

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

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Abstract — The Skraup reaction of amino-9H-xanthen-9-ones was conducted in the presence of glycerol, fuming sulfuric acid, nitrobenzene, iron (II) sulfate and boric acid. 1-Amino-9H-xanthen-9-one gave 12H-[1]benzopyrano[2,3-h]quinolin-12-one. 2- And 3-amino-9H-xanthen-9-ones gave angular-type products, 12H-[1]-benzopyrano[3,2-f]quinolin-12-one and 7H-[1]benzopyrano[3,2-g]quinolin-7-one respectively, without linear-type products. 4-Amino-9H-xanthen-9-one gave 7H-[1]benzopyrano[3,2-h]quinolin-7-one.

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.^{6,7}

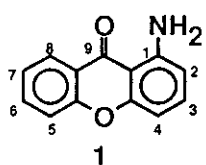
This paper describes the synthesis of several new heterocyclic compounds, 12*H*-[1]benzopyrano[2,3-*h*]quinolin-12-one, 12*H*-[1]benzopyrano[3,2-*f*]quinolin-12-one⁸, 7*H*-[1]benzopyrano[3,2-*g*]quinolin-7-one, and 7*H*-[1]benzopyrano[3,2-*h*]quinolin-7-one, from amino-9*H*-xanthen-9-ones by the Skraup reaction.

RESULTS AND DISCUSSION

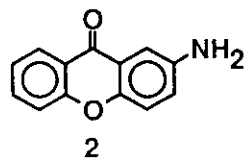
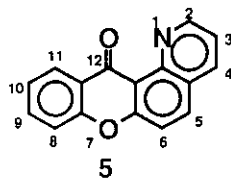
The synthesis of the starting materials, 1-amino- (1)⁹, 2-amino- (2)¹⁰, 3-amino- (3)¹⁰, and 4-amino-9*H*-xanthen-9-ones (4)¹¹ was previously described. Skraup reactions of amino-9*H*-xanthen-9-ones with glycerol, fuming sulfuric acid, and nitrobenzene were conducted in the presence of iron (II) sulfate and boric acid, and these products obtained were found to have the molecular formula C₁₆H₉NO₂ based on elemental analytical data and mass spectrum (ms) with *m/z* 247 (M⁺).

The Skraup reaction of 1 gave 12*H*-[1]benzopyrano[2,3-*h*]quinolin-12-one (5) in 78 % yield. The structure of 5 was determined by proton nuclear magnetic resonance (¹H-nmr) spectroscopy. The ¹H-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 9*H*-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.

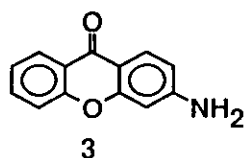
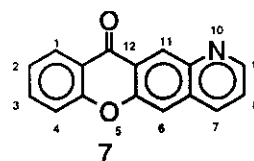
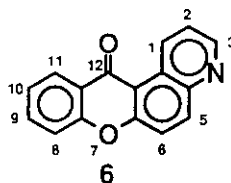
Although the Skraup reaction of 2 may possibly gave two products, 12*H*-[1]benzopyrano[3,2-*f*]quinolin-12-one (6)⁸ and 12*H*-[1]benzopyrano[2,3-*g*]quinolin-12-one (7), only 6 was obtained in 81 % yield. The ¹H-nmr spectrum of 6 showed proton signals at 7.63 (dd, *J*=3.9, 8.3 Hz, 2-H), 8.94 (dd, *J*=1.5, 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 9*H*-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-9*H*-xanthen-9-one (14) possessing a methyl group at



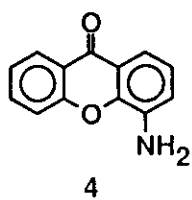
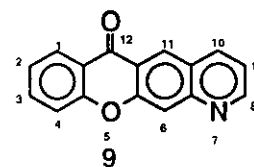
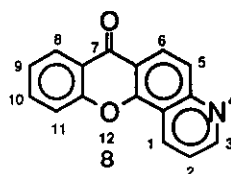
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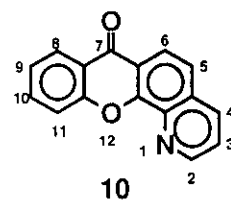
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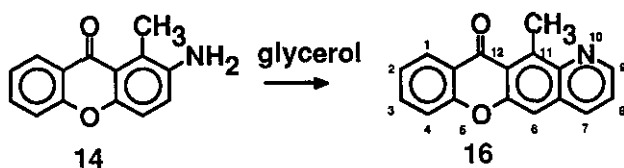
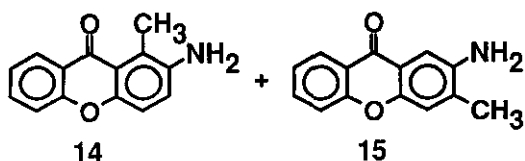
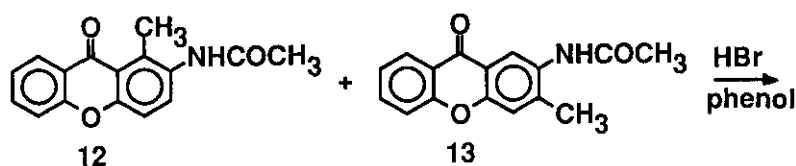
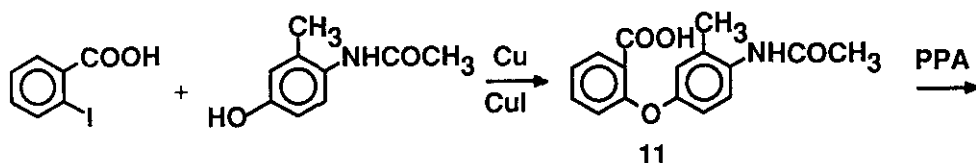


glycerol



glycerol

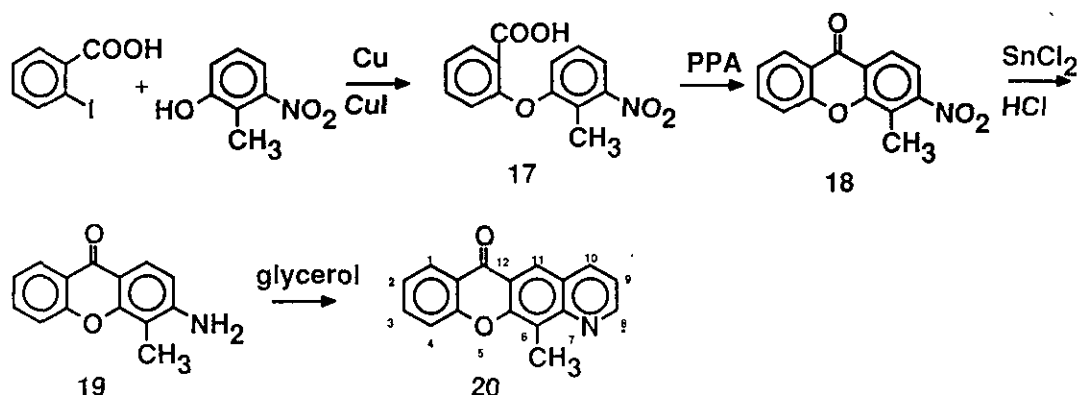




the 1-position of **2** was synthesized. The compound (**14**) was prepared by the following method.

2-(4-Acetamido-3-methylphenoxy)benzoic acid (**11**) obtained by the Ullmann reaction of 2-iodobenzoic acid with 4-acetamido-3-methylphenol was cyclized 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 mixture was treated with 47 % hydrobromic acid to obtain a mixture of **14** and **15** which was separated by column chromatography. Under the same conditions, 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, 7*H*-[1]benzopyrano[2,3-*f*]quinolin-7-one (**8**) and 12*H*-[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-9*H*-xanthen-9-one (**19**).



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-9*H*-xanthen-9-one (**18**), which was reduced to **19** with tin (II) chloride and hydrochloric acid. 6-Methyl-12*H*-[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 7*H*-[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. $^1\text{H-Nmr}$ 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-9H-xanthen-9-ones (1-4, 14, and 19)

A mixture of $\text{H}_2\text{SO}_4 \cdot \text{SO}_3$ (6.0 g, 50 mmol), nitrobenzene (1.23 g, 10 mmol), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.28 g, 1.0 mmol), and H_3BO_3 (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 % NH_4OH and the resulting precipitate was collected by filtration, and the precipitate extracted with CHCl_3 . The extract was dried over Na_2SO_4 , 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 $\text{C}_{16}\text{H}_9\text{NO}_2$: 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} . $^1\text{H-Nmr}$ 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, d, $J=9.3$ Hz, 5-H), 8.22 (1H, dd, $J=1.9, 8.3$ Hz, 4-H), 8.48 (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.,⁸ 191-192°C). Yield 81 %. Anal. Calcd for $\text{C}_{16}\text{H}_9\text{NO}_2$: 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} . $^1\text{H-Nmr}$ 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, 11-H), 8.94 (1H, dd, $J=1.5, 3.9$ Hz, 3-H), 10.33 (1H, dd, $J=1.5, 8.3$ Hz, 1-H). Ms: m/z 247 (M^+).

7H-[1]Benzopyrano[2,3-f]quinolin-7-one (8): Pale yellow needles (from MeOH), mp 216-217°C. Yield 72 %. Anal. Calcd for $C_{16}H_9NO_2$: 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} . 1H -Nmr δ : 7.46 (1H, t, $J=8.3$ Hz, 9-H), 7.59 (1H, dd, $J=4.4, 8.3$ Hz, 2-H), 7.64 (1H, d, $J=8.3$ Hz, 11-H), 7.78 (1H, t, $J=8.3$ Hz, 10-H), 7.98 (1H, d, $J=8.7$ Hz, 5-H), 8.38 (1H, d, $J=8.3$ Hz, 8-H), 8.49 (1H, d, $J=8.7$ Hz, 6-H), 8.92 (1H, dd, $J=1.5, 8.3$ Hz, 1-H), 9.09 (1H, dd, $J=1.5, 4.4$ Hz, 3-H). Ms: m/z 247 (M^+).

7H-[1]Benzopyrano[3,2-h]quinolin-7-one (10): Pale yellow needles (from MeOH), mp 221-222°C. Yield 84 %. Anal. Calcd for $C_{16}H_9NO_2$: 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} . 1H -Nmr δ : 7.48 (1H, t, $J=8.3$ Hz, 9-H), 7.66 (1H, dd, $J=4.4, 8.3$ Hz, 3-H), 7.75 (1H, d, $J=8.7$ Hz, 5-H), 7.83 (1H, t, $J=8.3$ Hz, 10-H), 7.93 (1H, d, $J=8.3$ Hz, 11-H), 8.29 (1H, dd, $J=1.4, 8.3$ Hz, 4-H), 8.40 (1H, d, $J=8.7$ Hz, 6-H), 8.43 (1H, d, $J=8.3$ Hz, 8-H), 9.17 (1H, dd, $J=1.4, 4.4$ Hz, 2-H). 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), K_2CO_3 (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 H_2O , 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 $NaHCO_3$, 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 CHCl_3 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 $\text{C}_{14}\text{H}_{11}\text{NO}_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.66; H, 4.99; N, 6.13. Ir (KBr): 3450, 3350, 1650, 1615, 1600 cm^{-1} . $^1\text{H-Nmr}$ δ : 2.80 (3H, s, CH_3), 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 $\text{C}_{14}\text{H}_{11}\text{NO}_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.88; H, 4.98; N, 6.21. Ir (KBr): 3400, 3350, 1655, 1620, 1600 cm^{-1} . $^1\text{H-Nmr}$ δ : 2.33 (3H, s, CH_3), 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]benzopyrano[2,3-g]quinolin-12-one (16): Pale yellow needles (from MeOH), mp 214-215°C. Yield 45 %. Anal. Calcd for $\text{C}_{17}\text{H}_{11}\text{NO}_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.00; H, 4.01; N, 5.28. Ir (KBr): 1660, 1600 cm^{-1} . $^1\text{H-Nmr}$ δ : 3.55 (3H, s, CH_3), 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), K_2CO_3 (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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Received, 27th September, 1993