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SULFONES. II. DERIVATIVES OF 4,4′-DIAMINODIPHENYL SULFONE

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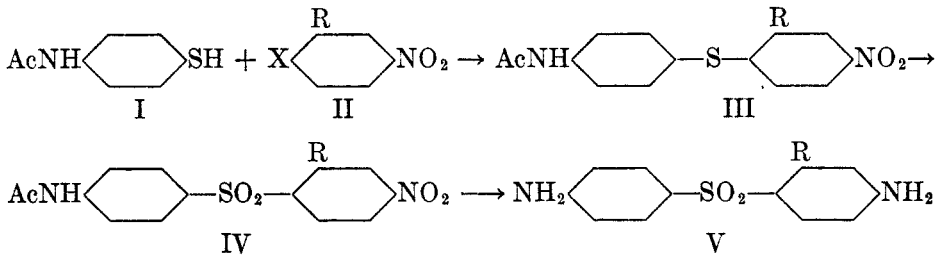
Since 4,4′-diaminodiphenyl sulfone is the only diaminodiphenyl sulfone which has chemotherapeutic activity (1), a number of C and N derivatives of it have been synthesized in order to determine the effect on the activity.[1]

4,4′-Diaminodiphenyl sulfones were prepared with substituents in the 2-position, namely: amino, chloro, sulfamyl, carbamyl, and methyl. The 2-amino derivative was synthesized by the condensation of *p*-acetaminobenzenesulfinic acid with 2,4-dinitrochlorobenzene followed by reduction of the nitro groups and hydrolysis. The remainder were synthesized by the condensation of the appropriately substituted *p*-nitrohalobenzene (II) with *p*-acetaminothiophenol (I) to the sulfides, III, then oxidation to the sulfones, IV. Reduction of the nitro group and hydrolysis gave the desired diamines, V. Similarly, 4-amino-1-naphthyl 4-aminophenyl sulfone[2] was prepared starting with 1-iodo-4-nitronaphthalene.



Nitration of 4-acetamino-4′-nitrodiphenyl sulfone led to 3,4′-dinitro-4-acetaminodiphenyl sulfone. After removal of the acetyl group, the nitro groups were reduced with stannous chloride to form 3,4,4′-triaminodiphenyl sulfone.

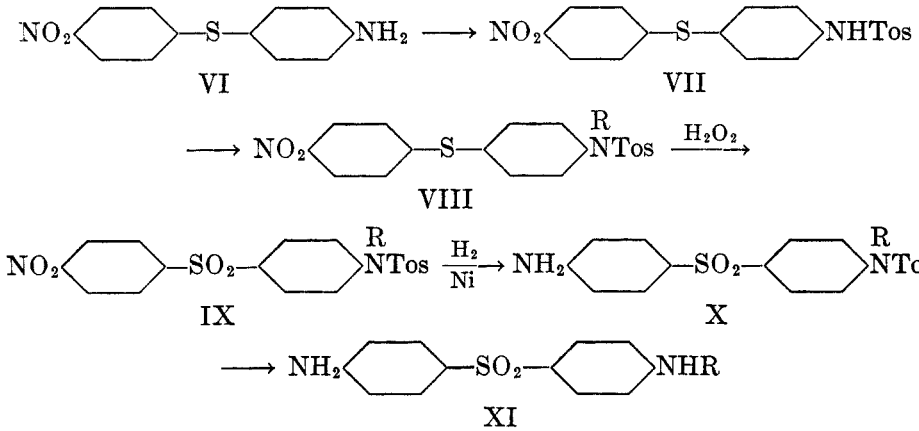
Since it seemed desirable to synthesize a number of N-alkyl derivatives, a general method was sought. 4-Amino-4′-nitrodiphenyl sulfide (VI) (7) was converted to the tosylamide, VII, with *p*-toluenesulfonyl chloride in pyridine. The amide, VII, was smoothly alkylated in Methyl Cellosolve with 10% aqueous potassium hydroxide and a variety of alkyl halides[3] including *n*- and isopropyl iodide, allyl bromide, octyl bromide, lauryl bromide, cetyl iodide, benzyl chloride, *p*-nitrobenzyl chloride, and α-chloroacetanilide to VIII. No difficulty was encountered in the sequence VIII → X.

[1] The biological studies will be reported elsewhere.

[2] Since the completion of this work the preparation of this sulfone by a different method has been described (11).

[3] Attempts to alkylate 4-tosylamino-4′-acetamino (or nitro) diphenyl sulfone with *n*-propyl iodide under similar conditions led to mixtures and much of the unalkylated sulfonamide could be recovered.

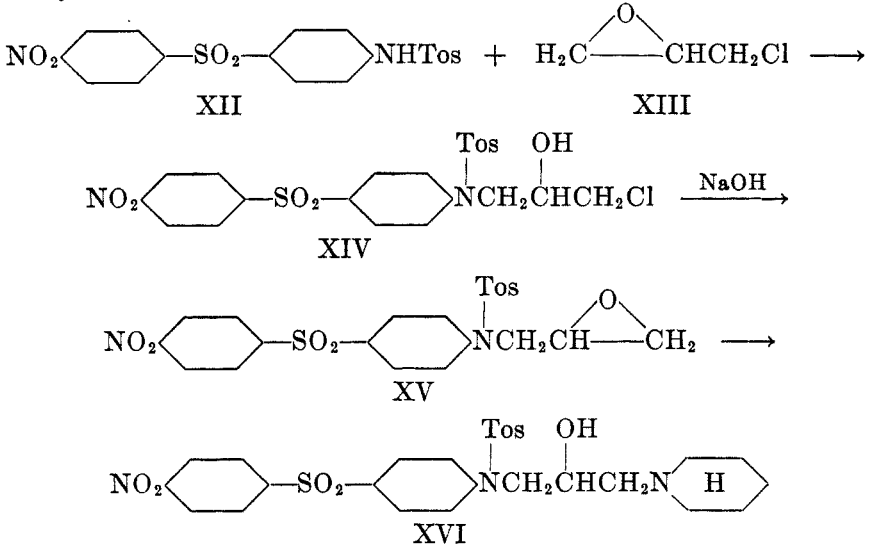
Acid hydrolysis of X to XI proceeded smoothly except in the cases of R = isopropyl, benzyl, and *p*-aminobenzyl. The latter two groups were rapidly cleaved to the corresponding alkyl chloride. 4-Amino-4′-benzylaminodiphenyl



VI VII VIII IX X XI

sulfone was then synthesized by condensation of benzaldehyde with 4-acetamino-4′-aminodiphenyl sulfone and catalytic reduction of the anil followed by hydrolysis of the acetyl group.

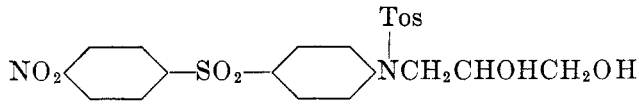
4-Tosylamino-4′-nitrodiphenyl sulfone (XII) readily condensed with epichlorohydrin (XIII) to form the chlorohydrin, XIV, in excellent yield according



XII XIII XIV XV XVI

to the method of Oehle and Haesler (2). With sodium hydroxide in Methyl Cellosolve, the chlorohydrin was converted to the oxide, XV. The latter, with piperidine, gave the amino alcohol, XVI. Catalytic reduction of the nitro group and hydrolysis of the sulfonamide linkage gave 4-(β-hydroxy-γ-piperidinopropylamino)-4′-aminodiphenyl sulfone.

Attempts to open the oxide ring of XV to the glycol, XVII, under a variety of conditions were unsuccessful. However, XVII could be prepared by the direct condensation of glycidol with the sulfone, XII, or by condensation of glycidol



XVII

with the sulfide, VII, followed by oxidation to the sulfone with hydrogen peroxide. The nitro group of XVII was smoothly reduced catalytically, but the 4-(β,γ-dihydroxypropylamino)-4′-aminodiphenyl sulfone obtained on hydrolysis under a variety of conditions could not be induced to crystallize.

Only one disubstituted 4,4′-diaminodiphenyl sulfone was synthesized, namely the 2,2′-dichloro derivative. This compound was prepared in the same manner as the 2-monochloro derivative. Oxidation of the intermediate 2,2′-dichloro-4-acetamino-4-nitrodiphenyl sulfide with hydrogen peroxide in acetic acid gave a mixture which was predominantly the sulfoxide. The oxidation was successfully carried out by the use of potassium permanganate in dilute acetic acid.

It is interesting to note that hydrogen peroxide oxidation of diphenyl sulfides unsubstituted in either 2-position takes place smoothly at 50° in excellent yield. With one substituent *ortho* to the sulfide linkage, the peroxide oxidation is incomplete at 50° and is finished by heating on the steam-bath. However, the yields are considerably lower than with the non-*ortho* substituted sulfides. As noted above, with groups in both the 2 and 2′-positions, hydrogen peroxide oxidation fails completely as a preparative method.

Acknowledgment. The authors wish to thank Mr. Louis Brancone and his staff for the microanalyses.

EXPERIMENTAL

2,4-Dinitro-4′-acetaminodiphenyl sulfone. To a solution of 40 g. of *p*-acetaminobenzenesulfinic acid in 200 cc. of alcohol containing 8 g. of reagent sodium hydroxide in 8 cc. of water was added 42 g. of 2,4-dinitrochlorobenzene. The mixture was refluxed for thirty minutes, during which the product separated. The mixture was cooled, the solid was removed and washed successively with alcohol, ether, and water; yield, 68 g. (93%), m.p. 222–225°. Recrystallization from Methyl Cellosolve afforded yellow crystals, m.p. 226–227°.

Anal. Calc'd for $C_{14}H_{11}N_3O_7S$: N, 11.5. Found: N, 11.7.

2,4,4′-Triaminodiphenyl sulfone. A mixture of 250 g. of stannous chloride dihydrate in 500 cc. of concentrated hydrochloric and 25 g. of 2,4-dinitro-4′-acetaminodiphenyl sulfone was stirred for fifteen minutes maintaining the temperature at 20–23° by occasional cooling. At the end of this time the tin complex separated; the mixture was diluted with 500 cc. of water, then heated on the steam-bath for thirty minutes after the temperature reached 85°. The product was isolated in the same manner as described for 3,4′-diaminodiphenyl sulfone (1), except that alcohol-water was used for purification; yield, 12.8 g. (71%), m.p. 118°, resolidifies and remelts at 150°. Recrystallization from dilute alcohol did not change the m.p.

Anal. Calc'd for $C_{12}H_{13}N_3O_2S$: C, 54.8; H, 5.0; N, 16.0.
Found: C, 54.5; H, 5.2; N, 16.1.

p-Acetaminothiophenol. A mixture of 344 g. of *p*-chloronitrobenzene, 1290 g. of sodium sulfide monohydrate, and 5.7 l. of water was refluxed for seven hours. Some insoluble oil was removed by washing the solution with benzene. The solution was cooled to 7° with stirring in an ice-bath and treated with 700 cc. of acetic anhydride in one portion. After being stirred in the ice-bath for thirty minutes during which the temperature rose to 21° then subsided, the *p*-acetylthioacetanilide was removed by filtration and washed with water; weight, 398 g., m.p. 125–130°.

The crude acetyl derivative was refluxed on the steam-bath with 1200 cc. of alcohol and 196 g. of sodium hydroxide in 1900 cc. of water for seventy-five minutes. The solution was concentrated *in vacuo* to cloudiness, diluted to about 4 l. with water, and cooled to 5°. The insoluble material was removed by filtration through Celite and the filtrate acidified. The product was washed with water; yield, 196 g. (54%), m.p. 148–150°. In other runs the yields were consistently 54–57%.

The thiophenol was also prepared by reduction of 4,4′-dinitrodiphenyl disulfide with stannous chloride, acetylation of the tin complex, and reprecipitation of the product from alkaline solution. Several reprecipitations were necessary to remove the tin; yield, 36%, m.p. 140–147°. Reduction of acetylsulfanilyl chloride with zinc according to Zincke and Jörg (3) gave inconsistent results. The highest yield obtained was 53%. Very frequently, for no explainable reason, no thiophenol was obtained and sometimes 4,4′-diacetaminodiphenyl disulfide was isolated. Zincke and Jörg (3) give the m.p. of *p*-acetaminothiophenol as 140–145°.

2-Methyl-4-nitro-4′-acetaminodiphenyl sulfide. 2-Methyl-4-nitroiodobenzene was prepared in 71% yield, m.p. 100–103°, from 2-methyl-4-nitroaniline according to the general procedure of Hodgson and Walker (4).

To a solution of 45 g. of *p*-acetaminothiophenol in 360 cc. of alcohol containing 10.8 g. of reagent sodium hydroxide in 11 cc. of water was added 72 g. of 2-methyl-4-nitroiodobenzene. After being refluxed for one hour on the steam-bath, the solution was cooled in an ice-bath. The product was collected and washed with cold alcohol until no more color was removed; yield, 63.5 g. (77%), m.p. 120° (dec.). For analysis a sample was recrystallized from 95% alcohol, yellow crystals of unchanged m.p. The sulfide could not be crystallized from anhydrous solvents and appeared to be a hydrate.

Anal. Calc'd for $C_{15}H_{14}N_2O_3S \cdot H_2O$: C, 56.3; H, 5.0; N, 8.8.
Found: C, 56.5; H, 5.4; N, 8.8.

Similarly, the condensation of 1-iodo-4-nitronaphthalene (4) with *p*-acetaminothiophenol gave a 77% yield of *4-nitro-1-naphthyl 4-acetaminophenyl sulfide*, m.p. 206–208°.

Anal. Calc'd for $C_{18}H_{14}N_2O_3S$: C, 63.9; H, 4.1; N, 8.3.
Found: C, 64.3; H, 4.7; N, 8.1.

2-Carbamyl-4-nitro-4′-acetaminodiphenyl sulfide. To a warm solution of 36 g. of *p*-acetaminothiophenol in 940 cc. of 50% alcohol containing 8.8 g. of reagent sodium hydroxide was added a hot solution of 47 g. of 2-chloro-5-nitrobenzamide (5) in 470 cc. of alcohol in portions over a period of five minutes. After standing for fifteen minutes, the product was washed successively with alcohol and water; yield, 66 g. (93%) m.p. 262–264°. Recrystallization from Methyl Cellosolve-water gave yellow crystals, m.p. 264–266°.

Anal. Calc'd for $C_{15}H_{13}N_3O_4S$: N, 12.7. Found: N, 12.6.

2-Sulfamyl-4-nitro-4′-acetaminodiphenyl sulfide. This compound was prepared from 2-chloro-5-nitrobenzenesulfonamide (6) in the same manner as the corresponding 2-methyl compound. The crude product was filtered from the hot reaction mixture and leached with boiling alcohol; yield, 80%, m.p. 258–263°. Recrystallization from Methyl Cellosolve-water gave yellow crystals, m.p. 266–268°.

Anal. Calc'd for $C_{14}H_{13}N_3O_5S_2$: C, 45.8; H, 3.6; N, 11.4.
Found: C, 45.9; H, 4.0; N, 11.5.

2-Chloro-4-amino-4′-nitrodiphenyl sulfide. A mixture of 75 g. of 3,4-dichloronitrobenzene, 245 g. of sodium sulfide nonahydrate, and 615 cc. of water was refluxed for nineteen hours. After the addition of 62 g. of *p*-nitrochlorobenzene, refluxing was continued for fifteen

hours longer. The insoluble product was recrystallized from alcohol; yield, 59.3 g. (54%), m.p. 145–147°. Recrystallization from alcohol gave orange crystals, m.p. 146–148°.

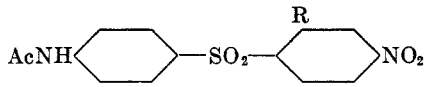
Anal. Calc'd for $C_{12}H_9ClN_2O_2S$: N, 10.0. Found: N, 9.8.

The procedure is patterned after that of Lantz for 4-amino-4'-nitrodiphenyl sulfide (7).

2-Methyl-4-nitro-4'-acetaminodiphenyl sulfone. A mixture of 63.5 g. of the corresponding sulfide, 550 cc. of acetic acid, and 150 cc. of 30% hydrogen peroxide was stirred in a bath at 50° for three hours, then heated on the steam-bath for two hours. The solution was evaporated to dryness *in vacuo* and the residue crystallized from alcohol. Additional compounds prepared in a similar manner are listed in table I.

2-Sulfamyl-4-amino-4'-acetaminodiphenyl sulfone. A mixture of 43.5 g. of 2-sulfamyl-4-nitro-4'-acetaminodiphenyl sulfone, 150 cc. of Cellosolve, and one teaspoon of Raney nickel was shaken with hydrogen at 2–3 atmospheres for 24 hours when reduction was complete. The mixture was heated on the steam-bath to dissolve the product, then filtered.

TABLE I



R	YIELD	M.P., °C.	SOLVENT	ANALYSES					
				Calc'd			Found		
				C	H	N	C	H	N
CH_3	80	160–163	Alc.			8.4			8.3
SO_2NH_2	78[a]	235–237	[b]			10.5			10.1
$CONH_2$	69[f]	254–256	[b]	49.7	3.6	11.6	49.4	3.7	11.5
Cl[g]	88[c]	[d]	Alc.	47.4	3.1	7.9	46.7	3.4	7.8
[e]	93[c]	199–200	Alc.	58.4	3.8	7.6	58.3	3.6	7.1

[a] The condensation of 2-chloro-5-nitrobenzenesulfonamide with sodium *p*-acetaminobenzenesulfinate in dilute alcohol (8) gave a product melting 80° low which was difficult to purify. [b] Methyl Cellosolve-water. [c] The product was isolated by dilution of the reaction mixture with water. [d] Partially melts at 115–120°, resolidifies and remelts at 178–180°. [e] 4-Nitro-1-naphthyl 4-acetaminophenyl sulfone. [f] Attempts to prepare this compound by the direct condensation of 2-chloro-5-nitrobenzamide and sodium *p*-acetaminobenzenesulfinate in dilute alcohol were unsuccessful. [g] The 2-chloro-4'-amino-4-nitrodiphenyl sulfide was acetylated with acetic anhydride in acetic acid, then hydrogen peroxide was added for the oxidation.

Dilution with alcohol gave 28 g. (70%) of product, m.p. 220–223°. Recrystallization of a sample from a large volume of alcohol gave nearly white crystals, m.p. 227–229°.

Anal. Calc'd for $C_{14}H_{15}N_3O_5S_2$: N, 11.4. Found: N, 11.6.

2-Sulfamyl-4,4'-diaminodiphenyl sulfone. A mixture of 28 g. of 2-sulfamyl-4-amino-4'-acetaminodiphenyl sulfone and 280 cc. of 6 *N* hydrochloric acid was refluxed for fifteen minutes. The solution was poured on ice and a slight excess of ammonia water. After acidification with acetic acid, the product was collected; yield, 21.5 g. (88%), m.p. 207–210° dec. Admixture with a sample prepared by an alternative method (8) gave no depression in m.p.

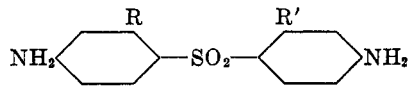
2-Carbamyl-4,4'-diaminodiphenyl sulfone. 2-Carbamyl-4-nitro-4'-acetaminodiphenyl sulfone (48 g.) was hydrogenated in Methyl Cellosolve in the same manner as described for the corresponding 2-sulfamyl derivative. The product crystallized out during reduction and could not be separated from the catalyst by the use of organic solvents. The solvent

was decanted, the precipitate was cooled with 250 cc. of water and then it was treated cautiously with 250 cc. of concentrated hydrochloric acid. After most of the nickel had dissolved, the mixture was refluxed for ten minutes and filtered hot. The filtrate was poured into ice and excess ammonia. The crude product was dissolved in 1 *N* hydrochloric acid, the solution was clarified with Norit, and again made basic with ammonia; yield, 27 g. (70%), m.p. 250° dec. This compound is insoluble in all the common organic solvents. For analysis a sample was continuously extracted with acetone for eight hours. The product was collected from the extract by filtration, white crystals, m.p. 250–252°.

Anal. Calc'd for $C_{13}H_{13}N_3O_3S$: C, 53.6; H, 4.5.
Found: C, 53.7; H, 4.6.

2,2'-Dichloro-4-amino-4'-nitrodiphenyl sulfide. From 100 g. of 3,4-dichloronitrobenzene, 100 g. of sodium sulfide nonahydrate, and 1500 cc. of water followed by 100 g. more of 3,4-

TABLE II



R	R'	YIELD[a]	M.P., °C.	SOLVENT	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
CH_3	H	65	150–153	Alc.	59.6	5.4	10.7	59.6	5.6	10.7
Cl	H	68	118–120	EtAc-C_6H_6	59.8[b]	4.7	7.8	59.8	5.0	7.5
[c]	H	84	261–262	Alc.	64.4	4.7	9.4	64.3	5.4	9.3
Cl	Cl	83	255–257	[d]			8.8			9.0

[a] These compounds were prepared by stannous chloride reduction of the corresponding nitro compounds (IV) in the same way as described for 2-nitro-2'-acetaminodiphenyl sulfone (1). [b] This compound is solvated with one molecule of benzene of crystallization. [c] 4-Amino-1-naphthyl 4-aminophenyl sulfone. The literature (11) records a m.p. of 265° for the compound prepared in a different manner. [d] Methyl Cellosolve and alcohol.

dichloronitrobenzene, was obtained 108 g. (66%) of orange crystals from alcohol, m.p. 136–138° in the same manner as described for 2-chloro-4-amino-4'-nitrodiphenyl sulfide.

Anal. Calc'd for $C_{12}H_8Cl_2N_2O_2S$: C, 45.7; H, 2.5; N, 8.9.
Found: C, 46.0; H, 3.1; N, 9.0.

The *acetyl* derivative formed hydrated yellow crystals from 95% alcohol, m.p. 133–135° dec.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_2O_3S \cdot H_2O$: C, 44.8; H, 3.3; N, 7.6.
Found: C, 45.1; H, 3.5; N, 7.7.

2,2'-Dichloro-4-acetamino-4'-nitrodiphenyl sulfone. A solution of 20 g. of 2,2'-dichloro-4-amino-4'-nitrodiphenyl sulfide in 80 cc. of acetic acid and 9 cc. of acetic anhydride was heated on the steam-bath for thirty minutes, then it was diluted with 120 cc. of acetic acid. The solution was treated at 40–50° with 26 g. of potassium permanganate dissolved in 200 cc. of water in portions. After standing for thirty minutes, the manganese dioxide was dissolved by the addition of sodium bisulfite. After dilution with water, the product was collected; yield, 20.5 g. (82%), m.p. 181–184°. Recrystallization from alcohol gave white crystals, m.p. 182–184°.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_2O_5S$: C, 43.2; H, 2.6; N, 7.2.
Found: C, 43.0; H, 3.3; N, 7.4.

3,4'-Dinitro-4-acetaminodiphenyl sulfone. 4-Acetamino-4'-nitrodiphenyl sulfone was

prepared according to Ferry, Buck, and Baltzly (9b) except that *p*-acetaminobenzenesulfinic acid and *p*-nitrochlorobenzene were condensed directly in the presence of the theoretical amount of sodium hydroxide. The over-all yield was the same.

To a stirred mixture of 50 g. of this sulfone and 200 cc. of concentrated sulfuric acid was added with ice-cooling 100 cc. of nitric acid (d = 1.42) at such a rate that the temperature was 10–15° (fifteen minutes). After removal of the ice-bath, the mixture was stirred for fifteen minutes longer, then poured on ice. The crude product was washed well with water, then leached with hot alcohol and recrystallized from Methyl Cellosolve; yield, 39 g. (68%) of yellow crystals, m.p. 194–195°.

Anal. Calc'd for $C_{14}H_{11}N_3O_7S$: N, 11.5. Found: N, 11.5.

3,4'-Dinitro-4-aminodiphenyl sulfone. A mixture of 38.8 g. of 3,4'-dinitro-4-acetaminodiphenyl sulfone, 388 cc. of 6 *N* hydrochloric acid, and 388 cc. of alcohol was refluxed for one hour, then cooled; yield, 32.8 g. (96%), m.p. 227–231°. Recrystallization from Methyl Cellosolve-water gave yellow crystals, m.p. 230–232°.

Anal. Calc'd for $C_{12}H_9N_3O_6S$: C, 44.6; H, 2.8; N, 13.0.
Found: C, 44.9; H, 3.3; N, 13.5.

3,4,4'-Triaminodiphenyl sulfone. To a solution of 330 g. of stannous chloride dihydrate in 660 cc. of concentrated hydrochloric acid and 620 cc. of alcohol was added 32.8 g. of 3,4'-dinitro-4-aminodiphenyl sulfone. The mixture was stirred for 75 minutes. At the end of twenty minutes solution had taken place and the temperature had risen to 60°. The solution was poured into 730 g. of sodium hydroxide in 730 cc. of water and excess ice. The solid was collected on a sintered-glass funnel. The filtrate was extracted with 800 cc. of butanol. The solid was dissolved in the butanol extract by warming on the steam-bath. After clarification withNorit, the solution was concentrated to about 400 cc. *in vacuo*, then cooled; yield, 18.6 g. (62%), m.p. 132–134°. Recrystallization from butanol gave nearly white crystals of the same m.p.

Anal. Calc'd for $C_{12}H_{13}N_3O_2S$: C, 54.8; H, 5.0; N, 16.0.
Found: C, 55.2; H, 5.4; N, 15.9.

4-Tosylamino-4'-nitrodiphenyl sulfide (VII). A solution of 310 g. of *p*-toluenesulfonyl chloride and 387 g. of 4-amino-4'-nitrodiphenyl sulfide (7) in 1220 cc. of reagent pyridine was allowed to stand for three hours. The mixture was warmed to dissolve the separated product. It was diluted with 2.4 l. of alcohol and 1.1 l. of water, then cooled in an ice-bath. The product was washed with water; yield, 572 g., m.p. 150–154°. From the filtrate was isolated an additional 43 g. (total 97%) of product, m.p. 148–152°. Recrystallization of a sample from alcohol gave yellow crystals, m.p. 154–155°.

Anal. Calc'd for $C_{19}H_{16}N_2O_4S_2$: C, 57.0; H, 4.0; N, 7.0.
Found: C, 57.1; H, 4.0; N, 7.0.

4-(N-Tosyl-n-propylamino)-4'-nitrodiphenyl sulfide (VIII). A mixture of 10 g. of 4-tosylamino-4'-nitrodiphenyl sulfide (VII), 14 cc. of 10% potassium hydroxide, 100 cc. of Methyl Cellosolve, and 2.5 cc. of *n*-propyl iodide was refluxed until the color changed from orange to yellow (two hours). The solution was then neutral. After the addition of 3.2 cc. of 10% potassium hydroxide and 0.6 cc. of *n*-propyl iodide, the solution was again refluxed until the color changed from orange to yellow (two hours). Water was added to turbidity and the solution was cooled in an ice-bath. The yellow product was collected and washed with cold 50% alcohol.

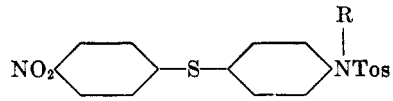
Similar alkylations are listed in Table III.

4-(N-Tosyl-n-propylamino)-4'-nitrodiphenyl sulfone (IX). A mixture of 37.5 g. of corresponding sulfide (VIII), 470 cc. of acetic acid, and 90 cc. of 30% hydrogen peroxide was stirred in a bath at 50° for three hours. The product was isolated by dilution with water. Similar oxidations are listed in Table IV.

4-(N-Tosyl-n-propylamino)-4'-aminodiphenyl sulfone (X). A mixture of 39.2 g. of the corresponding nitro sulfone (IX) and 150 cc. of Methyl Cellosolve was shaken with hydrogen at 2–3 atm. at 60–70° in the presence of Raney nickel until reduction was complete. The mixture was then heated on the steam-bath and enough Methyl Cellosolve was added

to dissolve the product which had separated. The filtered solution was diluted with water to turbidity and cooled. Similar reductions are listed in Table V.

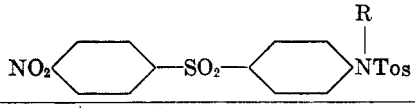
TABLE III



R[a]	YIELD	M.P., °C.	ANALYSES					
			Calc'd			Found		
			C	H	N	C	H	N
n-C_3H_7-	91	112–113			5.9			5.7
iso-C_3H_7-	64[b]	150–151	59.8	5.0	6.3	59.6	5.5	5.9
CH_2=$CHCH_2$-	96	91–93	60.0	4.6	6.4	60.3	4.8	6.4
$C_6H_5CH_2$-	87	121–122	63.7	4.5	5.7	63.6	4.8	5.6
p-$NO_2C_6H_4CH_2$-	65	187–190	58.3	4.0	7.8	57.9	4.2	7.8
-$CH_2CONHC_6H_5$	56	185–187	60.8	4.4	7.9	60.7	4.7	7.8

[a] R = octyl, lauryl, and cetyl were oils which were carried to the next step without further purification. Numbers 1, 2, and 3 were recrystallized from alcohol. Numbers 4, 5, and 6 were recrystallized from Methyl Cellosolve-water. [b] The crude yield, m.p. 124–126°. Considerable loss was entailed in purification.

TABLE IV



R	YIELD	M.P., °C.	ANALYSES					
			Calc'd			Found		
			C	H	N	C	H	N
n-C_3H_7-	98	156–158[c]			5.9			5.7
iso-C_3H_7-	44[a]	199–203[d]	55.7	4.7	5.9	55.8	5.0	5.6
CH_2=$CHCH_2$-	94	145–147[c]			5.9			5.7
C_8H_{17}-	84[b]	118–120[c]	59.7	5.9		59.6	5.9	
$C_{12}H_{25}$-	94[b]	100–102[e]	62.0	6.7	4.7	62.2	7.2	4.6
$C_{16}H_{33}$-	99[b]	96–98[e]			4.3			4.0
$C_6H_5CH_2$-	97	195–197[d]	59.8	4.3	5.4	60.2	4.7	5.4
p-$NO_2C_6H_5CH_2$-	92	183–185[d]	55.1	3.7	7.4	55.5	4.2	7.4
$HOCH_2CHOHCH_2$-	91	170–172[c]			5.5			5.3
H	90	174–176[c]			6.5			6.6

[a] The oxidation was carried out on crude sulfide, m.p. 124–126°. [b] Over-all yield including alkylation step. [c] Recrystallized from alcohol. [d] Recrystallized from Methyl Cellosolve-water. [e] Recrystallized from benzene-petroleum ether. These compounds were waxy solids.

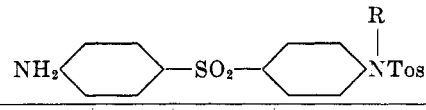
4-(N-Tosyl-N-allylamino)-4'-aminodiphenyl sulfone. To a solution of 18 g. of stannous chloride dihydrate in 18 cc. of concentrated hydrochloric was added 50 cc. of acetic acid

and 10 g. of the corresponding nitro sulfone (IX). The mixture was heated on the steam-bath for thirty minutes, then concentrated *in vacuo* until a solid began to separate. An excess of 40% sodium hydroxide and ice was added. The solid was dissolved in hot Methyl Cellosolve, the solution was clarified with Norit, then diluted with water to turbidity and cooled. The white crystals melted at 193–195°; yield, 7.1 g. (76%).

Anal. Calc'd for $C_{22}H_{22}N_2O_4S_2$: C, 59.7; H, 5.0; N, 6.3.
Found: C, 59.4; H, 5.6; N, 5.9.

4-(N-Tosyl-γ-chloro-β-hydroxypropylamino)-4'-nitrodiphenyl sulfone (XIV). A mixture of 47.4 g. of XII, 0.35 cc. of pyridine, and 14.2 cc. of epichlorohydrin was heated on the steam-bath for one hour. The oil was heated with alcohol when it crystallized. After cool-

TABLE V



R	YIELD	M.P., °C.	ANALYSES					
			Calc'd			Found		
			C	H	N	C	H	N
n-C_3H_7-	96	221–222[d]	59.5	5.5	6.3	59.2	5.2	6.3
iso-C_3H_7-	65	243–245[d]	59.5	5.5	6.3	59.0	5.6	6.0
C_8H_{17}-	99	88–90[e]			5.5			5.7
$C_{12}H_{25}$-	93	90–92[f]	65.2	7.4	4.9	65.2	7.7	4.9
$C_{16}H_{33}$-	94	48–50[f]	67.2	8.0	4.5	67.4	8.0	4.9
$C_6H_5CH_2$-	65	202–204[d]			5.7			5.7
p-$NH_2C_6H_4CH_2$-	72	125–127[e]			8.3			8.3
$HOCH_2CHOHCH_2$-	92	[b]			5.9			6.2
$C_5H_{10}NCH_2CHOHCH_2$-	66	75–78[c]	61.8	6.2	7.2	61.5	6.8	7.3
[a]	90	236–238						

[a] Reduction of 4-nitro-4'-acetaminodiphenyl sulfone. This method was found superior to the stannous chloride reduction described by Raiziss, *et al.* (9a). They record m.p. 242–243° and crude yield, 66%. [b] Melts at 165°, resolidifies and remelts at 185° when crystallized from alcohol. [c] Contains one-half molecule benzene of crystallization. Other solvents give an oil. Also obtained in 86% yield by stannous chloride reduction. [d] Recrystallized from Methyl Cellosolve. [e] Recrystallized from alcohol. [f] Recrystallized from benzene.

ing, the mixture was filtered and the product washed with alcohol; yield, 47.5 g. (85%), of yellow crystals, m.p. 165–167°.

Anal. Calc'd for $C_{22}H_{21}ClN_2O_7S_2$: N, 5.3. Found: N, 5.2.

4-(N-Tosyl-β,γ-oxidopropylamino)-4'-nitrodiphenyl sulfone (XV). To a solution of 46 g. of XIV in 460 cc. of Methyl Cellosolve containing a trace of phenolphthalein and heated on the steam-bath was added a 10% solution of reagent sodium hydroxide in Methyl Cellosolve over a period of ten minutes until a permanent color was obtained (35 cc.). The mixture was heated five minutes more, then diluted with water; yield, 33.3 g. (76%), m.p. 137–140°. Recrystallization from Methyl Cellosolve-water gave nearly white crystals, m.p. 147–149°.

Anal. Calc'd for $C_{22}H_{20}N_2O_7S_2$: C, 54.2; H, 4.1.
Found: C, 54.4; H, 4.5.

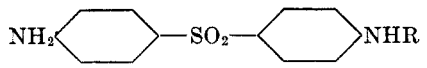
4-(N-Tosyl-β-hydroxy-γ-piperidinopropylamino)-4'-nitrodiphenyl sulfone (XVI). A mixture of 40 g. of XV and 40 cc. of piperidine was heated on the steam-bath to 80° with mix-

ing when the reaction proceeded with heat evolution and formation of a brown solution. After five minutes, during which time the temperature was not allowed to go above 100°, the oil was dissolved in alcohol and diluted with an equal volume of ether. After being cooled, the mixture was filtered and the product washed with alcohol-ether; yield, 37.5 g. (80%) of yellow crystals, m.p. 139–140°.

Anal. Calc'd for $C_{27}H_{31}N_3O_7S_2$: N, 7.3. Found: N, 7.7.

4-(N-Tosyl-β,γ-dihydroxypropylamino)-4'-nitrodiphenyl sulfide. A mixture of 10 g. of VII, 0.1 cc. of pyridine, and 2.5 cc. of glycidol (10) was heated on the steam-bath with mixing for thirty minutes. The temperature was maintained at 99–105° by removing the tube from the steam-bath when necessary. The oil was crystallized from dilute alcohol; yield, 9.2 g. (78%), m.p. 110–115°. Recrystallization from benzene gave yellow crystals, m.p. 120–122°.

TABLE VI



R	METHOD*	TIME (hours)	YIELD, %	M.P., °C.	SOLVENT	ANALYSES					
						Calc'd			Found		
						C	H	N	C	H	N
n-C_3H_7-	A	2	96	200–202[d]	Me Cell.-H_2O	62.2	6.2	9.7	62.2	6.6	9.7
	B[c]	20	80								
CH_2=$CHCH_2$-	B	2	80	154–156[d]	Alc.-H_2O			9.7			9.3
C_8H_{17}-	B	18	95	184–186[a]	MeOH-Et_2O	55.6	7.0	6.5	55.2	7.5	6.5
$C_{12}H_{25}$-	B	2	80	165–167	Alc.	69.2	8.7	6.7	68.9	9.4	6.8
$C_{16}H_{33}$-	A	17	86	159–161	Me Cell.-Alc.	71.2	9.4	5.9	71.0	9.0	6.0
$CH_2OHCHOHCH_2$-	C	3	81	[b]							
$C_5H_{10}NCH_2CHOHCH_2$-	C	2.5	78	150–155	Alc.-H_2O	61.7	7.0	10.8	62.0	7.4	10.8

* (A) Concentrated sulfuric acid (2 cc./g.) at room temperature. Poured on ice and excess ammonium hydroxide; (B) Refluxed with 15 cc. of 9 *N* HCl per g.; worked up as in A; (C) Refluxed with 10 cc. of 9 *N* H_2SO_4 per g., worked up as in A. [a] The dihydrochloride, which crystallized from the reaction mixture. [b] Light colored oil which could not be crystallized. [c] The corresponding isopropyl compound could not be prepared by any of the three methods. [d] This compound has been mentioned in the biological literature a number of times (13), but no description of its preparation or chemical properties has appeared.

Anal. Calc'd for $C_{22}H_{22}N_2O_6S$: C, 55.7; H, 4.7; N, 5.9.
Found: C, 55.6; H, 5.0; N, 5.9.

Glycidol could also be condensed with the sulfone, XII, in the same manner, but the yields were only 40–50% and in one run the reaction got out of control with a rise in temperature to 150° and the formation of a black tar.

4-Acetamino-4'-benzylaminodiphenyl sulfone. A mixture of 29 g. of 4-acetamino-4'-aminodiphenyl sulfone, 20 cc. of benzaldehyde, 2 g. of anhydrous sodium acetate, and 150 cc. of Methyl Cellosolve was heated on the steam-bath for thirty minutes with occasional shaking. The solution was hydrogenated at 2–3 atm. using 400 mg. of palladium chloride as a catalyst until a 20% excess of hydrogen was absorbed (100 minutes). The product, mixed with catalyst, was collected and recrystallized from Methyl Cellosolve; yield, 11 g. (29%), m.p. 230–240°. Further recrystallization gave buff-colored crystals, m.p. 242–247°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3S$: N, 7.4. Found: N, 7.1.

4-Benzylamino-4'-aminodiphenyl sulfone. A mixture of 8 g. of 4-acetamino-4'-benzylaminodiphenyl sulfone and 80 cc. of, 6 *N* hydrochloric acid was refluxed for ten minutes, the solution was clarified by filtration and the filtrate added to excess ammonia water and ice.

After standing overnight to complete crystallization, the product was recrystallized from alcohol-water; yield, 5.3 g. (75%), m.p. 172–174°. Further recrystallization gave buff crystals, m.p. 175–177° (uncorr.).

Anal. Calc'd for $C_{19}H_{18}N_2O_2S$: C, 67.4; H, 5.4; N, 8.3.
Found: C, 67.7; H, 6.1; N, 8.6.

After this work was completed, Jackson (12) prepared this compound in another manner and reported the m.p. 188.5–189° (corr.).

SUMMARY

Eight N-substituted and seven C-substituted derivatives of 4,4′-diaminodiphenyl sulfone have been synthesized by general methods for chemotherapeutic testing.

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