The Synthesis of 6,9-Difluorobenzo[*g*]quinoline-5,10-dione. Displacements of the Fluorides by Diamines Which Lead to 6,9-Bis[(aminoalkyl)amino]benzo[*g*]quinoline-5,10-diones

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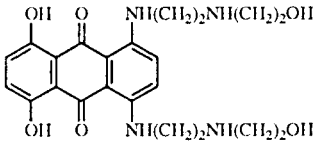
Received March 24, 1993

The synthesis of 6,9-difluorobenzo[*g*]quinoline-5,10-dione (**3b**) is described. Facile ipso substitutions of the fluorides from **3b** by diamines readily yield the corresponding 6,9-bis[(aminoalkyl)amino]benzo-[*g*]quinoline-5,10-diones **2**. The analogue **2d** has been synthesized by side arm modifications of dione **8a**.

J. Heterocyclic Chem., **30**, 1565 (1993).

Mitoxantrone (**1**) is an important new drug with demonstrated clinical efficacy in the treatment of human cancers [1-4]. Nevertheless, the need still exists for the synthesis and biological evaluations of additional anthracene-9,10-dione congeners in order to more fully define the mechanism of action of these chemotypes and to design new chemotherapeutic agents with improved therapeutic efficacies, lower host toxicities and increased effectiveness against MDR cell lines.



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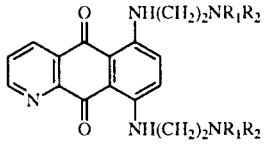
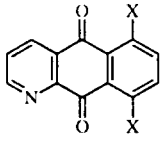
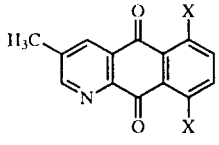


2

a, $R_1 = R_2 = CH_3$
b, $R_1 = R_2 = CH_2CH_3$
c, $R_1 = R_2 = H$
d, $R_1 = H$, $R_2 = (CH_2)_2OH$
e, $R_1 = H$, $R_2 = CO_2C(CH_3)_3$
f, $R_1 = H$, $R_2 = (CH_2)_2OSi(CH_3)_3$



3a, X = OH
b, X = F



4a, X = OTs
b, X = $NH(CH_2)_2N(CH_3)_2$

Antineoplastic comparisons of compounds with differing side arms in **1** [5] and those with nitrogen atom substitution in the anthracene-9,10-dione chromophore [6] have been examined. Several azaanthracene-9,10-diones analogues (*e. g.* **2a** and **2b**) have been synthesized in poor yield by treatment of **3a** with the appropriate diamines [6]. However, this methodology could not be applied to the preparation of analogues such as **2c** and **2d** in which the distal nitrogen of the ethylene diamine side chain is a primary or secondary amino functionality, respectively. In these cases, competitive cyclization of the distal nitrogen led to undesirable tetrahydroquinoxalines.

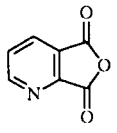
We wish to report a synthetic route which leads to analogues related to **2** in good overall yields.

Results and Discussion.

Since our previous studies have shown that the sequential displacements of the fluorides from 1,4-difluoroanthracene-9,10-diones [5,7,8] by nucleophilic diamines in pyridine at room temperature occur quite readily, 6,9-difluorobenzo[g]quinoline-5,10-dione (**3b**) appeared to be an attractive synthon. It might be noted that a previous study by Potts and co-workers [9] had reported that the displacements of the tosylate groups from **4a** by *N,N*-dimethylethylenediamine [pyridine, 70°, 16 hours] did not lead to any isolable bis-substitution product **4b**. The formal S_NAr substitutions of fluoride from **3b** would occur much more readily than tosylate group displacements.

Friedel-Crafts acylation of 1,4-difluorobenzene by anhydride **5** in the presence of aluminum chloride led to the regioisomeric keto acids **6a** and **6b** in an overall excellent yield (98%).The exceptional case of acylation of 1,4-difluorobenzene is of interest. Based on prior evaluations of the regioselectivity of **5** with other aromatic compounds [10], the predominant regioisomer is **6b**. Since either of these keto acids would cyclize to the

desired **3b**, no attempt was made to effect their separation. The cyclodehydration reaction proved to be difficult and conventional reagents such as polyphosphoric acid or concentrated sulfuric acid were not effective. Related types of hetero substituted keto acids have been reported to be extremely difficult to cyclodehydrate by other investigators [11-13]. For example, treatment of 3-benzoylpicolinic acid with hot sulfuric acid led to benzo[*g*]quinoline-5,10-dione in a 6% yield [12]. However, upon heating the keto acid mixture of **6a** and **6b** in fuming sulfuric acid (30% sulfur trioxide, 160°, 8 hours), **3b** was obtained in 30-40% yields. Variations of this procedure (see Experimental) raised the yields to 50 -70%.



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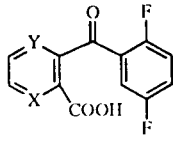
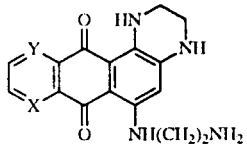
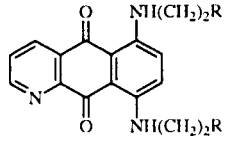


6a, X = CH, Y = N
b, X = N, Y = CH



7a, X = CH, Y = N
b, X = N, Y = CH



8a, R = OH
b, R = OSO_2CH_3

The reaction of **3b** with excess *N,N*-dimethylethylenediamine in pyridine at room temperature readily yielded **2a** (79%). On tlc monitoring (silica gel plates) of the reaction mixture, a magenta colored spot of high R_f formed rapidly and at longer reaction time this spot gradually disappeared and a blue spot corresponding to **2a** appeared. The magenta spot probably corresponds to a regioisomeric mixture of mono-substitution products from one fluoride substitution. The fluoride at position 9 of **3b** is more activated for nucleophilic displacement (S_NAr) than the fluoride at position 6. Under the reaction conditions employed for the substitution, regiospecific displacement would not be anticipated

Treatment of **3b** with ethylenediamine was then investigated for the preparation of **2c**. Upon removal of the pyridine from the reaction mixture of **3b** and ethylenediamine in pyridine at room temperature, crude **2c** was obtained. An examination of the ^1H nmr spectrum of this product indicated contamination by residual ethylenediamine and tetrahydroquinoxalines **7a** and **7b**. Of particular significance for the identification of **7a** and **7b** are the singlets at δ 6.1 and 6.3 for the aromatic protons *ortho* to the two amino substituents [14,15]. These tetrahydroquinoxalines arise from nucleophilic attack of the distal primary nitrogen on the quinone chromophore followed by air oxidation.

The unstable and hygroscopic nature of **2c** prevented purification by chromatographic techniques since these attempts led to decomposition. When chloroform was utilized as the solvent in the reaction of **3b** with ethylenediamine, the product **2c** was much easier to isolate but ^1H nmr analysis of the crude product indicated contamination by small amounts of **7a** and **7b**.

In order to avoid this undesirable cyclization, the reaction of **3b** with *N*-(*tert*-butoxycarbonyl)ethylenediamine in pyridine (or DMSO) led to **2e**. The removal of the BOC group was readily accomplished by treatment of **2e** with ethereal anhydrous hydrogen chloride. The hydrated trihydrochloride salt of **2c** was obtained quantitatively.

Our initial efforts to prepare the Mitoxantrone analogue **2d** by treatment of **3b** with 2-[(2- aminoethyl)amino]ethanol were met with difficulty. Analysis of the crude reaction mixture by tlc showed a very polar blue spot for **2d** (also based on ^1H nmr analysis) but the polarity and presence of the starting diamine prevented chromatographic separations. The stepwise construction of the sidearm was then utilized for the synthesis of **2d**. The diol **8a** (79%) was obtained by treatment of **3b** with 2-aminoethanol. The dimesylate **8b** (52%) was obtained by treatment of **8a** with methanesulfonyl chloride in pyridine. The displacement of the mesylate groups was accomplished by reaction of **8b** with 2-(trimethylsiloxy)ethylamine to yield **2f**. Attempted chromatographic purification of crude **2f** over silica gel resulted in the cleavage of the O-Si bond to yield **2d** which was converted to the dimaleate salt.

Conclusions

The difluoro analogue **3b** is a useful intermediate which undergoes facile stepwise ipso substitutions of the fluorides by amines to yield 6,9-bis-substitued benzo[*g*]-quinoline-5,10- diones. The use of **3b** in displacement reactions by other nucleophiles holds promise in other synthetic applications. The biological evaluations of the antitumor properties of the analogues reported here will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Thomas.Hoover apparatus and are uncorrected. Proton nmr spectra were run on a Bruker WP-270SY or WM-250 pulsed Fourier transform spectrometer. Chemical shifts are reported in δ units with TMS as an internal standard. The uv spectrum was determined on a Kontron Uvikon 860 and the hplc data were acquired using Perkin Elmer equipment which consisted of a series 3B liquid

chromatograph, an LC-85 spectrophotometric detector and an LCI-100 laboratory computing integrator. Precoated silica gel or alumina plates (Eastman Chromagram sheets) with fluorescent indicator were used for thin layer chromatography. Column chromatography was performed with Baker analyzed 80-200 mesh silica gel. Microanalyses were performed by Robertson Laboratory Madison, NJ. Pyridine-2,3-dicarboxylic acid, 1,4-difluorobenzene and the diamines were purchased from the Aldrich Chemical Co. The *N*-(*tert*-butoxycarbonyl)ethylenediamine [16] and 2-(trimethylsiloxy)ethylamine [17] were prepared following literature procedures.

6,9-Bis[[2-(dimethylamino)ethyl]amino]benzo[*g*]quinoline-5,10-dione (**2a**).

A solution of **3b** (25 mg, 0.10 mmole) and *N,N*-dimethylethylenediamine (88 mg, 1 mmole) in pyridine (0.5 ml) was stirred at room temperature for 94 hours. The pyridine and excess diamine were removed under a slow flow of nitrogen gas and the residual solid was placed under vacuum overnight. The residual blue solid was dissolved in 5% methanol/95% chloroform and added to a silica gel column. Elution with 10% methanol/90% chloroform led to small amounts of magenta colored compounds ((mono-substitution products). Gradient elution using 20% to 30% and then 50% methanol in chloroform gradually moved **2a** down the column. The **2a** eluted with 50% methanol/46% chloroform containing 4% concentrated aqueous ammonium hydroxide. Removal of the eluants yielded **2a**, 30 mg (79%), mp 165-167°, lit mp [6] 167°.

6,9.Bis[(2-aminoethyl)amino]benzo[*g*]quinoline-5,10-dione (**2c**).

A mixture of **3b** (102 mg, 0.42 mmole) and ethylenediamine (300 mg, 5 mmoles) in chloroform (2 ml) was allowed to stir at room temperature for 144 hours. The insoluble salts were removed by filtration and the chloroform was removed under a slow flow of nitrogen. The material was placed under vacuum to yield crude **2c**, 100 mg (73%) as a hygroscopic blue solid; ^{1}H nmr(dimethylsulfoxide-d_6): δ 11.5 and 11.3 (m, for H-bonded protons of **7a** and **7b**), 11.10 (m), 10,90 (m), 8.95 (d), 8.50 (dd), 7.75 (m), 7.45 (m), 6.1 and 6.2 (singlets for **7a** and **7b**), 3.7 (br s, hydrate), 2.5 (m), 2.9 (t), 2.7 (s, residual ethylenediamine).

Treatment of crude **2c** in a methanol/chloroform solution with a methanolic solution of maleic acid led to reasonably pure dimaleate salt; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.80 (m), 10.60 (m), 8.98 (d), 7.50 (d) 7.8 (m), 7.3 (m), 6.0 (s), 3.75 (m), 3.10 (m) [several other small extraneous peaks were also detectable].

6,9-Bis[(2-aminoethyl)amino]benzo[*g*]quinoline-5,10-dione Trihydrochloride Hydrate.

Under a nitrogen atmosphere at room temperature, 2 *N* hydrogen chloride in ether (32 ml, 64 mmoles) was added over a period of 5 minutes to a stirred solution of **2e** (1.59 g, 3.025 mmoles) in chloroform (500 ml, stabilized with 2% ethanol). The stirring was continued for 2 hours at room temperature, then the blue solid was collected by filtration under a nitrogen blanket, washed with *tert*-butyl methyl ether and dried under vacuum at room temperature. The product was obtained as a blue solid, 1.20 g (88%), mp 210° dec; tga 3.5% weight loss (35-120°), corresponding to approximately 1 mole of water; uv(water): λ max nm (E 1%) 289 (488), 342 (98), 647 (315); hplc, Lichrospher 100 RP18 (10 μm, 150mm); eluant sodium heptanesulfonate 20 m*M* in water/acetonitrile/dioxane (70/20/10), *p*H 3 by phosphoric acid; flow 1 ml/minute; λ 280 nm, > 99% purity (area), retention time 7.12 minutes; ^{1}H nmr (deuterium oxide): δ 8.95 (dd, 1H), 8.51 (dd, 1H), 7.97 (dd, 1H), 7.09 (br s, 2H), 3.87-3.70 (m, 4H), 3.37 (q, 4H).

Anal. Calcd. for $C_{17}H_{22}Cl_3N_5O_2 \cdot H_2O$: C, 45.10; H, 5.34; N, 15.47; Cl, 23.49. Found: C, 44.60; H, 5.40; N, 15.12; Cl, 23.78.

6,9-Bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]benzo[*g*]quinoline-5,10-dione (**2d**).

A solution of **8b** (0.245 g, 0.51 mmole) and 2-(trimethylsiloxy)ethylamine (1.35 g, 10.1 mmoles) in pyridine (2.5 ml) was stirred at room temperature under a nitrogen blanket for 26 hours. The pyridine was evaporated and the residue was dissolved in dichloromethane. This extract was washed with a saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. Evaporation of the solvent left a bluish oily residue of **2d** which was placed under vacuum overnight. Chromatography over silica gel with the eluant triethylamine/methanol/chloroform(1/5/5) followed by removal of the solvents led to **2d** as an oily blue material; ^{1}H nmr (deuteriochloroform): δ 11.10 (t, 1H), 10.82 (t, 1H), 8.91 (d, 1H), 8.46 (d, 1H), 7.54 (m, 1H), 6.80 (s, 2H), 3.85 (m, 4H), 3.48 (m, 4H), 3.00 (m, 8H) [peaks indicative of some residual triethylamine and solvent impurities were also present].

6,9-Bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]benzo[*g*]quinoline-5,10-dione Dimaleate salt.

The crude base was dissolved in a minimum amount of 50% chloroform/50% methanol and a solution of maleic acid (0.084 g, 0.72 mmole) in methanol (2 ml) was added. The addition of ether led to the separation of the dimaleate salt which was collected by filtration, 0.10 g (31%), mp 170-172°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.80 (t, 1H), 10.68 (t, 1H), 9.00 (m, 1H), 8.75 (br, 2H), 8.53 (d, 1H), 7.84 (m, 1H), 7.45 (s, 2H), 6.08 (s, 4H), 5.37 (br s, 2H), 3.89 (m, 4H), 3.76 (m, 4H), 3.42 (m, 4H), 3.10 (m, 4H).

Anal. Calcd. for $C_{21}H_{27}N_5O_4 \cdot 2C_4H_4O_4$: C, 53.95; H, 5.48; N, 10.84. Found: C, 53.60; H, 5.81; N, 10.44.

6,9-Bis[(2-*N*-*tert*-Butoxycarbonylaminoethyl)amino]-benzo[*g*]quinoline-5,10-dione (**2e**).

A. Pyridine as solvent at Room Temperature.

A mixture of **3b** (100 mg, 0.41 mmole) and *N*-(*tert*-Butoxycarbonyl)ethylenediamine (640 mg, 4.0 mmoles) in pyridine (4 ml) was stirred at room temperature for 187 hours. The pyridine was removed under a slow stream of nitrogen and water was added to the residual material. The crude blue solid was collected by filtration, 205 mg (95%). Chromatography over silica gel with the eluant 2% methanol/98% chloroform led to small amounts of the magenta colored mono substituted regioisomers. Elution with 5% methanol/95% chloroform gave blue **2e**, 110 mg (52%), mp 217-219°; ^{1}H nmr (deuteriochloroform): δ 11.24 (br t, 1H, exchangeable with deuterium oxide),

10.88 (br t, 1H, exchangeable with deuterium oxide), 9.04 (dd, 1H), 8.59 (d, 1H), 7.62 (dd, 1H), 7.34 (m, 2H), 5.22 (br m, 1H), 5.14 (br m, 1H, exchangeable with deuterium oxide), 3.60 (m, 4H), 3.47 (m, 4H), 1.48 (s, 9H), 1.46 (s, 9H).

Anal. Calcd. for $C_{27}H_{35}N_5O_6$: C, 61.70; H, 6.73; N, 13.32. Found: C, 61.52; H, 6.28; N, 13.02.

B. Pyridine as Solvent at 50-60°.

Under a nitrogen atmosphere a magnetically stirred mixture of **3b** (1.16 g, 4.73 mmoles) and *N*-(*tert*-butoxycarbonyl)ethylenediamine (5.77g, 36.0 mmoles) in dry pyridine (20 ml) was heated at 50° (external bath temperature) for 3.5 hours. The resulting thick suspension was diluted with dry pyridine (20 ml) and heated at 60° for an additional 2 hours. The reaction mixture was then partitioned between dichloromethane (200 ml) and 1.4 *M* sodium dihydrogen phosphate (300 ml). The organic phase was rapidly washed with 1.3 *N* hydrochloric acid (275 ml), then with 0.02 *N* hydrochloric acid (100 ml) and finally with a 0.04 *N* sodium bicarbonate solution. The extracts were dried over sodium sulfate, concentrated to dryness and the crude solid was purified by column chromatography over silica gel (230-400 mesh). The **2e** eluted with 2% methanol in chloroform (stabilized with 2% ethanol). Further purification was accomplished by a second column chromatography using dichloromethane: ethyl acetate: methanol mixture from 90:10:0 to 70:15:15 as eluants. The product **2e** was obtained as a blue solid, 1.62g (62%).

C. Dimethylsulfoxide as Solvent.

A mixture of **3b** (50 mg, 0.20 mmole) and *N*-(*tert*-butoxycarbony)ethylenediamine (320 mg, 2.0 mmoles) in dimethyl sulfoxide (1 ml) was stirred at room temperature for 88 hours. The mixture was quenched into water (100 ml) and the product collected by filtration, 85 mg. Pure **2e**, 55 mg (52%) was isolated by chromatography following the procedure described above using pyridine as the solvent.

6,9-Difluorobenzo[*g*]quinoline-5,10-dione (**3b**).

Run 1.

The keto acid mixture of **6a** and **6b** (0.40 g, 1.5 mmoles) in fuming sulfuric acid (1 ml, 30% sulfur trioxide) was heated in an oil bath at 155-165° for 6 hours. After cooling to room temperature, the mixture was poured over ice (50 ml) and then neutralized with solid sodium bicarbonate. Repeated extractions with methylene chloride and recrystallization from a mixture of chloroform and ligroine led to **3b** as yellow needles, 0.102 g (28%), mp 251-252°; ^{1}H nmr (deuteriochloroform): δ 9.13 (dd, 1H), 8.61 (dd, 1H), 7.75 (m, 1H), 7.54 (m, 2H).

Anal. Calcd. for $C_{13}H_5F_2NO_2$: C, 63.68; H, 2.06; N, 5.71. Found: C, 63.58; H, 1.98; N, 5.48.

Run 2.

A mixture of **6a** and **6b** (2.0 g, 7.5 mmoles) in fuming sulfuric acid (3 ml, 20% sulfur trioxide)was heated to 160°and then four portions (0.5 ml each)of fuming sulfuric acid were added at 25 minute intervals. At the end of the additions, the mixture was heated at 160° for an additional 30 minutes. A tlc analysis (silica gel; eluant of ethyl acetate/acetic acid 10/2) of a reaction aliquot which was quenched by a saturated solution of sodium dihydrogen phosphate and extracted with tetrahydrofuran indicated no starting material. While the mixture was still warm (about 80°, a temperature at which the mixture was still fluid) it was added slowly with stirring to a saturated solution of sodium dihydrogen phosphate (100 ml) which was being cooled in an ice bath. After stirring for 30 minutes the mixture was extracted with tetrahydrofuran (3 x 50 ml), the combined THF extracts were concentrated to yield crude **3b**, 1.3 g (70%). Purification was accomplished by dissolving crude **3b** in ethyl acetate/chloroform/triethylamine (3/1/0.1, 600 ml) and filtering through a silica gel column (70-230 mesh) and eluting with this solvent mixture. Upon removal of the eluants, the residue was taken up in hexane and filtered to yield **3b**.

Pyridine 2,3-DicarboxylicAnhydride (**5**).

A mixture of pyridine 2,3-dicarboxylic acid (10.0 g, 0.06 mole) and acetic anhydride (25 ml) was heated under reflux for 2 hours. Upon cooling to room temperature, carbon tetrachloride (50 ml) was added and the anhydride **5** was collected by filtration, 6.65 g (75%), mp 134-136°, lit [18] mp 134-135°; ^{1}H nmr (deuteriochloroform): δ 9.20 (d, 1H), 8.39 (m, 1H), 7.84 (m, 1H).

2-(2,5-Difluorobenzoyl)nicotinic Acid (**6a**) and 3-(2,5-Difluorobenzoyl)picolinic Acid (**6b**).

A mixture of **5** (2.4 g, 0.016 moles), aluminum chloride (8.4 g, 0.063 mole) and 1,4-difluorobenzene (35 ml) was heated in an oil bath at 110° for 22 hours. The excess 1,4-difluorobenzene was recovered by distillation of the reaction mixture. The residue was cooled by an ice bath and carefully quenched with hydrochloric acid (40 ml, 1 *N*). The product mixture was collected by filtration and air dried to yield an off-white solid, 4.1 g (98%). Recrystallization from methanol-chloroform led to the regioisomeric mixture of **6a** and **6b**, mp 159-163°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.50 (m), 8.45 (d), 8.05 (d), 7.75 (m), 7.60 (m).

Anal. Calcd. for $C_{13}H_7F_2NO_3$: C, 59.32; H, 2.66; N, 5.32. Found: C, 58.90; H, 2.34; N, 5.34.

6,9-Bis[(2-hydroxyethyl)amino]benzo[*g*]quinoline-5,10-dione (**8a**).

A solution of **3b** (0.125 g, 0.51 mmole) and ethanolamine (0.31 g, 5.10 mmoles) in pyridine (2.0 ml) was stirred at room temperature for 72 hours. The pyridine was removed under a slow stream of nitrogen and the residue quenched with water. The product **8a** was collected by filtration, 0.130 g (80%). Recrystallization from methanol gave a beautiful blue solid, mp 233-234°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.21 (br m, 1H), 11.03 (br m, 1H), 9.00 (dd, 1H), 8.60 (m, 1H), 7.78 (m, 1H), 7.55 (br s, 2H), 5.01 (t, 2H), 3.71 (m, 4H), 3.57 (m, 4H).

Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.25; N, 12.83. Found: C, 62.09; H, 5.04; N, 12.54.

6,9-Bis[(2-methanesulfonyloxyethyl)amino]benzo[*g*]quinoline-5,10-dione (**8b**).

Methanesulfonyl chloride (0.62 g, 5.4 mmoles) was added to a solution of **8a** (0.355 g, 1.1 mmoles) in pyridine (3.0 ml).

After stirring for 30 minutes, the reaction mixture was poured into ice water (20 ml) and **8b** was collected by filtration. Recrystallization from a chloroform/ligroin mixture yielded **8b** as a blue solid, 0.275 g (52%), mp 83-84°; ^{1}H nmr (deuteriochloroform): δ 11.05 (br m, 1H), 10.80 (br m, 1H), 9.04 (m, 1H), 8.64 (m, 1H), 7.64 (m, 1H), 7.29 (br s, 2H), 4.48 (m, 4H), 3.82 (m, 4H), 3.11 (s, 3H), 3.09 (s, 3H).

Anal. Calcd. for $C_{19}H_{21}N_3O_8S_2$: C, 47.20; H, 4.39; N, 8.69. Found: C, 46.91; H, 3.99; N, 8.33.

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