# The Synthesis of 1*H*-Benzimidazole Derivatives Containing a 9*H*-Xanthene or 9*H*-Thioxanthene Ring



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2-(9*H*-Xanthen-9-ylmethyl)-1*H*-benzimidazole (**2a**) was prepared by condensing 9*H*-xanthene-9-acetic acid (**1a**) with 1,2-benzenediamine. Similarly, 2-(9*H*-thioxanthen-9-ylmethyl)-1*H*-benzimidazole (**2b**) and its *S,S*-dioxide (**2d**) were obtained. Compound **2d** was also prepared by oxidizing **2b** with hydrogen peroxide in acetic acid. Heating of 9*H*-thioxanthene-9-acetic acid 10-oxide (**1c**) with 1,2-benzenediamine gave 9-methylene-9*H*-thioxanthene (**3**). 2-(9*H*-Thioxanthen-9-ylmethyl)-1*H*-benzimidazole *S*-oxide (**2c**) was obtained by oxidizing **2b** with *m*-chloroperbenzoic acid in acetone.

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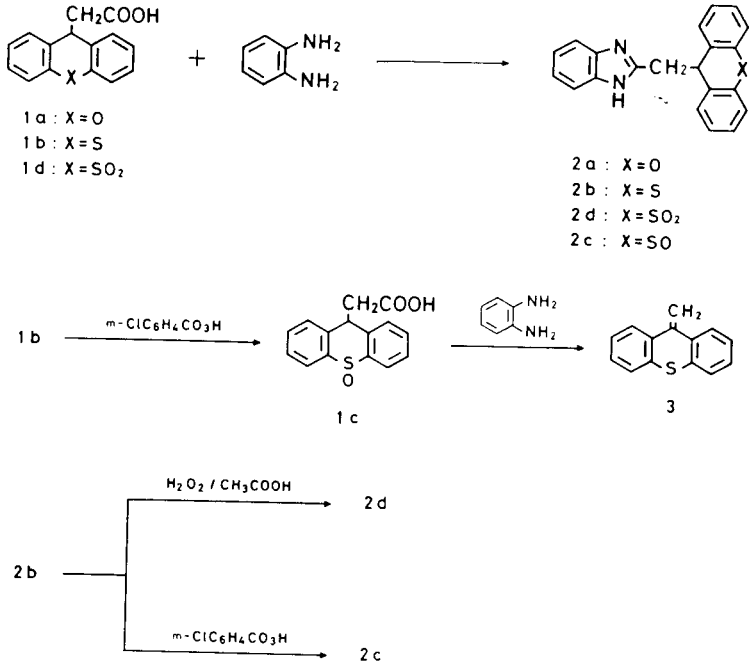
Imidazole derivatives are pharmacologically and biochemically important and interesting. Recently, 2-(2-pyridinyl)-1*H*-benzimidazole derivatives have been reported as an antiinflammatory agent [1]. In addition, 9*H*-xanthene or 9*H*-thioxanthene ring are contained in a variety of drugs such as Propantheline bromide, Methixene and Chlorprothixene.

In this paper, 2-(9*H*-xanthen-9-ylmethyl)- (**2a**), 2-(9*H*-thioxanthen-9-ylmethyl)-1*H*-benzimidazole (**2b**) and the derivatives of **2b**, **2c** and **2d**, were synthesized for the purpose of studying the pharmacological activity. With the expectation that these compounds exhibit the activity, the two carbon atoms were combined between the carbon atom of 9-position of either the 9*H*-xanthene or 9*H*-thioxanthene ring and the nitrogen atom (1- or 3-position) of 1*H*-benzimidazole as in various drugs, *e.g.* Naphazoline and Tolazoline.

9*H*-Xanthene-9-acetic acid (**1a**) [2] was obtained by heating a mixture of 9*H*-xanthen-9-ol and malonic acid in pyridine at 70° and then at 100°. 2-(9*H*-Xanthen-9-ylmethyl)-1*H*-benzimidazole (**2a**) was prepared in good yield by heating a mixture of **1a** and 1,2-benzenediamine at 190°.

In a similar way, 2-(9*H*-thioxanthen-9-ylmethyl)-1*H*-benzimidazole (**2b**) was obtained by condensing 9*H*-thioxanthene-9-acetic acid (**1b**) [3] with 1,2-benzenediamine.

9*H*-Thioxanthene-9-acetic acid 10-oxide (**1c**) was prepared by oxidizing **1b** with *m*-chloroperbenzoic acid in acetone at room temperature. When **1c** was heated with 1,2-benzenediamine in a manner similar to that used for the preparation of **2a**, the product was not 2-(9*H*-thioxanthen-9-ylmethyl)-1*H*-benzimidazole *S*-oxide (**2c**), but an oil which was easily oxidized to 9*H*-thioxanthen-9-one in the



air. The ir, $^1$H-nmr and mass spectra and the properties of the oily compound were identical with those of a sample of 9-methylene-9*H*-thioxanthene (**3**) [4] prepared by the reaction of 9*H*-thioxanthen-9-one with methylmagnesium iodide. Heating of **1c** alone under the same reaction conditions resulted in recovery of **1c**. Compound **2c** was obtained by oxidizing **2b** with *m*-chloroperbenzoic acid in acetone at room temperature.

Since 9*H*-thioxanthen-9-ol 10,10-dioxide [5] did not react with malonic acid as expected, 9*H*-thioxanthene-9-acetic acid 10,10-dioxide (**1d**) [6] was prepared by oxidizing **1b** with hydrogen peroxide in acetic acid, and then **1d** was condensed with 1,2-benzenediamine to give 2-(9*H*-thioxanthen-9-ylmethyl)-1*H*-benzimidazole *S,S*-dioxide (**2d**). Compound **2d** was also obtained by oxidizing **2b** with hydrogen peroxide in acetic acid at 50°.

## EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. The ir spectra were recorded with a Hitachi model 215 spectrometer. The $^1$H-nmr spectra were obtained on a Varian XL-200 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Mass spectra were measured with a Hitachi RMU-7M double focusing spectrometer.

2-(9*H*-Xanthen-9-ylmethyl)-1*H*-benzimidazole (**2a**).

A mixture of **1a** (1.20 g, 5 mmoles) and 1,2-benzenediamine (0.54 g, 5 mmoles) was heated in an oil bath slowly to 190° and held there for 3 hours. After cooling, the solid was extracted with 5% sodium carbonate solution, and the insoluble solid was collected and washed with water. The product (1.35 g, 87%) was recrystallized from ethanol and benzene and finally aqueous acetone to give colorless needles, mp 223-224° dec; ir (potassium bromide): 3380 $cm^{-1}$ (NH); nmr: $\delta$ 3.21 (d, $CH_2$, 2H, J = 7 Hz), 4.65 (t, xanthenyl H-9, 1H, J = 7 Hz), 6.86-7.27 (m, Ar*H*, 12H); ms: m/z 312 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.86; H, 5.16; N, 8.77.

2-(9*H*-Thioxanthen-9-ylmethyl)-1*H*-benzimidazole (**2b**).

This compound was prepared from **1b** (1.28 g, 5 mmoles) and 1,2-benzenediamine (0.54 g, 5 mmoles) in a manner similar to that used for the preparation of **2a**. The product (1.37 g, 84%) was recrystallized from ethanol and benzene and finally aqueous acetone to give colorless prisms, mp 245-246° dec; ir (potassium bromide): 3380 $cm^{-1}$ (NH); nmr: $\delta$ 3.30 (d, $CH_2$, 2H, J = 8 Hz), 4.72 (t, thioxanthenyl H-9, 1H, J = 8 Hz), 7.03-7.26 (m, Ar*H* except thioxanthenyl H-4 and H-5, 10H), 7.38-7.50 (m, thioxanthenyl H-4, H-5, 2H); ms: m/z 328 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 77.07; H, 5.05; N, 8.35.

9*H*-Thioxanthene-9-acetic Acid 10-Oxide (**1c**).

*m*-Chloroperbenzoic acid (0.87 g, 5 mmoles) dissolved in acetone (20 ml) was added to a stirred solution of **1b** (1.28 g, 5 mmoles) in acetone (20 ml). After stirring at room temperature for 9 hours, the resulting mixture was filtered; the precipitate and the solid obtained by evaporating the filtrate *in vacuo* were treated with benzene, and the insoluble solid was recrystallized from aqueous acetone to give 0.79 g (58%) of colorless needles, mp 210-211° dec; ir (potassium bromide): 3420 (NH), 1710 (C=O), 1010 $cm^{-1}$ (SO); nmr: $\delta$ 3.37 (d, $CH_2$, 2H, J = 7 Hz), 4.59 (t, thioxanthenyl H-9, 1H, J = 7 Hz), 7.42-7.65 (m, thioxanthenyl H-1, H-2, H-3, H-6, H-7, H-8, 6H), 7.90-7.96 (m, thioxanthenyl H-4, H-5, 2H); ms: m/z 272 ($M^+$).

*Anal.* Calcd. for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44. Found: C, 66.10; H, 4.36.

Heating of **1c** with 1,2-Benzenediamine.

A mixture of **1c** (0.27 g, 1 mmole) and 1,2-benzenediamine (0.11 g, 1 mmole) was heated in a manner similar to that described for the preparation of **2a**. The product was purified by preparative thin-layer chromatography (Kieselgel 60 $PF_{254}$, Merck) using hexane-ethyl acetate (10:1) as a developing solvent to give 9-methylene-9*H*-thioxanthene (**3**) as a pale yellow oil, which was easily oxidized to 9*H*-thioxanthen-9-one in the air; nmr: $\delta$ 5.53 (s, $CH_2$, 2H), 7.00-7.89 (m, Ar*H*, 8H); ms: m/z 210 ($M^+$).

2-(9*H*-Thioxanthen-9-ylmethyl)-1*H*-benzimidazole *S*-Oxide (**2c**).

*m*-Chloroperbenzoic acid (0.35 g, 2 mmoles) dissolved in acetone (8 ml) was added to a stirred solution of **2b** (0.66 g, 2 mmoles) in acetone (72 ml). After stirring at room temperature for 7 hours, the resulting mixture was filtered, the precipitate was treated with 5% sodium carbonate solution, and the insoluble solid was recrystallized from aqueous ethanol to give 0.28 g (40%) of colorless needles, mp 257-258° dec; ir (potassium bromide): 3340 (NH), 1005 $cm^{-1}$ (SO); nmr: $\delta$ 3.85 (d, $CH_2$, 2H, J = 8 Hz), 4.83 (t, thioxanthenyl H-9, 1H, J = 8 Hz), 7.07-7.49 (m, Ar*H* except thioxanthenyl H-4 and H-5, 10H), 7.85-7.97 (m, thioxanthenyl H-4, H-5, 2H); ms: m/z 344 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{16}N_2OS$: C, 73.23; H, 4.68; N, 8.13. Found: C, 72.97; H, 4.65; N, 7.99.

2-(9*H*-Thioxanthen-9-ylmethyl)-1*H*-benzimidazole *S,S*-Dioxide (**2d**).

a) A mixture of **1d** (1.44 g, 5 mmoles) and 1,2-benzenediamine (0.54 g, 5 mmoles) was heated in an oil bath slowly to 190° and held there for 3 hours. After cooling, the solid was extracted with 5% sodium carbonate solution, and the insoluble solid was collected and washed with water. The product (1.60 g, 89%) was recrystallized from ethanol and benzene and finally aqueous acetone to give colorless pillars, mp 287.5-288° dec; ir (potassium bromide): 3360 (NH), 1290, 1155 $cm^{-1}$ ($SO_2$); nmr: $\delta$ 3.67 (d, $CH_2$, 2H, J = 8 Hz), 4.88 (t, thioxanthenyl H-9, 1H, J = 8 Hz), 7.14-7.52 (m, Ar*H* except thioxanthenyl H-4 and H-5, 10H), 8.05-8.16 (m, thioxanthenyl H-4, H-5, 2H); ms: m/z 360 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{16}N_2O_2S$: C, 69.98; H, 4.47; N, 7.77. Found: C, 70.24; H, 4.59; N, 7.47.

b) To a solution of **2b** (0.66 g, 2 mmoles) in glacial acetic acid (10 ml) 30% hydrogen peroxide (0.70 g, 6 mmoles) was added. The mixture was heated on a water bath at 50° for 4 hours. After cooling, the mixture was poured into water (60 ml), and sodium chloride (4 g) was dissolved. The precipitate (0.70 g, 97%) was collected and washed with water and recrystallized from aqueous acetone to give colorless pillars, mp 285-287° dec, both alone and admixed with a sample obtained by method a). The ir spectrum was identical with that of a sample obtained by method a).

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