ported by Crum and Robinson[5c] and in addition, none of the objectionable thioether described by these authors was observed by us.

8-γ-(γ'-Morpholinopropylamino)-propylamino-6-methoxyquinoline (VIII).—A mixture of 10.0 g. of 8-(γ-chloropropylamino)-6-methoxyquinoline hydrochloride from above, 12 g. of γ-morpholinopropylamine[10] and 12 ml. of absolute ethanol was heated in a sealed tube at 147° for seven hours. The contents of the tube were mixed with 100 ml. of water and the aqueous layer saturated with potassium carbonate and extracted with five 150-ml. portions of benzene. The wet extracts were dried over potassium carbonate, the solvent removed on the steam-bath, and the residue distilled through a small Claisen flask to give 10.0 g. of material boiling at 235–236° (1.5 mm.), 90.7% yield. This was converted to the hydrochloride by bubbling dry hydrogen chloride into an anhydrous ether–alcohol solution of the base, and the precipitate recrystallized, after treating with Norit, from methanol–ether; light orange crystals, m. p. 226–227°. *Anal.* Calcd. for $C_{20}H_{30}O_2N_4 \cdot 3HCl \cdot 1/2H_2O$: C, 50.35; H, 7.19; N, 11.75. Found: C, 50.15; H, 7.19; N, 11.36. Although the original precipitated hydrochloride of this compound was very hygroscopic, after recrystallization it could be stored in the atmosphere indefinitely. Compounds 12, 13, and 14 in Table I were made by this same procedure.

8-(γ-Morpholinopropylamino)-6-chloroquinoline.—A homogeneous mixture of 20.8 g. of γ-morpholinopropyl chloride hydrochloride and 20.8 g. of 8-amino-6-chloroquinoline was heated with stirring in an oil-bath at 150° for five hours. The reaction mixture was taken up in 50 ml. of 2.5 *N* HCl, treated with Norit and made alkaline with potassium carbonate. The resultant heterogeneous mixture was extracted with ether and the ether extracts dried over anhydrous potassium carbonate, concentrated on the steam-bath, and distilled from a small Claisen flask at 2 mm. pressure to give 8.5 g. of recovered 8-amino-6-chloroquinoline and 17 g. of clear, yellow product boiling at 185–195° (2 mm.), yield 71%. The base was crystallized from hot methanol, m. p. 84.5–86.0°. *Anal.* Calcd. for $C_{16}H_{20}ON_3Cl$: N, 13.73. Found: N, 13.59. The hydrochloride salt made in the usual manner melted at 210–212°. *Anal.* Calcd. for $C_{16}H_{20}ON_3Cl \cdot 2HCl$: N, 11.10. Found: N, 10.89.

6-(γ-Diethylaminopropylamino)-8-methoxyquinoline.—A well-stirred mixture of 12.4 g. of 6-amino-8-methoxyquinoline hydrochloride, 9.3 g. of γ-diethylaminopropyl chloride hydrochloride and 8 ml. of pyridine was heated at 150° for twelve hours. After dissolving the reaction mixture in dilute hydrochloric acid, neutralizing with sodium hydroxide, extracting with ether, and distilling the ether extracts, 5.0 g. of 6-(γ-diethylaminopropylamino)-8-methoxyquinoline, b. p. 175–82° (1.5 mm.) was obtained. The hydrochloride was recrystallized from absolute ethanol and ether, orange crystals m. p. 205–7°. *Anal.* Calcd. for $C_{17}H_{25}ON_3 \cdot 2HCl$: N, 11.62. Found: N, 12.03.

In a similar fashion, 6-(γ-morpholinopropylamino)-8-methoxyquinoline hydrochloride was prepared, 37.4% yield, m. p. 230–5°. *Anal.* Calcd. for $C_{17}H_{23}O_2N_3 \cdot HCl$: N, 12.13. Found: N, 12.12.

Summary

1. A series of sixteen derivatives of 8-amino-6-methoxyquinoline has been reported along with the necessary intermediates for their preparation. Seven of these derivatives contain two or more basic groups in the side chain.

2. Two derivatives of 6-amino-8-methoxyquinoline were prepared.

3. One derivative of 8-amino-6-chloroquinoline was prepared.

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Some Chemotherapeutically Active Sulfones.[1] I

BY L. L. BAMBAS

The antistreptococcal activity of 4,4'-diaminodiphenyl sulfone was found to be approximately one hundred times that of sulfanilamide.[2] Rist, Block and Hamon[3] reported the inhibitory effect of this drug on experimental tuberculosis in animals. Feldman, Hinshaw and Moses[4,5,6] in studies on this compound and two derivatives which are readily decomposed to the parent 4,4'-diaminodiphenyl sulfone conclude that it has chemotherapeutic efficacy in experimental tuberculosis and that some modification of this compound should be made to obtain drugs more suitable for clinical application. Since the toxic manifestations of 4,4'-diaminodiphenyl sulfone preclude its use as a drug in clinical tuberculosis, analogs of this compound were prepared with the hope of reducing the toxicity and retaining the antistreptococcal and antitubercular activity. Thus one or both phenyl rings were replaced by heterocyclic rings.

Changing the amine from the 4-position to the 2- or 3-positions on one of the phenyl rings of 4,4'-diaminodiphenyl sulfone decreased the antibacterial activity of the resultant compounds.[7] Therefore, the compounds investigated were limited to heterocycles in which the amine could be placed in an equivalent para position to the sulfone. That principle of vinylogy was used in which the vinylene group (—CH=CH—) may be replaced by the thio (—S—), the iminomethylene (—N=CH—) and the hydrazo (=N—N=) groups. Thus substitution on the 2 and 5 positions on the pyridine, thiazole,[8] thiophene and

(1) Presented in part before the Division of Medicinal Chemistry, Memphis meeting of the American Chemical Society, April 20, (1942).

(2) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **1**, 1331 (1937).

(3) Rist, Block and Hamon, *Ann. Inst. Pasteur*, **64**, 203 (1940).

(4) Feldman, Hinshaw and Moses, *Am. J. Med. Sci.*, **207**, 290 (1944).

(5) Feldman, Hinshaw and Moses, *Am. Rev. Tuberc.*, **45**, 303 (1942).

(6) Feldman, Hinshaw and Moses, *Arch. Path.*, **36**, 64 (1943).

(7) Tullar and Banks, Abstracts of the St. Louis meeting of the American Chemical Society, Paper no. 5, The Division of Medicinal Chemistry, April, 1941.

(8) The preparation of the thiazole compounds will be given in a subsequent paper.

1,3,4-thiadiazole rings gave isoesters of 4,4′-diaminodiphenyl sulfone. The fact that many of these same heterocycles gave active N^1-substituted sulfanilamides was fortuitous.

Three general methods were used to prepare these compounds. First, sodium or silver-4-acetylaminobenzene sulfinate was condensed in a suitable solvent with a nitro or amino substituted halogenated heterocycle. The resulting compound was then converted to the diamine. One of the two possible pyridyl isomers was prepared from 2-chloro-5-nitropyridine and sodium 4-acetylaminobenzene sulfinate yielding 4-acetylaminophenyl-5′-nitropyridyl-2′ sulfone. The acetyl group was removed by hydrolysis and the nitro group was reduced with iron and dilute ammonium chloride to give 4-aminophenyl-5′-aminopyridyl-2′ sulfone. The monothienyl compound was prepared by refluxing 2-iodo-5-nitrothiophene[9] with sodium 4-acetylaminophenyl sulfinate in dilute alcohol to produce 4-acetylaminophenyl-5′-nitrothienyl-2′ sulfone. This compound on reduction with tin and hydrochloric acid, ammonium polysulfide, or iron and dilute acetic acid give black tars. This was probably due to the instability of the 2-aminothiophenes. Sodium *p*-acetylaminobenzene sulfinate on refluxing in dilute ethanol with 2-chloro-4,6-diamino-1,3,5-triazine gave 2-hydroxy-4,6-diamino-1,3,5-triazine. Sodium 4-nitrothiophenolate reacted with 2-chloro-4,6-diamino-1,3,5-triazine to give 4-nitrophenyl-4′,6′-diamino-1′,3′,5′-triazinyl-2′ sulfide. Oxidation of this compound with hydrogen peroxide to give the sulfone yielded 2-hydroxy-4,6-diamino-1,3,5-triazine.

The second method of preparation consisted in the reaction of sodium sulfide or sodium 4-nitrothiophenolate with a nitrohalogenated heterocycle. The resulting sulfide was oxidized to the sulfone and the nitro groups were reduced to the amine with iron and dilute acetic acid. Bis-(5-aminopyridyl-2) sulfone[10] and bis-(5-nitrothienyl-2) sulfone were prepared in this manner. 2-Nitro-5-bromopyridine[11] was prepared by oxidizing 2-amino-5-bromopyridine with Caro's acid according to the method of Kirpal and Bohn.[12] The reaction of 2-nitro-5-bromopyridine with sodium 4-nitrothiophenolate gave 4-nitrophenyl-2′-nitropyridyl-5′ sulfide.

The third method used involved the reaction between an aminothioheterocycle and 4′-nitrochloro- or 4-nitrobromobenzene. This reaction is very slow and requires refluxing for a considerable length of time and, in some instances, does not appear to proceed at all. Thus thioammeline as the sodium salt does not couple with 4-nitrobromobenzene in twenty-four hours at the reflux temperature of 80°.

(9) Rinkes, *Rec. trav. chim.*, **53**, 648 (1934).

(10) Surrey and Lindwall, THIS JOURNAL, **62**, 173 (1940).

(11) Since this work was finished, an article on the preparation of 2-nitro-5-bromopyridine by Bystritskaya and Kirsanov appeared in *J. Gen. Chem.* (U. S. S. R.), **10**, 1101 (1940).

(12) Kirpal and Bohn, *Ber.*, **64**, 767 (1931).

Experimental

Method I

Silver-4-acetylaminobenzene sulfinate[13] was prepared by dissolving 5.0 g. of 4-acetylaminobenzene sulfinic acid in 250 cc. of water containing sodium bicarbonate (1 eq.). The solution was acid to litmus. This solution was warmed to 50° under vacuum (water pump) to remove excess carbon dioxide; then a solution of silver nitrate (4.2 g. in 250 cc. of water) was added. The mixture was shaken vigorously for a few minutes, then filtered off, washed, and dried in a vacuum oven at 60°.

4-Acetylaminophenyl-5′-aminoquinolyl-8′ Sulfone.[13]—5-Amino-8-chloroquinoline (6.0 g.) was suspended in 10% ethanol (500 cc.) and after the mixture was heated to boiling, the silver 4-acetylaminobenzene sulfinate (10 g.) was added. The mixture was refluxed for two hours and filtered while hot. The acetylamino sulfone which separates on cooling was recrystallized from a mixture of isopropanol and amyl alcohol. 5-Amino-8-bromoquinoline also was used in place of the chloro compound in this reaction.

4-Aminophenyl-5′-aminoquinolyl-8′ sulfone[13] was prepared by boiling the acetyl derivative for five minutes with 100 cc. of dilute hydrochloric acid (5 *N*). The solution was then filtered, cooled, and neutralized to litmus with sodium hydroxide. The product was filtered off and recrystallized from 95% ethanol.

4-Acetylaminophenyl-5′-nitrothienyl-2′ sulfone was prepared by refluxing sodium 4-acetylaminobenzene sulfinate (20 g.) with 2-iodo-5-nitrothiophene[9] (15 g.) in 200 cc. 30% dioxane for two hours. The product was precipitated by the addition of water and filtered off. The crude material was recrystallized from isopropyl alcohol.

4-Aminophenyl-5′-nitrothienyl-2′ sulfone was prepared by refluxing the acetyl derivative for fifteen minutes in alcoholic hydrochloric acid. An equal volume of water was added and the solution was made alkaline to litmus. The precipitate was filtered off and recrystallized from isopropyl alcohol.

Method II

2-Nitro-5-bromopyridine was prepared by oxidizing 2-amino-5-bromopyridine[14] with Caro's acid. Concentrated (30%) hydrogen peroxide (500 cc.) was dissolved in 1000 cc. of cold concentrated sulfuric acid. The solution of the amine was added dropwise to the Caro's acid at 0–5° with vigorous stirring. The reaction mixture was allowed to stand for sixteen to eighteen hours at 10–15°, and then was poured on ice. The precipitate was filtered off and recrystallized from methanol.

2′,4-Dinitrophenylpyridyl-5′ sulfide was prepared by refluxing 10 g. of 2-nitro-5-bromopyridine and 10 g. of sodium *p*-nitrothiophenolate in 300 cc. of ethanol for two hours. The solution was cooled and the precipitate was filtered off and the filtrate was diluted with two volumes of water and a second crop was obtained. The combined precipitates were recrystallized from hot 30% ethanol.

2′,4-Dinitrophenylpyridyl-5′ sulfone was prepared by dissolving 7 g. of the 2′,4-dinitrophenylpyridyl-5′ sulfide in 100 cc. of 1:1 acetic anhydride:glacial acetic acid solution. Concentrated (30%) hydrogen peroxide (20 cc.) was added and the solution was allowed to stand. The solution heated up gradually. On cooling the solution was placed on a steam-bath for an hour. The reaction mixture was then cooled and the yellowish white precipitate was filtered off. Another crop was obtained by diluting the filtrate. The combined precipitates were recrystallized from acetone.

2′,4-Diaminophenylpyridyl-5′ sulfone was prepared by reducing 2′,4-dinitrophenylpyridyl-5′ sulfone in warm C. P. acetone with Raney nickel catalyst and hydrogen at 60 pounds pressure.

(13) W. F. Holcomb of this Laboratory, private communication.

(14) Tschitschibabin and Tjashelowa, *Chem. Zentr.*, [3] **94**, 1021 (1923).

TABLE I

CHEMOTHERAPEUTIC ACTIVITY[a]

Compound, sulfone	M. p., °C., uncor.	Toxicity[a] LD-50	Antistreptococcal[g]	Antipneumococcal[h]	Formula	N Analyses,[b] % Calcd.	Found	Ref.
4-Aminophenyl-5'-aminopyridyl-2'	185–186	60	Active	Active	$C_{11}H_{11}O_2N_3S$	16.9	16.5	*d, c, i*
4-Aminophenyl-5'-nitropyridyl-2'	161–163	60	Active	.....	$C_{11}H_9O_4N_3S$	15.05	14.9	...
4-Aminophenyl-2'-aminopyridyl-5'	222–224	40	Active	Sl. active	$C_{11}H_{11}O_2N_3S$	16.8	16.7	*d, i*
Bis-(5-aminopyridyl-2)	239–241	50	Inactive	.....	$C_{10}H_{10}O_2N_4S$	22.4	22.2	*d, e*
4-Aminophenyl-5'-aminoquinolyl-8'	295–297	75	Active	Sl. active	$C_{15}H_{13}O_3N_3S$	14.1	14.2	*d, f*
4-Aminophenyl-2'-nitrothienyl-5'	159–162	125	Sl. active	.....	$C_{10}H_8O_4N_2S_2$	9.5	9.4	*d, i*
Bis-(5-nitrothienyl-2)	158–160	40	V. sl. active	Inactive	$C_8H_4O_6N_2S_4$	8.8	8.5	*d*
4-Aminophenyl-2'-amino-(1',3',4'-thiadiazolyl-5')	211–214	100	Active	Sl. active	$C_8H_8O_2N_4S_2$	21.8	21.8	*d, i*

[a] Data supplied by O. M. Gruhzit of these Laboratories. Oral toxicity in white mice. [b] Microanalyses supplied by C. S. Chamberlain, L. Doub, A. W. Spang and M. McCarthy Ledyard. [c] Roblin, Williams and Anderson, THIS JOURNAL, **63,** 1930 (1941). [d] See experimental. [e] Surrey and Lindwall, *loc. cit.* [f] W. F. Holcomb, *loc. cit.* [g] β hemolytic streptococcal infections were used. [h] Type I pneumococcal infections were used. [i] Tuberculotherapeutic activity of these compounds will be reported by W. H. Feldman and H. C. Hinshaw, Mayo Foundation and Mayo Clinic.

TABLE II

Compound	M. p., °C. uncor.	Formula	N Analyses, %[a] Calcd.	Found	Yield, %
4-Acetylaminophenyl-5'-aminoquinolyl-8' sulfone	280–282	$C_{17}H_{15}O_3N_3S$	12.3	12.0	78
4-Nitrophenyl-5'-nitropyridyl-2' sulfide	124–126	$C_{11}H_7O_4N_3S$	15.15	14.9	55
4-Nitrophenyl-5'-nitropyridyl-2' sulfone	236–242	$C_{11}H_7O_6N_3S$	13.6	13.3	78
Bis-(5-nitropyridyl-2) sulfide	132–136	$C_{10}H_6O_4N_4S$	20.1	20.0	71
Bis-(5-nitropyridyl-2) sulfone	222–226	$C_{10}H_6O_6N_4S$	18.0	18.0	81
2-Nitro-5-bromopyridine[11]	150–152	$C_5H_3O_2N_2Br$	13.8	13.7	37
4-Nitrophenyl-2'-nitropyridyl-5' sulfide	112–113	$C_{11}H_7O_4N_3S$	15.2	15.2	66
4-Nitrophenyl-2'-nitropyridyl-5' sulfone	202–203	$C_{11}H_7O_6N_3S$	13.6	13.6	77
4-Nitrophenyl-2'-aminothiadiazolyl-5' sulfide	196–200	$C_8H_6O_2N_4S_2$	22.0	21.4	84
4-Nitrophenyl-2'-acetylaminothiadiazolyl-5' sulfone	250–254	$C_{10}H_8O_5N_4S_2$	17.05	17.25	86
4-Nitrophenyl-2'-aminothiadiazolyl-5' sulfone	228–232	$C_8H_6O_4N_4S_2$	19.6	19.2	93
4-Acetylaminophenyl-2'-nitrothienyl-5' sulfone	188–190	$C_{12}H_{10}O_5N_2S_2$	8.5	8.2	83
Bis-(5-nitrothienyl-2) sulfide	104–106	$C_8H_4O_4N_2S_3$	9.7	9.3	43

[a] Microanalyses by C. S. Chamberlain, L. Doub, A. W. Spang and M. McCarthy Ledyard.

Method III

4-Nitrophenyl-2'-amino-(1',3',4'-thiadiazolyl-5') sulfide was prepared by refluxing 150 g. of 2-mercapto-5-amino-1,3,4-thiadiazole[15] as the sodium salt with 150 g. of 4-nitrochlorobenzene in 1500 cc. of 80% ethanol for twenty hours. The solution was cooled and the precipitate was filtered off. The product was washed well with ether. The filter cake was recrystallized from 95% ethanol.

4-Nitrophenyl-2'-acetylamino-(1',3',4'-thiadiazolyl-5') sulfone was prepared by suspending 120 g. of 4-nitrophenyl-2'-amino-(1',3',4'-thiadiazolyl-5') sulfide in 1000 cc. of glacial acetic acid and 50 cc. of acetic anhydride. The suspension was gently warmed to 70° and 250 cc. of 30% hydrogen peroxide was added portionwise, care being taken that the temperature did not rise over 85°. The suspension went into solution and the 4-nitrophenyl-2'-acetylamino-(1',3',4'-thiadiazolyl-5') sulfone precipitates out as formed. The precipitate was collected and recrystallized from dioxane.

(15) Guha, THIS JOURNAL, **44,** 1516 (1922).

Summary

A series of 4-aminophenylaminoheterocycle sulfones, analogs of 4,4'-diaminodiphenyl sulfone, has been made with the object of obtaining compounds having high antistreptococcal and antipneumococcal activity and low toxicity. Only those compounds which had at least one benzene nucleus with nitrogen in para position to the sulfur were effective. Compounds in which the pyridyl, thiadiazolyl and quinolyl rings were substituted for one of the phenyl rings retained high anti-streptococcal activity but not as great as 4,4'-diaminodiphenyl sulfone. All the compounds were less toxic than 4,4'-diaminodiphenyl sulfone.

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