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THE SYNTHESIS OF POTENTIAL ANTIMALARIALS. SOME SUBSTITUTED N-PHENYLSULFONAMIDES[1]

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Drugs of the sulfonamide type have recently been extensively investigated as antimalarials. As part of this general program the compounds in Table I were prepared.[3]

As intermediates, several unreported aniline derivatives were required and their preparation is also described.

These compounds were prepared by coupling an appropriate sulfonyl chloride with the required aniline derivative and hydrolyzing or reducing the product to the final compound. The method of coupling and hydrolysis employed was essentially that of Long and Burger (1), but it was found that variations in the experimental details were of great importance in obtaining satisfactory yields of the products.

Two methods are described for the preparation of III. The coupling with 2,6-dibromo-4-aminoacetanilide was employed, since it was thought that the blocking of one amino group would be necessary to prevent formation of two products. When the removal of the blocking group gave difficulty, the alternate method with 2,6-dibromo-*p*-phenylenediamine was used, which gave satisfactory yields.

The preparation of 4-dimethylamino-3,5-dibromonitrobenzene presented some difficulty. Bromination of *p*-nitro-N,N-dimethylaniline, as described below, led to a monomethyl derivative, a result similar to that reported by Fries (2) in the bromination of dimethylaniline. Only starting material was recovered when an attempt was made to methylate 4-nitro-2,6-dibromoaniline with dimethyl sulfate as described by Evans and Williams (3) for the methylation of *p*-nitroaniline. The formaldehyde-formic acid method described by Clarke *et al* (4) for the methylation of 2,4,6-trisubstituted anilines gave similar results. The preparation was finally accomplished by the reaction of dimethylamine with 4-iodo-3,5-dibromonitrobenzene.

An attempt was made to prepare 4-cyano-3′,5′-dibromobenzenesulfonanilide from II following the procedure used by Miller *et al* (5) to prepare *p*-cyanoben-

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Instatute of Technology.

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[3] At the time this work was started compound II and the acetyl derivative of I were described in the patent literature (6), but they were not available for testing. Since the completion of this work compounds II and VIII have been briefly described by Kaplan and Leubner (10), while compound VI has been prepared by a different method by Cook *et al* (20).

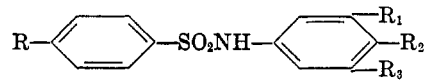
zenesulfonamide from sulfanilamide. The method failed because of the insolubility of both II and its diazonium salt. The required compound was then obtained by the reaction of *p*-cyanobenzenesulfonyl chloride with 3,5-dibromoaniline.

EXPERIMENTAL[4,5]

N^4-Acetyl-N^1-(3,5-dinitrophenyl)sulfanilamide (6). Twenty-eight grams of 3,5-dinitroaniline (7) was dissolved in 200 ml. of reagent pyridine, and 55 g. of acetylsulfanilyl chloride[6] was added in small portions while the solution was cooled and shaken. After standing at room temperature for one hour the solution was heated on a steam-bath for fifteen hours. It was then poured into a mixture of hydrochloric acid and ice, and the precipitated solid filtered and washed with dilute acid and water. For purification it was dissolved in 200 ml. of hot 2 *N* sodium carbonate solution, filtered, and precipitated with 2 *N* hydrochloric acid. After filtration, washing, and drying, the product weighed 55 g. (93%) and melted with decomposition at 280–281°.

N^1-(3,5-Dinitrophenyl)sulfanilamide (I), (SN 3863).[7] The acetyl group was removed by refluxing a solution of 55 g. of the amide in a mixture of 750 ml. of ethanol and 220 ml. of

TABLE I



	R	R_1	R_2	R_3
I	$-NH_2$	$-NO_2$	$-H$	$-NO_2$
II	$-NH_2$	$-Br$	$-H$	$-Br$
III	$-NH_2$	$-Br$	$-NH_2$	$-Br$
IV	$-NH_2$	$-Br$	$-NHCH_3$	$-Br$
V	$-NH_2$	$-Br$	$-N(CH_3)_2$	$-Br$
VI	$-NH_2$	$-CN$	$-H$	$-H$
VII	$-NH_2$	$-CN$	$-H$	$-CN$
VIII	$-CH_2NH_2$	$-Br$	$-H$	$-Br$

concentrated hydrochloric acid. After two hours the solution was poured into five volumes of water and made basic with ammonia. The amine after filtration, washing, and drying weighed 45 g. (90%). It melted at 214–215° after crystallization from ethanol.

Anal. Calc'd for $C_{12}H_{10}N_4O_6S$: C, 42.6; H, 3.0; N, 16.6.
Found: C, 42.7; H, 3.1; N, 16.5.

3,5-Dibromoaniline. 3,5-Dibromonitrobenzene (8) was reduced catalytically with Raney nickel at 50° and 50 lbs. pressure.[8] The catalyst was removed by filtration and the solution evaporated to dryness. The residue, after purification through the hydrochloride,

[4] All melting points reported have been corrected for exposed stem.

[5] The microanalyses reported have been carried out by Dr. Gertrude Oppenheimer and Mr. Alan Swinhart.

[6] We wish to thank Merck and Company for a generous gift of this compound.

[7] The Survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of the compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.

[8] This method of reducing halogenated nitrobenzenes was suggested by Dr. N. L. Drake of the University of Maryland in a private communication.

was obtained in an 86% yield and had the m.p. 47.5–50.5° in agreement with the literature (9).

N^4-Acetyl-N^1-(3,5-dibromophenyl)sulfanilamide (*6*). This compound was prepared from 3,5-dibromoaniline and acetylsulfanilyl chloride in the manner described above. After purification, the product was obtained in 93% yield and melted at 242–244°.

N^1-(3,5-Dibromophenyl)sulfanilamide (*II*) (*6, 10*), (*SN 187*). The acetyl compound was hydrolyzed as described above. The crystalline precipitate of the product was obtained in 79% yield and melted at 149.5–152°. A sample recrystallized from ethanol melted at 154–155°.

Anal. Calc'd for $C_{12}H_{10}Br_2N_2O_2S$: C, 35.5; H, 2.5; N, 6.9.
Found: C, 35.3; H, 2.4; N, 6.9.

2,6-Dibromo-4-aminoacetanilide. 2,6-Dibromo-4-nitroaniline prepared in 96% yield from *p*-nitroaniline under the conditions employed by Hartman and Dickey (11) for the bromination of *p*-nitrophenol was acetylated by the method of Smith and Orton (12, 13) and the nitro group reduced catalytically (64% yield) as described above for 3,5-dibromonitrobenzene. The product was crystallized from ethanol to give colorless crystals melting at 246.5–248.5°.

Anal. Calc'd for $C_8H_8Br_2N_2O$: C, 31.2; H, 2.6; N, 9.1.
Found: C, 31.5; H, 2.8; N, 8.9.

N^4-Acetyl-N^1-(3,5-dibromo-4-acetaminophenyl)sulfanilamide. The reaction was carried out in the usual fashion, with two and one-half hours' warming on a steam-bath. A yield of 81% of crude material was obtained. A sample crystallized from aqueous ethanol melted at 236–238°.

N^1-(3,5-Dibromophenyl-4-acetaminophenyl)sulfanilamide. The hydrolysis was carried out as described above. After one and one-half hours of refluxing, a compound melting at 210–213° was obtained in 76% yield.

Anal. Calc'd for $C_{14}H_{13}Br_2N_3O_3S$: C, 36.3; H, 2.8.
Found: C, 36.5; H, 3.1.

N^4-Acetyl-N^1-(3,5-dibromo-4-aminophenyl)sulfanilamide. Twenty grams of 2,6-dibromo-*p*-phenylenediamine (14) and 18.5 g. of acetylsulfanilyl chloride were coupled using one hour of heating. A sample crystallized from aqueous ethanol melted at 232–233.5°.

Anal. Calc'd for $C_{14}H_{13}Br_2N_3O_3S$: N, 9.1. Found: N, 9.5.

N^1-(3,5-Dibromo-4-aminophenyl)sulfanilamide (*III*), (*SN 3864*). The hydrolysis of N^1-(3,5-dibromo-4-acetaminophenyl)sulfanilamide required eight hours of additional refluxing. A product melting at 176–177° was obtained in 60% yield.

Anal. Calc'd for $C_{12}H_{11}Br_2N_3O_2S$: C, 34.2; H, 2.6; N, 9.8.
Found: C, 34.5; H, 2.7; N, 10.3.

The crude N^4-acetyl-N^1-(3,5-dibromo-4-aminophenyl)sulfanilamide was hydrolyzed by one hour of refluxing. Recrystallization from aqueous ethanol gave a yield of 85% of a compound identical with that reported above.

p-Nitro-N,N-dimethylaniline. A solution of 44.8 g. of *p*-nitrochlorobenzene, 40 ml. of dimethylamine, and 200 ml. of ethanol was heated for four hours at 160° in bomb tubes. On cooling, the product crystallized out and was collected by filtration. After recrystallization from ethanol 41.6 g. (88%) of *p*-nitro-N,N-dimethylaniline was obtained melting at 163–166° in agreement with the literature (15).

N-Methyl-2,6-dibromo-4-nitroaniline. The bromination of *p*-nitro-N,N-dimethylaniline was carried out as was the bromination of *p*-nitroaniline. On recrystallization of the crude product from ethanol, 30% of yellow crystals was obtained, m.p. 111–113° in agreement with the literature (16).

N^1-Methyl-2,6-dibromo-p-phenylenediamine. The nitro compound was reduced as usual, in 54% yield. An analytical sample of the amine crystallized from benzene melted at 103–104°.

Anal. Calc'd for $C_7H_8Br_2N_2$: C, 30.0; H, 2.9; N, 10.0.
Found: C, 29.9; H, 2.9; N, 10.0.

N^4-Acetyl-N^1-(3,5-dibromo-4-methylaminophenyl)sulfanilamide. The reaction between the amine and acetylsulfanilyl chloride required one hour of heating. The crude product was obtained in 92% yield. A sample recrystallized from aqueous ethanol melted at 220–221.5°.

Anal. Calc'd for $C_{15}H_{15}Br_2N_3O_3S$: C, 37.8; H, 3.2; N, 8.8.
Found: C, 38.4; H, 3.2; N, 8.3.

N^1-(3,5-Dibromo-4-methylaminophenyl)sulfanilamide (IV), (SN 3865). The hydrolysis and isolation were carried out in the usual manner. There was obtained an 80% yield of a product which melted at 147–148.5° after recrystallization from a chloroform-ligroin mixture.

Anal. Calc'd for $C_{13}H_{13}Br_2N_3O_2S$: C, 35.9; H, 3.0; N, 9.7.
Found: C, 36.3; H, 3.3; N, 9.8.

3,5-Dibromo-4-iodonitrobenzene. This compound was prepared from 2,6-dibromo-4-nitroaniline in the manner employed by Niemann and Redemann (17) to obtain 3,4,5-triiodonitrobenzene. After recrystallization from an ethanol-Cellosolve (2:1) mixture 75% of product melting at 150.5–152.5° was obtained. The previously reported melting point 135.5° (18) seems to be in error.

Anal. Calc'd for $C_6H_2Br_2INO_2$: C, 17.7; H, 0.5.
Found: C, 18.0; H, 0.9. 7.460 mg. compound gives 11.21 mg. AgX. Calculated 11.19 mg. AgX.

3,5-Dibromo-4-dimethylaminonitrobenzene. A mixture of 40.7 g. of 3,5-dibromo-4-iodonitrobenzene, 80 ml. of butanol, and 15 ml. of dimethylamine was heated in a sealed tube at 120–130° for seven hours. A homogeneous solution was obtained. On cooling, the product crystallized out and was filtered and washed with methanol. Recrystallization from ethanol yielded 25.3 g. of golden plates melting at 102–103.5°. A second crop was obtained from the mother liquors. The total yield was 27.5 g. (85%).

Anal. Calc'd for $C_8H_8Br_2N_2O_2$: C, 29.7; H, 2.5; N, 8.7.
Found: C, 29.8; H, 2.5; N, 8.5.

3,5-Dibromo-4-dimethylaminoaniline. The catalytic reduction of 4-dimethylamino-3,5-dibromonitrobenzene in the usual manner gave a quantitative yield. The free amine appeared to be unstable and was therefore immediately coupled with acetylsulfanilyl chloride.

N^4-Acetyl-N^1-(3,5-dibromo-4-dimethylaminophenyl)sulfanilamide. The crude amine from the reduction of 15 g. of the nitro compound was dissolved in 25 ml. of pyridine and coupled with acetylsulfanilyl chloride in the usual manner. The product weighed 21.7 g. (95% from the nitro compound), m.p. 248.5–250.5°. An analytical sample from aqueous ethanol melted at 252–253°.

Anal. Calc'd for $C_{16}H_{17}Br_2N_3O_3S$: C, 39.1; H, 3.5; N, 8.6.
Found: C, 39.5; H, 3.7; N, 8.6.

N^1-(3,5-Dibromo-4-dimethylaminophenyl)sulfanilamide (V), (SN 3866). The acetyl compound was hydrolyzed as usual, yielding 79% of colorless platelets, m.p. 194.5–196°, after crystallization from aqueous ethanol.

Anal. Calc'd for $C_{14}H_{15}Br_2N_3O_2S$: C, 37.4; H, 3.4; N, 9.4.
Found: C, 37.3; H, 3.3; N, 9.4.

p-Nitrobenzenesulfonyl-m-cyanoanilide. The reaction of *m*-cyanoaniline (19) with *p*-nitrobenzenesulfonylchloride was carried out in the same fashion as the couplings previously described. Two hours' heating were required. After crystallization from acetic acid 77% of colorless prisms, m.p. 198.5–199.5° was obtained.

Anal. Calc'd for $C_{13}H_9N_3O_4S$: C, 51.5; H, 3.0; N, 13.9.
Found: C, 51.5; H, 3.1; N, 13.3.

N^1-(3-Cyanophenyl)sulfanilamide (VI) (20), (SN 6947). To a suspension of 45 g. of iron powder in 150 ml. of 96% ethanol containing 1.5 ml. of dilute hydrochloric acid was added 14 g. of *p*-nitrobenzenesulfonyl-*m*-cyanoanilide, and the mixture was stirred and heated on the steam-bath for six hours. At the end of this period the suspension was filtered hot, and

the residue was washed with hot ethanol. The solution thus obtained was poured into about five volumes of water whereupon a colorless crystalline precipitate slowly appeared. It was filtered, washed, and dried to give 11.4 g. (90%) of product, m.p. 188–191°. After several recrystallizations from 30% ethanol the product melted at 191–192°.

Anal. Calc'd for $C_{13}H_{11}N_3O_2S$: C, 57.1; H, 4.1; N, 15.4.
Found: C, 57.3; H, 4.2; N, 15.6.

5-Nitroisophthalic acid. When 120 g. of isophthalic acid was heated with 600 ml. of fuming nitric acid, density 1.59–1.60, the solid went into solution in about eight hours. Evaporation of the solution and recrystallization of the product from water gave yields of 70–75% of 5-nitroisophthalic acid,[9] m.p. 254–258°.

3,5-Dicyanonitrobenzene. The preparation of the dicyano compound was carried out in ten-gram batches as larger runs tended to decrease the yield. An intimate mixture of 10 g. of 5-nitroisophthalamide (21) and 13 g. of phosphorus pentoxide was heated at 240–250° for eight hours. The residue was treated with water until it softened and was then filtered and dried. This material was extracted with a 50-ml. portion of boiling acetic acid. The filtrate on standing deposited yellow crystals which were filtered and dried. The solid residue from the first extraction was extracted twice more with the same portion of acetic acid, the yields thus obtained being combined. There was obtained 3.9 g. (46%) of yellow prisms, m.p. 203.5–205.5°.

3,5-Dicyanoaniline. To 3.5 g. of 3,5-dicyanonitrobenzene dissolved in 40 ml. of hot acetic acid was added 13 g. of stannous chloride dihydrate. Dry hydrogen chloride was passed into the hot suspension until a clear orange solution was obtained (about ten minutes). The solution was allowed to cool and then poured into 250 ml. of ether. Water was added and the mixture was shaken until two clear phases were obtained; then, with constant shaking, 40% sodium hydroxide solution was gradually added until the aqueous phase was strongly basic. The ethereal phase was washed and dried. Evaporation of the ether and crystallization of the residue from 30% ethanol gave 1.2 g. (41%) of colorless needles, m.p. 192–193°.

Anal. Calc'd for $C_8H_5N_3$: C, 67.1; H, 3.5; N, 29.4.
Found: C, 67.3; H, 3.5; N, 29.2.

p-Nitrobenzenesulfonyl-3,5-dicyanoanilide. The coupling of 3,5-dicyanoaniline with *p*-nitrobenzenesulfonyl chloride was effected in the manner employed for the monocyano compound. A yield of 91% of product melting above 300° was obtained. An analytical sample was prepared by crystallization from ethanol.

Anal. Calc'd for $C_{14}H_8N_4O_4S$: C, 51.2; H, 2.5; N, 17.1.
Found: C, 51.4; H, 2.9; N, 17.5.

N^1-(3,5-Dicyanophenyl)sulfanilamide (VII), (SN 6946). The nitro compound was reduced using iron powder and hydrochloric acid as described above for the monocyano compound. A yield of 76% of product, m.p. 222–224°, was obtained. After crystallization from aqueous ethanol it was recovered as light greenish-yellow prisms, m.p. 227.5–228.5°.

Anal. Calc'd for $C_{14}H_{10}N_4O_2S$: C, 56.4; H, 3.4; N, 18.8.
Found: C, 56.3; H, 3.8; N, 18.8.

4-Cyano-3',5'-dibromobenzenesulfonanilide. To a solution of 24.0 g. of 3,5-dibromoaniline in 48 ml. of dry pyridine was added 19.6 g. of *p*-cyanobenzenesulfonyl chloride (22, 23) in small portions. After standing at room temperature for 45 minutes the mixture was heated on a steam-bath for three hours. The product was then isolated in the usual fashion. The crude material was crystallized from 500 ml. of boiling ethanol by adding hot water (500 ml.) until crystallization began. After cooling, the product was filtered, washed, and dried, yielding 36.9 g. (93%) of colorless plates and flat prisms melting at 196.5–197.5°.

Anal. Calc'd for $C_{13}H_8Br_2N_2O_2S$: C, 37.5; H, 1.9; N, 6.7.
Found: C, 37.3; H, 2.0; N, 6.7.

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[9] Under the conditions described by Meyer and Wesche (24) and Storrs and Fittig (25) no reaction could be made to occur even when the reactants were refluxed together for seventy-two hours.

4-Aminomethyl-3′,5′-dibromobenzenesulfonanilide (VIII), (SN 8828), (10). A suspension of 37.5 g. of 4-cyano-3′,5′-dibromobenzenesulfonanilide in 920 ml. of absolute ethanol containing 0.112 mole of hydrochloric acid was catalytically reduced by shaking with 3.0 g. of platinum oxide under one atmosphere of hydrogen (5). The theoretical quantity of hydrogen was adsorbed in five hours. After the catalyst was filtered, the solvent was removed under reduced pressure. The residue was extracted with 1200 ml. of boiling water, and, on cooling, large, colorless, flat prisms were deposited weighing 30.4 g., m.p. 271–272° with decomposition and effervescence. A second crop of 2.7 g. was obtained from the mother liquors making a total yield of 78%. An analytical sample from water melted at 273–274°.

Anal. Calc'd for $C_{13}H_{13}Br_2ClN_2O_2S \cdot H_2O$: C, 32.9; H, 3.2; N, 5.9.
Found: C, 32.8; H, 3.4; N, 5.9.

The free base was obtained by neutralization of a hot solution of the hydrochloride with saturated potassium bicarbonate solution. Recrystallization from absolute ethanol resulted in colorless prisms melting at 214.5–215.5°.

Anal. Calc'd for $C_{13}H_{12}Br_2N_2O_2S$: C, 37.2; H, 2.9; N, 6.7.
Found: C, 37.0; H, 3.1; N, 6.6.

SUMMARY

The preparation of several new derivatives of aniline and of nitrobenzene is described and the synthesis of a group of substituted sulfonanilides is reported.

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