2,5-DIBA, 3,5-DIBA, and 2,3-DIBA. TIBA was present in the 78 to 90-hr. sample in a smaller proportion than in the 6 to 12-hr. sample, and accounted for only 10.2% of the extracted ^{14}C. However, the metabolites occurred in larger proportions in the later sample. The results of the metabolite study indicate that TIBA is metabolized to a significant extent by deiodination.

SUMMARY

In the authors' opinion, TIBA has a low probability of becoming an environmental health hazard for a number of reasons. Other investigators have reported the following: TIBA is applied to soybeans in very small quantities and only a minute fraction of the amount applied can be detected in the harvested beans; the toxicity of TIBA is relatively low in humans; and the major portion of TIBA ingested orally by rats, cows, goats, and chickens is excreted rapidly. The work reported here also shows rapid excretion of TIBA in chickens, and no egg or organ concentration of the compound.

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N-acyl Derivatives of Bis-(4-aminophenyl) Disulfide and its Thiolsulfinate

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Abstract □ Bis-(4-aminophenyl)-sulfone and several *N,N'*-diacyl derivatives have shown appreciable activity as antimalarials. With the assumption that a molecule more readily cleaved to a *p*-aminophenyl sulfur or oxidized sulfur anion, as a potential anti-PAB substance, might be a more effective antimalarial, a series of *N,N'*-diacyl derivatives of bis-(4-aminophenyl) disulfide was synthesized. Oxidation with peroxide followed by acylation gave the corresponding thiolsulfinates. Antimalarial activity was found for bis-(4-*p*-acetamidobenzenesulfonamidophenyl) disulfide and *N,N'*-bis-(α-aminoacyl) derivatives of bis-(4-aminophenyl)-sulfone.

Keyphrases □ Bis-(4-aminophenyl) disulfide and thiosulfinate—*N*-acyl derivatives synthesis □ Antimalarial activity—bis-(4-aminophenyl) disulfide derivatives □ IR spectrophotometry—structure □ UV spectrophotometry—structure

Diaminodiphenylsulfone (DDS) (1) and its *N,N'*-diacetyl derivative (2) have both shown appreciable antimalarial activity, particularly against strains of *P. falciparum* resistant to chloroquine and other widely used antimalarials. Evidence has been found to suggest that these compounds are effective by interfering with the utilization of PABA by the parasites (3). If this is the case, then compounds more readily cleaved *in vivo* to a *p*-aminophenyl sulfur or oxidized sulfur moiety might interfere more effectively with PABA utilization. Accordingly, a series of *N,N'*-diacyl derivatives of bis-(4-aminophenyl) disulfide and *S*-oxidized derivatives has been prepared for antimalarial evaluation. Other disulfides, including 5,5'-diacetamido-8,8'-diquinolyl disulfide, have shown antimalarial activity (4, 5).

Bis-(4-aminophenyl) disulfide was obtained by the procedure of Price and Stacy (6), in which sodium 4-aminophenylmercaptide was oxidized by 30% hydrogen peroxide to the disulfide. The product showed the expected IR absorption bands for an aromatic amine, in addition to two sharp bands at 1175 and 1065 $cm.^{-1}$. Bredereck (7) has attributed the presence of these bands in aromatic disulfides to the disulfide linkage and a 1,4-disubstituted aromatic ring, respectively. However, aliphatic disulfides have shown similar peaks in the 1050–1250 $cm.^{-1}$ region which were believed due to CH wag on the carbon adjacent to sulfur (8). UV absorption showed a peak at 256 mμ, characteristic of disulfides (9), with a shoulder at 290–295 mμ.

Peroxide oxidation of aliphatic disulfides has led to formation of thiolsulfinates, thiosulfonates, and α-disulfones, depending on reaction conditions (10). Also, percamphoric acid oxidation of alkyl or aryl disulfides gave mixtures of disulfides, thiolsulfinates, and thiolsulfonates (11). With bis-(4-aminophenyl) disulfide, peroxide oxidation gave only the thiolsulfinate, even on long standing. Heating resulted in decomposition. IR absorption of the product showed a peak at 1050 $cm.^{-1}$, in addition to those present for the disulfide, which is characteristic of thiolsulfinates (8, 12). UV

absorption was found at 254 mμ, but lacked the shoulder at 290 mμ of the disulfide.

Oxidation of bis-(4-nitrophenyl) disulfide at room temperature with 30% peroxide returned only starting material, but in refluxing acetic acid, an oxidation product was obtained. A low yield of bis-(4-nitrophenyl) sulfone was isolated; this result agrees with previous observations on the oxidation of either *p*-nitrothiophenol (13, 14) or bis-(4-nitrophenyl) disulfide (15) where only the sulfone was isolated. This unexpected product has been attributed both to the presence of bis-(4-nitrophenyl) sulfide as an impurity (15) and to cleavage of the C—S bond (14).

Since the toxicity of bis-(4-aminophenyl) sulfone was diminished by *N*-acylation (16), various acylation products of bis-(4-aminophenyl) disulfide and its thiolsulfinate were prepared. These included the acetyl, methanesulfonyl, *p*-toluenesulfonyl, *p*-acetamidobenzenesulfonyl, glycyl, α-phthalimidoacyl, and *N*-carbodithioate. Previously, introduction of α-aminoacyl and α-phthalimidoacyl groups reduced the toxicity of bis-(4-aminophenyl) sulfone without affecting antitubercular activity appreciably (17). The dithiocarbamate of bis-(4-aminophenyl) disulfide was obtained in the presence of a large excess of triethylamine, and showed characteristic IR absorption at 990 and 1010 $cm.^{-1}$ for the dithiocarbamate group (18). Similar IR absorption was shown by the dithiocarbamate of the thiolsulfinate, but confirming analytical data were not obtained for this compound.

Antimalarial Test Results—Antimalarial screening in mice using *Plasmodium berghei* has been carried out by the Walter Reed Army Institute of Research and reported to us by Dr. D. P. Jacobus. Bis-(4-*p*-acetamidobenzenesulfonamidophenyl) disulfide effected a cure in one of five mice (60-day survival) (three dying of drug toxicity) at a dose of 640 mg./kg. No activity was found for bis-(4-aminophenyl) disulfide, bis-(4-*p*-tolylsulfonamidophenyl) disulfide or the bis-(*N*-phthalimidoacetyl), bis-[*N*-(2-phthalimido-3-phenyl)-propionyl] or bis-(*N*-carbodithioate) derivatives of bis-(4-aminophenyl) disulfide. Also, of the thiolsulfinates, the 4-acetamidophenyl, 4-methylsulfonamidophenyl, 4-phthalimidoacetamidophenyl, and 4-(2-phthalimido-3-phenyl)-propionamidophenyl derivatives were inactive.

The bis-glycyl and bis-phenylalanyl derivatives of DDS, previously prepared (17), were described as curative, however. Bis-(4-nitrophenyl) sulfone was also curative.

EXPERIMENTAL

Analyses for carbon, hydrogen, and nitrogen were done by Weiler and Strauss, Oxford, England. Sulfur analyses were done by Parr bomb peroxide fusion. Melting points were taken on a Mel-Temp block and are uncorrected. IR absorption spectra were obtained with a Perkin-Elmer model 137B spectrometer.

Bis-(4-phthalimidoacetamidophenyl) Disulfide—To a solution of 2.5 g. (0.01 mole) of bis-(4-aminophenyl) disulfide (6) in 50 ml. of dry pyridine at 0° was added with stirring 4.5 g. (0.02 mole) of phthalimidoacetyl chloride (19) during a period of 10 min. The mixture was stirred for 4 hr. at 0°, and the resulting solution was poured into 250 ml. of cold water containing 25 ml. of sulfuric acid. The solid product was collected, washed with water, and digested in a mixture of 2-ethoxyethanol and water (4:1), giving 2.8 g. (45%) of cream-colored solid, m.p. 302–305° (dec.).

Anal.—Calcd. for $C_{32}H_{22}N_4O_6S_2$: C, 61.74; H, 3.57; N, 8.99; S, 10.29. Found: C, 62.13; H, 3.44; N, 9.19; S, 10.83.

Bis-(4-aminoacetamidophenyl) Disulfide Dihydrochloride—To a suspension of 0.62 g. (0.001 mole) of bis-(4-phthalimidoacetamidophenyl) disulfide in a mixture of 20 ml. of dimethylformamide and 5 ml. of water was added with stirring 3.0 ml. (0.0026 mole) of alcoholic hydrazine hydrate (1 *M*). Stirring was continued for 1 hr. and concentrated hydrochloric acid was added dropwise to distinct acidity. Water (50 ml.) was added, the mixture was chilled, and phthalazine-1,4-dione was removed. The filtrate was distilled under reduced pressure to a volume of 10 ml., methylene chloride was added, and the precipitate was collected and recrystallized from dilute hydrochloric acid, giving 0.1 g. of yellow solid, m.p. 255–257° (dec.).

Anal.—Calcd. for $C_{16}H_{20}Cl_2N_4O_2S_2$: C, 44.14; H, 4.63; N, 12.87. Found: C, 43.51; H, 4.65; N, 13.35.

Bis-[4-(2-phthalimido-3-phenyl)-propionamidophenyl] Disulfide—To a solution of 2.5 g. (0.01 mole) of bis-(4-aminophenyl) disulfide in 50 ml. of dry pyridine at 0° was added with stirring 6.4 g. (0.02 mole) of 2-phthalimido-3-phenylpropionyl chloride (19) during 10 min. The reaction was carried out as above, and 4.5 g. (56%) of pale yellow product was obtained; m.p. 267–269° (dec.).

Anal.—Calcd. for $C_{46}H_{34}N_4O_6S_2$: C, 68.80; H, 4.27; N, 6.97; S, 7.98. Found: C, 68.89; H, 4.30; N, 7.05; S, 8.24.

Bis-(4-methanesulfonamidophenyl) Disulfide—To a solution of 0.73 g. (0.003 mole) of bis-(4-aminophenyl) disulfide in 15 ml. of dry pyridine was added with stirring 1.0 ml. (0.012 mole) of methanesulfonyl chloride. The mixture was stirred for 15 min. and poured into cold water, and the precipitate was collected and digested in hot 95% ethanol, giving 1.0 g. (83%) of pale pink solid, m.p. 212–215°.

Anal.—Calcd. for $C_{14}H_{16}N_2O_4S_4$: C, 41.57; H, 3.99; N, 6.93; S, 31.70. Found: C, 41.23; H, 3.78; N, 7.10; S, 31.90.

Bis-(4-*p*-tolylsulfonamidophenyl) Disulfide—To a solution of 1.25 g. (0.005 mole) of bis-(4-aminophenyl) disulfide in 20 ml. of dry pyridine at 0° was added with stirring 1.91 g. (0.01 mole) of *p*-toluenesulfonyl chloride during 10 min. The reaction was carried out in the same fashion as with the phthalimidoacyl chlorides. The red solid which separated from dilute sulfuric acid was purified by dissolving in 5% sodium hydroxide solution, filtering, neutralizing with 5% hydrochloric acid, and removing all material which precipitated above pH 7. The resulting cream-colored solid was collected, giving 2.2 g. (80%), m.p. 300° (dec.).

Anal.—Calcd. for $C_{26}H_{24}N_2O_4S_2$: C, 56.09; H, 4.34; N, 5.03. Found: C, 56.24; H, 4.61; N, 5.11.

Bis-(4-*p*-acetamidobenzenesulfonamidophenyl) Disulfide—To a solution of 2.5 g. (0.01 mole) of bis-(4-aminophenyl) disulfide in 40 ml. of dry pyridine at 0° was added with stirring 4.7 g. (0.02 mole) of *p*-acetamidobenzenesulfonyl chloride during 10 min. The reaction was carried out as in the previous case, and 2.5 g. (40%) of cream-colored solid was obtained, m.p. 140° (with previous softening).

Anal.—Calcd. for $C_{28}H_{26}N_4O_6S_4$: C, 52.33; H, 4.08; N, 8.72; S, 19.96. Found: C, 52.27; H, 3.99; N, 8.72; S, 20.18.

Bis-(triethylammonium) Bis-[4-amino-(*N*-carbodithioate)-phenyl] Disulfide—To a solution of 2.5 g. (0.01 mole) of bis-(4-aminophenyl) disulfide in 25 ml. of absolute ethanol was added a 15-mole excess of carbon disulfide and 10-mole excess of triethylamine at room temperature. After the mixture was stirred and refrigerated overnight, the supernatant liquid was discarded and the residual oil was mixed repeatedly with ether–acetone (3:1). The oil was spread thinly on an evaporating dish, placed under vacuum, and the resulting yellow solid was triturated with ether–acetone (3:1) and filtered, giving 3.2 g. (52%) of product, m.p. 94–96°.

Anal.—Calcd. for $C_{26}H_{42}N_4S_6$: C, 51.80; H, 7.02; N, 9.29. Found: C, 52.06; H, 6.78; N, 8.98.

4-Aminophenyl 4-Aminobenzenethiolsulfinate—To a solution of 5.0 g. (0.02 mole) of bis-(4-aminophenyl) disulfide in 50 ml. of 95% ethanol was added an excess of 30% hydrogen peroxide. The flask was stoppered and allowed to stand at room temperature for 1 week. The precipitate was collected and purified by digesting in hot 95% ethanol, giving 3.6 g. (69%) of golden-brown product, m.p. 140–142°.

Anal.—Calcd. for $C_{12}H_{12}N_2OS_2$: C, 54.50; H, 4.58; N, 10.60. Found: C, 55.04; H, 4.82; N, 10.78.

The dihydrochloride was obtained by addition of absolute ethanol to its aqueous solution; m.p. 235° (dec.).

Anal.—Calcd. for $C_{12}H_{14}Cl_2N_2OS_2$: C, 42.73; H, 4.18; N, 8.31. Found: C, 42.90; H, 3.83; N, 8.12.

4-Phthalimidoacetamidophenyl 4-Phthalimidoacetamidobenzenethiolsulfinate—To a mixture of 20 ml. of dimethylformamide and 20 ml. of pyridine at 0° were added 1.32 g. (0.005 mole) of 4-aminophenyl 4-aminobenzenethiolsulfinate and 2.24 g. (0.01 mole) of phthalimidoacetyl chloride (19) during 10 min. The reaction was carried out in the same manner as for the corresponding disulfide, and 1.0 g. (32%) of product was obtained, m.p. 258–263° (dec.).

Anal.—Calcd. for $C_{32}H_{22}N_4O_7S_2$: C, 60.19; H, 3.47; N, 8.78. Found: C, 59.95; H, 3.75; N, 8.51.

4-(2-Phthalimido-3-phenyl)-propionamidophenyl 4-(2-Phthalimido-3-phenyl)-propionamidobenzenethiolsulfinate—To a mixture of 20 ml. of dimethylformamide and 20 ml. of pyridine at 0° were added 1.32 g. (0.005 mole) of 4-aminophenyl 4-aminobenzenethiolsulfinate and 3.15 g. (0.01 mole) of 2-phthalimido-3-phenylpropionyl chloride (19) during 10 min. The reaction was carried out as in the preceding case, and 3.3 g. (78%) of pale yellow product was obtained; m.p. 268–271° (dec.).

Anal.—Calcd. for $C_{46}H_{34}N_4O_7S_2$: C, 67.45; H, 4.19; N, 6.84. Found: C, 67.52; H, 4.43; N, 6.93.

4-Acetamidophenyl 4-Acetamidobenzenethiolsulfinate—To a solution of 1.32 g. (0.005 mole) of 4-aminophenyl 4-aminobenzenethiolsulfinate in 20 ml. of dimethylformamide was added an excess of acetic anhydride. The mixture was stirred for 15 min. and poured into cold water; further stirring coagulated the product. It was collected and recrystallized from glacial acetic acid, giving 1.0 g. (60%) of yellow solid, m.p. 200° (dec.).

Anal.—Calcd. for $C_{16}H_{16}N_2O_3S_2$: C, 55.15; H, 4.63; N, 8.04. Found: C, 55.08; H, 4.59; N, 8.26.

4-Methanesulfonamidophenyl 4-Methanesulfonamidobenzenethiolsulfinate—To a solution of 0.4 g. (0.0015 mole) of 4-aminophenyl 4-aminobenzenethiolsulfinate in 30 ml. of dry pyridine was added with stirring 0.5 ml. (0.006 mole) of methanesulfonyl chloride. The mixture was stirred for 15 min. and poured into cold water; the yellow product (0.47 g., 75%) was collected; m.p. 205–208° (dec.).

Anal.—Calcd. for $C_{14}H_{16}N_2O_5S_4$: C, 39.98; H, 3.83; N, 6.66. Found: C, 40.65; H, 3.90; N, 7.20.

Bis-(4-nitrophenyl) Sulfone—To a refluxing solution of 15.4 g. (0.05 mole) of bis-(4-nitrophenyl) disulfide (Eastman Organic Chemicals) (recrystallized from glacial acetic acid) in 100 ml. of glacial acetic acid was added 6.0 ml. of 30% hydrogen peroxide. An additional 6.0 ml. of 30% hydrogen peroxide was added after 2 hr. The reaction mixture was allowed to cool after 12 hr. of refluxing, and the precipitate was isolated. The pale yellow crystals were washed several times with water and dried *in vacuo*, giving 1.5 g. (10%) of product, m.p. 251–255° (lit. 252–253°) (14, 15).

Anal.—Calcd. for $C_{12}H_8N_2O_6S$: C, 46.75; H, 2.62; N, 9.09; S, 10.40. Found: C, 47.04; H, 2.78; N, 9.17; S, 10.90.

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