# Synthesis of Substituted Benzthiaxanthones for Possible Schistosomicidal Activity

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**Abstract** □ New substituted benzthiaxanthones were synthesized in an attempt to find new compounds that may have schistosomicidal activity.

**Keyphrases** □ Benzthiaxanthones, substituted—synthesized as possible schistosomicidal agents □ Thiaxanthones—synthesized containing methyl group *para* to diethylaminoethylamino side chain as possible schistosomicidal agents □ Schistosomicidal agents, potential—synthesis of substituted benzthiaxanthones

Some substituted thiaxanthones, represented by 1-(2-diethylaminoethylamino)-4-methylthiaxanthone[1], have shown schistosomicidal (1) and carcinostatic activity (2). The structural feature necessary for the biological activity of this agent is a methyl group *para* to a dialkylaminoalkylamino side chain on the aromatic ring (3). The reactivity of these groupings necessary for the biological activity was discussed previously (4–7).

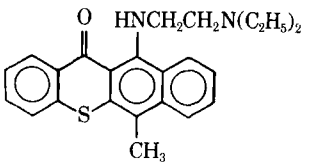
## DISCUSSION

These considerations suggested the synthesis of a new compound of the thiaxanthone type containing a methyl group *para* to the diethylaminoethylamino side chain and incorporating the naphthalene system. This was suggested since, in mammalian systems, molecular oxygen is directly incorporated in the naphthalene metabolism through an oxygenation process (8, 9). Such oxygen carriers may affect glycolysis in the parasite, which seeks its main source of energy for living and reproduction through this metabolic process.

Condensation of thiosalicylic acid with 2-bromo-1-methyl-4-nitronaphthalene (10, 11) in the presence of anhydrous sodium carbonate gave 1-methyl-4-nitro-2-naphthyl-*o*-carboxyphenyl sulfide (II).

Reduction of the nitro group in II, using iron and acetic acid, gave 4-amino-1-methyl-2-naphthyl-*o*-carboxyphenyl sulfide (III), which was cyclized under the effect of polyphosphoric acid to give 11-amino-6-methylbenz[*b*]thiaxanthen-12-one (IV). Upon condensation of IV with 2-diethylaminoethyl chloride, the desired product, 11-(2-diethylaminoethylamino)-6-methylbenz[*b*]thiaxanthen-12-one (V), was obtained.

Furthermore, it was observed that 1,4-naphthalenediamine killed adult *Schistosoma mansoni in vitro* at a drug concentration as low as 25 μg/ml (12). The potent chemotherapeutic effect of various *N*-(dialkylaminoalkyl)-1,4-naphthalenediamines (13–15) against infections of *S. mansoni* and *S. japonicum* in experimental animals was attributed to the affinity of these compounds to exist in the oxidation state as quinoid structures of the naphthoquinone types within these series (16). It was already known that naphthoquinone can reduce the rate of glycolysis in schistosomes substantially (17).




V

Condensation of thiosalicylic acid with 2-iodo-4-nitro-1-naphthylamine (18) in the presence of anhydrous sodium carbonate afforded 1-amino-4-nitro-2-naphthyl-*o*-carboxyphenyl sulfide (VI).

Reduction of VI with iron and acetic acid gave 1,4-diamino-2-naphthyl-*o*-carboxyphenyl sulfide (VII), which underwent ring closure with polyphosphoric acid to give 6,11-diaminobenz[*b*]thiaxanthen-12-one (VIII). This reacted with 4-diethylaminoethyl chloride to yield the product 6,11-bis(2-diethylaminoethylamino)benz[*b*]thiaxanthen-12-one (IX).

Upon acetylation of VI with acetic anhydride, 1-acetamido-4-nitro-2-naphthyl-*o*-carboxyphenyl sulfide (X) was obtained. This compound was similarly reduced to 1-acetamido-4-amino-2-naphthyl-*o*-carboxyphenyl sulfide (XI).

Cyclization of XI with polyphosphoric acid gave 6-acetamido-11-aminobenz[*b*]thiaxanthen-12-one (XII). Upon reaction with 2-diethylaminoethyl chloride and hydrolysis, XII gave 6-amino-11-(2-diethylaminoethylamino)benz[*b*]thiaxanthen-12-one (XIII).

Furthermore, *p*-aminophenols were found to undergo biological transformations to benzoquinone-type structures (19, 20). For this purpose, the present synthesis emphasized a benzthiaxanthone structure bearing a hydroxyl group *para* to the diamine side chain.

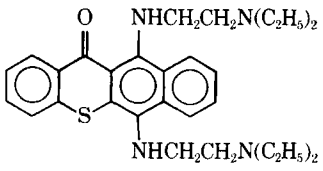
Condensation of 2-iodo-4-nitro-1-naphthol (18) with thiosalicylic acid gave 1-hydroxy-4-nitro-2-naphthyl-*o*-carboxyphenyl sulfide (XIV). However, this product, XIV, could also be obtained by boiling VI with alkali.

Reduction of the nitro group in XIV, using iron and acetic acid, afforded 4-amino-1-hydroxy-2-naphthyl-*o*-carboxyphenyl sulfide (XV). This was cyclized using polyphosphoric acid to give 11-amino-6-hydroxybenz[*b*]thiaxanthen-12-one (XVI). Finally, XVI was reacted with 2-diethylaminoethyl chloride to give 11-(2-diethylaminoethylamino)-6-hydroxybenz[*b*]thiaxanthen-12-one (XVII).

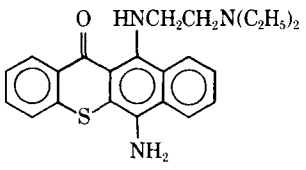
Biological studies on V, IX, XIII, and XVII will be presented in a separate report.

## EXPERIMENTAL[2]

**Compound II**—A mixture of thiosalicylic acid (5.8 g, 0.037



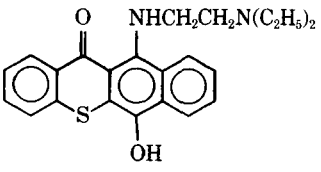

IX




XIII

[1] Lucanthone or Miracil D, Farbenfabriken Bayer AG, Leverkusen, West Germany.

[2] Melting points were taken in open capillary tubes by use of a sulfuric acid bath and a Gallenkamp melting-point apparatus and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, National Research Centre, Cairo, U.A.R. IR spectra were determined on a UR.10 Zeiss-Jean IR spectrophotometer using KBr pellets.




XVII

mole), 2-bromo-1-methyl-4-nitronaphthalene (10 g, 0.038 mole), anhydrous sodium carbonate (4.3 g, 0.041 mole), and amyl alcohol (60 ml) was refluxed at 140° for 16 hr. The alcohol was removed by steam distillation, and the reaction mixture was boiled with excess water and then filtered. The cold filtrate was acidified with acetic acid; the precipitated product was collected, washed with water, and dried to give 9 g (71%) of II, mp 153° (from ethanol).

*Anal.*—Calc. for $C_{18}H_{13}NO_4S$: C, 63.70; H, 3.86; N, 4.13. Found: C, 63.39; H, 3.74; N, 4.51.

**Compound III**—A suspension of II (7 g) in acetic acid (100 ml, 70%) was stirred on a steam bath, and then iron powder (7 g) was added portionwise. Stirring and heating were continued for 3 hr. The mixture was poured into ice-cold water. The solid product was collected, dissolved in boiling ammonium hydroxide solution, and filtered. The filtrate was acidified with acetic acid. The precipitated product was isolated to give 4.5 g (72%) of III, mp 190° (aqueous ethanol); IR: 700 (—S—), 1655 (—COOH), and 3330 (—$NH_2$) $cm^{-1}$.

*Anal.*—Calc. for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.67; H, 4.81; N, 4.70.

**Compound IV**—Compound III (2 g) was heated with polyphosphoric acid (20 g) at 140° for 2 hr. The reaction mixture was poured into ice-cold water, and the solid product was collected and washed with boiled ammonium hydroxide solution. After drying, it gave 1.7 g (90%) of IV, mp 151° (from ethanol).

*Anal.*—Calc. for $C_{18}H_{13}NOS$: C, 74.20; H, 4.50; S, 11.00. Found: C, 73.85; H, 4.21; S, 10.79.

**Compound V**—Compound IV (1 g) was treated with 2-diethylaminoethyl chloride (0.5 ml) at 160° for 4 hr. The reaction mixture was boiled with dilute hydrochloric acid and then filtered. The cooled filtrate was neutralized with dilute sodium hydroxide solution, and the solid precipitate was collected and dried to give 1 g (75%) of V, mp 113° (from aqueous ethanol).

*Anal.*—Calc. for $C_{24}H_{26}N_2OS$: C, 73.81; H, 6.71; N, 7.17. Found: C, 73.49; H, 6.53; N, 7.56.

**Compound VI**—A mixture of thiosalicylic acid (3.66 g, 0.0238 mole), 2-iodo-4-nitro-1-naphthylamine (7.6 g, 0.024 mole), anhydrous sodium carbonate (2.6 g, 0.0255 mole), copper powder (0.1 g), and amyl alcohol (60 ml) was refluxed at 150° for 15 hr. The alcohol was steam distilled, and the mixture was boiled with excess water and then filtered. The cold filtrate was neutralized with acetic acid and the formed precipitate was collected. After drying, it gave 6 g (75%) of VI, mp 230° (from ethanol); IR: 690 (—S—), 1505 (—$NO_2$), 1680 (—COOH), and 3330 (—$NH_2$) $cm^{-1}$.

*Anal.*—Calc. for $C_{17}H_{12}N_2O_4S$: C, 59.99; H, 3.56; S, 9.42. Found: C, 60.27; H, 3.88; S, 9.33.

**Compound VII**—A suspension of II (4.5 g) in acetic acid (60 ml, 70%) was stirred on a steam bath, and iron powder (4 g) was added portionwise. After 4 hr, the reaction mixture was poured into ice-cold water. The precipitated product was isolated, dissolved in boiling ammonium hydroxide solution, and filtered. The cold filtrate was acidified with acetic acid, and the formed precipitate was collected, washed with water, and dried to give 3 g (73%) of VII, mp 180° (from ethanol).

*Anal.*—Calc. for $C_{17}H_{14}N_2O_2S$: C, 65.78; H, 4.55; N, 9.04. Found: C, 65.54; H, 4.32; N, 9.28.

**Compound VIII**—Compound III (2 g) was treated with polyphosphoric acid (20 g) at 140° for 3 hr, and the reaction was poured into ice water. The solid product was isolated, washed with boiling ammonium hydroxide solution, washed with water, and dried to give VIII in 82% yield, mp 165° (from ethanol).

*Anal.*—Calc. for $C_{17}H_{12}N_2OS$: C, 69.84; H, 4.14; N, 9.58. Found: C, 69.68; H, 4.31; N, 9.36.

**Compound IX**—A mixture of IV (1.5 g, 0.005 mole) and 2-diethylaminoethyl chloride (1.4 g, 0.11 mole) was heated at 160° for 4 hr. The reaction mixture was boiled with excess water and a few milliliters of dilute hydrochloric acid and then filtered while hot. The cold filtrate was made basic with sodium hydroxide solution. The formed precipitate was collected, washed with water, and dried to give 1.7 g (61%) of IX, mp 144° (from aqueous ethanol).

*Anal.*—Calc. for $C_{29}H_{38}N_4OS$: C, 72.41; H, 7.81; S, 6.53. Found: C, 72.15; H, 7.63; S, 6.78.

**Compound X**—A solution of VI (5 g) in acetic acid (30 ml) and acetic anhydride (3 ml) was heated under reflux for 5 hr. The cooled reaction mixture was poured into ice water, and the formed precipitate was collected and recrystallized from aqueous ethanol to give 5 g (89%) of X, mp 246°.

*Anal.*—Calc. for $C_{19}H_{14}N_2O_5S$: C, 59.69; H, 3.69; N, 7.33. Found: C, 59.38; H, 3.61; N, 7.59.

**Compound XI**—Reduction of VI (4 g) with acetic acid (50 ml, 60%) and iron powder (4 g), as described for III, gave 3 g (82%) of XI, mp 216° (from aqueous ethanol).

*Anal.*—Calc. for $C_{19}H_{16}N_2O_3S$: C, 64.77; H, 4.58; N, 7.98. Found: C, 64.45; H, 4.39; N, 8.26.

**Compound XII**—This compound was prepared by the cyclization of XI with polyphosphoric acid, as described for VIII, in 83% yield, mp 158° (from ethanol).

*Anal.*—Calc. for $C_{19}H_{14}NO_2S$: C, 71.23; H, 4.40; N, 4.37. Found: C, 70.86; H, 4.13; N, 4.69.

**Compound XIII**—A mixture of XII (2 g) and 2-diethylaminoethyl chloride (1 ml) was heated at 170° for 4 hr. The reaction mixture was refluxed with dilute hydrochloric acid (20 ml) for 10 hr and then filtered after the addition of water. The cold filtrate was neutralized with aqueous sodium hydroxide. The precipitated product was collected, washed with water, and dried to give 1.8 g (75%) of XIII, mp 106° (from aqueous ethanol).

*Anal.*—Calc. for $C_{23}H_{25}N_3OS$: C, 70.55; H, 6.44; N, 10.73. Found: C, 70.36; H, 6.47; N, 10.58.

**2-Iodo-4-nitro-1-naphthol (17)**—To a solution of 4-nitro-1-naphthol (6 g) in acetic acid (50 ml) was added iodine monochloride (5.5 g) in acetic acid (12 ml). The mixture was kept at room temperature for 3 days and then poured into ice water. The precipitated product was collected, washed with water, and dried to give 7 g (70%) of practically pure 2-iodo-4-nitro-1-naphthol, mp 115° (17).

**Compound XIV**—*Method A* —A mixture of 2-iodo-4-nitro-1-naphthol (4.5 g, 0.0143 mole), thiosalicylic acid (2.2 g, 0.0142 mole), anhydrous sodium carbonate (16 g, 0.015 mole), and amyl alcohol (45 ml) was heated under reflux for 15 hr. The product was isolated as described for VI to give 3.5 g (72%), mp 200° (from ethanol); IR: 700 (—S—), 1505 (—$NO_2$), 1690 (—COOH), and 3400 (—OH) $cm^{-1}$.

*Anal.*—Calc. for $C_{17}H_{11}NO_5S$: C, 59.73; H, 3.25; N, 4.11. Found: C, 60.03; H, 3.44; N, 4.36.

*Method B*—A solution of VI (2 g) in sodium hydroxide solution (40 ml, 10%) was refluxed for 8 hr. The hot mixture was filtered, cooled, and acidified with dilute hydrochloric acid. The precipitated product was collected and dried to give 1.6 g (80%) of XIV identified by melting point and mixed melting point.

**Compound XV**—Reduction of XI with iron and acetic acid, as described for VII, gave XV in 74% yield, mp 211° (from aqueous ethanol).

*Anal.*—Calc. for $C_{17}H_{13}NO_3S$: C, 65.64; H, 4.21; S, 10.31. Found: C, 65.43; H, 4.26; S, 10.53.

**Compound XVI**—Cyclization of XV with polyphosphoric acid, as described for VIII, and washing with sodium carbonate solution gave XVI in 68% yield, mp 186° (from ethanol).

*Anal.*—Calc. for $C_{17}H_{11}NO_2S$: C, 69.76; H, 3.78; S, 10.93. Found: C, 69.53; H, 3.61; S, 10.79.

**Compound XVII**—Compound XVI (2 g) was treated with 2-diethylaminoethyl chloride (1 ml) at 160° for 5 hr. The reaction mixture was boiled with dilute hydrochloric acid and then filtered. The cold filtrate was neutralized with sodium carbonate solution, and the formed precipitate was isolated and dried to give 1.9 g (74%) of XVII, mp 122° (from aqueous ethanol).

*Anal.*—Calc. for $C_{23}H_{24}N_2OS$: C, 70.38; H, 6.16; N, 7.14. Found: C, 70.16; H, 6.23; N, 7.42.

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# Characterization of Silver Sulfadiazine and Related Compounds

**B. J. SANDMANN*, R. U. NESBITT, Jr.*, and R. A. SANDMANN**

**Abstract** □ Silver sulfonamides can be successfully recrystallized from strong ammonia solution. The spectral characterization of silver sulfadiazine, silver sulfamethazine, silver sulfanilamide, and silver sulfapyridine indicates that the silver sulfonamide formed on reaction of silver nitrate with the free sulfonamide or its sodium salt is correctly represented by a classical salt structure. Complexations of silver sulfonamides with morpholine yield 1:1 crystalline complexes, which can be analyzed by NMR spectroscopy directly. Spectral studies of the silver sulfonamides were carried out using an indirect NMR technique.

**Keyphrases** □ Silver sulfadiazine and related compounds—recrystallization and spectral characterization, structure determination □ Silver sulfonamides—recrystallization and spectral characterization, structure determination □ Sulfonamides, silver—recrystallization and spectral characterization, structure determination □ NMR spectroscopy—structure determination, silver sulfonamides

Since 1968, interest in silver sulfadiazine has increased steadily due to its effectiveness in the topical treatment of *Pseudomonas* infections associated with thermal burns. The compound contains both silver with its oligodynamic effect and sulfonamide antibiotic activity to give a broad range of effectiveness against microorganisms. Silver ion in solution is toxic, but salts of silver have been shown to be safe and effective against bacteria in concentrations as small as 1 ppb. When used in combination with, or when reacted with, a sulfonamide, silver offers additional advantages in the treatment of burns. These include the lack of sensitization characteristics of antibiotics usually employed for these conditions, the broader range of antibacterial activity as well as activity against mycotic and viral infections, and the failure of organisms to develop resistant strains to silver-ion activity.

Silver sulfadiazine offers many therapeutic advantages in topical use over other silver salts. Fox (1) reported that, unlike silver nitrate, silver sulfadiazine is odorless, stainless, easy to apply, and painless and often reduces the need for skin grafts. In addition, the compound does not deplete the applied area of essential body salts and, therefore, does not require simultaneous administration of supplementary fluids as is necessary with silver nitrate. Sulfonamides used as sodium salts are also inferior to their silver salts, because the sodium derivatives have been shown to cause extensive tissue damage because of their high alkalinity.

The proven efficacy of silver sulfadiazine in the treatment of *Pseudomonas* infections in burns has been reported (2–4), but little information about the physical and chemical properties of this compound is available. It was reported (5) that silver sulfadiazine is poorly water soluble and that the silver ion is firmly bound to the nitrogen, but no positive evidence for this claim was given. Wruble (6) prepared colloidal silver preparations of sulfadiazine and other sulfonamides and indicated structural formulas but without any supportive spectral or analytical data. A silver–sulfadiazine chelate ring complex was reported (7) for the precipitate obtained after mixing a sodium sulfadiazine solution with a silver nitrate solution. The chelate structure is just one of several proposed structures for silver sulfadiazine and related