Ethyl (4-*N*-Acylaminopyridin-3-yl)glyoxylate and 5-Azaisatin as New Synthons for a Route to Various New Polyheterocycles

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From 4-*N*-protected-aminopyridines which were functionalized at their 3-position, 5-azaisatin and equivalent synthons where obtained. *Via* the use of the Pfitzinger reaction, these compounds provided an easy route to new and various polyheterocyclic compounds.

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For several years, isatins **1** have been important intermediates in both pharmaceutical and dye synthesis [1]. One of the common uses is their condensation as alkali isatates **2** with α-methyleneketones to provide 4-quinolinecarboxylic acids (Pfitzinger reaction). With respect to the various structures built up *via* these synthons, it is surprising to see that the single report in the litterature of an azaisatin concerns the 7-azaisatin (**3**) [2] obtained by oxidation of 3-aminooxindole (Figure 1).

In this paper, we report on the synthesis of ethyl 4-acylaminopyridineglyoxylates **4** which correspond to the useful 5-azaisatin (**5**), which are synthons for an easy route to various new polyheterocyclic compounds.

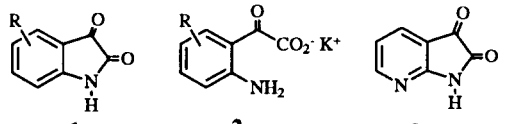


Figure 1.

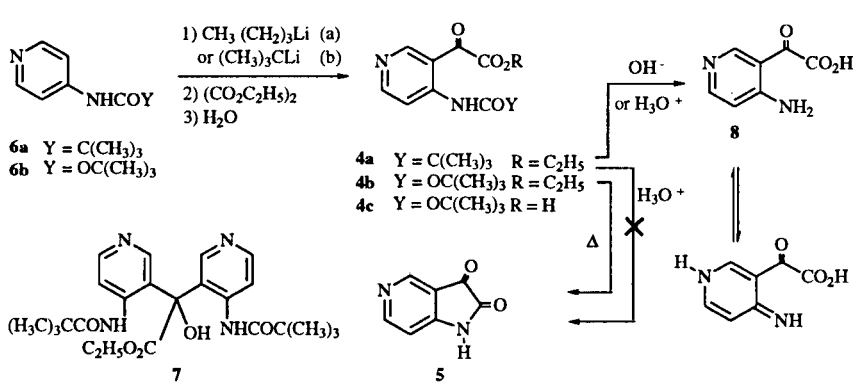
Results and Discussion.

While this work was already in progress, a general method for the synthesis of isatins has been described [3] which started from *ortho*-lithiated anilines. Thus for the preparation of aza derivatives by a similar proposed scheme, the described lithiation [4] of 4-*N*-pivaloylaminopyridine (**6a**), followed by reaction with diethyl oxalate in excess at -78°, provided pyridine **4a** bearing an α-ketoester at the 3 position (37%) (Scheme 1). However, it must be pointed out that if this reaction was performed at higher temperature (0°), the tertiary alcohol **7** was obtained as a result of normal reaction of **4a** with the 3-metallated pyridine species.

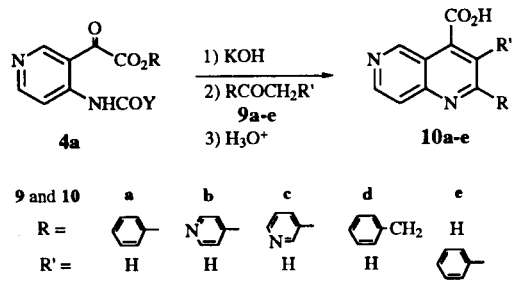
At first, we attempted to prepare 5-azaisatin (**5**) *via* a saponification-hydrolysis process and subsequent ring closure of the resulting intermediate **8** (Scheme 1). This pathway, however, totally failed, in contrast to what was observed in the aniline series [3]. The weak basicity of the 4-amino group of compound **8** probably accounts for this result. Nevertheless, pyridine **4a** appeared as a convenient synthon since its treatment with aqueous potassium hydroxide led to the intermediate alkali salt which corresponded to alkali isatates **2** generated from isatins **1**. Thus, when treated with potassium hydroxide, pyridine **4a** gave, with ketones or aldehydes bearing an α-methylene group in compounds **9a-e**, the 1,6-naphthyridine-4-carboxylic acids **10a-e** by the facile route to these types of heterocyclic compounds (Scheme 2). It is worth to noting that the structure of acid **10d**, obtained from ketone **9d**, gave clear indication of the steric hindrance factors. Indeed, in agreement with the literature [5], the less hindered methylene group reacts with the ketone function .

When the α-methyleneketone was β-tetralone (**11**), the obtained Pfitzinger product was thus dihydronaphtho-[1,6]naphthyridinecarboxylic acid **12**, which probably corresponded to a mixture of isomers **12a-c** due to an acid

Scheme 1

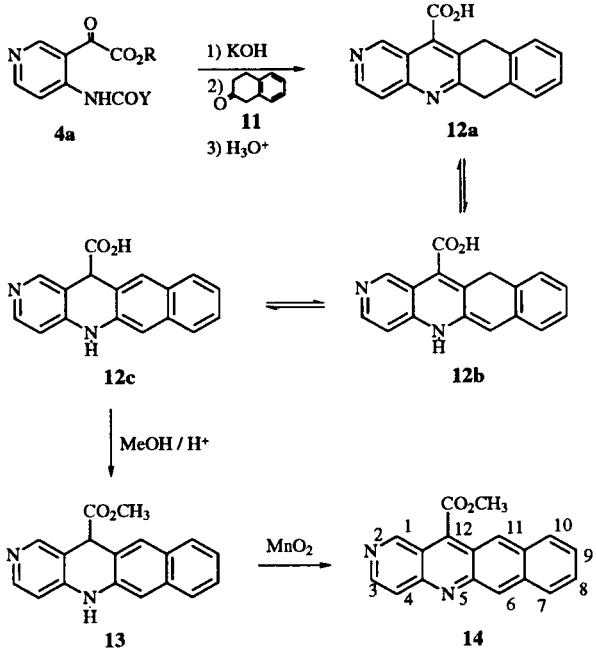


Scheme 2



induced tautomerism **12a** *vs* **12c** (Scheme 3). However, esterification of the mixture in acidic medium led to a compound corresponding to a single isomer **13**, whose manganese dioxide oxidation-aromatization furnished the linear tetracyclic aromatic compound **14**.

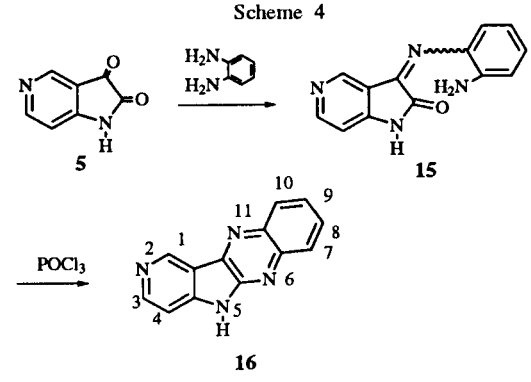
Scheme 3



In order to obtain 5-azaisatin (**5**) we then proceeded by starting from *N*-Boc protected 4-aminopyridine **6b** [6]. Its lithiation [6] took place under the usual conditions, and reaction of the corresponding lithio derivative with diethyl oxalate obviously gave the expected ketoester **4b** (33%) after flash chromatography, whereas the corresponding acid **4c** was obtained from the last fraction in low yield (3.5%). In contrast to our attempts to cyclise the intermediate compound *via* the protic species which totally failed, thermal cyclisation of ketoester-carbamate **4b** took place at 190° under vacuum, giving the expected 5-azaisatin (**5**) in a 68% yield (Scheme 1).

Obviously, pyridine **4b** and azaisatine **5** reacted with 2-methylene ketones as pyridine **4a** did in the Pfitzinger reaction. Moreover, like isatins **1** [6], 5-azaisatin (**5**) also was allowed to react with o-phenylenediamine to give intermediate **15** which provided, after cyclization by phosphorus oxychloride, another new heterocyclic system, namely 5*H*-pyrido[3',4':4,5]pyrrolo[2,3-*b*]quinoxaline (**16**) (Scheme 4).

Scheme 4



In conclusion, this work allowed us to provide 5-azaisatine (**5**) and ethyl 4-acylaminopyridineglyoxylates **4** which can be used as synthons in the Pfitzinger reaction in order to obtain various 1,6-naphthyridinecarboxylic acids as well as other new polyheterocyclic compounds.

EXPERIMENTAL

Melting points were measured with Kofler apparatus and are uncorrected. The ^{1}H nmr spectra were obtained in DMSO-d_6 using an AC-200 MHz Bruker spectrometer. Chemical shifts are reported in ppm (δ) relative to the deuteriated solvent as the internal standard and all coupling constants (J) are given in Hz. The mass spectra were recorded on AEI.MS-50 (MS-EI) spectrometer and as elemental analyses they were performed in ICSN/CNRS, Gif sur Yvette, France.

Ethyl (4-*N*-Pivaloylaminopyridin-3-yl)glyoxylate (**4a**).

Under argon, pyridine **6a** [4] (2.6 g, 14.6 mmoles) was dissolved in dry THF (30 ml) and the solution was stirred at -78°. *n*-Butyllithium (1.6 *M* solution in hexane, 22.8 ml, 36.5 mmoles) was added through a dropping funnel at such a rate that the temperature did not arise over -60°. After complete addition, the mixture was stirred for 3 hours at -10°. Then, at -78°, a solution of diethyl oxalate (5.5 g, 37.6 mmoles) in dry THF (7 ml) was added dropwise by a syringe. After 15 minutes at -78°, then 15 minutes at room temperature, the mixture was poured into ice-water and extracted with diethylether. The organic layer was washed with water, dried (magnesium sulfate), and evaporated under reduced pressure (1 mm of Hg) at 90°. The residue was chromatographed on a silica gel column with methylene chloride ethanol (100:0 then 90:10) as eluent. Product **5a** (1.5 g, 37%) was obtained as an oil; ^{1}H nmr (DMSO-d_6): δ 1.2 (s, 9H, $C(CH_3)_3$), 1.29 (t, 3H, J = 7.5 Hz, CH_3), 4.35 (q, 2H, J = 7.5 Hz, CH_2), 8.08 (d, 1H, J = 5.6 Hz, H-5), 8.72 (d, 1H, J = 5.6 Hz, H-6), 8.87 (s, 1H, H-2), 10.72 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60,72; H, 6.82; N, 9.88.

Ethyl Bis-(4-*N*-pivaloylaminopyridin-3-yl)glycolate (**7**).

This compound was prepared by the above preceeding procedure but diethyl oxalate was added at 0°. After work-up, the residue was taken up in ethanol to provide **7** (3.5%) as beige crystals, mp >260°; ^{1}H nmr (DMSO-d_6): δ 1.07 (s, 18H, 2 *t*-Bu), 1.15 (t, 3H, J = 7.2 Hz, CH_3), 4.35 (q, 2H, J = 7.2 Hz, OCH_2), 7.94 (2H, 2 x H-1), 8.32 (d, 1H, J = 5.6 Hz, H-5), 8.56 (d, 1H, J = 5.6 Hz, H-6), 9.6 and 9.7 (2 br. s, 2 x 1H, 2NH); ms: (DCI, NH_3) 457 (M+1).

Anal. Calcd. for $C_{24}H_{32}N_4O_5$: C, 63.14; H, 7.07; N, 12.27. Found: C, 62.96; H, 7.00; N, 12.11.

Ethyl (4-*N*-*tert*-Butoxycarbonylaminopyridin-3-yl)glyoxylate (**4b**) and (4-*N*-*tert*-Butoxycarbonylaminopyridin-3-yl)glyoxylic Acid (**4c**).

Compound **4b** was prepared from **6b** [6] with *tert*-butyllithium instead of *n*-butyllithium as described for **4a** above. It was obtained as an oil (33%); ^{1}H nmr (DMSO-d_6): δ 1.32 (t, 3H, J = 7.2 Hz, CH_3), 1.49 (s, 9H, $(CH_3)_3C$), 4.33 (q, 2H, J = 7.2 Hz, OCH_2), 7.66 (d, 1H, J = 5.8 Hz, H-5), 8.63 (d, 1H, J = 5.8 Hz, H-6), 8.69 (s, 1H, H-2), 10.30 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 57.13; H, 6.14; N, 9.26.

Evaporation of the last fractions obtained from chromatography gave a residue which was washed with acetone to provide **4c** (3.5%) as beige crystals, mp >260°; ^{1}H nmr (DMSO-d_6): δ 1.53 (s, 9H, $(CH_3)_3C$), 8.23 (d, 1H, J = 5.9 Hz, H-5), 8.56 (d, 1H, J = 5.9 Hz, H-6), 8.81 (s, 1H, H-2), 11.19 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{14}N_2O_5 \cdot 1.5H_2O$: C, 49.14; H, 5.84; N, 9.55. Found: C, 48.83; H, 5.74; N, 9.46.

2,3-Dihydro-*1H*-pyrrolo[3,2-*c*]pyridine-2,3-dione (**5**).

Pyridine **4b** (450 mg, 15.3 mmoles) was heated at 192° for 25 minutes under vacuum (10 Torr) in a micro-furnace (GKR51-Büchi). The solid formed was taken up in ethanol at room temperature to provide the 5-azaisatin **5** (140 mg, 68%) as yellow-green crystals, mp >260°; ^{1}H nmr (DMSO-d_6): δ 7.02 (d, 1H, J = 5.05 Hz, H-7), 8.60 (d, 1H, J = 5.05 Hz, H-3), 8.60 (s, 1H, H-4), 11.47 (s, 1H, NH); ms: (70 eV) m/z 148 (M^+, 100%).

Anal. Calcd. for $C_7H_4N_2O_2$: C, 56.76; H, 2.72; N, 18.91. Found: C, 56.81; H, 2.88; N, 18.71.

(4-Aminopyridin-3-yl)glyoxylic Acid (**8**).

A solution containing pyridine **4a** (578 mg, 2 mmoles) and potassium hydroxide (250 mg, 4.4 mmoles) in ethanol-water (5:1, 6 ml) was refluxed for 2 hours. After cooling and acidification (*p*H = 5) with acetic acid, the mixture was evaporated to dryness. The residue was taken up in a minimum ammount of ethanol to provide acid **8** (150 mg, 43%), mp 180°; ^{1}H nmr (DMSO-d_6): δ 6.99 (d, 1H, J = 6.9 Hz, H-5), 8.15 (d, 1H, J = 6.9 Hz, H-6), 8.69 (s, 1H, H-2), 8.90 (s, 2H, NH_2).

Anal. Calcd. for $C_7H_6N_2O_3 \cdot H_2O$: C, 45.65; H, 4.37; N, 15.21. Found: C, 45.31; H, 4.35; N, 15.31.

General Procedure for Preparation of Acids **10a-e** and **12**.

An ethanol-water (1:4, 20 ml) mixture containing pyridine **4a**, **4b** or 5-azaisatin (**5**) (5 mmoles) and potassium hydroxide (1.12 g, 20 mmoles) was refluxed for 2 hours. After addition of keto compound **10a-e** (10 mmoles), reflux was continued for a 24 hour period. After evaporation under reduced pressure, the residue was taken up in water and extracted with methylene chloride. The aqueous layer was cooled acidified with acetic acid and the solid was filtered, washed with water and recrystallized.

2-Phenyl-1,6-naphthyridine-4-carboxylic Acid (**10a**).

After recrystallization from ethanol, product **10a** was obtained (89%) as beige crystals, mp >260°; ^{1}H nmr (DMSO-d_6): δ 7.60 (m, 3H, 3H-Ph), 7.95 (d, 1H, J = 5.8 Hz, H-8), 8.30 (s, 1H, H-3), 8.33 (s, 2H, 2H-Ph), 8.73 (d, 1H, J = 5.9 Hz, H-7), 10.07 (s, 1H, H-5).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 72.00; H, 4.00; N, 11.20. Found: C, 71.91; H, 4.19; N, 10.90.

2-(Pyridin-4-yl)-1,6-naphthyridine-4-carboxylic Acid (**10b**).

After recrystallization from ethanol, product **10b** was obtained (54%) as beige crystals, mp >260°; ^{1}H nmr (DMSO-d_6): δ 7.88 (d, 1H, J = 5.9 Hz, H-8), 8.07 (dd, 2H, J = 4.6, 1.5 Hz, H-3', 5'), 8.42 (s, 1H, H-3), 8.62 (m, 2H, H-2', 6'), 8.65 (d, 1H, J = 5.9 Hz, H-7), 9.86 (s, 1H, H-5).

Anal. Calcd. for $C_{14}H_9N_3O_2 \cdot H_2O$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.15; H, 4.08; N, 15.37.

2-(Pyridin-3-yl)-1,6-naphthyridine-4-carboxylic Acid (**10c**).

After recrystallization from ethanol, product **10c** was obtained (44%) as beige crystals, mp >260°; ^{1}H nmr (DMSO-d_6): δ 7.43 (dd, 1H, J = 7.9, 4.6 Hz, H-5'), 7.82 (d, 1H, J = 5.8 Hz, H-8), 8.31 (s, 1H, H-3), 8.48 (dt, 1H, J = 8, 0.6 Hz, H-4'), 8.55 (m, 1H, H-6'), 8.59 (d, 1H, J = 5.9 Hz, H-7), 9.27 (d, 1H, J = 0.6 Hz, H-2'), 9.84 (s, 1H, H-5).

Anal. Calcd. for $C_{14}H_9N_3O_2 \cdot 0.25H_2O$: C, 65.75; H, 3.74; N, 16.43. Found: C, 65.89; H, 3.62; N, 16.26.

2-Benzyl-1,6-naphthyridine-4-carboxylic Acid (**10d**).

After recrystallization from ethanol, the product **10d** was obtained (25%) as beige crystals, mp 245°; ^{1}H nmr (DMSO-d_6): δ 4.43 (s, 2H, CH_2), 7.32 (m, 5H, 5H-Ph), 7.98 (s, 1H, H-7), 8.01 (d, 1H, J = 5.8 Hz, H-8), 8.81 (d, 1H, J = 5.8 Hz, H-7), 10.02 (s, 1H, H-5).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.49; H, 4.35; N, 10.83.

3-Phenyl-1,6-naphthyridine-4-carboxylic Acid (**10e**).

After recrystallization from ethanol, product **10e** was obtained (34%) as beige crystals, mp >260°; ^{1}H nmr (DMSO-d_6): δ 7.65 (m, 5H, H-Ph), 8.89 (d, 1H, J = 5.8 Hz, H-7), 8.90 (dd, 1H, J = 5.8, 0.6 Hz, H-8), 9.29 (d, 1H, H-2), 9.39 (d, 1H, J = 0.6 Hz, H-5).

Anal. Calcd. for $C_{15}H_{10}N_2O_2 \cdot H_2O$: C, 67.16; H, 4.51; N, 10.44. Found: C, 66.92; H, 4.56; N, 10.31.

6,11-Dihydronaphtho[2,3-*b*][1,6]naphthyridine-12-carboxylic Acid (**12a**).

Compound **12a**, which was air dried, was obtained (38%) as a crude product resulting from the acidified mixture without further purification, mp >280°. It probably corresponded to two or more tautomer forms and ^{1}H nmr (DMSO-d_6) showed: δ 4.18 (s, 2H, CH_2), 6.73 (d, 1H, J = 5.4 Hz, H-4), 8.09 (d, 1H, J = 5.4 Hz, H-3), 9.55 (s, 1H, H-1).

Anal. Calcd. for $C_{17}H_{10}N_2O_2 \cdot CH_3CO_2H \cdot 0.5H_2O$: C, 66.47; H, 4.40; N, 8.16. Found: C, 66.65; H, 4.70; N, 7.90.

Methyl 5,12-Dihydronaphtho[2,3-*b*][1,6]naphthyridine-12-carboxylate (**13**).

A solution containing the preceeding crude carboxylic acid **12** (556 mg, 1.2 mmoles) in methanol saturated with hydrochloric acid was refluxed for 2 hours. Methanol was evaporated, the residue was dissolved in water (50 ml) and the resulting aqueous layer was basified with 1*M* aqueous ammonia. The precipitate was filtered and recrystallized from toluene to obtain compound **13** (310 mg, 66%) as yellow crystals, mp 232° dec; ^{1}H nmr (DMSO-d_6): δ 3.59 (s, 3H, OCH_3), 5.45 (s, 1H, H-12), 6.87 (d, 1H, J = 5.5 Hz, H-4), 7.31 (s, 1H, H-6), 7.33 (td, 1H, J = 6.8, 1.3 Hz, H-9 or H-8), 7.46 (td, 1H, J = 6.8, 1.3 Hz, H-8 or H-9), 7.81 (m, 2H, H-7 and H-10), 7.88 (s, 1H, H-11), 8.22 (d,1H, J = 5.5 Hz, H-3), 8.31 (s, 1H, H-1), 9.84 (s, 1H, N-H).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.53; H, 4.58; N, 9.35.

Methyl Naphtho[2,3-*b*][1,6]naphthyridine-12-carboxylate (**14**).

A mixture of the ester **13** (298 mg, 1.03 mmoles) and freshly prepared manganese dioxide [7] (1.5 g) in dry methylene chloride (100 ml) was stirred at reflux for 1 hour. The hot mixture was filtered and washed with methylene chloride. After evaporation under reduced pressure and recrystallization from toluene, the fully aromatized ester **14** was obtained (221 mg, 75%) as red crystals, mp 212°; ^{1}H nmr (DMSO-d_6): δ 4.36 (s, 3H, OCH_3), 7.70 (m, 2H, H-8 and H-9), 8.32 (m, 2H, H-7 and H-10), 8.78 (d, 1H, J = 6.3 Hz, H-3), 9.04 (s, 1H, H-11 or H-6), 9.09 (s, 1H, H-6 or H-11), 9.69 (d, 1H, J = 1 Hz, H-1).

Anal. Calcd for $C_{18}H_{12}N_2O_2 \cdot 0.33H_2O$: C, 73.47; H, 4.33; N, 9.52. Found: C, 73.21; H, 4.29; N, 9.75.

3-(2-Aminophenylimino)-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridin-2-one (**15**).

A solution containing 5-azaisatin **5** (134 mg, 1 mmole) and *o*-phenylenediamine (118 mg, 1.1 mmole) in dimethylformamide (1 ml) was stirred at 100° for one day. The precipitate obtained after addition of water was collected and washed with water then acetone. The expected product **15** was obtained (155 mg, 65%) as a beige solid, mp >260°; ^{1}H nmr (DMSO-d_6): δ 6.75 (d, 1H, J = 5.7 Hz, H-7), 7.27 (2H, s, NH_2), 7.6-7.3 (m, 3H, H-3', 4', 5'), 7.90 (dd, 1H, J = 9.1 Hz, H-6'), 8.04 (d, 1H, J = 5.7 Hz, H-6), 9.14 (s, 1H, H-4), 12.56 (s, 1H, NH); ms: (DCI, NH_3) m/z 239 (M+1).

Anal. Calcd. for $C_{13}H_{10}N_4O \cdot 0.5H_2O$: C, 63.15; H, 4.48; N, 22.66. Found: C, 63.38; H, 4.44; N, 22.73.

5*H*-Pyrido[3',4':4,5]pyrrolo[2,3-*b*]quinoxaline (**16**).

A solution of the preceeding compound **15** (137 mg, 0.555 mmole) in phosphorus oxychloride (2 ml) was refluxed for 20 hours. After evaporation under reduce pressure water was added and the aqueous layer was basified with 1*M* ammonia. The precipitate was filtered and recrystallized from ethanol to provide product **16** (35 mg, 27%) as beige crystals, mp >260°; ^{1}H nmr (DMSO-d_6): δ 7.64 (d, 1H, J = 5.6 Hz, H-4), 7.83 (td, 1H, J = 6.8, 1.5 Hz, H-9 or H-8), 7.92 (td, 1H, J = 6.8, 1.5 Hz, H-8 or H-9), 8.18 (dd, 1H, J = 6.9, 1.5 Hz, H-10 or H-7), 8.35 (dd, 1H, J = 6.9, 1.5 Hz, H-7 or H-10), 8.75 (d, 1H, J = 5.7 Hz, H-3), 9.53 (s, 1H, H-1), 12.54 (s, 1H, NH); ms: (DCI, NH_3) m/z 221 (M+1).

Anal. Calcd. for $C_{13}H_{18}N_4 \cdot 0.66H_2O$: C, 67.26; H, 4.05; N, 24.14. Found: C, 67.34; H, 4.21; N, 24.45.

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