Synthesis of Novel Heterocycles from 2-Amino-3-cyanomethylsulfonyl-4,5-dimethylfuran

Chad E. Stephens and J. Walter Sowell, Sr.*

University of South Carolina, College of Pharmacy, Department of Basic Pharmaceutical Sciences, Division of Medicinal Chemistry, Columbia, SC 29208

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The synthesis and selected reactions of the versatile heterocycle 2-amino-3-cyanomethylsulfonyl-4,5-dimethylfuran is reported. In particular, cyclization reaction of the aminofuran yielded a number of novel furo[3,2-*b*]thiazine 1,1-dioxides. Additionally, a novel tetracyclic system, namely a pyrrolo[2',3':5,6]-[1,4]thiazino[3,2-*b*]quinoline 4,4-dioxide, is prepared *via* an intramolecular triple-cyclization in which the furan ring is opened and reclosed as a pyrrole.

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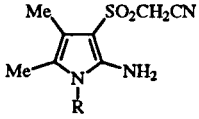
Previously we have reported the synthesis of substituted 2-amino-3-cyanomethylsulfonyl-4,5-dimethylpyrroles (**I**) [1] and their subsequent cyclization to a number of novel pyrrolo[3,2-*b*][1,4]thiazines [2] and pyrrolo[2,3-*e*][1,3,4]-thiadiazines [3]. During the course of work with the 3-arylsulfonyl derivatives of **I**, we discovered that the analogous furans could be prepared by condensation of acetoin with an (arylsulfonyl)acetonitrile under basic conditions [4]. Such methodology is similar to that first reported by Gewald with the condensation of acetoin or benzoin with malononitrile leading to 4,5-disubstituted-2-amino-3-cyanofurans [5]. Utilizing this methodology, we now report the synthesis of 2-amino-3-cyanomethylsulfonyl-4,5-dimethylfuran (**II**), a versatile heterocycle which has served as an immediate precursor to a number of novel furo[3,2-*b*]thiazine 1,1-dioxides. Furthermore, **II** has also served as a precursor in the synthesis of a novel tetracyclic system, namely a pyrrolo[2',3':5,6][1,4]thiazino[3,2-*b*]quinoline 4,4-dioxide.

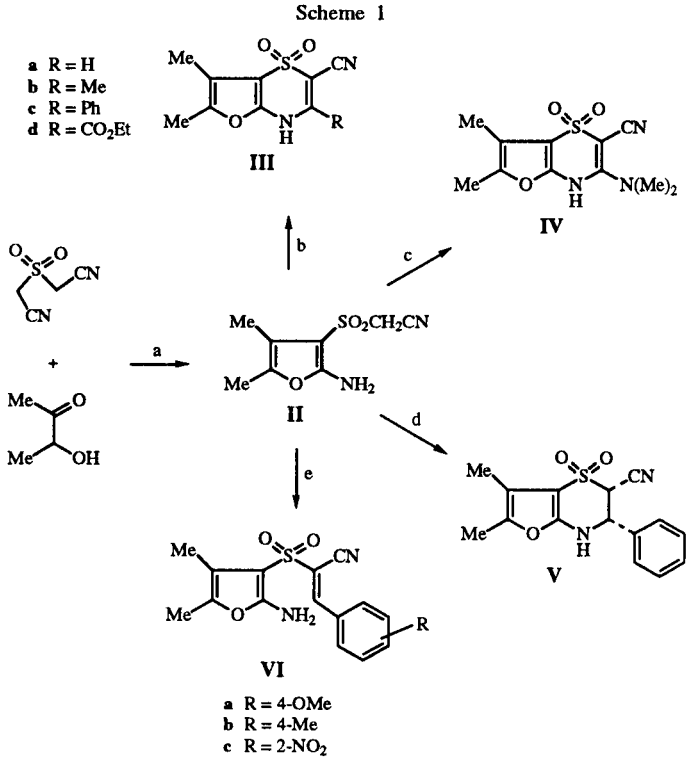


I

Condensation of acetoin with sulfonyldiacetonitrile in methanol utilizing 4-dimethylaminopyridine as the catalyst gave aminofuran **II** in 70% yield following recrystallization. Substitution of benzoin for acetoin however was unsuccessful in yielding the analogous diphenylfuran, consistent with previously reported difficulties with the condensation of sulfonylacetonitriles with aryl alkyl ketones [6].

As shown in Scheme 1, reaction of aminofuran **II** neat with ortho esters followed by addition of triethylamine in ethanol resulted in cyclization to various furo[3,2-*b*][1,4]-thiazine 1,1-dioxides. In particular, reaction with triethyl orthoformate, trimethyl orthoacetate, trimethyl orthobenzoate, or ethyl triethoxyacetate gave furothiazines **IIIa-d**,

Scheme 1

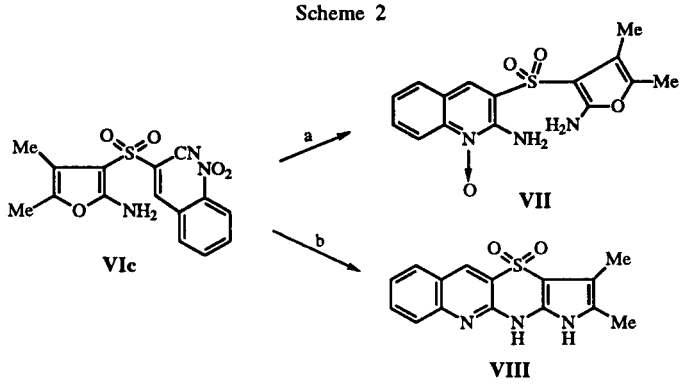


(a) 4-Dimethylaminopyridine, methanol, Δ; (b) 1. $(EtO)_3CR$ or $(MeO)_3CR$, Δ 2. Triethylamine, ethanol, Δ; (c) 1. Phosgene iminium chloride, dichloromethane, Δ 2. Triethylamine; (d) Benzaldehyde, ammonium acetate, ethanol, Δ; (e) Substituted benzaldehydes, ammonium acetate, ethanol, Δ.

respectively. The low yield (10%) obtained with the orthobenzoate is likely due to the steric demand of this bulky reagent. In a similar reaction, treatement of **II** with phosgene iminium chloride in dichloromethane followed by addition of triethylamine gave the dimethylamino-furothiazine **IV**. Additionally, condensation of **II** with benzaldehyde in ethanol in the presence of ammonium acetate [7] yielded the dihydrofurothiazine **V** in an approximate 2:1 mixture of cis:trans diastereomers as determined by nmr. In contrast to this, condensation with substituted benzaldehydes under identical conditions led

to isolation of the uncyclized cinnamonitriles **VIa-c**, with structural determination based on the presence of a free amino group in both the infrared and nmr spectra.

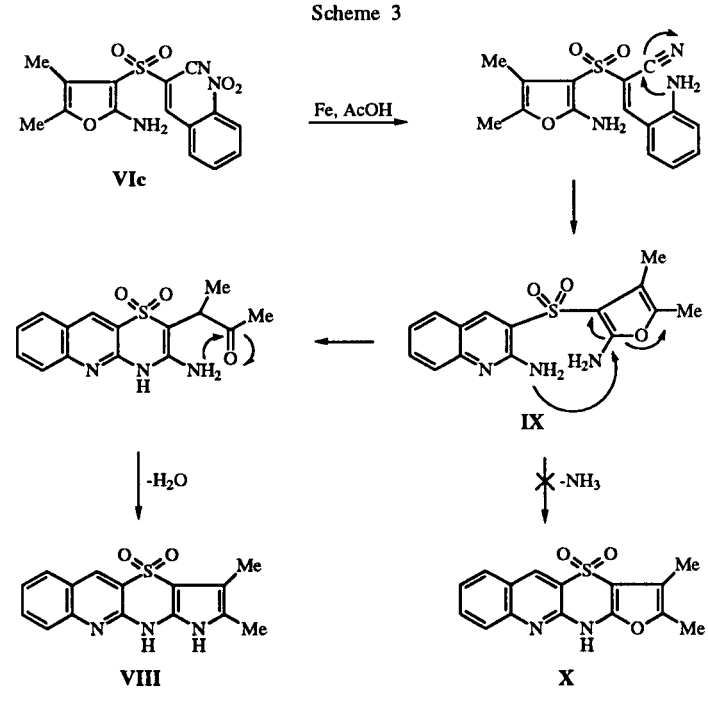
Scheme 2



(a) H_2, Pd/C, ethanol/DMF; (b) Fe, acetic acid, Δ.

As shown in Scheme 2, reductive cyclization of 2-nitrocinnamonitrile **VIc** under varying conditions led to two different products. First, catalytic hydrogenation using palladium on carbon gave the 2-aminoquinoline *N*-oxide **VII**, with the presence of the *N*-oxide confirmed by elemental analysis and mass spectroscopy. Upon review of the literature, such reductive cyclization of 2-nitrocinnamonitriles appears to be a well documented route to quinoline *N*-oxides [8]. Alternatively, reduction of **VIc** with iron in acetic acid gave the novel tetracyclic **VIII**, with structural assignment made on the basis of nmr and infrared spectra, elemental analysis, and mass spectrometry [9].

Scheme 3



Formation of the tetracyclic heterocycle evidently proceeds as shown in Scheme 3. Thus, the initial reductive cyclization to aminoquinoline **IX** is followed by an addition-elimination to the furan nucleus which results in opening of the ring and subsequent formation of the pyrrole to give **VIII**. Based on several reports of the acid-catalyzed elimination of ammonia from amino heterocycles [9,10], we initially considered furan-derivative **X** as product of the reduction; however, the presence of an additional NH resonance in the nmr spectrum and the determination of molecular formula clearly supports the assignment of structure **VIII**.

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus (capillary method) and are uncorrected. The nmr and mass spectra were determined on a Brucker WH-400 spectrometer and a VG-70 SQ instrument, respectively. Infrared spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique. Elemental analysis were performed by Atlantic Microlab, Inc., Norcross, Georgia. The tlc were performed on Baker Si250F silica plates. Sulfonyldiacetonitrile was synthesized according to a literature procedure [11]. Ethyl triethoxyacetate was synthesized as a 66% mixture with diethyl oxalate following simple distillation and used as such [12].

2-Amino-3-cyanomethylsulfonyl-4,5-dimethylfuran (**II**).

A mixture of sulfonyldiacetonitrile (1.44 g, 0.01 mole), acetoin (1.10 g, 0.0125 mole) and 4-dimethylaminopyridine (0.1 g) in methanol (10 ml) was heated at gentle reflux for 2 hours. The solution was then diluted with water (10 ml), stirred, and chilled to give a tan solid. Recrystallization from methanol:water (1:1) gave tan crystals (1.5 g, 70%). An analytical sample recrystallized from methanol:water (1:1) had mp 86-87°; ir: ν 3455 and 3355 (NH_2), 2240 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.00 and 2.08 (2s, 6H, $-CH_3$ at C4 and C5), 3.96 (s, 2H, SO_2-CH_2), 5.36 (br s, 2H, NH_2).

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.71; N, 13.08; S, 14.97. Found: C, 44.75; H, 4.72; N, 13.02; S, 14.90.

The procedure given for the synthesis of **IIIa** was adapted for the preparation of **IIIb-d**.

2-Cyano-6,7-dimethyl-4*H*-furo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**IIIa**).

A mixture of 2-amino-3-cyanomethylsulfonyl-4,5-dimethylfuran (**II**) (0.428 g, 0.002 mole) and triethyl orthoformate (1.2 g, 0.008 mole) was heated at 120-130° for 2 hours. After cooling, triethylamine (0.20 g, 0.002 mole) and ethanol (4 ml) were added and the mixture was refluxed for 30-45 minutes. The excess reagent was removed *in vacuo* and the oily residue was dissolved in sodium hydroxide (1*N*) and extracted with ethyl acetate. Acidification of the aqueous layer with concentrated hydrochloric acid gave an olive green solid (0.25 g, 56%). Recrystallization from methanol gave light golden crystals, mp chars >250°; mp 306-307° dec heating from 295° (to minimize dec); tlc R_f, ethyl acetate, 0.30; ir: ν 3200 (NH), 2210 (CN)

cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.08 and 2.25 (2s, 6H, -CH_3 at C6 and C7), 8.18 (s, 1H, 3-H).

Anal. Calcd. for $C_9H_8N_2O_3S$: C, 48.20; H, 3.60; N, 12.50; S, 14.30. Found: C, 48.25; H, 3.61; N, 12.43; S, 14.23.

2-Cyano-3,6,7-trimethyl-4*H*-furo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**IIIb**).

Prepared using trimethyl orthoacetate to give a tan solid (0.19 g, 40%). Recrystallization from methanol gave fine tan crystals, mp dec >300°; tlc R_f, ethyl acetate, 0.55; ir: ν 3200 (NH), 2200 (CN) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.07 and 2.25 (2s, 6H, -CH_3 at C6 and C7), 2.37 (s, 3H, 3-CH_3).

Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76; S, 13.46. Found: C, 50.32; H, 4.30; N, 11.67; S, 13.39.

2-Cyano-6,7-dimethyl-3-phenyl-4*H*-furo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**IIIc**).

Prepared using trimethyl orthobenzoate (1.5 equivalents). The oily product following acidification was extracted into ethyl acetate, dried (magnesium sulfate), and concentrated *in vacuo*. Chromatography (ethyl acetate) followed by recrystallization from ethyl acetate:hexanes gave a tan powder (0.12 g, 10%), mp 254-255° dec; tlc R_f, ethyl acetate, 0.33; ir: ν 3200 (NH), 2205 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.12 and 2.21 (2s, 6H, -CH_3 at C6 and C7), 7.48-7.58 (m, 5H, ArH), 9.21 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.98; H, 4.03; N, 9.33; S, 10.68. Found: C, 59.86; H, 4.11; N, 9.35; S, 10.61.

2-Cyano-3-ethoxycarbonyl-6,7-dimethyl-4*H*-furo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**IIId**).

Prepared using ethyl triethoxyacetate (66%, 1.3 equivalents) at 110° for 1 hour followed by triethylamine/ethanol for 30 minutes. The dark oil obtained following the initial concentration was redissolved in ethanol and then acidified with concentrated hydrochloric acid to give, after rinsing with a little 50% ethanol, a yellow crystalline solid (1.1 g, 37%). A sample was recrystallized from ethyl acetate to give bright yellow crystals, mp 232-234°; tlc R_f, ethyl acetate:methanol (4:1), 0.33; ir: ν 3130 (NH), 2210 (CN), 1740 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.31 (t, 3H, -CH_2-CH_3), 2.07 and 2.23 (2s, 6H, -CH_3 at C6 and C7), 4.32 (q, 2H, -CH_2-CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O_5S$: C, 48.64; H, 4.08; N, 9.46; S, 10.82. Found: C, 48.70; H, 4.11; N, 9.41; S, 10.71.

2-Cyano-3-dimethylamino-6,7-dimethyl-4*H*-furo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**IV**).

To a solution of 2-amino-3-cyanomethylsulfonyl-4,5-dimethylfuran (**II**) (1.29 g, 6.0 mmoles) in dichloromethane (30 ml) was added phosgene iminium chloride (1.22 g, 7.5 mmoles) and the suspension was stirred under argon at 35-40° for 1.5 hours. The red reaction mixture was then washed with saturated sodium bicarbonate solution, brine, and dried (magnesium sulfate). Triethylamine (1.2 g, 0.012 mole) was then added and the solution was stirred at ambient temperature overnight and then at reflux for 1 hour. Extraction with sodium hydroxide (1*N*) followed by acidification of the aqueous layer with concentrated hydrochloric acid gave an orange/brown solid (1.0 g, 62%). A sample was recrystallized from methanol to give golden colored crystals, mp 254-255° dec, with darkening >225°; tlc R_f, ethyl acetate, 0.32; ir: ν 3190 (NH), 2190 (CN) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.05 and 2.22 (2s, 6H, -CH_3 at C6 and C7), 3.10 (s, 6H, N-$(CH_3)_2$).

Anal. Calcd. for $C_{11}H_{13}N_3O_3S$: C, 49.42; H, 4.90; N, 15.72; S, 12.00. Found: C, 49.34; H, 4.97; N, 15.70; S, 11.95.

The procedure given for the synthesis of **V** was utilized for the preparation of **VIa-c**.

2-Cyano-3,4-dihydro-6,7-dimethyl-3-phenyl-2*H*-furo[3,2-*b*]-[1,4]thiazine 1,1-Dioxide (**V**).

A mixture of 2-amino-3-cyanomethylsulfonyl-4,5-dimethylfuran (**II**) (1.07 g, 0.005 mole), benzaldehyde (0.53 g, 0.005 mole), and ammonium acetate (0.39 g, 0.005 mole) in absolute ethanol (10 ml) was refluxed for 1 hour. The warm solution was then diluted with water (2 ml) and chilled to give a yellow solid (1.03 g, 68%). A sample was recrystallized from 95% methanol to give light yellow crystals, mp 200-201° dec; tlc R_f, ethyl acetate:hexanes (1:1), 0.75; ir: ν 3310 (NH), 2240 (CN, very weak) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.02 and 2.03 (2s, 3H, -CH_3 at C6 or C7), 2.12 and 2.15 (2s, 3H, -CH_3 at C6 or C7), 5.09 (d, 0.32H, 3-H), 5.21 (d, 0.68H, 3-H), 5.53 (d, 0.68H, 2-H), 5.72 (d, 0.32H, 2-H), 7.46-7.59 (m, 5H, ArH), 8.71 and 8.75 (2s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.58; H, 4.67; N, 9.27; S, 10.61. Found: C, 59.43; H, 4.70; N, 9.18; S, 10.55.

α-[(2-Amino-4,5-dimethyl-3-furanyl)sulfonyl]-4-methoxycinnamonitrile (**VIa**).

Prepared using *p*-anisaldehyde and isolated by chilling the reaction mixture as a yellow solid (0.37 g, 56%). Recrystallization from methanol gave yellow/orange crystals, mp 146-147°; tlc R_f, ethyl acetate:hexanes (1:1), 0.67; ir: ν 3400 and 3320 (NH_2), 2200 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.88 (s, 3H, -CH_3), 2.05 (s, 3H, -CH_3), 3.87 (s, 3H, OCH_3), 5.34 (s, 2H, NH_2), 6.97 (d, 2H, ArH), 7.88 (d, 2H, ArH), 7.97 (s, 1H, βH).

Anal. Calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.43; S, 9.65. Found: C, 57.89; H, 4.89; N, 8.35; S, 9.66.

α-[(2-Amino-4,5-dimethyl-3-furanyl)sulfonyl]-4-methylcinnamonitrile (**VIb**).

Prepared using *p*-tolualdehyde and isolated by chilling the reaction mixture as a yellow/orange solid (0.27 g, 43%). Recrystallization from methanol gave orange crystals, mp 150-152°; tlc R_f, ethyl acetate:hexanes (1:1), 0.8; ir: ν 3460 and 3350 (NH_2), 2210 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.89 (s, 3H, -CH_3), 2.05 (s, 3H, -CH_3), 2.42 (s, 3H, 4-CH_3), 5.36 (s, 2H, NH_2), 7.27 (d, 2H, ArH), 7.78 (d, 2H, ArH), 8.01 (s, 1H, βH).

Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.86; S, 10.13. Found: C, 60.74; H, 5.14; N, 8.79; S, 10.16.

α-[(2-Amino-4,5-dimethyl-3-furanyl)sulfonyl]-2-nitrocinnamonitrile (**VIc**).

Prepared using 2-nitrobenzaldehyde with a reaction time of 30 minutes. This compound precipitated during the course of the reaction and was isolated after chilling the reaction mixture as a red solid (0.35 g, 40%). The insoluble compound was then boiled in methanol (30 ml) and recollected. The filtrate upon cooling gave brick red crystalline flakes, mp 195-196°; tlc R_f, ethyl acetate:hexanes (3:2), 0.65; ir: ν 3460 and 3345 (NH_2), 2200 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.03 (s, 3H, -CH_3), 2.07 (s, 3H, -CH_3), 5.43 (s, 2H, NH_2), 7.68-7.72 (m, 1H, ArH), 7.79-7.81 (m, 3H, ArH), 8.27 (d, 1H, ArH), 8.56 (s, 1H, βH).

Anal. Calcd. for $C_{15}H_{13}N_3O_5S$: C, 51.87; H, 3.77; N, 12.10; S, 9.23. Found: C, 51.72; H, 3.83; N, 12.02; S, 9.16.

2-Amino-3-[(2-amino-4,5-dimethyl-3-furanyl)sulfonyl]quinoline 1-Oxide (**VII**).

A solution of the 2-nitrocinnamonitrile (**VIc**) (0.19 g, 0.55 mmole) in ethanol (10 ml) and DMF (5 ml) with palladium on carbon (10%, 50 mg) was hydrogenated at 45 psi for 1.75 hours. The mixture was then filtered over celite, partially concentrated *in vacuo*, and diluted with water to give a yellow solid (0.125 g, 69%). Recrystallization from ethyl acetate yielded bright yellow crystals, mp 204-206° dec; ir: ν 3440 and 3330 (NH_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.73 (s, 3H, $-CH_3$), 1.96 (s, 3H, $-CH_3$), 7.31 (s, 2H, NH_2), 7.34 (br s, 2H, NH_2), 7.52 (t, 1H, ArH), 7.86 (t, 1H, ArH), 8.16 (d, 1H, ArH), 8.30 (d, 1H, ArH), 8.51 (s, 1H, ArH); hrms (fab+): Calcd. for $C_{15}H_{16}N_3O_4S$: 334.0862. Found: 334.0860.

Anal. Calcd. for $C_{15}H_{15}N_3O_4S$: C, 54.04; H, 4.54; N, 12.61; S, 9.62. Found: C, 54.11; H, 4.59; N, 12.50; S, 9.54.

1,10-Dihydro-2,3-dimethylpyrrolo[2',3':5,6][1,4]thiazino[3,2-*b*]-quinoline 4,4-dioxide (**VIII**).

To a gently refluxing solution of the 2-nitrocinnamonitrile (**VIc**) (0.695 g, 0.002 mole) in acetic acid (15 ml) and water (2 ml) was added iron powder (0.6 g) and the mixture was stirred vigorously at the same temperature for 30 minutes. A yellow solid separated after about 5 minutes. The mixture was then cooled and the solid was collected and rinsed with methanol. The highly insoluble compound was purified by dissolving in hot pyridine, filtering, and then diluting with methanol until cloudy. After storing in the freezer, the solid was collected and washed with methanol to give a yellow powder (0.24 g, 40%), mp chars >225; ir: ν 3260, with faint shoulder at 3240 (2NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.12 and 2.14 (2s, 6H, $-CH_3$ at C2 and C3), 7.47 (d, 1H, ArH), 7.81 (s, 2H, ArH), 8.15 (d, 1H, ArH), 9.15 (s, 1H, ArH), 10.85 (s, 1H, NH), 11.83 (broader s, 1H, NH); hrms (ei): Calcd. for $C_{15}H_{13}N_3O_2S$: 299.0728. Found: 299.0721.

Anal. Calcd. for $C_{15}H_{13}N_3O_2S \cdot 0.33H_2O$: C, 59.01; H, 4.51; N, 13.76; S, 10.50. Found: C, 59.21; H, 4.45; N, 13.67; S, 10.38.

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