Synthesis of New Heterocyclic Compounds by the Skraup Reaction of Amino-9*H*-thioxanthen-9-ones

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The Skraup reaction of amino-9*H*-thioxanthen-9-ones was conducted in the presence of glycerol, fuming sulfuric acid, nitrobenzene, iron(II) sulfate and boric acid. 1-Amino-9*H*-thioxanthen-9-one (1) gave 12*H*-[1]benzothiopyrano[2,3-*h*]quinolin-12-one (5). 2-Amino-(2) and 3-amino-9*H*-thioxanthen-9-ones (3) gave angular-type products, 12*H*-[1]benzothiopyrano[3,2-*f*]quinolin-12-one (6) and 7*H*-[1]benzothiopyrano[2,3-*f*]quinolin-7-one (8), but did not give linear-type products. 4-Amino-9*H*-thioxanthen-9-one (4) gave 7*H*-[1]benzothiopyrano[3,2-*h*]quinolin-7-one (10).

Keywords 9*H*-thioxanthen-9-one analogue; Skraup reaction; heterocyclic compound; quinoline derivative

DNA intercalating agents, one of the most important classes of antitumor drugs, usually possess a planar aromatic or hetero-aromatic polycyclic system. Acridine derivatives are a good example,[1-3] and some thioxanthene derivatives are also effective.[4,5] We are interested in preparing compounds with a new chromophore instead of the acridine and thioxanthene moieties. This new chromophore is the thioxanthene ring condensed with an additional pyridine ring. The most generally useful method for preparing substituted quinolines is the Skraup reaction.[6,7] In this paper, we describe the synthesis of several new heterocyclic compounds, 12*H*-[1]benzothiopyrano-[2,3-*h*]quinolin-12-one (**5**), 12*H*-[1]benzothiopyrano[3,2-*f*]quinolin-12-one (**6**), 7*H*-[1]benzothiopyrano[2,3-*f*]quinolin-7-one (**8**), and 7*H*-[1]benzothiopyrano[3,2-*h*]quinolin-7-one (**10**), from amino-9*H*-thioxanthen-9-ones by means of the Skraup reaction.

Results and Discussion

Synthesis of the starting materials, 1-amino- (**1**),[8] 2-amino- (**2**),[9] 3-amino- (**3**),[9] and 4-amino-9*H*-thioxanthen-9-ones (**4**)[10] was previously described. The Skraup reactions of amino-9*H*-thioxanthen-9-ones with glycerol, fuming sulfuric acid, and nitrobenzene were conducted in the presence of iron(II) sulfate and boric acid, and the products obtained were found to have the molecular formula $C_{16}H_9NOS$ based on elemental analytical data and the mass spectra (MS), with *m/z* 263 ($M^{+\cdot}$).

The Skraup reaction of **1** gave 12*H*-[1]benzothiopyrano[2,3-*h*]quinolin-12-one (**5**) in 87% yield. The structure of **5** was determined by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. The ^{1}H-NMR spectrum showed the proton signals of the pyridine ring at δ 7.50 (dd, $J=4$, 8 Hz, 3-H), δ 8.17 (d, $J=8$ Hz, 4-H) and δ 9.21 (d, $J=4$ Hz, 2-H), and two doublet proton signals of the 9*H*-thioxanthen-9-one skeleton at δ 7.55 (d, $J=8$ Hz, 6-H) and δ 7.91 (d, $J=8$ Hz, 5-H).

Although the Skraup reaction of **2** may give two products, 12*H*-[1]benzothiopyrano[3,2-*f*]quinolin-12-one (**6**) and 12*H*-[1]benzothiopyrano[2,3-*g*]quinolin-12-one (**7**), in fact a sole product **6** was formed in 73% yield. The ^{1}H-NMR spectrum of **6** showed the proton signals of the new ring at δ 7.64 (dd, $J=4$, 8 Hz, 2-H), δ 8.96 (δ, $J=4$ Hz, 3-H) and δ 10.27 (d, $J=8$ Hz, 1-H) and two doublet proton signals of the 9*H*-thioxanthen-9-one skeleton as in the case of **5**.

Similarly, the Skraup reaction of **3** may give two prod-

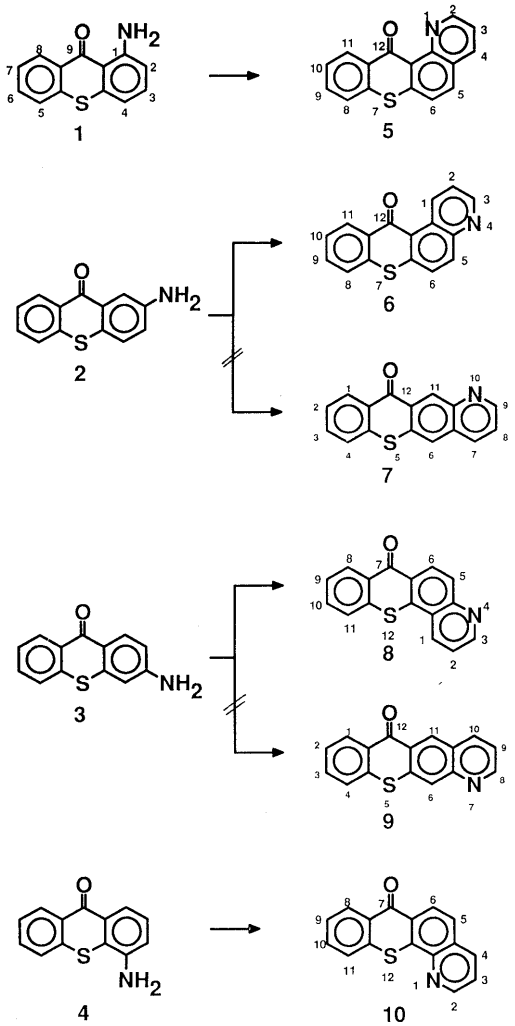

Chart 1

The paper is dedicated to Professor Yasumitsu Tamura on the occasion of his 70th birthday.

ucts, 7*H*-[1]benzothiopyrano[2,3-*f*]quinolin-7-one (**8**) and 12*H*-[1]benzothiopyrano[3,2-*g*]quinolin-12-one (**9**), but in fact only **8** was obtained in 85% yield. The structure of **8** was confirmed by the ^{1}H-NMR spectrum as in the case of **6**.

Finally, the Skraup reaction of **4** gave 7*H*-[1]benzothiopyrano[3,2-*h*]quinolin-7-one (**10**) in 80% yield. The structure of **10** was determined from the ^{1}H-NMR spectrum as in the case of **6**.

Since the Skraup reaction of **2** did not give the linear-type product **7**, 2-amino-1-methyl-9*H*-thioxanthen-9-one (**14**) possessing a methyl group at the 1-position of **2** was synthesized by the following method. 2-(4-Acetamido-3-methylphenylthio)benzoic acid (**11**) obtained by the Ullmann reaction between 2-mercaptobenzoic acid and 4-bromo-2-methylacetanilide was cyclized with polyphosphoric acid (PPA) to give a mixture of 2-acetamido-1-methyl- (**12**) and 2-acetamido-3-methyl-9*H*-thioxanthen-9-ones (**13**). The mixture was treated with 47% hydrobromic acid to give a mixture of 2-amino-1-methyl- (**14**) and 2-amino-3-methyl-9*H*-thioxanthen-9-ones (**15**), which was separated by column chromatography. Under the same conditions as employed in the preparation of **2**, the Skraup reaction of **14** gave a linear product, 11-methyl-12*H*-benzothiopyrano[2,3-*g*]quinolin-12-one (**16**) in 45% yield. The MS showed the molecular ion peak at *m/z* 277. The ^{1}H-NMR spectrum showed a singlet proton signal of the methyl group at δ 3.40, a signal due to the 9-proton at δ 9.02 (d, J=4 Hz, 9-H) and a singlet signal due to the 6-proton at δ 7.87. From the results, the ring closure of **2** occurs preferentially at the 1-position, rather than the 3-position.

The Skraup reaction of **3** did not give **9**, and thus the reactivity at the 2-position of **3** was examined with 3-amino-4-methyl-9*H*-thioxanthen-9-one (**19**). For the synthesis of **19**, 2-(2-methyl-3-nitrophenylthio)benzoic acid (**17**) prepared from 2-mercaptobenzoic acid and 2-bromo-6-nitrotoluene was cyclized with PPA to give 4-methyl-3-nitro-9*H*-thioxanthen-9-one (**18**), which was reduced to **19** with tin(II) chloride and hydrochloric acid. 6-Methyl-12*H*-[1]benzothiopyrano[3,2-*g*]quinolin-12-one (**20**) was obtained by the Skraup reaction of **19**. The structure of **20** was determined from the MS and ^{1}H-NMR spectrum in the same way as in the case of **16**. It was found that the ring closure of **3** occurs preferentially at the 4-position, rather than the 2-position.

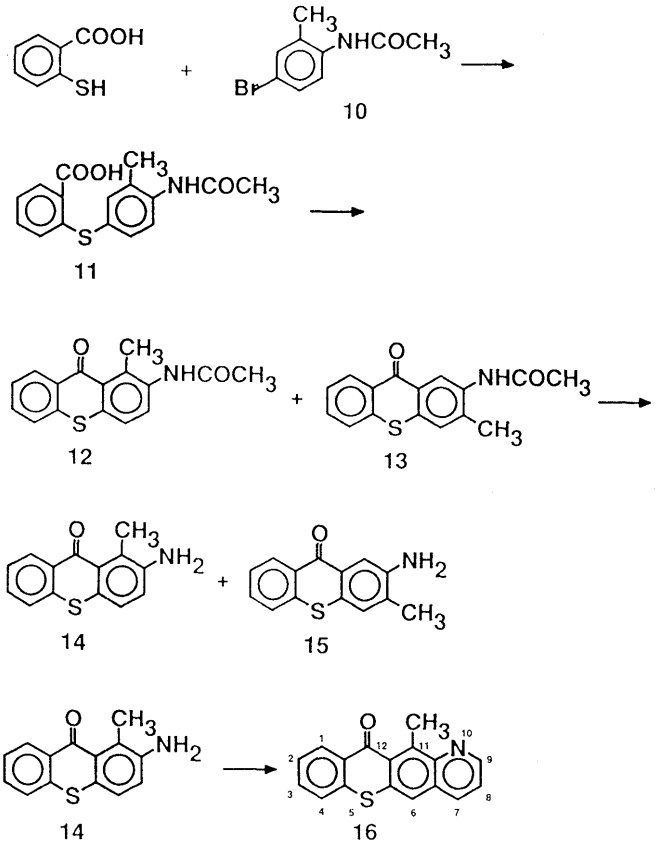

Chart 2

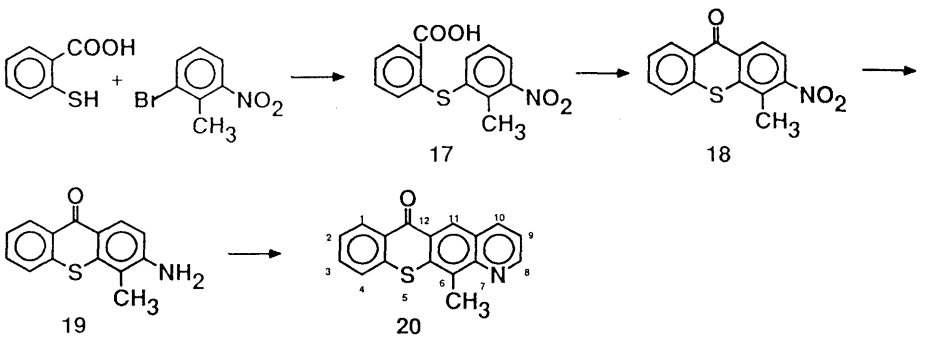

Chart 3

Experimental

Melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrophotometer. ^{1}H-NMR spectra were measured on a JEOL FX-400 instrument using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. MS were taken with a Hitachi RMU-7MG spectrometer.

General Procedure for the Skraup Reaction of Amino-9*H*-thioxanthen-9-ones (1—4) A mixture of $H_2SO_4 \cdot SO_3$ (6.0 g), nitrobenzene (1.35 g), $FeSO_4 \cdot 7H_2O$ (0.2 g), and H_3BO_3 (0.3 g) was chilled to 0—5 °C, and glycerol (1.55 g) was added to the mixture, followed by addition of amino-9*H*-thioxanthen-9-one (1.06 g) and H_2O (2.5 ml). The mixture was heated at 130 °C for 5 h. The reaction mixture was neutralized with 28% NH_4OH and the resulting precipitate was collected by filtration, and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, the solvent was evaporated, and the residue was recrystallized from MeOH to give [1]benzothiopyranoquinoline as colorless needles.

12*H*-[1]Benzothiopyrano[2,3-*h*]quinolin-12-one (5) Pale yellow needles (from MeOH), mp 152—153 °C. Yield 87%. IR (KBr): 1640, 1600 cm^{-1}. ^{1}H-NMR δ: 7.50 (1H, dd, J=4, 8 Hz, 3-H), 7.55 (1H, d, J=8 Hz, 6-H), 7.56 (1H, t, J=8 Hz, 10-H), 7.58 (1H, d, J=8 Hz, 8-H), 7.62 (1H, t, J=8 Hz, 9-H), 7.91 (1H, d, J=8 Hz, 5-H), 8.17 (1H, d, J=8 Hz, 4-H), 8.61 (1H, d, J=8 Hz, 11-H), 9.21 (1H, d, J=4 Hz, 2-H).

MS *m/z*: 263 ($M^{+\cdot}$). *Anal.* Calcd for $C_{16}H_9NOS$: C, 73.00; H, 3.45; N, 5.32. Found: C, 72.86; H, 3.47; N, 5.26.

12*H*-[1]Benzothiopyrano[3,2-*f*]quinolin-12-one (6) Pale yellow needles (from MeOH), mp 171—172 °C. Yield 73%. IR (KBr): 1620, 1590 cm^{-1}. ^{1}H-NMR δ: 7.58 (1H, t, J=8 Hz, 10-H), 7.64 (1H, dd, J=4, 8 Hz, 2-H), 7.67 (1H, t, J=8 Hz, 9-H), 7.76 (1H, d, J=8 Hz, 8-H), 7.79 (1H, d, J=8 Hz, 6-H), 8.26 (1H, d, J=8 Hz, 5-H), 8.67 (1H, d, J=8 Hz, 11-H), 8.96 (1H, d, J=4 Hz, 3-H), 10.27 (1H, d, J=8 Hz, 1-H). MS *m/z* 263: ($M^{+\cdot}$). *Anal.* Calcd for $C_{16}H_9NOS$: C, 73.00; H, 3.45; N, 5.32. Found: C, 72.63; H, 3.47; N, 5.25.

7*H*-[1]Benzothiopyrano[2,3-*f*]quinolin-7-one (8) Pale yellow needles (from MeOH), mp 224—225 °C. Yield 85%. IR (KBr): 1620, 1600 cm^{-1}. ^{1}H-NMR δ: 7.57 (1H, t, J=8 Hz, 9-H), 7.59 (1H, dd, J=4, 8 Hz, 2-H), 7.69 (1H, t, J=8 Hz, 10-H), 7.72 (1H, d, J=8 Hz, 11-H), 8.10 (1H, d, J=8 Hz, 5-H), 8.66 (1H, d, J=8 Hz, 8-H), 8.71 (1H, d, J=8 Hz, 1-H), 8.83 (1H, d, J=8 Hz, 6-H), 9.09 (1H, d, J=4 Hz, 3-H). MS *m/z*: 263 ($M^{+\cdot}$). *Anal.* Calcd for $C_{16}H_9NOS$: C, 73.00; H, 3.45; N, 5.32. Found: C, 73.06; H, 3.50; N, 5.32.

7*H*-[1]Benzothiopyrano[3,2-*h*]quinolin-7-one (10) Pale yellow needles (from MeOH), mp 225—226 °C. Yield 80%. IR (KBr): 1630, 1600 cm^{-1}. ^{1}H-NMR δ: 7.55 (1H, t, J=8 Hz, 9-H), 7.62 (1H, dd, J=4, 8 Hz, 3-H), 7.68 (1H, t, J=8 Hz, 10-H), 7.78 (1H, d, J=8 Hz, 11-H), 7.80 (1H, d, J=8 Hz, 5-H), 8.26 (1H, d, J=8 Hz, 4-H), 8.66 (1H, d, J=8 Hz, 8-H), 8.70 (1H, d, J=8 Hz, 6-H), 9.02 (1H, d, J=4 Hz, 2-H). MS *m/z*: 263 ($M^{+\cdot}$). *Anal.* Calcd for $C_{16}H_9NOS$: C, 73.00; H, 3.45; N, 5.32. Found: C, 72.59; H, 3.15; 5.30.

Preparation of 2-Amino-1-methyl-9*H*-thioxanthen-9-one (14) A mixture of 2-mercaptobenzoic acid (7.70 g, 0.05 mol), 4-bromo-2-methylacetoanilide (10.80 g, 0.05 mol), K_2CO_3 (13.80 g, 0.10 mol), Cu powder (0.95 g), CuI (1.00 g), and *N*,*N*-dimethylformamide (DMF) (100 ml) was refluxed for 14 h. The cooled mixture was filtered, and the filtrate was concentrated *in vacuo* to a small volume. The residue was treated with hot H_2O, and then filtered. The filtrate was acidified with diluted HCl, and the precipitated solid was collected by filtration, washed with H_2O, and dried to give 2-(4-acetamido-3-methylphenylthio)benzoic acid (**11**) (13.00 g, 86%). The product **11** (9.03 g, 0.03 mol) was stirred with PPA (500 g) and heated at 130 °C for 5 h. After the reaction, the hot mixture was poured into ice-water. The precipitate was collected by filtration, washed with aqueous $NaHCO_3$ and H_2O, and dried to give a mixture (7.44 g, 88%) of 2-acetamido-1-methyl-9*H*-thioxanthen-9-one (**12**) and 2-acetamido-3-methyl-9*H*-thioxanthen-9-one (**13**). The mixture of **12** and **13** in 47% HBr in the presence of phenol was refluxed for 3 h, then poured in 20% NaOH solution. The precipitate was collected by filtration, washed with H_2O, and dried to give a yellow powder (7.02 g, 97%) consisting of **14** and **15**. The mixture of **14** and **15** was separated by alumina column chromatography using chloroform to give 2-amino-1-methyl-9*H*-thioxanthen-9-one (**14**) (3.60 g, 51%) and 2-amino-3-methyl-9*H*-thioxanthen-9-one (**15**) (2.67 g, 38%).

2-(4-Acetamido-3-methylphenylthio)benzoic Acid (11) Colorless powder (from aqueous MeOH), mp 270—271 °C. IR (KBr): 1680, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.28 (3H, s, CH_3), 3.95 (3H, s, $COCH_3$), 6.82 (1H, d, J=8 Hz, 3-H), 7.10 (1H, t, J=7 Hz, 5-H), 7.23 (1H, t, J=7 Hz, 4-H), 7.39 (1H, s, 2′-H), 7.40 (1H, d, J=8 Hz, 6′-H), 7.96 (1H, d, J=8 Hz, 6-H), 7.98 (1H, d, J=8 Hz, 5′-H). MS *m/z*: 301 ($M^{+\cdot}$). *Anal.* Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.76; H, 4.88; N, 4.51.

2-Amino-1-methyl-9*H*-thioxanthen-9-one (14) Yellow needles (from MeOH), mp 149—150 °C. IR (KBr): 3450, 3350, 1610, 1590 cm^{-1}. ^{1}H-NMR δ: 2.64 (3H, s, CH_3), 3.83 (2H, br s, NH_2), 6.97 (1H, d, J=8 Hz, 3-H), 7.27 (1H, d, J=8 Hz, 4-H), 7.40 (1H, t, J=8 Hz, 7-H), 7.50 (1H, t, J=8 Hz, 6-H), 7.52 (1H, d, J=8 Hz, 5-H), 8.39 (1H, d, J=8 Hz, 8-H). MS *m/z*: 241 ($M^{+\cdot}$). *Anal.* Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.59; H, 4.81; N, 5.71.

2-Amino-3-methyl-9*H*-thioxanthen-9-one (15) Yellow needles (from aqueous MeOH), mp 216—217 °C. IR (KBr): 3400, 3350, 1655, 1620, 1600 cm^{-1}. ^{1}H-NMR δ: 2.30 (3H, s, CH_3), 7.29 (1H, s, 4-H), 7.30—7.60 (2H, m, 5-H, 6-H), 7.68 (1H, t, J=8 Hz, 7-H), 7.98 (1H, s, 1-H), 8.60 (1H, d, J=8 Hz, 8-H). MS *m/z*: 241 ($M^{+\cdot}$). *Anal.* Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.53; H, 4.71; N, 5.74.

11-Methyl-12*H*-[1]benzothiopyrano[2,3-*g*]quinolin-12-one (16) The title compound was prepared according to the general procedure for the Skraup reaction of amino-9*H*-thioxanthen-9-ones. Pale yellow needles (from MeOH), mp 205—206 °C. Yield 45%. IR (KBr): 1660, 1600 cm^{-1}. ^{1}H-NMR δ: 3.40 (3H, s, CH_3), 7.44 (1H, t, J=8 Hz, 2-H), 7.49 (1H, dd, J=4, 8 Hz, 8-H), 7.50 (1H, d, J=8 Hz, 4-H), 7.57 (1H, t, J=8 Hz, 3-H), 7.87 (1H, s, 6-H), 8.10 (1H, d, J=8 Hz, 7-H), 8.38 (1H, d, J=8 Hz, 1-H), 9.02 (1H, d, J=4 Hz, 9-H). MS *m/z*: 277 ($M^{+\cdot}$). *Anal.* Calcd for $C_{17}H_{11}NOS$: C, 73.62; H, 4.00; N, 5.05. Found: C, 73.62; H, 4.30; N, 4.89.

Preparation of 3-Amino-4-methyl-9*H*-thioxanthen-9-one (19) A mixture of 2-mercaptobenzoic acid (3.08 g, 0.02 mol), 2-bromo-6-nitrotoluene (4.32 g, 0.02 mol), K_2CO_3 (3.31 g, 0.04 mol), Cu powder (0.25 g), CuI (1.00 g), and DMF (50 ml) was refluxed for 14 h. The cooled mixture was filtered and the filtrate was concentrated *in vacuo* to a small volume. The residue was treated with H_2O and then filtered. The filtrate was acidified with 10% HCl, and the precipitated solids were collected by filtration, washed with H_2O, and dried to give 2-(2-methyl-3-nitrophenylthio)benzoic acid (**17**) (4.28 g, 74%). A mixture of **17** (2.89 g, 0.01 mol) and H_2SO_4 (25 ml) was heated and stirred at 100 °C for 30 min. After the reaction the hot mixture was poured into ice-water, and the precipitated solids were collected by filtration, washed with aqueous $NaHCO_3$ and H_2O, and dried to give 4-methyl-3-nitro-9*H*-thioxanthen-9-one (**18**) (2.38 g, 88%). The crude **18** (2.38 g) in acetic acid (30 ml) was treated with $SnCl_2 \cdot 2H_2O$ (9.00 g) in concentrated HCl (13 ml), and the mixture was heated in a boiling water bath for 3 h. After cooling, 20% aqueous NaOH (150 ml) was added. The precipitate was collected by filtration, washed with water, and dried to give **19** (1.97 g, 93%).

2-(2-Methyl-3-nitrophenylthio)benzoic Acid (17) Pale yellow powder, mp 196—197 °C. IR (KBr): 1680, 1520 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.63 (1H, d, J=8 Hz, 3-H), 7.28 (1H, t, J=8 Hz, 5-H), 7.41 (1H, t, J=8 Hz, 4-H), 7.56 (1H, t, J=8 Hz, 5′-H), 7.86 (1H, d, J=8 Hz, 6′-H), 7.97 (1H, d, J=8 Hz, 6-H), 8.02 (1H, d, J=8 Hz, 4′-H). MS *m/z*: 289 ($M^{+\cdot}$). *Anal.* Calcd for $C_{14}H_{11}NO_4S$: C, 58.12; H, 3.84; N, 4.84. Found: C, 57.86; H, 3.64; N, 4.57.

4-Methyl-3-nitro-9*H*-thioxanthen-9-one (18) Yellow plates (from aqueous MeOH), mp 228—229 °C. IR (KBr): 1640, 1520, 1350 cm^{-1}. NMR δ: 2.65 (3H, s, CH_3), 7.56 (1H, t, J=8 Hz, 7-H), 7.67 (1H, d, J=8 Hz, 5-H), 7.70 (1H, t, J=8 Hz, 6-H), 7.77 (1H, d, J=9 Hz, 2-H), 8.60 (1H, d, J=8 Hz, 8-H), 8.64 (1H, d, J=9 Hz, 1-H). MS *m/z*: 271 ($M^{+\cdot}$). *Anal.* Calcd for $C_{14}H_9NO_3S$: C, 61.99; H, 3.35; N, 5.17. Found: C, 62.28; H, 3.21; N, 5.00.

3-Amino-4-methyl-9*H*-thioxanthen-9-one (19) Yellow needles (from aqueous MeOH), mp 205—206 °C. IR (KBr): 3495, 3350, 1630, 1600, 1570 cm^{-1}. ^{1}H-NMR δ: 2.66 (3H, s, CH_3), 4.26 (2H, br s, NH_2), 7.57 (1H, t, J=8 Hz, 7-H), 7.68 (1H, d, J=8 Hz, 5-H), 7.71 (1H, t, J=8 Hz, 6-H), 7.78 (1H, d, J=8 Hz, 2-H), 8.60 (1H, d, J=8 Hz, 8-H), 8.64 (1H, d, J=8 Hz, 1-H). MS *m/z*: 241 ($M^{+\cdot}$). *Anal.* Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.42; H, 4.84; N, 5.73.

6-Methyl-12*H*-[1]benzothiopyrano[3,2-*g*]quinolin-12-one (20) The title compound was prepared according to the general procedure for the Skraup reaction of amino-9*H*-thioxanthen-9-ones. Pale yellow needles (from MeOH), mp 228—229 °C. Yield 70%. IR (KBr): 1660, 1605 cm^{-1}. ^{1}H-NMR δ: 3.00 (3H, s, CH_3), 7.47 (1H, t, J=8 Hz, 2-H), 7.48 (1H, d, J=8 Hz, 4-H), 7.50 (1H, dd, J=4, 8 Hz, 9-H), 7.60 (1H, t, J=8 Hz, 3-H), 8.36 (1H, d, J=8 Hz, 1-H), 8.60 (1H, d, J=8 Hz, 10-H), 9.05 (1H, s, 11-H), 9.06 (1H, d, J=4 Hz, 8-H). MS *m/z*: 277 ($M^{+\cdot}$). *Anal.* Calcd for $C_{17}H_{11}NOS$: C, 73.62; H, 4.00; N, 5.05. Found: C, 73.35; H, 4.20; N, 4.94.

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