromic acid in acetic acid did not proceed beyond the stage of the sulfoxide. The reaction of *p,p'*-dichlorodiphenyl sulfone with cuprous cyanide in the presence of pyridine was considered as a possible route to the dinitrile but no crystalline product could be isolated from the reaction mixture.

The reaction between I and cyanamide to yield the N-phenyldiguanido compound could not be accomplished. When the amine hydrochloride was heated in alcohol with cyanamide in the usual manner, no crystalline material could be recovered. Arndt's method[18] of treating the amine and excess cyanamide with concentrated hydrochloric acid gave only unchanged starting material. Heating I with guanidine thiocyanate was equally unsuccessful. Bischoff[19] reports similar difficulties in preparing guanidines from negatively substituted aromatic amines.

In an attempt to prepare a higher homolog of I the bromination of *p,p'*-ditolyl sulfone[9,20] was investigated. Genvresse[21] reports a *p,p'*-bisbromomethyldiphenyl sulfone, melting at 108°, which he obtained by treating ditolylsulfone with bromine at 160–180°. Neither by his method nor by working in boiling carbon tetrachloride in the sunlight were we able to secure a homogeneous bromination product, from which the desired *p,p'*-bisaminomethyldiphenyl sulfone might have been prepared.

Biological tests are being performed by Dr. John Maier of the International Health Division of the Rockefeller Foundation, and details of the results will be published elsewhere. Tests on all compounds except XI, XIII, XIV, XV and III have been completed; compound III was not submitted for testing. All acyl compounds and urea derivatives except compound X were without appreciable effect and gave poor blood levels. Substances X and XII were found to be active. The activity of XII is surprising because it is known that in the sulfanilamide series the activity is greatly diminished or disappears completely if the amino nitrogen is alkylated. Compound XII gave good blood levels, determined by the Marshall diazotization technique, indicating demethylation in the organism.[22] While the activity of X and XII is about equal in the test used by Dr. Maier, the dimethyl compound XII is non-toxic at dosage levels where the diformyl derivative X kills the experimental animal. Among compounds submitted for testing were the following substances, which have been recorded previously: *p,p'*-biscinnamylideneaminodiphenyl sulfone,[23] *p,p'*-bis-phenylpropylaminodiphenyl sulfone tetrasodium $\alpha,\gamma,\alpha',\gamma'$-tetrasulfonate,[23] and the condensation product of I with sodium formaldehyde sulfoxylate.[24] Both the anil and the sulfoxylate showed a certain activity without being toxic at relatively high dosage levels, a fact which in conjunction with the other results seems to indicate that more success may be expected from N-alkyl- and similar derivatives than from those containing acylated amino groups.

The action of these drugs seems to depend on the liberation of the parent sulfone. A suitable derivative should be non-toxic yet readily convertible to the active agent, and this conversion

(15) Hodgson and Crook, *J. Chem. Soc.*, 1812 (1932).

(16) Donald and Reade, *ibid.*, 53 (1935).

(17) Ashley, Barber, Ewins, Newbery and Self, *J. Chem. Soc.*, 103 (1942).

(18) Arndt, *Ber.*, **46**, 3525 (1913); Arndt and Rosenau, *ibid.*, **50**, 1260 (1917).

(19) Bischoff, *J. Biol. Chem.*, **80**, 354 (1928).

(20) Böeseken, *Rec. trav. chim.*, **30**, 137 (1911).

(21) Genvresse, *Bull. soc. chim.*, [3] **11**, 504 (1894).

(22) A number of examples for biological demethylations of aromatic amines is given by Stevenson, Dobriner and Rhoads, *Cancer Research*, **2**, 160 (1942).

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

(24) Bauer, THIS JOURNAL, **61**, 617 (1939).

should take place at a location in the animal body where the liberated drug can exert its best effect. Our knowledge of the chemical changes necessary to adapt a given compound to these conditions is scant. Therefore the unexpected activity of XII is encouraging and we plan to investigate further alkyl derivatives of the parent sulfone.

The mode of action of the active principle is unknown. Maier's findings[2] suggest the possibility that the drug supplants a metabolite vital to the microörganisms.

We are indebted to Dr. Oliver Kamm of the Parke Davis Company for a generous supply of starting material.

Experimental Part[25]

p,p'-Dichlorodiphenyl Sulfone.—Meyer's procedure[9] was modified by the use of standard-taper ground-glass and spherical joints. Concentrated sulfuric acid (50 cc.) was heated in a Wood's metal-bath at 200° and chlorobenzene was vaporized by means of an electric bowl heater. After twenty-eight hours the reaction did not seem to proceed any further and the product was worked up according to Meyer. After recrystallization from alcohol 108 g. (42% based on sulfuric acid) of p,p'-dichlorodiphenyl sulfone was obtained; m. p. 147.8–149.2°. Longer heating did not increase the yield.

p,p'-Diaminodiphenyl Sulfone (I).—Into the copper liner of an Adkins rocking bomb was placed 20 g. of p,p'-dichlorodiphenyl sulfone, 1 g. of cuprous bromide, 0.5 g. copper bronze and 170 cc. of 28% aqueous ammonia. The bomb was shaken at 200° for 39.5 hours and shaking was continued during the cooling period to avoid solidification of the product as a solid cake. The solid was filtered from the ammoniacal liquid, washed with water, and dissolved in 10% hydrochloric acid. A small amount of tar and the copper bronze were removed by treatment with Darco and filtration. The solution was cooled and the clear brownish liquid was basified with ammonia. The collected precipitate was washed with ammonium hydroxide and water and dissolved in 150 cc. of ethanol and 50 cc. of water. A voluminous precipitate of ferric hydroxide was left undissolved, and it was filtered with addition of Supercel. The slightly brownish filtrate was clarified with Darco and diluted with boiling water to a volume of about 800 cc. Beautiful flat needles of I crystallized on cooling (13.5 g., 78%), m. p. 175–176.8°. The fully purified base melts at 176.3–177.5°.

p-Chloro-p'-aminodiphenyl Sulfone (Ia).—When a larger run of the described ammonolysis was carried out in a technical laboratory, a mixture resulted. The crude reaction product was dissolved in the minimum volume of boiling 10% hydrochloric acid and a white crystalline hydrochloride was deposited on cooling. The crystals were redissolved in warm 10% hydrochloric acid and the base was precipitated with ammonium hydroxide. The solid was dried and recrystallized from ethanol from which it appears in the form of white needles. The mixture in our hands yielded 9.8 g. of Ia, m. p. 183–187°, from 50 g. of the crude product. After recrystallization to constant melting point the substance melts at 187.8–188.4°.

Anal.[26] Calcd. for $C_{12}H_{10}O_2NClS$: C, 52.61; H, 3.76; Cl, 13.24. Found: C, 52.21; H, 3.83; Cl, 13.02.

Conversion of Ia to p,p'-Dichlorodiphenyl Sulfone.—A suspension of the acetate corresponding to 2 g. of Ia in 24 cc. of glacial acetic acid was added to the solution of 0.6 g. of sodium nitrite in 6 cc. of concentrated sulfuric acid, according to the method of diazotization described by Hodgson and Walker.[27] The mixture was maintained at room temperature throughout the diazotization. A sample of the clear, yellow solution was miscible with water without turbidity and excess nitrous acid was found to be present. The mixture was poured into the solution of 1.5 g. of cuprous chloride in 15 cc. of concentrated hydrochloric acid. After standing for one hour the liquid was poured into much water, the light yellow precipitate was collected, digested with warm dilute ammonium hydroxide, boiled up with 10% hydrochloric acid, collected and dried; yield of crude product 2.0 g., m. p. 138–146°. To remove the colored impurity the material was dissolved in hot alcohol and treated with the solution of 3.5 g. of stannous chloride in 10 cc. of concentrated hydrochloric acid. The product was recovered from the solution and after two recrystallizations from ethanol it melted at 146.7–148.1°; when mixed with authentic p,p'-dichlorodiphenyl sulfone the melting point was 146.6–148.1°.

p-Chloro-p'-acetylaminodiphenyl Sulfone (Ib).—A mixture of 3 g. of Ia, 5 cc. of glacial acetic acid and 2 cc. of acetic anhydride was boiled under reflux for one hour. The cooled mixture was poured into much water, the solid was collected, washed and dried; it amounted to 3.4 g. (99%) of Ib, melting at 193–196°. On recrystallization from ethanol 3.1 g. of leaflets was obtained, m. p. 185–197°. The long melting interval is due to the existence of two melting points. The analytical sample, obtained by crystallization from alcohol melted at 186.6–188.2°, 196.6–197.8°. A sample was sublimed in high vacuum at 170°; when introduced to a bath at 190° it sintered, resolidified and melted 196.2–197.4°.

Anal.[26] Calcd. for $C_{14}H_{12}O_3NSCl$: C, 54.27; H, 3.90; N, 4.52. Found: C, 54.13; H, 3.94; N, 4.73.

p,p'-Bissuccinoylaminodiphenyl Sulfone (II).—A solution of 10 g. of I and 8.6 g. of succinic anhydride in 350 cc. of dry dioxane was boiled under reflux for three hours. The solution turned faintly yellow and after two hours of boiling a precipitate began to crystallize. The solid was filtered after cooling; the crystals seemed to contain dioxane of crystallization as indicated by the neutralization equivalent. The product was boiled with 400 cc. of ethanol in which it slowly dissolved. Two crops of stout needles, totaling 9.75 g. were obtained, which withered at 170° and melted with decomposition at 233–235°, the temperature depending on the rate of heating. The dioxane mother liquor was freed from solvent under reduced pressure, the residue was taken up in ethanol and decolorized with Darco, yielding 5.6 g. of material decomposing at 220–225°. Total yield was 77%. An analytical sample was obtained by repeated recrystallization from ethanol. The crystals become opaque and lose their structure on prolonged keeping. Analysis and neutralization equivalent indicate the presence of one molecule of alcohol of crystallization, which is lost on drying at 170°.

Neut. equiv. 1. Crude product from dioxane: calcd. for $C_{20}H_{20}O_8N_2S\cdot C_4H_8O_2$: 268. Found: 259, 263. 2. Sample crystallized from alcohol, calcd. for $C_{20}H_{28}O_8N_2S\cdot C_2H_6O$: 247. Found: 248, 248. 3. Sample crystallized from alcohol and dried *in vacuo* at 175° for one hour: calcd. for $C_{20}H_{20}O_8N_2S$: 224. Found: 227, 224. *Anal.*[26] Calcd. for $C_{20}H_{20}O_8N_2S\cdot C_2H_6O$: C, 55.43; H, 5.30. Found: C, 53.16; H, 5.22.

Conversion of II to the Half Sodium Salt.—To the hot alcoholic solution of 13 g. of II was added the hot alcoholic solution of 2.16 g. of anhydrous sodium acetate. The crystalline precipitate which appeared on cooling was suspended in water, the mixture was acidified and the solid was dissolved in alcohol and reprecipitated as described, yielding 10.8 g. (83%) of the half sodium salt of II containing one molecule of ethanol of crystallization for 2 molecules of the salt.

Neut. equiv. Calcd. for $2\ C_{20}H_{19}O_8N_2SNa\cdot C_2H_6O$: 493. Found: 494, 496. *Anal.*[26] Calcd. for $2\ C_{20}H_{19}O_8N_2SNa\cdot C_2H_6O$: C, 51.11; H, 4.49. Found: C, 50.84; H, 4.11.

Diphenyl Sulfone p,p'-Bisisocyanate (III).—Into the warm solution of 5 g. of I in 80 cc. of pure, dry dioxane was passed dry hydrogen chloride until the precipitation ceased. Phosgene from a cylinder was passed through linseed oil and sulfuric acid and introduced to 100 cc. of

(25) All melting points are corrected.

(26) Microanalysis by E. Werble.

(27) Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

dry, pure dioxane until 7.8 g. (1 molecule excess) was dissolved. The phosgene solution was added to the suspension of amine salt and the mixture was boiled under reflux with mechanical stirring and exclusion of moisture while a slow stream of phosgene was passed through. After three-fourths hour a clear yellowish solution had formed, the phosgene cylinder was closed, and dioxane was distilled until the volume of the solution had decreased to about 10 cc. Dry benzene was added in four successive 50-cc. portions, each portion being distilled before addition of the next one. The evolution of hydrogen chloride ceased during distillation of the last portion of benzene; the solution was concentrated to a volume of about 30 cc. and 5 g. (82.5%) of III was isolated in two crops of large yellowish crystals, which when introduced to a bath at 149° melted, resolidified and remelted at 153–156°. Recrystallization from dry benzene yielded an analytical sample consisting of a mixture of colorless needles and plates, both melting at 156–158.8° with previous softening.

It is not necessary to precipitate the base hydrochloride before the addition of phosgene; likewise there is no advantage in adding a solution of the base to a solution of phosgene. An excess of 10–30% over the calculated amount of phosgene was found to be sufficient. In an experiment using a sample of the dihydrochloride of I, which had been obtained in aqueous solution, the reaction proceeded very slowly and the yield was poor. In general the yields of III are quite reproducible although the time necessary for the reaction to proceed may vary. In several cases it was found convenient not to isolate III but rather to use it in benzene solution for the next reaction.

Anal.[26] Calcd. for $C_{14}H_8O_4N_2S$: C, 55.99; H, 2.94. Found: C, 56.41; H, 2.84.

p,p'-Bisureidodiphenyl Sulfone (IV).—A solution of III was prepared from 15 g. of I as described. After distillation of the dioxane 500 cc. of dry benzene was added and the solution was boiled under reflux until the evolution of hydrogen chloride subsided. The solution was clarified with Darco and cooled, filtered from a small amount of precipitation and made up to a volume of 600 cc. Dry ammonia was passed into the cold solution for twenty minutes, and a white precipitate settled with slight evolution of heat. It amounted to 19.5 g. of a solvated product, which lost the solvent at about 170° and melted at 264° with decomposition. By digestion of the product with warm ethanol it was transformed into crystalline, non-solvated material (17.4 g., 84%), m. p. 264–265° with decomposition. A sample was recrystallized from 150 parts of a 6:1 alcohol–water mixture, then dissolved in the necessary amount of a 5:1 pyridine–water mixture and poured into 10 volumes of hot water. On standing fine needles appeared which soon became opaque; decomposition point, 265°.

Anal.[26] Calcd. for $C_{14}H_{14}O_4N_4S$: C, 50.29; H, 4.22; N, 16.76. Found: C, 50.59; H, 4.12; N, 16.61.

p,p'-Bisethylcarbamyldiphenyl Sulfone (V).—A solution of 0.5 g. of III in 10 cc. of dry hot dioxane was filtered from a small amount of insoluble material and 3 cc. of commercial absolute ethanol was added. A crystalline solid appeared soon and after warming the mixture on the steam-bath for twenty minutes the supernatant liquid was clear. After cooling 0.48 g. (74%) of faintly tan-colored, small prisms was isolated, decomposing at about 270°. After two recrystallizations from aqueous pyridine the sample was colorless, m. p. 268–274°, with decomposition.

Anal.[26] Calcd. for $C_{18}H_{20}O_6N_2S$: C, 55.09; H, 5.13. Found: C, 55.41; H, 5.37.

Diphenyl Sulfone p,p'-Bisureidoacetic Acid (IV).—To the solution of 5 g. (14% excess) of glycine in 37.9 cc. of 1.76 *N* sodium hydroxide were added 8.6 g. of crude III and a few drops of dioxane. The suspension was stirred and a slight evolution of heat ensued which subsided after ten minutes, when only a small amount of a fluffy solid was left undissolved. The solution was treated with Norite and Supercel and acidified after cooling, yielding 12.2 g. (91.5%) of the hydrate of VI. On acidification of a hot solution of the acid in alkali and 500 parts of water the hydrate crystallizes on cooling in long slender needles. When the hydrate is warmed with a little water or ethanol or on drying *in vacuo* a prismatic, anhydrous form results, melting at 222–227° with gas evolution. The hydrate may be dissolved without dehydration by quickly bringing it into excess hot water, from which it crystallizes as described. The anhydrous form is insoluble in alcohol and in water but it dissolves in a 2:1 mixture of alcohol and water, from which it crystallizes with one molecule of alcohol of crystallization.

The diethyl ester of VI was prepared by treating the filtered solution of 1.93 g. of III in 50 cc. of hot, dry benzene with a solution of 2 g. of ethyl glycinate in 5 cc. of dry benzene and boiling the resulting suspension for fifteen minutes under reflux. The white crystalline solid was filtered and dried (2.9 g.), m. p. 215–225° with decomposition. The material was insoluble in most solvents; from a 5:1 mixture of dioxane and water it crystallizes in the form of small prisms which wither at 180° and melt at 223–225° with decomposition. The analysis indicates the presence of one molecule of water of crystallization, which is lost on drying *in vacuo* at 180°. The ester is readily saponified by digestion with *N* sodium hydroxide at room temperature.

Neut. equiv. 1. Anhydrous acid, calcd. for $C_{18}H_{18}O_4N_4S$: 225. Found: 224, 226. 2. Hydrate of acid, calcd.: 234. Found: 234, 236. 3. Alcoholate of acid, calcd.: 248. Found: 248, 248.

Anal.[26] Calcd. for $C_{18}H_{18}O_8N_4S$: C, 48.00; H, 4.02. Found: C, 48.28; H, 4.07. Calcd. for hydrated ester, $C_{22}H_{26}O_8N_4S\cdot H_2O$: C, 50.37; H, 5.38. Found: C, 50.59; H, 5.31. Calcd. for anhydrous ester: C, 52.16; H, 5.17. Found: C, 52.41; H, 5.34.

p,p'-Bis-β-diethylaminoethylureidodiphenyl Sulfone (VII).—A solution of III in 600 cc. of dry benzene was prepared from 10 g. of I as described above. To the cold solution was added 10 g. of β-diethylaminoethylamine in a small amount of benzene. A white solid settled immediately with slight evolution of heat; after standing for one hour and brief warming on the steam-bath it was collected and dried. The yield was 20.45 g. (95.4%), m. p. 214–216° with decomposition. After repeated crystallization from commercial absolute ethanol VII appeared in the form of large colorless prisms, melting at 215–216° with discoloration and decomposition. The substance is readily soluble in dilute hydrochloric acid.

Anal.[28] Calcd. for $C_{26}H_{40}O_4N_6S$: C, 58.62; H, 7.57; N, 15.78. Found: C, 58.90, 58.74; H, 7.45, 7.61; N, 15.84, 15.52.

Neut. equiv., calcd.: 262. Determined with methyl orange in alcoholic–aqueous solution, found: 268, 265.

p,p'-Bisstearylaminodiphenyl Sulfone (VIII).—A mixture of 50 g. of stearic acid (Eastman) and 30 cc. of purified thionyl chloride was warmed on the steam-bath for one hour. Thionyl chloride was distilled and the residue was heated with a free flame in the vacuum of the water pump until beginning of ebullition, cooled and quickly dissolved in 75 cc. of dry pyridine. The mixture was treated with a solution of 22 g. of I in 75 cc. of dry pyridine and the resulting red solution was warmed on the steam-bath for one hour. After cooling it was diluted with 1000 cc. of ether and the precipitated material was collected, washed well with ether, and dried. After recrystallization from chloroform 41.4 g. (60%) of VIII was obtained in the form of colorless, hair-fine needles, m. p. 143–146°. After several recrystallizations from commercial absolute ethanol the substance formed microscopic leaflets, m. p. 145–146° with slight softening at 142°.

Anal.[26] Calcd. for $C_{48}H_{80}O_4N_2S$: C, 73.80; H, 10.32; N, 3.59. Found: C, 74.26; H, 10.32; N, 3.72.

p,p'-Bischaulmoogrylaminodiphenyl Sulfone (XI).—Chaulmoogric acid was regenerated from ethyl chaulmoograte according to Shriner and Adams.[29] A mixture of 1.5

(28) Microanalysis by Dr. Carl Tiedcke.

(29) Shriner and Adams, THIS JOURNAL, 47, 2727 (1925).

g. of chaulmoogric acid, 10 cc. of ligroin (b. p. 70–90°), and 1 cc. of phosphorus trichloride was boiled under reflux for one hour with exclusion of moisture. A yellowish semi-solid was deposited, the solution was decanted and the low-boiling material was distilled at atmospheric pressure, then *in vacuo*, with nitrogen passing through the boiling capillary. Two additional portions of ligroin were added and distilled and the residue was dissolved in chloroform. The solution was added to a suspension of 0.64 g. of I in 3 cc. of dry pyridine and 10 cc. of chloroform. Soon a clear brownish solution resulted, leaving a brown resin on the bottom of the flask. A white precipitate began to appear and the mixture stood at room temperature for twenty hours. Solution and precipitate were decanted from the resin, chloroform was distilled and the remaining pyridine solution was poured into excess 10% hydrochloric acid. The resulting flocculent precipitate was collected, dried and recrystallized from ethanol, yielding 1.1 g. (53%) of XI in the form of small warts, melting at 135.8–138°. Immersed in a bath at 130° the substance melts, resolidifies and remelts at the given temperature. Several recrystallizations from commercial absolute alcohol yielded an analytical sample, m. p. 135.9–137.5°. In a larger run, using 21.4 g. of fatty acid and 9.55 g. of I, the solution was warmed during the condensation and no resin was observed in this case. However, the yield of pure product was only 12.6 g. (42.5%). The distillation of chloroform from the decanted condensation mixture was omitted in one run and the product was filtered immediately, yield 44%, m. p. 134–136°.

Anal.[26] Calcd. for $C_{48}H_{72}O_4N_2S$: C, 74.56; H, 9.38; N, 3.62. Found: C, 74.51; H, 9.32; N, 3.72.

p,p'-Bisformylaminodiphenyl Sulfone (X).—A solution of 10 g. of I in 100 cc. of 98% formic acid was boiled under reflux for three and one-half hours, allowed to cool and poured into 1.5 liters of water. The milky suspension soon coagulated and the precipitate was collected, washed until free from acid and dried in an evacuated desiccator over concentrated sulfuric acid and potassium hydroxide. The yield was 11.4 g. (93%), m. p. 268–270°. The product was dissolved in 450 cc. of ethanol and 300 cc. of water, treated with Darco and diluted with 750 cc. of hot water. On cooling 8.7 g. of X crystallized in the form of blades, m. p. 268–270°. The analytical sample melts at 268–270° with slight decomposition.

Anal.[26] Calcd. for $C_{14}H_{12}O_4N_2S$: C, 55.25; H, 3.97; N, 9.20. Found: C, 55.57; H, 3.90; N, 9.09.

Disodium p,p'-Bisbenzensulfonylaminodiphenyl Sulfone (XI).—**(A)** To a solution of 21.8 g. of I in 100 cc. of pyridine was added quickly a mixture of 34.4 g. (10% excess) of benzenesulfonyl chloride and 50 cc. of pyridine. A red color developed and heat was evolved. After standing at room temperature for three hours a green fluorescence had appeared which vanished when the mixture was warmed on the steam-bath for half an hour. The viscous solution was poured with stirring into ice water containing excess hydrochloric acid and the resulting amorphous precipitate was collected and washed free from acid. The cake was dissolved in 400 cc. of hot water containing the calculated amount of sodium hydroxide and the brownish solution was clarified with Darco. It was concentrated on the steam-bath until a solid began to crystallize, 1000 cc. of ethanol was added and after cooling the salt was precipitated by slowly adding 2000 cc. of ether. The disodium derivative XI appeared in the form of hairlike needles, yield 44.75 g. (89%). For further purification 15 g. of the salt was dissolved in 100 cc. of hot water. Addition of 500 cc. of ethanol and 700 cc. of ether precipitated 12.5 g. of XI. Aqueous solutions of XI have a *p*H of 8–9; they cannot be neutralized without precipitation of the free Hinsberg derivative. The analytical sample consists of a mass of colorless hairlike needles which have no characteristic melting point.

Anal.[26] Calcd. for $C_{24}H_{18}O_6N_2S_2Na_2$: S, 16.79; N, 4.89; Na, 8.03. Found: S, 16.77; N, 5.09; Na, 7.88.

(B) To the solution of 50 g. of I in 200 cc. of pyridine was added with stirring the solution of 80 g. of benzenesulfonyl chloride in 70 cc. of pyridine. The addition took twenty minutes and the temperature stayed between 60–70°. After standing for one and one-half hours the dark red, slightly fluorescent solution was boiled under reflux for one-half hour. A solution of 40 g. of sodium hydroxide in 200 cc. of water was added while at the same time pyridine–water mixture was distilled. The alkali was added over one hour during which 177 cc. of liquid distilled and the mixture set to a stiff paste. Distilling was continued until 475 cc. of distillate had been collected, containing most of the pyridine, while a suitable amount of solvent was maintained in the reaction vessel by gradual addition of 650 cc. of water. During the addition of alkali and the distillation the color of the mixture changed to a faint tan. The mass was allowed to cool, the solid was filtered, pressed, washed with 100 cc. of ice water, and 50 cc. of ethanol and dried. The yield was 98 g. (85%) of a whitish microcrystalline powder. Purity and identity were examined by converting 5 g. of the product into the dimethyl derivative by the procedure described below. A yield of 3.55 g. (73%) of the methylation product was obtained, m. p. 187–189°. A recrystallized sample did not depress the melting point of authentic N,N'-dibenzenesulfonyl-p,p'-bismethylaminodiphenyl sulfone.

N,N'-Dibenzenesulfonyl-p,p'-bismethylaminodiphenyl Sulfone.—To a solution of 29.75 g. of XI in 300 cc. of water and 600 cc. of ethanol was added 15 cc. of methyl iodide and the mixture was boiled under reflux. After forty-five minutes a crystalline solid appeared. The solution was heated for altogether two hours, allowed to cool and filtered. The product amounted to 23.5 g. (81.5%), melting at 188–192°. No satisfactory material was isolated from the mother liquor. The compound was recrystallized from 30 parts of ethyl acetate; the recovery is poor unless the mother liquors are worked extensively. In pure state the substance forms stout needles, m. p. 192.8–193.7°. Sometimes another modification is isolated in the form of thin needles, melting below 188°, resolidifying and melting at the temperature given.

Anal.[26] Calcd. for $C_{26}H_{24}O_6N_2S_3$: C, 56.10; H, 4.34; N, 5.03. Found: C, 55.77; H, 4.15; N, 5.36.

p,p'-Bismethylaminodiphenyl Sulfone (XII).—**(A)** To 8.55 of the described benzenesulfonyl derivative was added 15 cc. of concentrated sulfuric acid. The solid dissolved rapidly and the solution stood for one hour at room temperature. It was poured into 450 cc. of ice water and soon XII crystallized in the form of needles or sometimes small plates. The precipitation was completed by neutralizing at ice-temperature with sodium hydroxide, the product was collected, washed until free from alkali and dried. The yield was 4.15 g. (98%), m. p. 179–181.4°. On recrystallization from commercial absolute ethanol the substance may appear as rhombic plates, melting in the pure state at 180.8–182.3°, or in the form of slender needles which melt below 177°, resolidify and remelt at the temperature given (literature,[8] m. p. 179–180°).

Anal.[26] Calcd. for $C_{14}H_{16}O_2N_2S$: C, 60.84; H, 5.83; N, 10.14. Found: C, 61.17; H, 5.45; N, 9.90.

(B) A mixture of 5 g. of p,p'-dichlorodiphenyl sulfone, 30 cc. of 33% aqueous methylamine, and a pinch of each cuprous bromide and copper bronze was shaken in a copper-lined rocking bomb for thirty-six hours at 200–210°. The product was isolated as described for I, but the crude material was dried and crystallized from alcohol, yielding 4.06 g. of XII, m. p. 172–177°. Purification from ethanol was unsatisfactory. The diacetyl derivative prepared as described below (90.7%, m. p. 162–163.5°), could be brought to a constant melting point at 162.8–164.1°, but this melting point is lower than that obtained by acetylation of a sample of XII prepared according to procedure A. The regenerated and recrystallized base melted at 179.8–180.8°, also lower than the melting point of the product in A. A mixture of samples of XII prepared according to A and B melted at 179.4–181.8°.

N,N'-Diacetyl-p,p'-bismethylaminodiphenyl Sulfone (XIII).—A solution of 9.8 g. of XII in 70 cc. of acetic anhydride was boiled under reflux for two hours. After

cooling the mixture was stirred into 300 cc. of water and a clear homogeneous solution was formed. An aqueous solution of 60 g. of sodium hydroxide was added slowly with mechanical stirring while the temperature was kept below 10° by addition of ice, and a crystalline solid settled during the neutralization. When exact neutrality had been reached, the crystallization was allowed to go to completion, the product was collected and dried *in vacuo* over concentrated sulfuric acid. The yield was 11.9 g. (93%), m. p. 164–165.8°. The product can be recrystallized from very dilute ethanol or from a large volume of water, forming small leaflets which melt when introduced to a bath at 159°, resolidify and remelt at 164.4–165.8°.

Anal.[26] Calcd. for $C_{16}H_{20}O_4N_2S$: C, 59.98; H, 5.60; N, 7.77. Found: C, 60.23; H, 5.34; N, 7.73.

p,p'-Bismethylaminodiphenyl Sulfone Dinitrosamine.—To a solution of 170 mg. of XII in 2 cc. of 10% hydrochloric acid was added quickly the solution of 90 mg. of sodium nitrite in a little water. A semi-solid settled, which soon solidified completely, yielding 195 mg. of a light yellow powder, decomposing at 195–204°. The compound decomposes on attempted purification from boiling toluene or acetic acid. By dissolving the product in 17.5 cc. of warm chloroform and precipitating the solution with 30 cc. of ethanol, fine light yellow needles of the dinitrosamine were obtained, decomposing at 207–212°. The substance did not lose weight on drying *in vacuo* at 70° for three hours:[26] Nitrogen analyses by two different laboratories gave low and varying values, and the expected amount of nitrogen was evolved only when the Dumas determination was carried out in the presence of potassium chlorate. The regeneration of the parent amine from the nitrosamine by reduction with tin and hydrochloric acid confirms the structure of the nitroso compound.

Anal. Calcd. for $C_{14}H_{14}O_4N_4S$: C, 50.29; H, 4.22; N, 16.76. Found:[26] C, 50.44, 50.73; H, 3.97, 4.14; N, 14.52, 14.81, 16.72. Found:[28] N, 16.00, 16.15.

Regeneration of XII from the Dinitrosamine.—A mixture of 1 g. of tin granules, 230 mg. of the dinitroso compound, 5 cc. of concentrated hydrochloric acid and 5 cc. of water was boiled under reflux. After five minutes a clear, colorless solution was formed, boiling was continued for five additional minutes and the cooled solution was decanted from unused tin. The liquid was made alkaline with a solution of 4.8 g. of sodium hydroxide in water and the base was collected, washed until free from alkali and dried. The yield of 190 mg. had a m. p. of 180–181.6°. After one recrystallization from commercial absolute ethanol the regenerated XII melted at 180.8–182.1°, not depressed by admixture of authentic material.

p,p'-Bisdimethylaminodiphenyl Sulfone Dimethiodide (XIV).—A mixture of 10 g. of I, 25 cc. of dry methanol and 17 cc. of methyl iodide in a sealed tube was heated at 120° for nine and one-half hours. Considerable pressure was discharged on opening the tube. The product consisted mainly of a brown crystalline mass, which was collected, washed with methanol and ground in a mortar. The solid was extracted by digestion with 250 cc. of water for two hours at room temperature. The filtrate with the washings amounted to 400 cc. On addition of 3800 cc. of acetone 12 g. (46%) of XIV crystallized slowly. The analysis indicated one molecule of acetone of crystallization, and the product gave a positive iodoform test. By repeated crystallization in the described manner faintly yellow prisms were obtained which lost their crystalline structure on heating and melted at 267.4–268.8°. The purified material may also be recrystallized from hot water. On extracting the water-insoluble part of the reaction mixture and the material dissolved in the methyl alcoholic filtrate with 10% hydrochloric acid, basifying and recrystallizing the base from alcohol, 0.65 g. (5.5%) of impure XV was isolated, m. p. 264–267°.

Anal.[28] Calcd. for $C_{18}H_{26}O_2N_2I_2S \cdot C_3H_6O$: C, 39.02; H, 4.99; I, 39.27. Found: C, 39.17; H, 5.23; I, 39.28.

p,p'-Bisdimethylaminodiphenyl Sulfone (XV).—Into a round-bottom flask was placed 5 g. of the methiodide XIV and the flask was evacuated with an aspirator pump. The vessel was immersed into a bath at 110° and the temperature was raised to 270° during fifteen minutes. Gas evolution began at 200° and ceased when at 270° the mass had changed to a clear, light brown melt. The product solidified to a loose crust of tan crystals, yield 2.3 g. (97%), m. p. 264–268°. A sample was crystallized from pyridine, then from dioxane and sublimed in high vacuum at 220–230°, yielding a white crystalline powder, m. p. 265.8–267.8° with slight previous softening (literature,[8] m. p. 259–260°). A convenient way of purifying the base consists in dissolving it in 10% hydrochloric acid and reprecipitating it in crystalline form by dilution with water.

Anal.[26] Calcd. for $C_{16}H_{20}O_2N_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.35; H, 6.26; N, 9.12.

When 1 g. of XV, 1 cc. of methyl iodide and 5 cc. of absolute methanol were heated at 110–120° in a sealed tube for ten hours, 560 mg. (52%) of XIV was isolated in the described manner, melting at 266–267.8° after previous decomposition. A mixture of the residue from the decomposition and a sample of XV, melted at the same temperature.

Nitrosation of XV.—To a solution of 400 mg. of XV in 60 cc. of concentrated hydrochloric acid and 40 cc. of water was added slowly a solution of 600 mg. (6 molecules) of sodium nitrite in water. The resulting yellow solution was allowed to stand overnight and a yellow solid settled, which was collected and washed with 100 cc. of hydrochloric acid of the specified concentration. The product was digested with 2 cc. of ice-cold concentrated hydrochloric acid, collected, washed with ice-cold concentrated and then with 10% hydrochloric acid. The yield was 300 mg. of a light yellow powder, decomposing at 190–195°. The material was recrystallized from 250 cc. of boiling ethanol, from chloroform–ethanol and finally from ethanol, yielding 80 mg. of fine yellow needles of p,p'-bismethylaminodiphenylsulfone dinitrosamine, decomposing at 207–214°. The color of this product was a distinctly darker yellow than that of the material prepared by direct nitrosation of XII. The nitroso compound was reduced with tin and hydrochloric acid as described and on recrystallization of the product from commercial absolute ethanol 65 mg. of XII was isolated in two crops, m. p. 177.5–180.2°. One recrystallization raised the melting point to 179–180.6°, not depressed by admixture of authentic material.

When 550 mg. of XV in 25 cc. of 10% hydrochloric acid was nitrosated with 130 mg. (3 molecules) of sodium nitrite, a yellow powder was precipitated, from which after two recrystallizations 280 mg. of large, flat, yellow needles was isolated, decomposing at 207–217° to a wine-red liquid. The substance gave a green color in the Liebermann test, changing to cherry-red on dilution. The analysis indicates elimination from XV of one methyl group by a nitroso group. The substance is soluble in cold concentrated hydrochloric acid. However, on reduction with tin and hydrochloric acid the product gave rise to a white, basic solid, which showed the melting range 229–245°, and repeated crystallization has not yet yielded a pure homogeneous substance, so that the homogeneity of the mononitroso compound is not rigorously established.

Anal. The substance did not lose weight on drying *in vacuo* at 70° for three hours.[26] Calcd. for $C_{15}H_{17}O_3N_3S$: C, 56.41; H, 5.31; N, 13.15. Found:[26] C, 56.56; H, 5.10; N, 12.91 (potassium chlorate added). Found:[28] N, 12.62, 12.85.

p,p'-Dicyanodiphenyl Sulfide.—To the ice-cooled mixture of 18.7 g. of concentrated sulfuric acid, 50 cc. of water and 10 g. of thioaniline was quickly added an aqueous solution of 6.6 g. of sodium nitrite with mechanical stirring. After one-half hour only a small amount of material was left undissolved; the orange solution was filtered through glass wool and neutralized with sodium hydroxide. A catalyst solution was prepared by adding the solution of 46 g. of cupric sulfate in 250 cc. of water to 52 g. of potassium cyanide in 120 cc. of water. The diazo solution was introduced to the catalyst at 65° and a dark solid was de-

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.

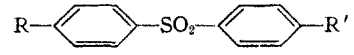
CAMBRIDGE, MASS. RECEIVED SEPTEMBER 1, 1945

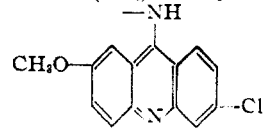
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

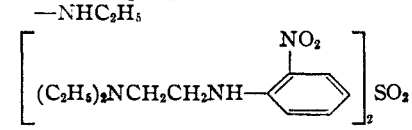
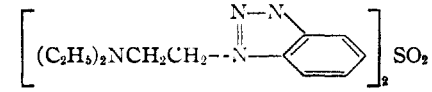
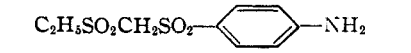
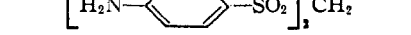
Derivatives of *p,p'*-Diaminodiphenyl Sulfone. II[1]

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).

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