Synthesis of 3*H*-Pyrazol-3-one Derivatives Containing a 9*H*-Thioxanthene Ring

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2,4-Dihydro-5-methyl-2-phenyl-4-(9*H*-thioxanthen-9-yl)-3*H*-pyrazol-3-one (**3**) was prepared by condensing 9*H*-thioxanthen-9-ol (**1**) with 2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one (**2**), or by cyclizing ethyl α-acetyl-9*H*-thioxanthene-9-acetate (**4**) with phenylhydrazine. 2,4-Dihydro-5-methyl-2-phenyl-4-(9*H*-thioxanthen-9-yl)-3*H*-pyrazol-3-one 10,10-dioxide (**8**) was prepared by cyclizing ethyl α-acetyl-9*H*-thioxanthene-9-acetate 10,10-dioxide (**7**) with phenylhydrazine. Compound **8** was also obtained by oxidizing **3** with hydrogen peroxide in acetic acid. 5-Amino-2,4-dihydro-2-phenyl-4-(9*H*-thioxanthen-9-yl)-3*H*-pyrazol-3-one (**10**) was obtained by condensing **1** with 5-amino-2,4-dihydro-2-phenyl-3*H*-pyrazol-3-one (**9**).

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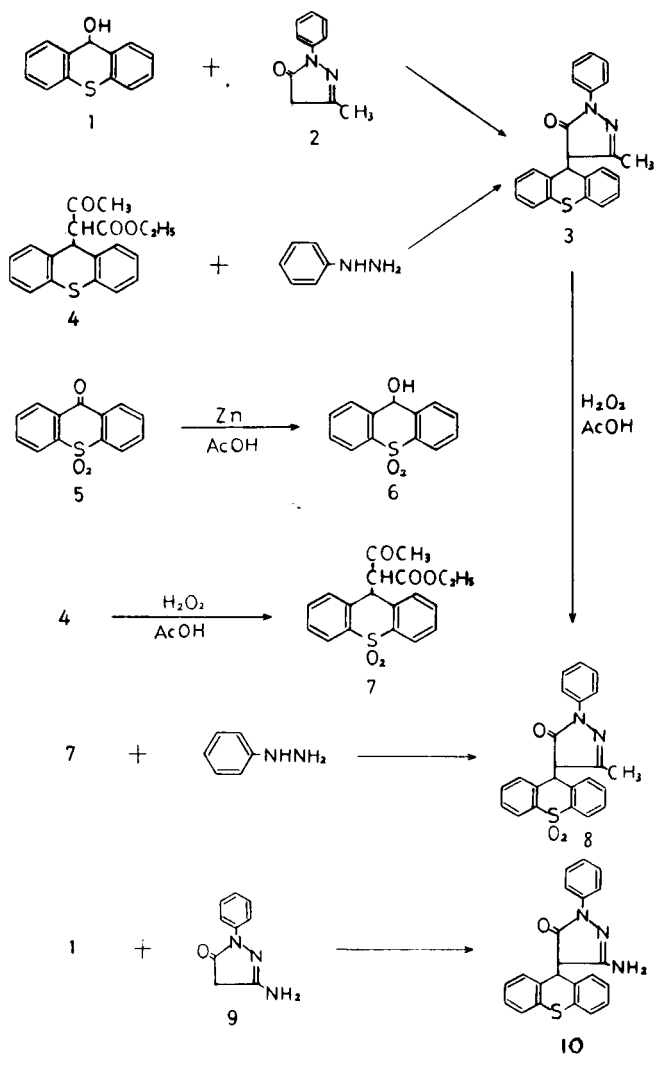
In the previous paper (1), the author reported the synthesis of 3*H*-pyrazol-3-one derivatives containing a 9*H*-xanthene ring. 9*H*-Xanthen-9-ol was condensed with 2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one (**2**) and 5-amino-2,4-dihydro-2-phenyl-3*H*-pyrazol-3-one (**9**) in acetic acid at 100° to give 2,4-dihydro-5-methyl-2-phenyl-4-(9*H*-xanthen-9-yl)-3*H*-pyrazol-3-one and 5-amino-2,4-dihydro-2-phenyl-4-(9*H*-xanthen-9-yl)-3*H*-pyrazol-3-one, respectively.

Recently, the author has found that both 9*H*-xanthen-9-ol and 9*H*-thioxanthen-9-ol (**1**) react readily with **2** and **9** in a mixture of acetic acid and ethanol at room temperature to form the crystalline condensation products in good yields. In this paper, 3*H*-pyrazol-3-one derivatives containing a 9*H*-thioxanthene ring were synthesized for the purpose of comparing the pharmacological activity with the corresponding derivatives containing a 9*H*-xanthene ring.

9*H*-Thioxanthen-9-ol (**1**) (2) was condensed with 2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one (**2**) (3) in a mixture of acetic acid and ethanol at room temperature to give 2,4-dihydro-5-methyl-2-phenyl-4-(9*H*-thioxanthen-9-yl)-3*H*-pyrazol-3-one (**3**) in 95% yield. The product, obtained by heating a mixture of phenylhydrazine and ethyl α-acetyl-9*H*-thioxanthene-9-acetate (**4**) (4) prepared from **1** and ethyl acetoacetate, was identical with **3**.

9*H*-Thioxanthen-9-one, as well as 9*H*-xanthen-9-one, was reduced with sodium amalgam and ethanol to **1** (2). On the other hand, 9*H*-thioxanthen-9-one 10,10-dioxide (**5**) (5) was not reduced with the same reagents. 9*H*-Thioxanthen-9-ol 10,10-dioxide (**6**) (6) was obtained by reducing **5** with zinc and acetic acid. Since compound **6**, however, did not react with ethyl acetoacetate and **2**, as expected, **6** was not useful for the preparation of ethyl α-acetyl-9*H*-thioxanthene-9-acetate 10,10-dioxide (**7**) and 2,4-dihydro-5-methyl-2-phenyl-4-(9*H*-thioxanthen-9-yl)-3*H*-pyrazol-3-one 10,10-dioxide (**8**). Consequently, compound **7** was prepared by oxidizing **4** with hydrogen peroxide in acetic acid, and then **7** was heated with phenylhydrazine to give **8**. Compound **8** was also obtained by oxidizing **3** with hydrogen peroxide in acetic acid at 70°.

Furthermore, 5-amino-2,4-dihydro-2-phenyl-4-(9*H*-thioxanthen-9-yl)-3*H*-pyrazol-3-one (**10**) was obtained in 78% yield by condensing **1** with 5-amino-2,4-dihydro-2-phenyl-3*H*-pyrazol-3-one (**9**) (7) in a manner similar to that described for the preparation of **3**.



EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Ir spectra were obtained in potassium bromide disks on a Hitachi model 215 spectrometer. The ^{1}H nmr spectra were obtained on a Varian XL-200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi RMU-7M double focusing spectrometer.

2,4-Dihydro-5-methyl-2-phenyl-4-(9*H*-thioxanthen-9-yl)-3*H*-pyrazol-3-one (**3**).

a) To a solution of 0.87 g (0.005 mole) of **2** in a mixture of 3 ml of acetic acid and 3 ml of ethanol (8), a solution of 1.07 g (0.005 mole) of **1** in 4 ml of the same solvent was added. The mixture was allowed to stand at room temperature for 3 days. The crystalline product (1.75 g, 95%) was collected by filtration, washed with methanol, and recrystallized from 65% ethanol giving 1.40 g (76%) of colorless prisms, mp 214-216° dec; ir: 1610 (CO) cm^{-1}; nmr (DMSO-d_6): δ 1.86 (s, CH_3, 3H), 4.98 (s, thioxanthenyl H-9, 1H), 7.10-7.52 (m, aromatic H, 12H), 7.70-7.84 (m, phenyl H-2, 6, 2H); ms: m/z 370 (M^+).

Anal. Calcd. for $C_{23}H_{18}N_2OS$: C, 74.57; H, 4.90; N, 7.56. Found: C, 74.67; H, 5.09; N, 7.52.

b) A mixture of 1.63 g (0.005 mole) of **4** and 0.54 g (0.005 mole) of phenylhydrazine was heated in an oil bath (160°) for 2 hours. After cooling, the solid was powdered and treated with a small portion of ether and then with benzene. The insoluble crystals were collected by filtration, washed with benzene, and recrystallized from aqueous ethanol twice giving 0.40 g (22%) of colorless prisms, mp 214-216° 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).

Ethyl α-Acetyl-9*H*-thioxanthene-9-acetate 10,10-Dioxide (**7**).

To a solution of 0.98 g (0.003 mole) of **4** in 12 ml of acetic acid, 0.80 g (0.007 mole) of 30% hydrogen peroxide was added. The mixture was stirred at 100° for 4 hours. After cooling, the mixture was poured into 100 ml of water. The resulting solid was collected by filtration, washed with water, and recrystallized from ethanol giving 0.95 g (88%) of colorless prisms, mp 178.5-179.5°; ir: 1740 (CO-O), 1710 (C=O), 1290, 1160 (SO_2) cm^{-1}; nmr (deuteriochloroform): δ 1.09 (t, CH_3CH_3, 3H, J = 7 Hz), 1.92 (s, $COCH_3$, 3H), 4.03 (q, CH_2CH_3, 2H, J = 7 Hz), 4.87 (d, CHCHCO, 1H, J = 11 Hz), 4.96 (d, CHCHCO, 1H, J = 11 Hz), 7.48-7.70 (m, thioxanthenyl H-1,2,3,6,7,8, 6H), 8.06-8.18 (m, thioxanthenyl H-4,5, 2H); ms: m/z 358 (M^+).

Anal. Calcd. for $C_{19}H_{18}O_3S$: C, 63.67; H, 5.06. Found: C, 63.97; H, 5.27.

2,4-Dihydro-5-methyl-2-phenyl-4-(9*H*-thioxanthen-9-yl)-3*H*-pyrazol-3-one 10,10-Dioxide (**8**).

a)A mixture of 0.72 g (0.002 mole) of **7** and 0.22 g (0.002 mole) of phenylhydrazine was heated in an oil bath (180°) for 2 hours. The solid was powdered and a small portion of ether was added. The insoluble product was collected by filtration, washed with ether, and recrystallized from 50% acetone twice giving 0.41 g (51%) of colorless needles, mp 252-254° dec; ir: 1610 (CO), 1310, 1165 (SO_2) cm^{-1}; nmr (DMSO-d_6): δ 1.75 (s, CH_3, 3H), 5.70 (s, thioxanthenyl H-9, 1H), 7.28 (t, phenyl H-4, 1H, J = 7 Hz), 7.35-7.78 (m, aromatic H, 9H), 7.78-7.90 (d, phenyl H-2,6, 2H, J = 7 Hz), 8.04-8.20 (m, thioxanthenyl H-4,5, 2H); ms: m/z 402 (M^+).

Anal. Calcd. for $C_{23}H_{18}N_2O_3S$: C, 68.64; H, 4.51; N, 6.96. Found: C, 68.92; H, 4.69; N, 6.85.

b)To a solution of 0.37 g (0.001 mole) of **3** in 15 ml of acetic acid, 0.34 g (0.003 mole) of 30% hydrogen peroxide was added. The mixture was stirred at 70° for 6 hours. After cooling, the mixture was poured into 250 ml of water. The resulting solid was collected by filtration, washed with water, and recrystallized from 50% acetone twice giving 0.26 g (65%) of colorless needles, mp 252-254° 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).

5-Amino-2,4-dihydro-2-phenyl-4-(9*H*-thioxanthen-9-yl)-3*H*-pyrazol-3-one (**10**).

To a solution of 0.88 g (0.005 mole) of **9** in a mixture of 9 ml of acetic acid and 9 ml of ethanol (8), a solution of 1.07 g (0.005 mole) of **1** in 4 ml of the same solvent was added. The mixture was allowed to stand at room temperature for 3 days. The crystalline product (1.45 g, 78%) was collected by filtration, washed with 50% methanol, and recrystallized from 65% ethanol giving 1.13 g (61%) of colorless prisms, mp 210-212° dec; ir: 3325, 3250 (NH_2), 1620 (CO) cm^{-1}; nmr (DMSO-d_6): δ 4.67 (s, thioxanthenyl H-9, 1H), 6.37 (s, NH_2, 2H, exchangeable with deuterium oxide), 7.07 (t, phenyl H-4, 1H, J = 7 Hz), 7.18-7.56 (m, aromatic H, 11H), 7.66-7.78 (d, phenyl H-2,6, 2H, J = 7 Hz); ms: m/z 371 (M^+).

Anal. Calcd. for $C_{22}H_{17}N_3OS$: C, 71.14; H, 4.61; N, 11.31. Found: C, 71.02; H, 4.76; N, 11.06.

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(8) Compound **2** or **9** was dissolved at 80°, and then the solution was cooled to room temperature.