TABLE I

No.	Order of introduction of groups (names indicated)	M. p., °C.	Nitrogen, % Calcd.	Found
1a	PhNH(*o*-Tol:)C—NHPh	93	13.94	13.89
1b	PhNH(PhN:)C—NH—*o*-Tol	110.5	13.94	13.87
2a	PhNH(*m*-TolN:)CNHPh	101	13.94	14.01
2b	PhNH(PhN:)CNH—*m*-Tol	92	13.94	13.93
3a	PhNH(*p*-TolN:)C—NH—Ph	104.5	13.94	13.95
3b	PhNH(PhN:)C—NH—*p*-Tol	121	13.94	13.86
4a	*o*-TolNH(PhN:)C—NH—*o*-Tol	93.5	13.32	13.30
4b	*o*-TolNH(*o*-TolN:)C—NH—Ph	97	13.32	13.17
5a	*o*-TolNH(*m*-TolN:)C—NH-*o*-Tol	88	12.76	12.80
5b	*o*-TolNH(*o*-TolN:)C—NH—*m*-Tol	86	12.76	12.76
6a	*o*-TolNH(*p*-TolN:)C—NH—*o*-Tol	70.5	12.76	12.77
6b	*o*-TolNH(*o*-TolN:)C—NH—*p*-Tol	83	12.76	12.77
7a	*m*-TolNH(PhN:)C—NH—*m*-Tol	92	13.32	13.32
7b	*m*-TolNH(*m*-TolN:)C—NH—Ph	86	13.32	13.35
8a	*m*-TolNH(*o*-TolN:)C—NH—*m*-Tol	90	12.76	12.63
8b	*m*-TolNH(*m*-TolN:)C—NH—*o*-Tol	84	12.76	12.77
9a	*m*-TolNH(*p*-TolN:)C—NH—*m*-Tol	103	12.76	12.81
9b	*m*-TolNH(*m*-TolN:)C—NH—*p*-Tol	93	12.76	12.80
10a	*p*-TolNH(PhN:)C—NH—*p*-Tol	62	13.32	13.27
10b	*p*-TolNH(*p*-TolN:)C—NH—Ph	82.5	13.32	13.35
11a	*p*-TolNH(*o*-TolN:)C—NH—*p*-Tol	77.5	12.76	12.74
11b	*p*-TolNH(*p*-TolN:)C—NH—*o*-Tol	89.5	12.76	12.86
12a	*p*-TolNH(*m*-TolN:)C—NH—*p*-Tol	83.5	12.76	12.74
12b	*p*-TolNH(*p*-TolN:)C—NH—*m*-Tol	101	12.76	12.76

pure lower melting isomer. Thus both isomers could be obtained pure.

In Table I are given twelve pairs of isomers, (a) and (b), in all combinations of phenyl and the tolyl groups, and in conformity with the general formulas (a) and (b). The compounds are arranged to show the order of introduction of groups. The first group indicates the mustard oil used to form the thiourea. The first two groups indicate the thiourea used to form the carbodiimide. The third group indicates the primary base used to yield the guanidine. In the table isomers are adjacent, the established locations of double bonds are given, also the melting points and analytical data. All of these compounds crystallize as needles or as rosettes of needles. Analyses were made by the Kjeldahl method. In general the symmetrical carbodiimides yield the higher melting isomers. When a *m*-tolyl group is present, this does not always hold true.

Summary

When a primary base adds to a carbodiimide to yield a guanidine, only one hydrogen atom of the base shifts to a nitrogen atom of the carbodiimide. This rule is established by study of the lone isomer obtained with a symmetrical carbodiimide and also of the two isomers always obtained with the symmetrical carbodiimide. This knowledge leads to determination of location of gamma double bonds. Twelve pairs of isomers were prepared and their structural relations were established.

SEATTLE, WASHINGTON RECEIVED AUGUST 31, 1940

[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH FOUNDATION OF THE FRANKLIN INSTITUTE]

The Preparation of Some 2-Pyridyl and 8-Quinolyl Phenyl Sulfides and Sulfones

BY HARRY C. WINTER AND FRANCIS E. REINHART

The discovery of the powerful antistreptococcal properties of sulfanilamide, 4,4′-dinitrodiphenyl sulfone, and some of their derivatives has led to the investigation of a large number of related compounds of the benzene series. Very little attention, however, has been directed to the pyridine and quinoline analogs of these active therapeutic agents. In fact, only two such compounds, 6-sulfonamidoquinoline[1] and 2,2′-dipyridyl sulfide,[2] had been studied when an investigation of these analogs was begun in this Laboratory. Recently, there has been reported the preparation of a number of sulfonamides,[3] sulfides[4,5] and sulfones[5] of pyridine and of quinoline. The value of these compounds as antistreptococcal agents has not yet been established.

The compounds prepared in this investigation have been chiefly 2-pyridyl or 8-quinolyl sulfides and sulfones in which a phenyl or *p*-nitrophenyl group was present as the second substituent. In all of these, a nitro or amino group occupied that position in the heterocyclic nucleus para to the sulfur linkage thus simulating the relative

(1) J. Tréfouël, Mme. J. Tréfouël, F. Nitti and D. Bovet, *Ann. Inst. Pasteur*, **58**, 30 (1937).

(2) J. A. Kolmer, H. Brown and G. W. Raiziss, *J. Pharmacol.*, **61**, 253 (1937).

(3) C. Naegeli, W. Kündig and H. Brandenburger, *Helv. Chim. Acta*, **21**, 1746 (1938); **22**, 912 (1939).

(4) M. Colonna, *Gazz. chim. ital.*, **70**, 154 (1940).

(5) A. R. Surrey and H. G. Lindwall, THIS JOURNAL, **62**, 173 (1940).

TABLE I

PROPERTIES AND ANALYSES OF COMPOUNDS

		M. p., °C. (uncor.)	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
	( ) Disulfide							
I	5,5′-Dinitro-8,8′-diquinolyl	245	83	$C_{18}H_{10}N_4O_4S_2$	13.7	13.7	15.6	15.7
	( ) Sulfide							
II	5-Nitro-2-pyridyl phenyl[6]	121	80	$C_{11}H_8N_2O_2S$	12.1	12.1		
III	5-Amino-2-pyridyl phenyl[6]	125–7	84	$C_{11}H_{10}N_2S$	13.9	13.8		
IV	5-Nitro-2-pyridyl *p*-nitrophenyl	126–9	71	$C_{11}H_7N_3O_4S$	15.2	15.0	11.6	11.7
V	5-Nitro-8-quinolyl phenyl	100	89	$C_{15}H_{10}N_2O_2S$	9.9	10.0	11.4	11.2
VI	5-Amino-8-quinolyl phenyl	128	43	$C_{15}H_{12}N_2S$	11.1	11.2	12.7	12.6
VII	5-Acetamino-8-quinolyl phenyl	97–8		$C_{17}H_{14}N_2OS$	9.5	9.6		
VIII	5-Nitro-8-quinolyl *p*-nitrophenyl	223	85	$C_{15}H_9N_3O_4S$	12.8	12.7	9.8	9.9
	( ) Sulfoxide							
IX	5-Nitro-8-quinolyl phenyl	145–6	60	$C_{15}H_{10}N_2O_3S$	9.4	9.2	10.8	11.0
	( ) Sulfone							
X	5-Nitro-2-pyridyl phenyl	151–3	93	$C_{11}H_8N_2O_4S$	10.6	10.7	12.1	12.2
XI	5-Amino-2-pyridyl phenyl	169–70	68	$C_{11}H_{10}N_2O_2S$	12.0	12.0	13.7	13.8
XII	5-Nitro-2-pyridyl *p*-nitrophenyl	217	90	$C_{11}H_7N_3O_6S$	13.6	13.8	10.4	10.5
XIII	5-Nitro-2-pyridyl *m*-nitrophenyl	169–70	93	$C_{11}H_7N_3O_6S$	13.6	13.6	10.4	10.3
XIV	5-Nitro-8-quinolyl phenyl	180–1	96	$C_{15}H_{10}N_2O_4S$	8.9	8.8	10.2	10.4
XV	5-Amino-8-quinolyl phenyl	224	55	$C_{15}H_{12}N_2O_2S$	9.9	9.8	11.3	11.4
XVI	5-Acetamino-8-quinolyl phenyl	268–9		$C_{17}H_{14}N_2O_3S$	8.6	8.7		
XVII	5-Nitro-8-quinolyl *p*-nitrophenyl	237	55	$C_{15}H_9N_3O_6S$	11.7	11.8	8.9	9.0

positions of these groups in the active antistreptococcal compounds of the benzene series.

The sulfides were made by condensing 2-chloro-5-nitropyridine or 5-nitro-8-chloroquinoline with thiophenol or its *p*-nitro derivative. Although an alkaline medium was generally used for this reaction, 2-chloro-5-nitropyridine was found to react readily with thiophenol at 135–150° in the absence of solvents and alkaline agents to yield 5-nitro-2-pyridyl phenyl sulfide (II).[6] Reduction of (II) and 5-nitro-8-quinolyl phenyl sulfide (V) by stannous chloride gave the corresponding amino sulfides (III)[6] and (VI). The disulfide (I) has been prepared by the reaction of 5-nitro-8-chloroquinoline with sodium disulfide in alcoholic solution.

The oxidation of the nitro sulfides with hydrogen peroxide has led to the formation of the corresponding sulfones (X, XII, XIV) and, with a shorter period of oxidation, the intermediate sulfoxide (IX). In the case of the sulfide (VIII) it was found necessary to use chromic acid to obtain the sulfone (XVII). Nitration of (X) gave a dinitro sulfone (XIII) which is considered to be 5-nitro-2-pyridyl *m*-nitrophenyl sulfone, since nitration would be expected to proceed as in the case of the alkyl phenyl sulfones, where meta substitution occurs. The reduction of (XIV) with the required amount of stannous chloride and the oxidation of (III) with hydrogen peroxide gave the amino sulfones (XV) and (XI), respectively.

8-Quinolinesulfonyl sulfanilic acid (XVIII) was made from 8-quinolinesulfonyl chloride by the method described by Crossley, Northey and Hultquist[7] for the preparation of sulfanilyl derivatives of aminoaryl sulfonic acids.

Several known compounds of related structure were prepared for evaluation as antistreptococcal agents. These were potassium 5-nitro-2-pyridinesulfonate,[8] 5-amino-2-pyridinesulfonic acid,[8] 8-quinolinesulfonic acid,[9] 8-quinolinesulfonamide[10] and 8-aminoquinoline-5-sulfonic acid.[11] 5,5′-Dinitro-2,2′-dipyridyl and 5,5′-dinitro-8,8′-diquinolyl sulfides were prepared as subsequently described by Surrey and Lindwall.[5] It was found that the latter compound could also be obtained by the reaction of 5-nitro-8-chloroquinoline with thiourea in absolute alcohol in the presence of sodium ethylate. A similar method has very recently been described by Surrey and Lindwall[12] for the preparation of 5-nitro-2-pyridyl sulfides.

(6) Previously described, German Patent 550,327 (1930), *C. A.* **26**, 4062 (1932).

(7) M. L. Crossley, E. H. Northey and M. E. Hultquist, THIS JOURNAL, **60**, 2220 (1938).

(8) E. Plazek, *Roczniki Chem.*, **17**, 97 (1937).

(9) A. Claus, *J. prakt. Chem.*, [2] **37**, 258 (1888).

(10) S. Hoogewerff and W. A. van Dorp, *Rec. trav. chim.*, **8**, 173 (1889).

(11) K. Cybulski, E. Sucharda, C. Troskiewiczówna and W. Turska, *Roczniki Chem.*, **14**, 1172 (1934).

(12) A. R. Surrey and H. G. Lindwall, THIS JOURNAL, **62**, 1697 (1940).

These known compounds as well as (II), (III), (VI), (X), (XI), (XIV), (XV), and (XVIII) have been tested in mice for antistreptococcal activity and found to be ineffective.[13]

Experimental

5,5'-Dinitro-8,8'-diquinolyl Disulfide (I).—A solution of sodium disulfide, prepared by dissolving sulfur (0.48 g.) in a saturated alcoholic solution of crystallized sodium sulfide (3.6 g.), was added to 5-nitro-8-chloroquinoline (4.17 g.) in hot alcohol (350 cc.). After the red reaction mixture had been refluxed for six hours, the precipitated disulfide was separated and washed with water and alcohol. The crude product crystallized from a large volume of acetic acid in greenish-yellow needles.

The disulfide was reduced readily by a hot solution of sodium sulfide in 50% alcohol. On cooling this solution, red needles, probably the sodium salt of the thiol, separated. These quickly oxidized to the disulfide on exposure to air.

5-Nitro-2-pyridyl Phenyl Sulfide (II).—2-Chloro-5-nitropyridine (79 g.) was thoroughly mixed with thiophenol (55 g.) and heated to 135–150° until the evolution of hydrogen chloride ceased (three hours). After traces of thiophenol had been removed by steam distillation, the residue crystallized from alcohol in glistening white plates. These were soluble in the common organic solvents but insoluble in water. The melting point, 121°, was identical with that reported.[6]

5-Amino-2-pyridyl Phenyl Sulfide (III).—A solution of stannous chloride dihydrate (35 g.) in concentrated hydrochloric acid (80 cc.) was added during one-half hour to a solution of 5-nitro-2-pyridyl phenyl sulfide (12 g.) in concentrated hydrochloric acid (100 cc.). External cooling was necessary to prevent the mixture from boiling. After standing for twelve hours at 25°, the tin complex was separated by filtration and dissolved in water (400 cc.). The amino sulfide was precipitated by the addition of an excess of sodium hydroxide solution. It crystallized as white needles from a large volume of ligroin or water, and was found to be soluble in alcohol, acetone, and dilute acids but insoluble in cold water. Its melting point, 125–127°, was higher than the one reported (120°).[6]

5-Nitro-2-pyridyl *p*-Nitrophenyl Sulfide (IV).—A solution of *p*-nitrothiophenol was prepared by refluxing *p,p'*-dinitrodiphenyl disulfide (5.5 g.) in a solution of crystallized sodium sulfide (2.6 g.) and sodium hydroxide (1.4 g.) in 60% alcohol (150 cc.) for twenty minutes.[14] Refluxing was continued for thirty minutes after a solution of 2-chloro-5-nitropyridine (6 g.) in hot absolute alcohol (125 cc.) had been added. The sulfide, which precipitated on cooling, crystallized from alcohol in bright yellow needles which were soluble in acetone or ether but insoluble in water.

5-Nitro-8-quinolyl Phenyl Sulfide (V).—A solution of 5-nitro-8-chloroquinoline (8.3 g.), thiophenol (4.5 g.) and sodium acetate (5.4 g.) in alcohol (150 cc.) was refluxed for thirty minutes. The reaction mixture was then cooled and the crystalline sulfide separated and washed with water and alcohol. The almost pure product crystallized from alcohol in long dark yellow needles. These were insoluble in water, and only slightly soluble in cold alcohol, acetone, or acetic acid.

5-Amino-8-quinolyl Phenyl Sulfide (VI).—To a solution of 5-nitro-8-quinolyl phenyl sulfide (5.6 g.) in cold concentrated hydrochloric acid (90 cc.) there was added slowly with stirring a solution of stannous chloride dihydrate (13.8 g.) in concentrated hydrochloric acid (100 cc.). After standing for three hours with occasional agitation, the yellow tin complex was separated, dissolved in boiling water (500 cc.), and treated with hydrogen sulfide. The tin sulfide was then filtered off and the amine precipitated from the acid filtrate by the addition of dilute sodium hydroxide. The precipitate crystallized from dilute alcohol in yellow leaflets.

5-Acetamino-8-quinolyl Phenyl Sulfide (VII).—5-Amino-8-quinolyl phenyl sulfide (0.5 g.) was added to acetic anhydride (10 cc.) and the solution warmed on the water-bath for ten–fifteen minutes. The reaction mixture was then poured into ice water and, after complete hydrolysis of the anhydride, the precipitate was separated and washed with water. The crude product crystallized from dilute alcoholic solution in colorless, irregular plates.

5-Nitro-8-quinolyl *p*-Nitrophenyl Sulfide (VIII).—To a solution of *p*-nitrothiophenol, prepared as described under (IV) above, 5-nitro-8-chloroquinoline (9.1 g.) dissolved in hot alcohol (500 cc.) was added and the reaction mixture boiled for fifteen–twenty minutes. The precipitated sulfide was then separated and washed with water and hot alcohol. It crystallized from glacial acetic acid as a yellow powder.

5-Nitro-8-quinolyl Phenyl Sulfoxide (IX).—A suspension of 5-nitro-8-quinolyl phenyl sulfide (1.5 g.) in glacial acetic acid (25 cc.) was treated with 30% hydrogen peroxide (2.5 cc.). After standing at room temperature for twenty-four hours, the 5-nitro-8-quinolyl phenyl sulfide was completely dissolved. The clear solution was poured into water and the precipitate was separated and washed free of acetic acid. The crude product crystallized from alcohol in yellow needles which were soluble in alcohol and in acetic acid but insoluble in water.

5-Nitro-2-pyridyl Phenyl Sulfone (X).—5-Nitro-2-pyridyl phenyl sulfide (8 g.) was suspended in glacial acetic acid (70 cc.) and stirred while 30% hydrogen peroxide (17 cc.) was added. After standing for several days at 25° the sulfone which had precipitated was separated by filtration and washed with ether. It was combined with an additional amount obtained by pouring the acetic acid filtrate into water and on recrystallization from alcohol gave colorless prisms which were soluble in benzene but insoluble in water.

5-Amino-2-pyridyl Phenyl Sulfone (XI).—5-Amino-2-pyridyl phenyl sulfide (3 g.) was dissolved in glacial acetic acid (24 cc.) and 30% hydrogen peroxide (7 cc.) added. After twenty-four hours the clear solution was poured into water (60 cc.) and the sulfone precipitated by the gradual addition of anhydrous sodium carbonate (21 g.). It was purified by dissolving in dilute hydrochloric acid, filtering, reprecipitating by the addition of sodium carbonate and, finally, recrystallizing from a large volume of water. The

(13) We are indebted to Mr. R. Lloyd Phillips of this Laboratory for the biological testing of these compounds.

(14) H. H. Hodgson and E. Leigh, *J. Chem. Soc.*, 1033 (1938).

cream-colored plates, which turn dark on exposure to light, were soluble in alcohol, slightly soluble in ether and insoluble in benzene and in water.

5-Nitro-2-pyridyl *p*-Nitrophenyl Sulfone (XII).—A suspension of 5-nitro-2-pyridyl *p*-nitrophenyl sulfide (1 g.) in glacial acetic acid (10 cc.) was treated with 30% hydrogen peroxide (2 cc.). After two days the crystalline sulfone was separated by filtration, washed with ether, and recrystallized from dry benzene. White needles, soluble in hot alcohol and insoluble in water, were obtained.

5-Nitro-2-pyridyl *m*-Nitrophenyl Sulfone (XIII).—5-Nitro-2-pyridyl phenyl sulfone (3 g.) was added to a mixture of concentrated sulfuric acid (6 cc.) and concentrated nitric acid (2 cc.). The solution was heated to 100° for ten minutes, cooled and then poured into ice water (100 cc.). The precipitate, after being separated and washed with water, crystallized from alcohol in fine white needles which were soluble in benzene and in dioxane and insoluble in water.

5-Nitro-8-quinolyl Phenyl Sulfone (XIV).—A hot solution of 5-nitro-8-quinolyl phenyl sulfide (5.6 g.) in glacial acetic acid (50 cc.) was cooled to 40°, treated with 30% hydrogen peroxide (8.5 cc.) and allowed to stand at room temperature. Within twenty-four hours all of the sulfide had dissolved and crystals of the sulfone began to appear. After standing for four days (longer periods of oxidation result in diminished yields), the reaction mixture was poured into water and the precipitated sulfone separated. It crystallized from alcohol in long white needles which were insoluble in water and only slightly soluble in alcohol and in acetic acid.

5-Amino-8-quinolyl Phenyl Sulfone (XV).—To a solution of 5-nitro-8-quinolyl phenyl sulfone (5 g.) in concentrated hydrochloric acid (100 cc.) was added stannous chloride dihydrate (11 g.) dissolved in concentrated hydrochloric acid (45 cc.). After standing for two hours with occasional agitation, the precipitated yellow tin complex was separated, suspended in a small quantity of water and enough 40% sodium hydroxide was added to make the solution strongly alkaline. The precipitate was transferred to a filter, washed with water, and redissolved in hot 5% hydrochloric acid. Remaining traces of tin were removed by passing hydrogen sulfide through this solution and filtering off the tin sulfide. The amine was precipitated from the filtrate by the addition of dilute sodium hydroxide, redissolved in hot alcohol, and decolorized with bone black. On cooling, it crystallized in fine white needles. Alcoholic solutions of this compound exhibited a blue fluorescence.

5-Acetamino-8-quinolyl Phenyl Sulfone (XVI).—5-Amino-8-quinolyl phenyl sulfone was acetylated by the procedure described for the preparation of (VII) above. The compound crystallized from alcoholic solution in colorless prisms.

5-Nitro-8-quinolyl *p*-Nitrophenyl Sulfone (XVII).—5-Nitro-8-quinolyl *p*-nitrophenyl sulfide (1 g.) suspended in glacial acetic acid (25 cc.) was treated with chromium trioxide (1 g.) and the reaction mixture heated, gently at first, then boiled for fifteen minutes. The resulting solution was poured into water and the precipitated sulfone separated and washed with water. The crude product crystallized from acetone in flat needles.

8-Quinolinesulfonyl Sulfanilic Acid. (XVIII).—To a solution of sulfanilic acid (4.2 g.), sodium hydroxide (1 g.) and sodium carbonate (0.5 g.) in water (50 cc.) maintained at 30–40°, 8-quinolinesulfonyl chloride (4.9 g.) was added with mechanical stirring over a period of one hour. The *p*H of the solution was maintained slightly on the alkaline side by the gradual addition of sodium hydroxide (0.8 g.) in water (5 cc.) during the course of the reaction. After two and one-half hours the solution was filtered from a small quantity of undissolved solid and the 8-quinolinesulfonyl sulfanilic acid precipitated by acidifying with hydrochloric acid. The precipitate was separated, washed with water and redissolved in a boiling solution of sodium hydroxide (0.6 g.) in water (100 cc.). The colorless solution was filtered and the hot filtrate made slightly acid by the addition of concentrated hydrochloric acid (3 cc.). On cooling, 5.3 g. (64% of the theoretical yield) of the sulfonic acid monohydrate crystallized in light yellow leaflets.

Anal. Calcd. for $C_{15}H_{12}N_2O_5S_2 \cdot H_2O$: N, 7.3; S, 16.8. Found: N, 7.4; S, 16.7.

8-Quinolinesulfonyl sulfanilic acid was found to be insoluble in water and in alcohol. Its sodium salt crystallized from water in fine white needles.

Summary

1. Eighteen pyridine and quinoline compounds, some of which are analogs of active antistreptococcal agents of the benzene series, have been prepared. They were chiefly 2-pyridyl and 8-quinolyl phenyl sulfides and sulfones in which (a) a nitro, amino or acetamino group occupied the 5-position of the heterocyclic nucleus or (b) a nitro group para to the sulfur linkage was present in each nucleus. 5-Nitro-2-pyridyl *m*-nitrophenyl sulfone, 5-nitro-8-quinolyl phenyl sulfoxide, 5,5′-dinitro-8,8′-diquinolyl disulfide, and 8-quinolinesulfonyl sulfanilic acid have also been made.

2. Preliminary to the preparation of these compounds, a number of known compounds of related structure were prepared.

3. Some of the compounds prepared were tested for antistreptococcal activity and were found to be ineffective.

PHILADELPHIA, PA. RECEIVED AUGUST 3, 1940