under vacuum at 30°, the product separated and recrystallized from ethyl alcohol (I), or (II and III) from glacial acetic acid.

Compounds IV, V, and VI from I, II, and III, respectively.—Compound I (or II or III) (25.3 g.) was suspended in 100 cc. of concentrated hydrochloric acid and mossy tin (41.6 g.) was added slowly, keeping the temperature below 60°. In one-half hour all of the nitro compound had gone into solution. Then 50 cc. of concentrated hydrochloric acid and 41.6 g. of mossy tin were added and the mixture was boiled for twenty hours. The unused tin was then filtered off, the solution was diluted to 1600 cc. with water, and tin was removed as the sulfide. The product was obtained by evaporation to dryness on the steam-bath. Purification of IV was by dissolving in water and saturating with hydrogen chloride; of VI by crystallization from alcohol; V could not be recrystallized.

The Benzoyl Derivatives of IV, V, and VI (VII, VIII, and IX).—Compound IV (or V or VI) (0.5 g.) was dissolved in 10 cc. of water and 1 g. of sodium carbonate and 1.5 g. of benzoyl chloride were added. The product separated after standing two hours at room temperature; recrystallized from ethyl alcohol.

The Urethan Derivatives of IV, V, and VI (X, XI, and XII).—Compound IV (or V or VI) (0.5 g.) was dissolved in 10 cc. of water and 1 g. of sodium carbonate and 0.7 g. of ethyl chloroformate were added. The products were crystallized from ethyl alcohol.

The Urea Derivatives of IV, V, and VI (XIII, XIV and XV).—Compound IV (or V or VI) (1.0 g.) was dissolved in 7 cc. of water and 1 g. of potassium cyanate dissolved in 3 cc. of water was added. The crystalline product separated after twelve hours standing in ice; in each case the product was recrystallized from water after treatment with bone coal.

Compounds XVI, XVII and XVIII.—Nitromethane (9 g.) and 7-carbomethoxy-isatin (12 g.) were placed in 12 cc. of absolute ethyl alcohol and the mixture was cooled to −15°. Diethylamine (15 drops) was added with stirring. The mixture was held at −15° for one hour, and part of the solvent was then removed to cause fairly complete separation of XVI. Compounds XVII and XVIII were prepared, respectively, by substituting 1-methyl-7-carbomethoxy-isatin and 1-ethyl-7-carbomethoxy-isatin in this procedure.

Compound XIX (from XVI).—Compound XVI (9.5 g.) was suspended in 50 cc. of concentrated hydrochloric acid and mossy tin (17 g.) was added slowly, keeping the temperature below 60°. After boiling the mixture for two hours it was diluted with water and tin was removed as the sulfide. The solution was evaporated until a solid separated; it was recrystallized from ethyl alcohol. Treatment of XIX with benzoyl chloride yielded **compound XX;** with ethyl chloroformate, **compound XXI;** with potassium cyanate, **compound XXII.**

Summary

Oxindole and N-alkylated-oxindole derivatives have been prepared in which the 3-position holds the hydroxyl and the aminomethyl groups, and the 5- or 7-position is occupied, respectively, by the amino or carboxyl group. For certain of these products benzoyl, urethan, and urea derivatives are described.

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Sulfides and Sulfones of Pyridine and Quinoline

BY A. R. SURREY AND H. G. LINDWALL

The similarity of therapeutic effect to sulfanilamide of the dinitro- and diaminodiphenyl sulfides and sulfones,[1,2,3] suggested the preparation of like compounds in the pyridine and quinoline series.

The chemotherapy of these diphenyl compounds[4,5] showed that while some of them possess greater activity than sulfanilamide, in general they have a greater toxicity. The introduction of the pyridine ring in sulfanilamide not only enhances the activity but also adds desirable features absent from sulfanilamide. Encouraging results were obtained with certain other pyridine compounds[6] including the dihydrobromide of 2,2′-dipyridyl sulfide. Recently, sulfonamides of some aminoquinolines have been synthesized.[7] It therefore seemed desirable to prepare pyridine and quinoline analogs of the dinitro and diamino diphenyl sulfides and sulfones.

5,5′-Dinitro 2,2′-dipyridyl sulfide (I) has been prepared by the action of sodium sulfide on 2-chloro-5-nitropyridine. This is essentially the method used by Nietzki and Bothof[8] for the preparation of the diphenyl analog. The diquinolyl sulfides (IV) and (V) (see Table I) were prepared in the same way starting with 5-chloro-8-nitro-

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(7) Bobranski, *Arch. Pharm.*, **277**, 75 (1939).

(8) Nietzki and Bothof, *Ber.*, **27**, 3261 (1894).

TABLE I

PROPERTIES AND ANALYSES OF COMPOUNDS

Sulfide	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I 5,5′-Dinitro-2,2′-dipyridyl	136–137	$C_{10}H_6N_4O_4S$	20.14	20.13	...	...	..	..
II 5,5′-Diamino-2,2′-dipyridyl	130–131.5	$C_{10}H_{10}N_4S$	25.69	25.53	55.05	54.96	4.59	4.74
III 5,5′-Diacetylamino-2,2′-dipyridyl	265–266.5	$C_{14}H_{14}N_4O_2S$	18.54	18.52	...	...	..	..
IV 8,8′-Dinitro-5,5′-diquinolyl	280–281	$C_{18}H_{10}N_4O_4S$	14.81	14.92	57.14	57.47	2.64	2.91
V 5,5′-Dinitro-8,8′-diquinolyl	288.5–290	$C_{18}H_{10}N_4O_4S$	14.81	14.79	57.14	57.40	2.64	2.62
Sulfone								
VI 5,5′-Dinitro-2,2′-dipyridyl-	218.5–220.5	$C_{10}H_6N_4O_6S$	18.06	18.20	...	...	..	..
VII 5,5′-Diamino-2,2′-dipyridyl-	238–239	$C_{10}H_{10}N_4O_2S$	22.40	22.14	48.00	48.42	4.00	4.30
VIII 5,5′-Diacetylamino-2,2′-dipyridyl-	276–278	$C_{14}H_{14}N_4O_4S$	16.77	16.69	...	...	..	..
IX 5,5′-Dinitro-8,8′-diquinolyl-	260[a]	$C_{18}H_{10}N_4O_6S$	13.66	13.73	52.68	53.06	2.44	2.37

[a] Begins to decompose at 245°, completely black at 260°.

quinoline and 8-chloro-5-nitroquinoline, respectively. The latter were made from the corresponding chloroquinolines by nitration. The dinitrodipyridylsulfone (VI) was prepared by oxidation of (I) with potassium dichromate. 5,5′-Dinitro-8,8′-diquinolylsulfone (IX) was formed from (V) by oxidation with chromic acid.

Reduction of the dinitrodipyridyl compounds (I and VI), to yield the corresponding amino compounds (II and VII), was carried out using stannous chloride. Two forms of 5,5′-diamino-2,2′-dipyridyl sulfide were obtained, one melting at 80–81°, the other at 130–131.5°. By heating the lower melting compound in the oven at 90° the higher melting variety was obtained. Both gave the same diacetylamino derivative (III). A calculated amount of stannous chloride was used in the reduction of (VI) to give 5,5′-diamino-2,2′-dipyridylsulfone (VII). An excess of stannous chloride reduced the sulfone group to give (II).

Certain of these compounds will be tested to determine their therapeutic effect.

Experimental Part

I, IV and V.—To a nearly saturated solution of 2-chloro-5-nitropyridine (or 5-chloro-8-nitroquinoline or 8-chloro-5-nitroquinoline) in hot alcohol was added a slight excess of a saturated aqueous solution of sodium sulfide. In each case the reaction mixture turned red and heat was evolved. After the initial reaction had subsided, the solution was refluxed for four hours on the steam-bath. The product which separated was filtered and washed with alcohol; yield: (I) 73%, yellow needles from alcohol; (IV) 90%, small yellow needles from acetone and water; (V) 85%, small orange crystals from pyridine.

5,5′-Dinitro-2,2′-dipyridylsulfone (VI).—A solution of 6 g. of potassium dichromate in 80 cc. of water was added with shaking to a solution of 4.5 g. of I in 80 cc. of water and 60 cc. of concd. sulfuric acid. In a short time a fine white precipitate began to separate. After all the dichromate solution had been added, the reaction mixture was allowed to stand for a few minutes and then diluted with four times its volume of water. The precipitate was filtered and washed with water until a clear filtrate was obtained, and then dried; yield, 4.5 g. (90%). The material crystallized from propyl alcohol in small white needles.

II and VII.—Compound I (or VI) (3 g.) was added slowly with cooling to a solution of 24 g. (or 14 g.) of stannous chloride in 30 cc. (or 17 cc.) of concd. hydrochloric acid. The solution was then heated on the steam-bath for one hour. The clear solution was allowed to cool and the tin salt which separated was filtered. To a solution of the tin salt in a small amount of water, 40% sodium hydroxide was added until the solution was strongly alkaline. The brown oil which separated was cooled until it solidified and then was filtered. The crude amine was dissolved in hot water and treated with bone black: yield, (II) 68%; (VII) 67%. Both were obtained as white needles after repeated recrystallizations from water.

5,5′-Diacetylamino-2,2′-dipyridyl Sulfide (III).—Compound II (0.5 g.) was added to 10 cc. of acetic anhydride. Heat was evolved and the diacetylamino compound (III) separated as a fine white powder. The product was purified by dissolving in alcohol, treating with bone black and allowing most of the alcohol to evaporate; yield, almost quantitative.

5,5′-Diacetylamino-2,2′-dipyridylsulfone (VIII).—Compound VII (0.5 g.) was added to 10 cc. of acetic anhydride. The solution was warmed until all of the amine went into solution. On cooling, light yellow needles separated out. The material was purified by recrystallizing from water.

5,5′-Dinitro-8,8′-diquinolylsulfone (IX).—Chromic acid (1.0 g.) was added to a solution of 1.0 g. of V in 30 cc. of glacial acetic acid. After the initial vigorous reaction, which was induced by warming, the solution was refluxed for fifteen minutes and then poured into ice. A yellow precipitate separated; yield, 0.6 g. (54%); small yellow needles from acetone.

Summary

Methods are described for the preparation of the 5,5′-dinitro, the 5,5′-diamino, the 5,5′-diacetylamino-2,2′-dipyridyl sulfides, and their respective sulfones, as well as the 5,5′-dinitro-8,8′-diquinolyl sulfide and its sulfone, and the 8,8′-dinitro-5,5′-diquinolyl sulfide.

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