Synthesis of 1,8-, 1,6- and 3,6-Dichloro-9*H*-thioxanthen-9-ones

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Cyclization of 2-chloro-6-[(3-chlorophenyl)thio]benzoic acid (**2**) gave a mixture of 1,8-, **3**, and 1,6-dichloro-9*H*-thioxanthen-9-ones **4**. The mixture was converted to 1,8-diamino- **7**, and 1-amino-6-chloro-9*H*-thioxanthen-9-ones **8**, from which **3** and **4** were prepared separately, respectively. From a mixture of **4** and 3,6-dichloro-9*H*-thioxanthen-9-one (**11**) obtained by cyclizing 4-chloro-2-[(3-chlorophenyl)thio]benzoic acid (**10**) was separated **11** by conversion of **4** to **8**.

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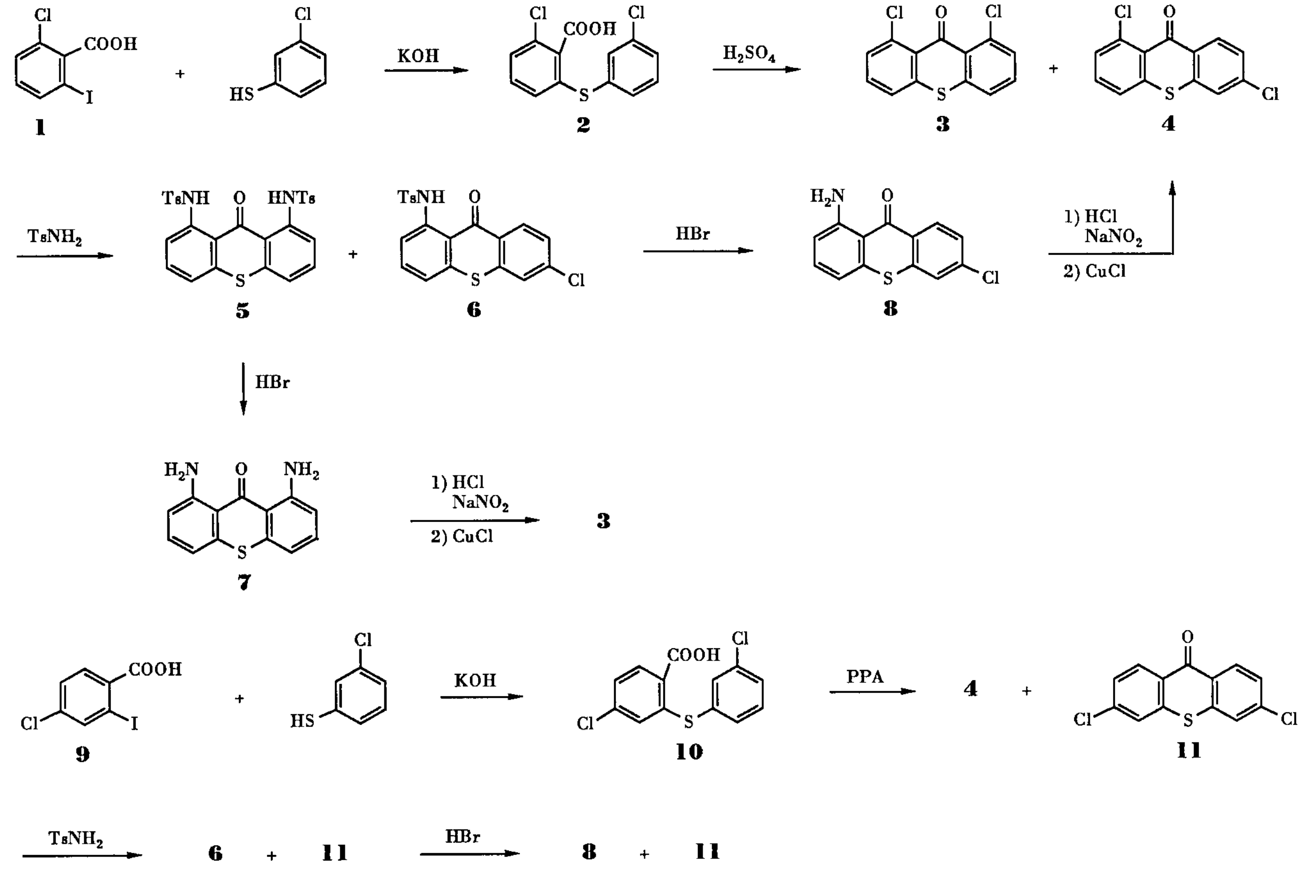
In the previous paper [1], we reported the synthesis of 1,5- and 1,7-dichloro-9*H*-thioxanthen-9-ones. Since cyclization of 3-chloro-2-[(3-chlorophenyl)thio]benzoic acid gave a mixture of 1,5- and 3,5-dichloro-9*H*-thioxanthen-9-ones whose mutual separation is difficult on a preparative scale, 1,5-dichloro-9*H*-thioxanthen-9-one was prepared by cyclization of 2-chloro-6-[(2-chlorophenyl)thio]benzoic acid. Similarly 1,7-dichloro-9*H*-thioxanthen-9-one was prepared by cyclization of 2-chloro-6-[(4-chlorophenyl)thio]benzoic acid, as the cyclization of 5-chloro-2-[(3-chlorophenyl)thio]benzoic acid gave a similar troublesome mixture of 1,7- and 2,6-dichloro isomers.

This paper is concerned with the synthesis of the still unknown isomers of dichloro-9*H*-thioxanthen-9-ones, 1,8- **3**, 1,6- **4**, and 3,6-dichloro-9*H*-thioxanthen-9-ones **11**. Of these compounds **3** is particularly interesting as a starting material of the 1,8-disubstituted 9*H*-thioxanthen-9-ones.

Unlike the above 1,5- and 1,7-dichloro-9*H*-thioxanthen-9-ones, 1,8- **3**, 1,6- **4**, and 3,6-dichloro isomers **11** respectively, cannot be obtained solely even through the device of the combination of materials used in the Ullmann reaction. The reason why is as follows: in order to synthesize **3** and **4**, it is necessary to cyclize 2-chloro-6-[(3-chlorophenyl)thio]benzoic acid (**2**), and the cyclization of 4-chloro-2-[(3-chlorophenyl)thio]benzoic acid (**10**) is required for the



synthesis of **11**, and it is inevitable that the cyclizations of these benzoic acids will give mixtures of isomers. That is, **3** should be formed together with **4**, and **11** should be accompanied by **4**. These expections do not cast doubt upon a comparison with our previous results [1-3].

Compound **2** was prepared by condensing 2-chloro-6-iodobenzoic acid (**1**) [4] with 3-chlorobenzenethiol, as the Ullmann reaction of 2,6-dichlorobenzoic acid with 3-chlorobenzenethiol gave predominantly the disubstitution product. Similarly, compound **10** was prepared from 4-chloro-2-iodobenzoic acid (**9**) [4,5] and 3-chlorobenzenethiol. The method using **9** gave a far higher yield of **10** than that [6] using 2,4-dichlorobenzoic acid.

Cyclization of **2** was carried out with sulfuric acid or polyphosphoric acid (PPA) in good yield. In the case of cyclization of **10** polyphosphoric acid was effective, as **10** was rather insoluble in sulfuric acid.

The proton magnetic resonance spectrum of the cyclization product of **2** showed that the product was a mixture of **3** and **4** in a ratio of 1 to 3. On the other hand, the proton magnetic resonance spectrum of the cyclization product of **10** showed that the product was an equimolecular mixture of **4** and **11**.

For the purpose of separating **3** and **4**, the cyclization product of **2** was treated with *p*-toluenesulfonamide ($TsNH_2$) to give a mixture of 1,8-bis(*p*-toluenesulfonamido)- **5**, and 6-chloro-1-(*p*-toluenesulfonamido)-9*H*-thioxanthen-9-ones **6**, which was separated into each compound. Compounds **5** and **6** were hydrolyzed with 47% hydrobromic acid in the presence of phenol to afford 1,8-diamino- **7**, and 1-amino-6-chloro-9*H*-thioxanthen-9-ones **8** respectively, from which **3** and **4** were prepared respectively by the Sandmeyer reaction.

Compound **4** had a melting point of 202-204°. This is different from that (219-220°) of the cyclization product (a mixture of **4** and **11**) of **10** reported as **4** by Nargund *et al.* [6].

The cyclization product of **10** was treated with *p*-toluenesulfonamide and the resulting mixture of **6** and unreacted **11** was hydrolyzed with 47% hydrobromic acid in the presence of phenol to give a mixture of **8** and **11**, from which **11** was separated.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. The ir spectra were recorded with a Hitachi 260-10 spectrophotometer in potassium bromide disks. The ^{1}H nmr spectra were obtained on a JEOL JNM-FX 200 spectrometer in deuteriochloroform, unless otherwise stated, using tetramethylsilane as an internal standard. The mass spectra were measured with a Hitachi RMU-7MG double focusing spectrometer.

2-Chloro-6-[(3-chlorophenyl)thio]benzoic Acid (**2**).

Compound **4** (8.47 g, 30 mmoles) and copper powder (0.2 g) were added to a solution of 3-chlorobenzenethiol (4.34 g, 30 mmoles) and potassium hydroxide (5.61 g, 100 mmoles) in water (100 ml). The solution was heated at reflux for 6 hours, cooled and filtered. The filtrate was acidified with hydrochloric acid. The resulting oily precipitate was solidified by rodding with glass rod. The solid (8.34 g, 93%) was recrystallized from aqueous acetic acid to give **2** as colorless prisms, mp 123-126°; ir: 3050-2550, 1700, 1300, 947 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 7.20-7.56 (7H, m, ArH); ms: m/z 298 ($M^{+\cdot}$).

Anal. Calcd. for $C_{13}H_8Cl_2O_2S$: C, 52.19; H, 2.70. Found: C, 52.27; H, 2.65.

1,8-Bis(*p*-toluenesulfonamido)-9*H*-thioxanthen-9-one (**5**) and 6-Chloro-1-(*p*-toluenesulfonamido)-9*H*-thioxanthen-9-one (**6**).

A mixture of **2** (2.99 g, 10 mmoles) and concentrated sulfuric acid (18 ml) was heated at 100° for 40 minutes. After cooling, the solution was poured into ice-water (500 ml). The resulting precipitate was collected, washed with water, and treated with 5% aqueous sodium bicarbonate. The insoluble product (2.59 g, 92%) was heated at reflux with *p*-toluenesulfonamide (9.54 g), anhydrous sodium acetate (4.58 g), copper(II) acetate (0.6 g) and 1-pentanol (75 ml) for 4 hours. After cooling, the solid was collected, washed with ether and then with water, dried, dissolved in chloroform and filtered. The filtrate was evaporated under reduced pressure. The residue was boiled with benzene and the insoluble crystals of **5** (0.80 g) were collected hot, which were recrystallized from chloroform-acetone to give yellow needles, mp >300°; ir: 1590, 1365, 1155 cm^{-1}, ^{1}H nmr: δ 2.35 (6H, s, 2 x CH_3), 7.12 (2H, d, J = 8 Hz, 2,7-H), 7.26 (4H, d, J = 8 Hz, 2 x tosyl 3,5-H), 7.44 (2H, t, J = 8 Hz, 3,6-H), 7.62 (2H, d, J = 8 Hz, 4,5-H), 7.82 (4H, d, J = 8 Hz, 2 x tosyl 2,6-H); ms: m/z 550 ($M^{+\cdot}$).

Anal. Calcd. for $C_{27}H_{22}N_2O_5S_3$: C, 58.89; H, 4.03; N, 5.09. Found: C, 58.59; H, 3.90; N, 4.96.

Evaporation of the above benzene mother liquor from which **5** was obtained gave **6** (1.0 g), which was purified by silica gel column chromatography with chloroform as an eluent to give yellow needles, mp 254-257°; ir: 1595, 1280, 1155 cm^{-1}; ^{1}H nmr: δ 2.34 (3H, s, CH_3), 7.16 (1H, d, J = 8 Hz, 2-H), 7.23 (2H, d, J = 8 Hz, tosyl 3,5-H), 7.43 (1H, d, J = 8 Hz, 7-H), 7.44 (1H, t, J = 8 Hz, 3-H), 7.50 (1H, s, 5-H), 7.65 (1H, d, J = 8 Hz, 4-H), 7.82 (2H, d, J = 8 Hz, tosyl 2,6-H), 8.48 (1H, d, J = 8 Hz, 8-H); ms: m/z 415 ($M^{+\cdot}$).

Anal. Calcd. for $C_{20}H_{14}ClNO_3S_2$: C, 57.76; H, 3.39; N, 3.37. Found: C, 57.84; H, 3.34; N, 3.37.

1,8-Diamino-9*H*-thioxanthen-9-one (**7**).

A mixture of **5** (1.10 g, 2 mmoles), 47% hydrobromic acid (10 ml) and phenol (1 g) was heated at reflux for 2 hours. After cooling, the mixture was alkalinized with 10% aqueous sodium hydroxide to give a yellow solid (0.45 g, 93%), which was recrystallized from aqueous ethanol to afford **7** as yellow leaflets, mp 163-166°; ir: 3450, 3315, 1600 cm^{-1}; ^{1}H nmr: δ 6.48 (2H, d, J = 8 Hz, 2,7-H), 6.65 (2H, d, J = 8 Hz, 4,5-H), 6.81 (4H, br s, 2 x NH_2), 7.17 (2H, t, J = 8 Hz, 3,6-H); ms: 242 ($M^{+\cdot}$).

Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.15; H, 4.05; N, 11.24.

1,8-Dichloro-9*H*-thioxanthen-9-one (**3**).

A mixture of **7** (0.48 g, 2 mmoles) and 5 *N* hydrochloric acid (26 ml) was cooled to 0-5°. To the stirred mixture was added dropwise a solution of sodium nitrite (0.29 g, 4.2 mmoles) in water (1 ml). The diazonium solution was added slowly to a stirred solution of copper(I) chloride (2.0 g) in 10 *N* hydrochloric acid (12 ml) at 40°. After 15 minutes the mixture was heated at 100° with stirring for 1 hour. The resulting precipitate (0.49 g, 88%) was collected and recrystallized from aqueous ethanol to give **3** as yellow needles, mp 176-179°; ir: 1670 cm^{-1}; ^1H nmr: δ 7.30-7.50 (6H, m, ArH); ms: m/z 280 ($M^{+\cdot}$).

Anal. Calcd. for $C_{13}H_6Cl_2OS$: C, 55.54; H, 2.15. Found: C, 55.23; H, 2.10.

1-Amino-6-chloro-9*H*-thioxanthen-9-one (**8**).

This compound was prepared from **6** (0.83 g, 2 mmoles), 47% hydrobromic acid (7 ml) and phenol (0.8 g) in a manner similar to that described for the preparation of **7**. The product (0.51 g, 98%) was recrystallized from aqueous ethanol to give **8** as yellow needles, mp 177-180°; ir: 3425, 3300, 1607 cm^{-1}; ^1H nmr: δ 6.57 (1H, d, J = 8 Hz, 2-H), 6.74 (1H, d, J = 8 Hz, 4-H), 6.98 (2H, br s, NH_2), 7.26 (1H, t, J = 8 Hz, 3-H), 7.34 (1H, d, J = 8 Hz, 7-H), 7.43 (1H, s, 5-H), 8.41 (1H, d, J = 8 Hz, 8-H); ms: m/z 261 ($M^{+\cdot}$).

Anal. Calcd. for $^{9}{}_{13}H_8ClNOS$: C, 59.66; H, 3.08; N, 5.35. Found: C, 59.65; H, 3.06; N, 5.01.

1,6-Dichloro-9*H*-thioxanthen-9-one (**4**).

This compound was prepared from **8** (0.52 g, 2 mmoles) in a manner similar to that described for the preparation of **3**. The product (0.48 g, 86%) was recrystallized from aqueous ethanol to give **4** as yellow needles, mp 202-204°; ir: 1640 cm^{-1}; ^1H nmr: δ 7.26 (1H, s, 5-H), 7.34-7.50 (4H, m, 2,3,4,7-H), 8.38 (1H, d, J = 8 Hz, 8-H); ms: m/z 280 ($M^{+\cdot}$).

Anal. Calcd. for $C_{13}H_6Cl_2OS$: C, 55.54; H, 2.15. Found: C, 55.68; H, 2.18.

4-Chloro-2-[(3-chlorophenyl)thio]benzoic Acid (**10**).

This compound was prepared from **9** (5.65 g, 20 mmoles) and 3-chlorobenzenethiol (2.90 g, 20 mmoles) in a manner similar to that described for the preparation of **2**. The product (5.92 g, 99%) was recrystallized from aqueous acetic acid to give **10** as colorless needles, mp 200-201° (lit [6] mp 209-210°).

3,6-Dichloro-9*H*-thioxanthen-9-one (**11**).

A mixture of **10** (2.99 g, 10 mmoles) and polyphosphoric acid (150 g) was heated at 120° with stirring for 5 hours. After cooling, the solution was poured into ice-water (2.5 ℓ). The resulting precipitate was collected, washed with water and treated with 5% aqueous sodium bicarbonate. The insoluble product (2.02 g, 72%) was heated at reflux with *p*-toluenesulfonamide (2.48 g), anhydrous sodium acetate (1.19 g), copper(II) acetate (0.1 g) and 1-pentanol (25 ml) for 4 hours, then the solvent was evaporated under reduced pressure and the residue was washed with ether and then with water to give a mixture (1.6 g) of **6** and **11**. The mixture and phenol (0.8 g) in 47% hydrobromic acid (8 ml) were heated at reflux for 2 hours, cooled and extracted with chloroform and the chloroform layer was separated from the acidic layer. The chloroform layer was washed with 10% aqueous sodium hydroxide and then with water, dried (sodium sulfate) and evaporated under reduced pressure to give **11** (0.56 g). Recrystallization from chloroform-ethanol afforded yellow needles, mp 241-242°; ir: 1635 cm^{-1}; ^1H nmr: δ 7.45 (2H, d, J = 8 Hz, 2,7-H), 7.57 (2H, s, 4,5-H), 8.53 (2H, d, J = 8 Hz, 1,8-H); ms: m/z 280 ($M^{+\cdot}$).

Anal. Calcd. for $C_{13}H_6Cl_2OS$: C, 55.54; H, 2.15. Found: C, 55.20; H, 2.19.

The above acidic layer was alkalinized to give **8** (0.47 g), which was identical with the product obtained from **2**.

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