SYNTHESIS OF HETEROCYCLIC COMPOUNDS BY THE SKRAUP REACTION OF AMINO-9H-XANTHEN-9-ONES

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DNA intercalating agents, which are very important classes of antitumor drugs, usually possess planar aromatic and heteroaromatic polycyclic systems. Acridine derivatives are good examples of DNA intercalating agents.1-3 Some thioxanthene derivatives are effective against tumors.4,5 For the synthesis of xanthene derivatives, we have planned preparation of a new chromophore moiety instead of acridine and thioxanthene moieties. This new chromophore moiety was the xanthone ring condensed with an additional pyridine ring. The most generally useful method for preparing
substituted quinolines is the Skraup reaction.\textsuperscript{6,7}

This paper describes the synthesis of several new heterocyclic compounds, 12H-[1]benzopyrano[2,3-h]quinolin-12-one, 12H-[1]benzopyrano[3,2-f]quinolin-12-one\textsuperscript{8}, 7H-[1]benzopyrano[3,2-g]quinolin-7-one, and 7H-[1]benzopyrano[3,2-h]quinolin-7-one, from amino-9H-xanthen-9-ones by the Skraup reaction.

RESULTS AND DISCUSSION

The synthesis of the starting materials, 1-amino- (1)\textsuperscript{9}, 2-amino- (2)\textsuperscript{10}, 3-amino- (3)\textsuperscript{10}, and 4-amino-9H-xanthen-9-ones (4)\textsuperscript{11} was previously described. Skraup reactions of amino-9H-xanthen-9-ones with glycerol, fuming sulfuric acid, and nitrobenzene were conducted in the presence of iron (II) sulfate and boric acid, and these products obtained were found to have the molecular formula C\textsubscript{16}H\textsubscript{9}NO\textsubscript{2} based on elemental analytical data and mass spectrum (ms) with m/z 247 (M\textsuperscript{+}).

The Skraup reaction of 1 gave 12H-[1]benzopyrano[2,3-h]quinolin-12-one (5) in 78\% yield. The structure of 5 was determined by proton nuclear magnetic resonance (\textsuperscript{1}H-nmr) spectroscopy. The \textsuperscript{1}H-nmr spectrum showed proton signals of the pyridine ring at 7.53 (dd, J=4.4, 8.3 Hz, 3-H), 8.22 (dd, J=1.9, 8.3 Hz, 4-H) and 9.29 (dd, J=1.9, 4.4 Hz, 2-H) ppm, and proton signals of the 9H-xanthen-9-one skeleton at 7.67 (d, J=9.3 Hz, 6-H) and 8.10 (d, J=9.3 Hz, 5-H) ppm.

Although the Skraup reaction of 2 may possibly gave two products, 12H-[1]benzopyrano[3,2-f]quinolin-12-one (6)\textsuperscript{8} and 12H-[1]benzopyrano[2,3-g]quinolin-12-one (7), only 6 was obtained in 81\% yield. The \textsuperscript{1}H-nmr spectrum of 6 showed proton signals at 7.63 (dd, J=3.9, 8.3 Hz, 2-H), 8.94 (dd, J=1.5, 3.9 Hz, 3-H) and 10.33 (dd, J=1.5, 8.3 Hz, 1-H) ppm, and two doublet proton signals of the 9H-xanthen-9-one skeleton as in the case of 5. The Skraup reaction of 2 did not give linear-type product (7), and thus 2-amino-1-methyl-9H-xanthen-9-one (14) possessing a methyl group at
the 1-position of 2 was synthesized. The compound (14) was prepared by
the following method.

2-(4-Acetamido-3-methylphenoxy)benzoic acid (11) obtained by the Ullmann
reaction of 2-iodobenzoic acid with 4-acetamido-3-methylphenol was cy-
clized with polyphosphoric acid (PPA) to give a mixture of 2-acetamido-1-
methyl- (12) and 2-acetamido-3-methyl-9H-xanthen-9-ones (13). This mix-
ture was treated with 47 % hydrobromic acid to obtain a mixture of 14 and
15 which was separated by column chromatography. Under the same condi-
tions, the Skraup reaction of 14 gave a linear-type product, 11-methyl-12H-[1]benzopyrano[2,3-g]quinolin-12-one (16). The ms of 16 showed a
molecular ion peak at m/z 261 and the 1H-nmr spectrum, a methyl group at
3.55 ppm and proton signals of the 9-position at 9.00 ppm (dd, J=1.9, 3.9
Hz) and 6-position at 7.72 ppm (1H, s). The ring closure of 2 thus occurs
preferentially at the 1-position, compared to the 3-position.
Similarly, the Skraup reaction of 3 has possibility to give two products, 7H-1]benzopyrano[2,3-f]quinolin-7-one (8) and 12H-1]benzopyrano[3,2-g]-quinolin-12-one (9). But that of 3 produced only product (8) in 72% yield, and the structure of 8 was confirmed by the 1H-nmr spectrum as the case of 6. 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-9H-xanthen-9-one (19).

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\begin{align*}
\text{COOH} & \quad \text{Cu} \quad \text{CuI} \\
& \quad \text{PAA} \quad \text{SnCl}_2 \quad \text{HCl}
\end{align*}
\]

For the synthesis of 19, 2-(2-methyl-3-nitrophenoxy)benzoic acid (17) prepared from 2-iodobenzoic acid and 2-methyl-3-nitrophenol was cyclized with PPA to give 4-methyl-3-nitro-9H-xanthen-9-one (18), which was reduced to 19 with tin (II) chloride and hydrochloric acid. 6-Methyl-12H-1]benzopyrano[3,2-g]quinolin-12-one (20) was obtained by the Skraup reaction of 19. The structure of 20 was determined from its ms and 1H-nmr spectrum in the same way as in the case of 16. Based on the present results, the Skraup reaction of 3 affords the corresponding angular-type product without the linear-type product.

Skraup reaction of 4 gave 7H-1]benzopyrano[3,2-h]quinolin-7-one (10) in 84% yield.

**EXPERIMENTAL**

Melting points were measured on a Yanagimoto micro-melting point apparatus...
and are uncorrected. Infrared (ir) spectra were recorded with a Hitachi 260-10 spectrophotometer. H-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 RMU-7MG spectrometer.

**General procedure for the Skraup reaction of amino-9H-xanthen-9-ones (1-4, 14, and 19)**

A mixture of H₂SO₄·SO₃ (6.0 g, 50 mmol), nitrobenzene (1.23 g, 10 mmol), FeSO₄·7H₂O (0.28 g, 1.0 mmol), and H₃BO₃ (0.31 g, 5.0 mol) was chilled to 0-5°C, and glycerol (1.84g, 20 mmol) was added to the mixture, followed by addition of amino-9H-xanthen-9-one (1.06 g, 5 mmol) and water (2.5 ml). The mixture was heated at 130°C for 5 h. The reaction mixture was neutralized with 28 % NH₄OH and the resulting precipitate was collected by filtration, and the precipitate extracted with CHCl₃. The extract was dried over Na₂SO₄, the solvent was evaporated and the residue was recrystallized from MeOH to give the corresponding benzopyranoquinoline as colorless needles.

12H-[1]Benzopyrano[2,3-h]quinolin-12-one (5): Pale yellow needles (from MeOH), mp 189-190°C. Yield 73 %. Anal. Calcd for C₁₆H₁₃NO₂: C, 77.72; H, 3.67; N, 5.67. Found: C, 77.65; H, 3.81; N, 5.65. Ir (KBr): 1600, 1615 cm⁻¹. H-Nmr δ: 7.46 (1H, t, J=8.3 Hz, 10-H), 7.53 (1H, dd, J=4.4, 8.3 Hz, 3-H), 7.56 (1H, d, J=8.3 Hz, 8-H), 7.67 (1H, d, J=9.3 Hz, 6-H), 7.73 (1H, t, J=8.3 Hz, 9-H), 8.10 (1H, dd, J=9.3 Hz, 5-H), 8.22 (1H, dd, J=1.9, 8.3 Hz, 4-H), 8.36 (1H, d, J=8.3 Hz, 11-H), 9.29 (1H, dd, J=1.9, 4.4 Hz, 2-H). Ms: m/z 247 (M⁺).

12H-[1]Benzopyrano[3,2-f]quinolin-12-one (6): Pale yellow needles (from MeOH), mp 194-195°C (lit., 18191-192°C). Yield 81 %. Anal. Calcd for C₁₆H₁₃NO₂: C, 77.72; H, 3.67; N, 5.67. Found: C, 77.88; H, 3.70; N, 5.65. Ir (KBr): 1645, 1615 cm⁻¹. H-Nmr δ: 7.45 (1H, t, J=8.3 Hz, 10-H), 7.54 (1H, d, J=8.3 Hz, 8-H), 7.63 (1H, dd, J=3.9, 8.3 Hz, 2-H), 7.73 (1H, t, J=8.3 Hz, 9-H), 7.78 (1H, d, J=9.3 Hz, 6-H), 8.36 (1H, d, J=9.3 Hz, 5-H),
8.39 (1H, d, J=8.3 Hz, 11H), 8.94 (1H, dd, J=1.5, 3.9 Hz, 3H), 10.33 (1H, dd, J=1.5, 8.3 Hz, 1H). Ms: m/z 247 (M^+).

7H-[1]Benzopyran-2,3-fquinolin-7-one (8): Pale yellow needles (from MeOH), mp 216-217°C. Yield 72 %. Anal. Calcd for C_{16}H_{12}N_2O_2: C, 77.72; H, 3.67; N, 5.67. Found: C, 77.80; H, 3.48; N, 5.65. Ir (KBr): 1660, 1630 cm⁻¹. \(^1\)H-Nmr δ: 7.46 (1H, t, J=8.3 Hz, 9H), 7.59 (1H, dd, J=4.4, 8.3 Hz, 2H), 7.64 (1H, d, J=8.3 Hz, 11H), 7.78 (1H, t, J=8.3 Hz, 10H), 7.98 (1H, d, J=8.7 Hz, 5H), 8.38 (1H, d, J=8.3 Hz, 8H), 8.49 (1H, d, J=8.7 Hz, 6H), 8.92 (1H, dd, J=1.5, 8.3 Hz, 1H), 9.09 (1H, dd, J=1.5, 4.4 Hz, 3H). Ms: m/z 247 (M^+).

7H-[1]Benzopyran-3,2-hquinolin-7-one (10): Pale yellow needles (from MeOH), mp 221-222°C. Yield 84 %. Anal. Calcd for C_{16}H_{12}N_2O_2: C, 77.72; H, 3.67; N, 5.67. Found: C, 77.66; H, 3.70; N, 5.66. Ir (KBr): 1650, 1610 cm⁻¹. \(^1\)H-Nmr δ: 7.48 (1H, t, J=8.3 Hz, 9H), 7.66 (1H, dd, J=4.4, 8.3 Hz, 3H), 7.75 (1H, d, J=8.7 Hz, 5H), 7.83 (1H, t, J=8.3 Hz, 10H), 7.93 (1H, d, J=8.3 Hz, 11H), 8.29 (1H, dd, J=1.4, 8.3 Hz, 4H), 8.40 (1H, d, J=8.7 Hz, 6H), 8.43 (1H, d, J=8.3 Hz, 8H), 9.17 (1H, dd, J=1.4, 4.4 Hz, 2H). Ms: m/z 247 (M^+).

2-Amino-1-methyl-9H-xanthen-9-one (14): A mixture of 2-iodobenzoic acid (12.4 g, 50 mmol), 4-acetamido-3-methylphenol (8.25 g, 50 mmol), K₂CO₃ (13.80 g, 100 mmol), Cu powder (0.95 g, 15 mmol), CuI (1.00 g, 5 mmol), and n-amyl alcohol (10 ml, 93 mmol) was heated at 180°C for 5 h. The mixture was cooled and diluted with hot water and filtered. The filtrate was acidified with diluted HCl and the resulting precipitate was collected by filtration, washed with H₂O, and dried to give 2-(4-acetamido-3-methylphenoxy)benzoic acid (11) (10.82 g, 76 %). The product (11) was stirred in PPA (500 g) and heated at 130°C for 5 h, and the hot mixture was poured into ice-water. The precipitate was collected by filtration, washed with 10 % aqueous NaHCO₃, water, and dried to give a mixture (5.19 g, 36 %) of 2-acetamido-1-methyl-9H-xanthen-9-one (12) and 2-acetamido-3-methyl-9H-
xanthen-9-one (13). A mixture (5.19 g, 19.4 mmol) of 12 and 13 in 47% HBr and phenol (15.6 g, 58 mmol) was refluxed for 3 h. The mixture was poured in 10% NaOH solution. The precipitate was collected by filtration, washed with water, and dried to give a yellow powder (4.12 g, 94%) of 14 and 15. The mixture of 14 and 15 was separated by alumina column chromatography using CHCl₃ to give 2-amino-1-methyl-9H-xanthen-9-one (14) (1.80 g, 41%) and 2-amino-3-methyl-9H-xanthen-9-one (15) (2.00 g, 46%).

Compound 14: Yellow needles (from MeOH), mp 147-148°C. Anal. Calcd for C₁₄H₁₁N₂O₂: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.66; H, 4.99; N, 6.13. 1H-Nmr δ: 2.80 (3H, s, CH₃), 7.08 (1H, d, J=8.8 Hz, 3-H), 7.23 (1H, d, J=8.8 Hz, 4-H), 7.30 (1H, t, J=8.3 Hz, 7-H), 7.39 (1H, d, J=8.3 Hz, 5-H), 7.64 (1H, t, J=8.3 Hz, 6-H), 8.27 (1H, d, J=8.3 Hz, 8-H). Ms: m/z 225 (M⁺).

Compound 15: Yellow needles (from aqueous MeOH), mp 216-217°C. Anal. Calcd for C₁₄H₁₁N₂O₂: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.88; H, 4.98; N, 6.21. 1H-Nmr δ: 2.33 (3H, s, CH₃), 7.25 (1H, s, 4-H), 7.33 (1H, t, J=8.3 Hz, 6-H), 7.45 (1H, d, J=8.3 Hz, 5-H), 7.52 (1H, s, 1-H), 7.68 (1H, t, J=8.3 Hz, 7-H), 8.32 (1H, d, J=8.3 Hz, 8-H). Ms: m/z 225 (M⁺).

11-Methyl-12H-[1]benzopyano[2,3-g]quinolin-12-one (16): Pale yellow needles (from MeOH), mp 214-215°C. Yield 45%. Anal. Calcd for C₁₇H₁₁NO₂: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.00; H, 4.01; N, 5.28. 1H-Nmr δ: 3.55 (3H, s, CH₃), 7.35 (1H, t, J=8.3 Hz, 2-H), 7.44 (1H, d, J=8.3 Hz, 4-H), 7.50 (1H, dd, J=3.9, 8.3 Hz, 8-H), 7.70 (1H, t, J=8.3 Hz, 3-H), 7.72 (1H, s, 6-H), 8.16 (1H, dd, J=1.9, 8.3 Hz, 7-H), 8.33 (1H, d, J=8.3 Hz, 1-H), 9.00 (1H, dd, J=1.9, 3.9 Hz, 9-H). Ms: m/z 261 (M⁺).

3-Amino-4-methyl-9H-xanthen-9-one (19): A mixture of 2-iodobenzoic acid (4.96 g, 20 mmol), 2-methyl-3-nitrophenol (3.06 g, 20 mmol), K₂CO₃ (3.31 g, 40 mmol), Cu powder (0.25 g, 4 mmol), CuI (1.00 g, 5 mmol), and n-amyl
alcohol (5 ml, 46 mmol) was heated at 180°C for 3 h. The mixture was cooled, diluted with hot water, and filtered. The filtrate was acidified with 10% HCl, and the precipitate was collected by filtration, washed with H2O, and dried to give 2-(2-methyl-3-nitrophenoxy)benzoic acid (17) (2.80 g, 51%). A mixture of 17 (2.80 g) and PPA (150 g) was heated and stirred at 130°C for 3 h. After the reaction, the hot mixture was poured into ice-water, and the precipitate was collected by filtration, washed with aqueous NaHCO3, water, and dried to give 2.16 g (85%) of 4-methyl-3-nitro-9H-xanthen-9-one (18). Crude 18 (2.16 g) in acetic acid (30 ml) was added to a mixture of SnCl2·2H2O (9.00 g) and 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 filtered, washed with water, and dried and recrystallized from aqueous MeOH to give 19 (1.70 g, 90%).

3-Amino-4-methyl-9H-xanthen-9-one (19): Yellow needles (from aqueous MeOH), mp 204-205°C. Anal. Calcd for C14H11NO2: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.76; H, 4.79; N, 6.25. Ir (KBr): 3495, 3350, 1630, 1600, 1570 cm⁻¹. 1H-Nmr δ: 2.28 (3H, s, CH₃), 6.68 (1H, d, J=8.3 Hz, 2-H), 7.32 (1H, t, J=8.3 Hz, 7-H), 7.46 (1H, d, J=8.3 Hz, 5-H), 7.64 (1H, t, J=8.3 Hz, 6-H), 8.05 (1H, d, J=8.3 Hz, 1-H), 8.30 (1H, d, J=8.3 Hz, 8-H). Ms: m/z 225 (M⁺).

6-Methyl-12H-[1]benzopyrano[3,2-g]quinolin-12-one (20): Pale yellow needles (from MeOH), mp 248-249°C. Yield 84%. Anal. Calcd for C17H11NO2: C, 78.15; H, 4.24; N, 5.36. Found: C, 77.88; H, 4.00; N, 5.33. Ir (KBr): 1660, 1605 cm⁻¹. 1H-Nmr δ: 3.00 (3H, s, CH₃), 7.38 (1H, t, J=7.8 Hz, 2-H), 7.43 (1H, dd, J=4.4, 8.3 Hz, 9-H), 7.58 (1H, d, J=8.3 Hz, 4-H), 7.77 (1H, t, J=8.3 Hz, 3-H), 8.35 (1H, dd, J=1.5, 8.3 Hz, 10-H), 8.36 (1H, d, J=8.3 Hz, 1-H), 8.77 (1H, s, 11-H), 9.07 (1H, dd, J=1.5, 4.4 Hz, 8-H). Ms: m/z 247 (M⁺).
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