

Synthesis of [1]Benzopyrano[2,3,4-*kl*]acridin-3-ol and Its Analogues as Pentacyclic Compounds

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A new heterocyclic compound, [1]benzopyrano[2,3,4-*kl*]acridin-3-ol was synthesized by cyclization of xanthone derivatives. The key compound, 1-(3'-methoxyanilino)-xanthone, was prepared from 1-aminoxanthone. [1]benzopyrano[2,3,4-*kl*]acridin-3-ol analogues, [1]benzothiopyrano[2,3,4-*kl*]acridin-3-ol, pyrido[3',2':5,6]-pyrano[2,3,4-*kl*]acridin-3-ol and pyrido[3',2':5,6]thiopyrano[2,3,4-*kl*]acridin-3-ol were synthesized by the same method.

Key words heterocyclic compound; [1]benzopyrano[2,3,4-*kl*]acridin-3-ol; [1]benzothiopyrano[2,3,4-*kl*]acridin-3-ol; pyrido[3',2':5,6]pyrano[2,3,4-*kl*]acridin-3-ol; pyrido[3',2':5,6]thiopyrano[2,3,4-*kl*]acridin-3-ol

A number of polycyclic aromatic alkaloids that may have various types of biological activity have been isolated from natural marine organisms. In particular, these compounds are attractive with respect to anti-tumor activity. From this perspective, our investigation of synthesizing xanthene derivatives focused on synthesis of [1]benzopyrano[2,3,4-*kl*]acridin-3-ol (**1**) and its analogues, because of their structural similarity to shermilamine and norse goline, an inhibitor of DNA topoisomerase type-II (Chart 1).

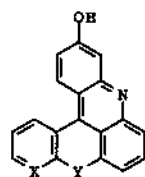
The [1]benzopyrano[2,3,4-*kl*]acridine derivative possesses the fused ring system which contains xanthene skeleton. In retrosynthetic analysis of **1**, a number of bond disconnections are possible, one of which is shown in Chart 2. Disconnection of carbon-carbon double bond would require the preparation of 1-(3'-methoxyanilino)xanthone (**5**) from 1-chloroxanthone or 1-aminoxanthone (**6**).

Results and Discussion

We chose to investigate two synthetic routes to 1-(3'-methoxyanilino)xanthone (**5**). The first route utilizes the reaction of 1-chloroxanthone with 3-methoxyaniline and the second (route B, in Chart 3) is the condensation of 1-aminoxanthone with 1-iodo-3-methoxybenzene.

1-Chloroxanthone was prepared according to Okabayashi's method.¹⁾ The obtained chloroxanthone was a mixture of 1- and 3-chloroxanthone which could not be separated by recrystallization or column chromatography. For this reason, the mixture of 1- and 3-chloroxanthones was used with the following reaction. 1-Aminoxanthone was prepared from a mixture of 1- and 3-chloroxanthone by a modification of the

method of 1-aminothioxanthone.²⁾ A mixture of 1- and 3-chloroxanthones was reacted with *p*-toluenesulfonamide to give a mixture of 1-(*p*-toluenesulfonamido)xanthone and 3-chloroxanthone. The mixture was hydrolyzed with 47% hydroboric acid to give a mixture of 1-aminoxanthone and 3-chloroxanthone. The mixture was easily separated by silica gel column chromatography to give **6**. Initially, a mixture of



- 1: X=CH, Y=O: [1]benzopyrano[2,3,4-*kl*]acridin-3-ol
 2: X=CH, Y=S: [1]benzothiopyrano[2,3,4-*kl*]acridin-3-ol
 3: X=N, Y=O: pyrido[3',2':5,6]pyrano[2,3,4-*kl*]acridin-3-ol
 4: X=N, Y=S: pyrido[3',2':5,6]thiopyrano[2,3,4-*kl*]acridin-3-ol

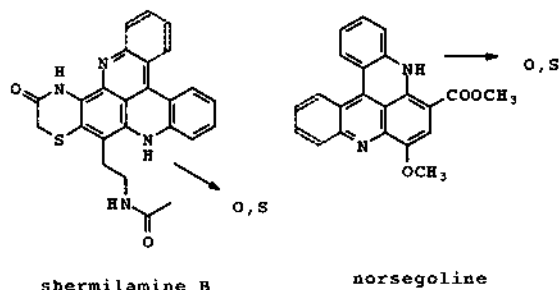


Chart 1

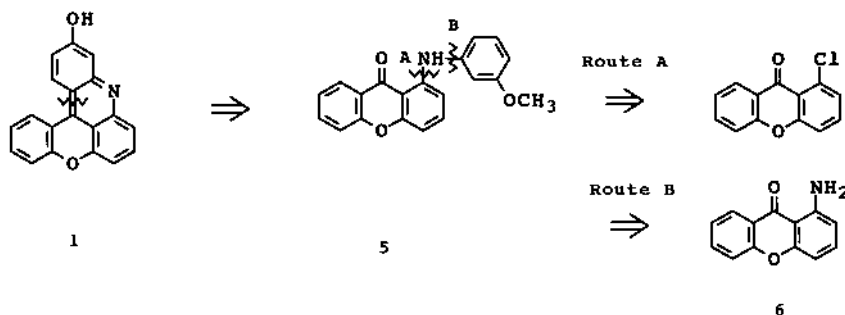


Chart 2

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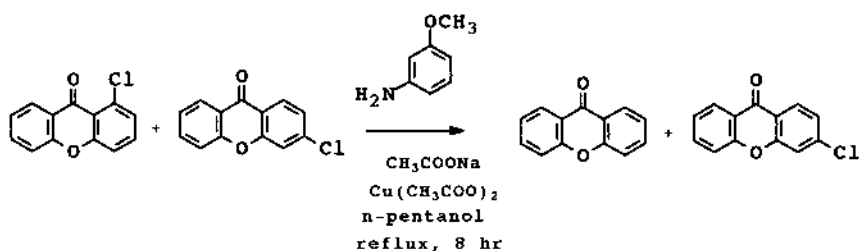


Chart 3

route B

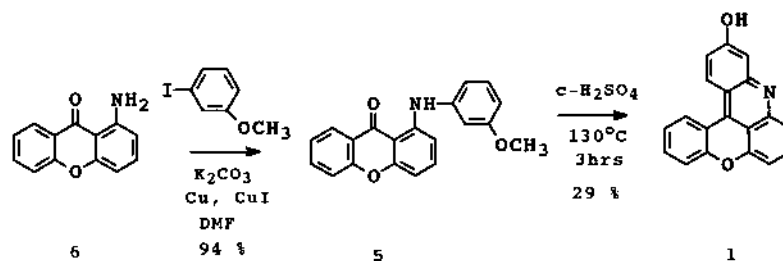


Chart 4

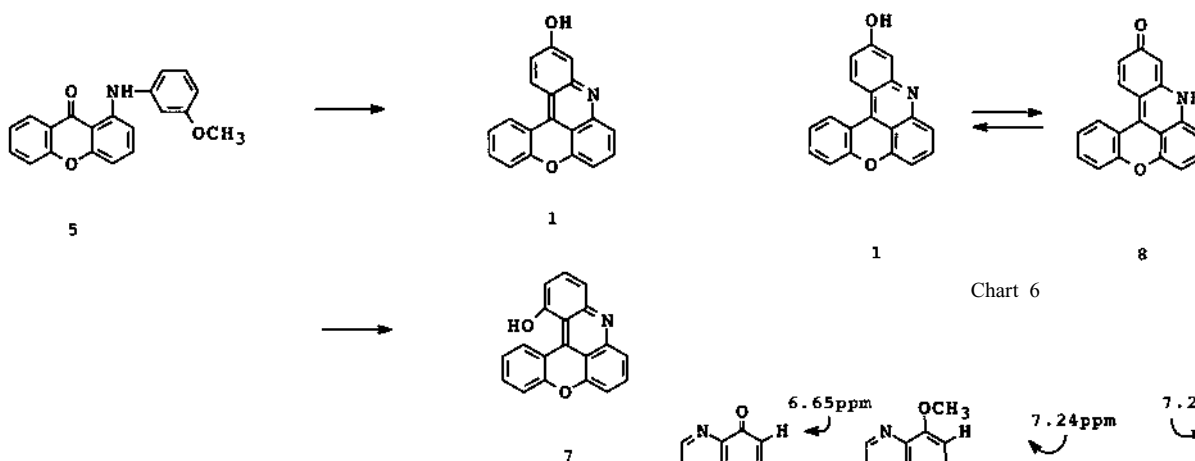


Chart 5

Chart 6

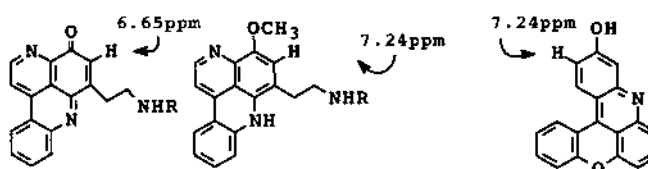


Chart 7

1- and 3-chloroxanthone was reacted with 3-methoxyaniline to give a mixture of xanthone and 3-chloroxanthone. From these results, 1-chloroxanthone gave xanthone by dechlorination. The reaction did not afford the objected compound (5).

On the other hand, in route B reaction of 1-aminoxanthone with 1-iodo-3-methoxybenzene gave **5** in a 94% isolated yield, Chart 4. Analysis of the $^1\text{H-NMR}$ spectrum of **2** suggests this is the structure, due to the presence of methoxy protons at δ 3.82 ppm and aromatic protons at δ 7.0–8.5 ppm.

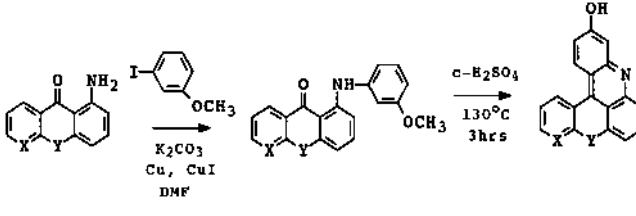
The obtained **5** was reacted under conc.-sulfuric acid at 130°C for 8 h to give **1**. The reaction was considered with the possibility of two compounds, **1** and [1]benzopyrano[2,3,4-*kl*]acridin-1-ol (**7**), by condensation orientation (Chart 5). However, only compound **1** was obtained.

Furthermore, **1** had the possibility of 3*H*,5*H*-[1]benzopyrano[2,3,4-*kl*]acridin-3-one structure (**8**) which was the keto form of the relationship of keto–enol tautomerism (Chart 6). In cystodytin A,³⁾ the proton at the 2-position was indicated

with the signal at δ 6.65 ppm and in cystodytin A methyl ether, the proton at the 2-position was indicated with the signal at δ 7.24 ppm (Chart 7). From these results, the structure of **1** was determined for the enol type in the presence of aromatic proton of δ 7.24 ppm corresponding to the proton at the 2-position of cystodytin A.

In addition, synthesis of [1]benzopyrano[2,3,4-*kl*]acridin-3-ol analogous, [1]benzothiopyrano[2,3,4-*kl*]acridin-3-ol (**2**), pyrido[3',2':5,6]pyrano[2,3,4-*kl*]acridin-3-ol (**3**) and pyrido[3',2':5,6]thiopyrano[2,3,4-*kl*]acridin-3-ol (**4**) were examined by the procedure described above. We prepared the starting materials, 1-aminothioxanthone (**9**),⁴⁾ 1-amino-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (**10**)⁵⁾ and 1-amino-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**11**)⁶⁾ by a modification of the method described by literatures. Then, **9**, **10** and

Table 1



	Yield		Yield
6: X=CH, Y=O	94%	5	29%
9: X=CH, Y=S	73%	12	15%
10: X=N, Y=O	94%	13	47%
11: X=N, Y=S	50%	14	46%

11 were reacted with 3-iodo-1-methoxybenzene to give 1-(3'-methoxyanilino)thioxanthone (**12**), 1-(3'-methoxyanilino)-benzopyrano[2,3-*b*]pyridin-5-one (**13**) and 1-(3'-methoxyanilino)benzothiopyrano[2,3-*b*]pyridin-5-one (**14**) in good yields, respectively. The reaction of these compounds with conc.-sulfuric acid afforded **2—4**, as shown in Table 1. These structures were determined by a method similar to that for **1**.

Experimental

Melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer FT-IR 1720. ¹H-NMR spectra were measured on a JEOL FX-400 instrument using CDCl₃ as a solvent and tetramethylsilane as an internal standard. MS were taken with a Hitachi M-2500 spectrometer.

1-(3'-Methoxyanilino)xanthone (5) A mixture of 1-aminoxanthone (2.11 g, 0.01 mol), 3-iodo-1-methoxybenzene (2.34 g, 0.01 mol), copper (0.1 g), copper iodine (0.1 g), K₂CO₃ (2.76 g, 0.02 mol), and DMF (50 ml) was stirred under reflux for 5 h. The reaction mixture was filtered. The filtrate was concentrated. The residue was mixed with hot water, filtered, and dried. The obtained solid was purified by silica gel column chromatography with benzene to give **5** (3.00 g, 94%).

Compound **5**: Yellow crystal (MeOH), mp 100–101 °C, IR (KBr) cm⁻¹: 1640, 1597, ¹H-NMR (CDCl₃) δ: 3.83 (3H, s, OCH₃), 6.69 (1H, dd, *J*=2.44, 8.29 Hz, 4'-H), 6.71 (1H, dd, *J*=0.98, 8.29 Hz, 4-H), 6.90 (1H, d, *J*=2.44 Hz, 2'-H), 6.96 (1H, dd, *J*=1.46, 7.81 Hz, 6'-H), 7.07 (1H, dd, *J*=0.98, 8.29 Hz, 2-H), 7.28 (1H, t, *J*=7.81 Hz, 5'-H), 7.34 (1H, t, *J*=7.81 Hz, 7-H), 7.40 (1H, dd, *J*=1.95, 8.29 Hz, 5-H), 7.42 (1H, t, *J*=8.29 Hz, 3-H), 7.68 (1H, t, *J*=7.81 Hz, 6-H), 8.26 (1H, dd, *J*=1.46, 7.81 Hz, 8-H), 11.30 (1H, s, NH). *Anal.* Calcd for C₂₀H₁₅NO₃: C, 75.69; H, 4.76; N, 4.41. Found: C, 75.66; H, 4.75; N, 4.19. MS: *m/z* 317 [M⁺].

1-(3'-Methoxyanilino)thioxanthone (12) A mixture of 1-aminothioxanthone (2.27 g, 0.01 mol), 3-iodo-1-methoxybenzene (2.34 g, 0.01 mol), copper (0.1 g), copper iodine (0.1 g), K₂CO₃ (2.76 g, 0.02 mol), and DMF (50 ml) was stirred under reflux for 5 h. The reaction mixture was filtered. The filtrate was concentrated. The residue was mixed with hot water, filtered, and dried. The obtained solid was purified by silica gel column chromatography with benzene to give **12** (2.43 g, 73%).

Compound **12**: Yellow needles (MeOH), mp 98–99 °C. IR (KBr) cm⁻¹: 1603, 1590, 1559. ¹H-NMR (CDCl₃) δ: 3.82 (3H, s, OCH₃), 6.70 (1H, dd, *J*=2.44, 8.29 Hz, 4'-H), 6.83 (1H, dd, *J*=0.98, 7.81 Hz, 4-H), 6.90 (1H, d, *J*=2.44 Hz, 2'-H), 6.94 (1H, d, *J*=7.81 Hz, 6'-H), 7.18 (1H, dd, *J*=0.98, 8.29 Hz, 2-H), 7.28 (1H, t, *J*=7.81 Hz, 5'-H), 7.28 (1H, t, *J*=7.81 Hz, 3-H), 7.43 (1H, t, *J*=8.29 Hz, 7-H), 7.47 (1H, dd, *J*=0.98, 8.29 Hz, 5-H), 7.56 (1H, t, *J*=8.29 Hz, 6-H), 8.52 (1H, dd, *J*=0.98, 7.81 Hz, 8-H), 11.83 (1H, s, NH). *Anal.* Calcd for C₂₀H₁₅NO₂S: C, 72.06; H, 4.54; N, 4.20. Found: C, 71.88; H, 4.60; N, 4.14. MS: *m/z* 333 [M⁺].

1-(3'-Methoxyanilino)-5H-[1]benzopyrano[2,3-*b*]pyridin-5-one (13) A mixture of 1-amino-5H-[1]benzopyrano[2,3-*b*]pyridin-5-one (2.12 g,

0.01 mol), 3-iodo-1-methoxybenzene (2.34 g, 0.01 mol), copper (0.1 g), copper iodine (0.1 g), K₂CO₃ (2.76 g, 0.02 mol), and DMF (50 ml) was stirred under reflux for 5 h. The reaction mixture was filtered. The filtrate was concentrated. The residue was mixed with hot water, filtered, and dried. The obtained solid was purified by silica gel column chromatography with benzene to give **13** (2.98 g, 94%).

Compound **13**: Yellow needles (MeOH), mp 139–140 °C. IR (KBr) cm⁻¹: 1641, 1595, 1572. ¹H-NMR (CDCl₃) δ: 3.82 (3H, s, OCH₃), 6.72 (1H, d, *J*=1.95, 8.29 Hz, 4'-H), 6.82 (1H, d, *J*=8.3 Hz, 4-H), 6.89 (1H, s, 2'-H), 6.93 (1H, d, *J*=8.29 Hz, 6'-H), 7.08 (1H, d, *J*=8.30 Hz, 2-H), 7.28 (1H, t, *J*=7.8 Hz, 5'-H), 7.37 (1H, dd, *J*=4.88, 7.81 Hz, 7-H), 7.43 (1H, t, *J*=8.29 Hz, 3-H), 8.62 (1H, dd, *J*=1.95, 7.81 Hz, 8-H), 8.68 (1H, dd, *J*=1.95, 4.88 Hz, 6-H), 11.11 (1H, s, NH). *Anal.* Calcd for C₁₉H₁₄N₂O₂: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.46; H, 4.35; N, 8.81. MS: *m/z* 318 [M⁺].

1-(3'-Methoxyanilino)-5H-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (14) A mixture of 1-amino-5H-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (2.28 g, 0.01 mol), 3-iodo-1-methoxybenzene (2.34 g, 0.01 mol), copper (0.1 g), copper iodine (0.1 g), K₂CO₃ (2.76 g, 0.02 mol), and DMF (50 ml) was stirred under reflux for 5 h. The reaction mixture was filtered. The filtrate was concentrated. The residue was mixed with hot water, filtered, and dried. The obtained solid was purified by silica gel column chromatography with benzene to give **14** (1.68 g, 50%).

Compound **14**: Yellow needles (MeOH), mp 147–148 °C. IR (KBr) cm⁻¹: 1603, 1594, 1573. ¹H-NMR (CDCl₃) δ: 3.82 (3H, s, OCH₃), 6.72 (1H, dd, *J*=1.95, 8.30 Hz, 4'-H), 6.86 (1H, dd, *J*=0.98, 7.81 Hz, 4-H), 6.88 (1H, s, 2'-H), 6.93 (1H, d, *J*=7.81 Hz, 6'-H), 7.17 (1H, dd, *J*=0.98, 8.30 Hz, 2-H), 7.28 (1H, t, *J*=7.81 Hz, 5'-H), 7.30 (1H, t, *J*=8.30 Hz, 3-H), 7.36 (1H, dd, *J*=4.39, 7.81 Hz, 7-H), 8.69 (1H, dd, *J*=1.95, 4.39 Hz, 6-H), 8.71 (1H, dd, *J*=1.95, 7.81 Hz, 8-H), 11.71 (1H, s, NH). *Anal.* Calcd for C₁₉H₁₄N₂OS: C, 68.25; H, 4.22; N, 8.38. Found: C, 68.00; H, 4.26; N, 8.15. MS: *m/z* 334 [M⁺].

[1]Benzopyrano[2,3,4-*k*]acridin-3-ol (1) A solution of **5** (3.17 g, 0.01 mol) in 94% H₂SO₄ was heated at 130 °C for 3 h. The cooled solution was poured ice-water and filtered, and the filter cake was washed with water and dried. The residue was purified by silica gel column chromatography using CHCl₃–MeOH as eluent to give **1** (0.83 g, 29%).

Compound **1**: Dark red powder, mp 283–284 °C, IR (KBr) cm⁻¹: 1642, 1620, 1595. ¹H-NMR (DMSO-*d*₆) δ: 7.04 (1H, dd, *J*=0.98, 7.56 Hz, 8-H), 7.23 (1H, d, *J*=2.44 Hz, 4-H), 7.24 (1H, dd, *J*=2.44, 9.27 Hz, 2-H), 7.39 (1H, t, *J*=8.55 Hz, 12-H), 7.42 (1H, dd, *J*=1.47, 8.30 Hz, 10-H), 7.58 (1H, dd, *J*=0.98, 8.79 Hz, 6-H), 7.62 (1H, t, *J*=8.55 Hz, 11-H), 7.71 (1H, t, *J*=8.79 Hz, 7-H), 8.42 (1H, dd, *J*=1.47, 8.30 Hz, 13-H), 8.59 (1H, d, *J*=9.27 Hz, 1-H). *Anal.* Calcd for C₁₉H₁₁NO₂: C, 79.99; H, 3.89; N, 4.91. Found: C 79.73; H, 4.02; N, 4.71. MS: *m/z* 285 [M⁺]. HR-EI-MS Calcd for C₁₉H₁₁NO₂: 285.0789. Found: 285.0808.

[1]Benzothiopyrano[2,3,4-*k*]acridin-3-ol (2) A solution of **12** (3.33 g, 0.01 mol) in 94% H₂SO₄ was heated at 130 °C for 3 h. The cooled solution was poured ice-water and filtered, and the filter cake was washed with water and dried. The residue was purified by silica gel column chromatography using CHCl₃–MeOH as eluent to give **2** (0.45 g, 15%).

Compound **2**: Dark red powder, mp 273–274 °C. IR (KBr) cm⁻¹: 1636, 1596. ¹H-NMR (DMSO-*d*₆) δ: 7.23 (1H, dd, *J*=2.44, 9.27 Hz, 2-H), 7.28 (1H, d, *J*=2.44 Hz, 4-H), 7.43 (1H, dd, *J*=0.98, 8.78 Hz, 8-H), 7.47 (1H, t, *J*=7.81 Hz, 12-H), 7.53 (1H, t, *J*=7.81 Hz, 11-H), 7.63 (1H, t, *J*=8.78 Hz, 7-H), 7.67 (1H, dd, *J*=1.47, 7.81 Hz, 10-H), 7.75 (1H, dd, *J*=1.98, 8.78 Hz, 6-H), 7.97 (1H, dd, *J*=1.47, 7.81 Hz, 13-H), 8.30 (1H, d, *J*=9.27 Hz, 1-H). *Anal.* Calcd for C₁₉H₁₁NOS: C, 75.72; H, 3.68; N, 4.65. Found: C, 75.83; H, 3.79; N, 4.44. MS: *m/z* 301 [M⁺]. HR-EI-MS Calcd for C₁₉H₁₁NOS: 301.0561. Found: 301.0590.

Pyrido[3',2':5,6]pyrano[2,3,4-*k*]acridin-3-ol (3) A solution of **13** (3.18 g, 0.01 mol) in 94% H₂SO₄ (40 ml) was heated at 130 °C for 3 h. The cooled solution was poured ice-water and filtered, and the filter cake was washed with water and dried. The residue was purified by silica gel column chromatography using CHCl₃–MeOH as eluent to give **3** (1.34 g, 47%).

Compound **3**: Red powder, mp 310–311 °C. IR (KBr) cm⁻¹: 1640, 1595. ¹H-NMR (DMSO-*d*₆) δ: 7.10 (1H, dd, *J*=8.78 Hz, 8-H), 7.27 (1H, d, *J*=2.44 Hz, 4-H), 7.28 (1H, d, *J*=2.44, 9.27 Hz, 2-H), 7.45 (1H, dd, 4.39, 7.80, 12-H), 7.63 (1H, d, *J*=8.78 Hz, 6-H), 7.74 (1H, t, *J*=8.78 Hz, 7-H), 8.46 (1H, d, *J*=4.39 Hz, 11-H), 8.57 (1H, d, *J*=9.27 Hz, 1-H), 8.87 (1H, d, *J*=7.80 Hz, 13-H). *Anal.* Calcd for C₁₈H₁₀N₂O₂: C, 75.51; H, 3.52; N, 9.79. Found: C, 75.37; H, 3.56; N, 9.84. MS: *m/z* 286 [M⁺]. HR-EI-MS Calcd for C₁₈H₁₀N₂O₂: 286.0741. Found: 286.0715.

Pyrido[3',2':5,6]thiopyrano[2,3,4-*k*]acridin-3-ol (4) A solution of **14** (3.34 g, 0.01 mol) in 94% H₂SO₄ (40 ml) was heated at 130 °C for 3 h. The

cooled solution was poured ice-water and filtered, and the filter cake was washed with water and dried. The residue was purified by silica gel column chromatography using CHCl_3 –MeOH as eluent to give **4** (1.39 g, 46%).

Compound **4**: Red powder, mp 297–298 °C. IR (KBr) cm^{-1} : 1636, 1597. ^1H -NMR ($\text{DMSO}-d_6$) δ : 7.24 (1H, dd, $J=2.44, 9.27$ Hz, 2-H), 7.28 (1H, d, $J=2.44$ Hz, 4-H), 7.46 (1H, dd, $J=0.98, 8.78$ Hz, 8-H), 7.46 (1H, dd, $J=4.39, 7.80$ Hz, 12-H), 7.66 (1H, t, $J=8.78$ Hz, 7-H), 7.78 (1H, dd, $J=0.98, 8.78$ Hz, 6-H), 8.22 (1H, d, $J=9.27$ Hz, 1-H), 8.32 (1H, d, $J=1.46, 7.80$ Hz, 13-H), 8.57 (1H, d, $J=1.46, 4.39$ Hz, 11-H). *Anal.* Calcd for $\text{C}_{18}\text{H}_{10}\text{NO}_2\text{S}$: C, 71.52; H, 3.33; N, 9.27. Found: C, 71.78; H, 3.46; N, 9.00. MS: m/z 302 $[\text{M}^+]$. HR-EI-MS Calcd for $\text{C}_{20}\text{H}_{15}\text{NO}_3$: 302.0514. Found: 302.0554.

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