Synthesis of Novel Cyclic Sulfone Dihydropyridines Facilitated by a Selective Ethyl Diazoacetate Ring Expansion

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A series of novel cyclic sulfone dihydropyridines with five to nine membered rings have been synthesized. Anomalous intermediates isolated from the Hantzch condensation were found to vary depending on the sulfone ring size and aromatic substitution. Tin tetrachloride has been shown to be a superior Lewis acid catalyst for ethyl diazoacetate ring expansion of the requesite β-keto cyclic sulfone precursors.

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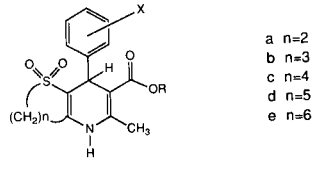
Introduction.

The utility of 4-aryl-1,4-dihydropyridines as therapeutic agents for angina and hypertension is well known [1]. The structural variations explored in this class are extensive, with most compounds being claimed as calcium antagonists with cardiovascular applications. Reviews on the general structure activity relationship of dihydropyridines suggest that ester moieties are the most potent substitution for the 3,5 position [2]. It is also generally accepted that branched chain alkanes increase receptor affinity over simple methyl and ethyl esters. We felt that a sulfone moiety tied back to the dihydropyridine ring could mimick a bulky ester moiety. We wish to report the synthesis and anomalous chemistry which occurred while making the novel cyclic sulfone dihydropyridines shown in structure **1**.

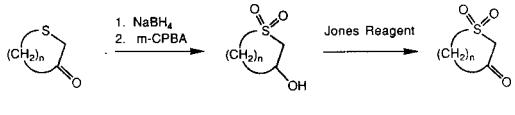


a n=2
b n=3
c n=4
d n=5
e n=6

1

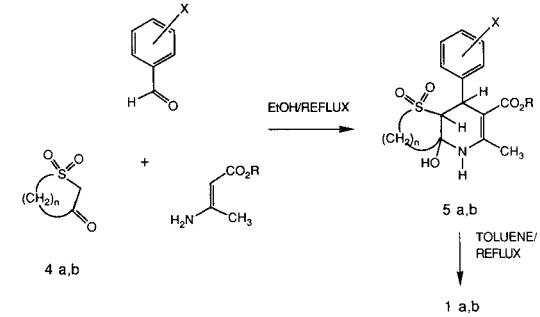
Results and Discussion.

The synthetically most accessible members of this series were the five and six membered sulfones (n = 2,3). To synthesize the five membered compound commercially available tetrahydrothiophen-3-one (**2a**) was reduced with sodium borohydride followed by oxidation with *m*-chloroperoxybenzoic acid to give tetrahydrothiophen-3-ol 1,1-dioxide (**3a**). This was oxidized with Jones reagent to give the five membered β-keto sulfone **4a** necessary for Hantzch condensation. This rather circuitous route was necessary since direct oxidation of tetrahydrothiophen-3-one to the β-keto sulfone using hydrogen peroxide or *m*-chloroperoxybenzoic acid met with no success.



2 a,b 3 a,b 4 a,b

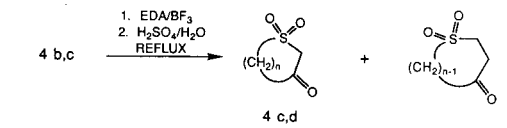
By reacting the five membered β-keto cyclic sulfone, methyl 3-aminocrotonate and a substituted benzaldehyde we initially obtained products which had failed to dehydrate. This Hantzch condensation intermediate, **5a** was somewhat difficult to identify because the hydrogens at positions 3 and 4 showed no coupling in the nmr spectrum and the parent peak was not observed in the EI mass spectrum. The desired dihydropyridine **1a** was obtained by refluxing **5a** in toluene.



4 a,b 5 a,b 1 a,b

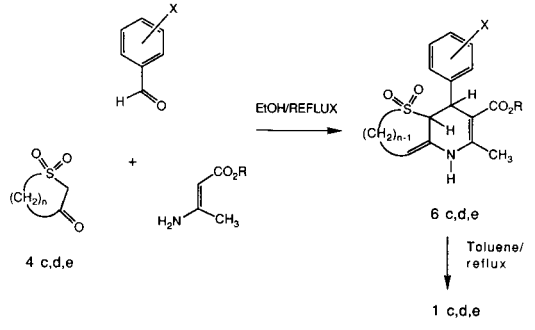
Although Fehnel reported a direct oxidation of **2b** to **4b** [3] the same three step procedure employed in the five membered series was used since the direct oxidation was difficult to reproduce. Hantzch condensation in this series led directly to the desired dihydropyridines **1** (n = 3) except in the case where X = 2-NO_2. This particular compound gave under usual refluxing ethanol conditions a 1:1 mixture of the desired dihydropyridine **1b** and the hydroxy substituted precursor **5b**. Dehydration of this intermediate required heating in dry dimethyl sulfoxide or heating in ethanol containing hydrochloric acid.

Synthesis of the seven membered β-keto sulfone was accomplished by using the procedure of Eistert [4]. Ring expansion of **4b** with ethyl diazoacetate and boron trifluoride followed by hydrolysis and decarboxylation gave a 2:1 mixture of 3-keto and 4-keto seven membered cyclic sulfone. Chromatographic separation afforded the 3-keto isomer suitable for use in the Hantzch condensation.



4 c,d

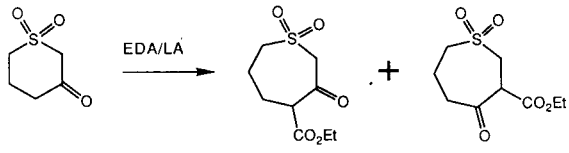
The Hantzch condensation was uneventful except in the case of bulky *ortho* substituted phenyl groups such as X = 2-nitro, 2-trifluoromethyl and 2,3-dichloro. Rather than obtaining the conventional 1,4-dihydropyridine we found that the double bond was endo to the sulfone ring as in structure **6c**. Heating in toluene at reflux isomerized these compounds to the apparently more themodynamically stable 1,4-dihydropyridine **1c**.



Ring expansion followed by hydrolysis and decarboxylation of **4c** proceeded in a fashion identical to the ring expansion of **4b** affording a 2:1 mixture of the 3-keto and 4-keto eight membered sulfone. This mixture again required chromatography to separate the regioisomers. During Hantzch condensation we found formation of **6d** in the eight membered series to be even more prominent than in the seven membered series. In all cases it was necessary to reflux the product in toluene to obtain the desired regioisomer **1d**.

Although we carried out one more expansion to obtain the nine membered sulfone it was apparent that a linear synthesis which contained steps that gave an appreciable amount of the undesirable regioisomer would severely limit the number of analogs and the quantity of material that could be prepared. For this reason we synthesized only one nine membered sulfone dihydropyridine where X = 3-NO_2. This reaction formed the desired target **1e** under similar Hantzch conditions necessary in the eight membered series.

Since the most biologically interesting compounds in this series were the seven, eight and nine membered cyclic sulfone dihydropyridines it was critical to our program to improve the yield and selectivity of the ring expansion. Work by Warnhoff [5] had demonstrated that ketones with electron withdrawing groups in the *alpha* position resulted in selective ring expansion away from the electron withdrawing substituent. They found that the reaction with ethyl diazoacetate and boron trifluoride proceeded very slow and excess reagent and catalyst in addition to refluxing the reaction mixture was necessary to effect the expansion in 1-2 days. In the case of cyclic beta sulfones Eistert had found preference for expansion away from the electron withdrawing sulfone moiety. Since this reaction with boron trifluoride was completed in less than one hour we felt a milder Lewis acid catalyst could give better selectivity and still achieve practical reaction times. Table 1 shows the selectivity and reaction times for various catalysts. We



LEWIS ACID	Ratio of isomers [a] 3-keto	4-keto	Rx time
BF_3	65 (67) [4]	35 (33)	2 hrs. (48hr)
$ZnCl_2$	100	0	> 3 days
SbF_5	60	40	< 1 hr.
$SnCl_4$	99	trace [b]	3-4 hrs.

Table 1

[a] Product ratios were determined by the ratio of isolated yields of each isomer after decarboxylation was carried out. [b] Small quantities of the 4-keto isomer were detected in mother liquors which had large quantities of the 3-keto isomer removed.

found tin tetrachloride to be extremely selective and to proceed at a rate which allowed the reaction and workup to be completed in one day. Elimination of the chromatography necessary for separation of the isomers allowed large scale synthesis of the desired medium ring cyclic sulfones.

Summary.

We have synthesized a series of novel dihydropyridines containing a cyclic sulfone with five to nine membered rings. Synthesis of the required seven, eight or nine membered β-keto sulfone was found to be facilitated by use of an extremely selective ring expansion reaction.

EXPERIMENTAL

Melting points were determined on a Meltemp Melting Point apparatus and are uncorrected. Proton nmr spectra were recorded on a Varian XL 400, General Electric QE 300 or Bruker WP100SY spectrometer. All ^1H nmr were run in DMSO-d_6 unless otherwise noted. Mass spectra were recorded on a Finnigan 8230 spectrometer in the DCI mode using isobutane as the ionizing gas. Infrared spectra were recorded on a Nicolet 5DXB FT-IR spectrophotometer. Elemental analysis was recorded on a Perkin Elmer 2400 CHN elemental analyzer. Chromatography was carried out using Merck 9385 (230-400 mesh) silica gel.

General Procedure for Three Step Conversion of **2a,b** into **4a,b**.

Tetrahydrothiopyran-3-one 1,1-Dioxide (**4b**).

To a solution of tetrahydrothiopyran-3-one (**2b**) (10.0 g, 81.6 mmoles) in 100 ml of absolute ethanol was added sodium borohydride (3.25 g, 8.6 mmoles) over a five minute period. After stirring for 30 minutes, a 1.0*N* solution of hydrochloric acid was added until *p*H 5 was achieved. The reaction mixture was diluted with water and extracted with dichloromethane (6 x 50 ml). The organic phase was dried over magnesium sulfate, filtered, concentrated *in vacuo* and distilled (100 mm Hg, 158°) to give 6.8 g of tetrahydrothiopyran-3-ol.

A solution of tetrahydrothiopyran-3-ol (6.8 g, 0.058 mole) and chloroform (250 ml) was cooled to 0° and treated with *m*-chloroperoxybenzoic acid (23.4 g, 0.135 mole) at a rate which would not cause the temperature to rise above 10°. After addition was complete, the thickened mixture was stirred at 0° for 1 hour and then at room temperature for 30 minutes. The resulting solid was removed by filtration and the filtrate evaporated *in vacuo* to remove remaining chloroform. The resulting solid was diluted with water (150 ml) and filtered. The filtrate was evaporated *in vacuo* and residual water was removed by repeated evaporation with toluene. This afforded 7.5 g of tetrahydrothiopyran-3-ol 1,1-dioxide as a colorless oil.

To a solution of tetrahydrothiopyran-3-ol 1,1-dioxide (**3b**) (7.5 g, 0.05 mole) and acetone (150 ml) was slowly added enough Jones reagent to maintain a brown color for at least 10 minutes without need for additional reagent. The excess reagent was reduced by addition of 2-propanol (5 ml). The mixture was filtered through Celite and the chromium salts were washed 3x with acetone. The solvent was removed *in vacuo* to give a solid which was triturated with ethanol. The resulting crystals were isolated by filtration and rinsed 3x with diethyl ether. After drying, 5.0 g of product was obtained identical to material obtained by the method of Fehnel.

General Procedure for the Synthesis of **1a**.

Methyl 2,3,3a,4,7,7a-Hexahydro-3a-hydroxy-5-methyl-7-(2-nitrophenyl)-1,1-dioxothieno[3,2-*b*]pyridine-6-carboxylate (**5a**) (R = CH_3, n = 2, X = NO_2).

A solution of tetrahydrothiophene-3-oxo 1,1-dioxide (**4a**) (1.3 g, 10.0 mmoles), 2-nitrobenzaldehyde (1.5 g, 10.0 mmoles) in ethanol (20 ml) was stirred overnight. The resulting crystals were isolated by filtration and washed 2x with ethanol and 2x with diethyl ether. After drying under high vacuum for 24 hours 2.54 g of product was obtained, mp 175-179° dec; ^{1}H nmr: δ 2.27 (s, 3H), 1.8-3.2 (m, 4H), 3.26 (s, 3H), 3.49 (s, 1H), 4.64 (s, 1H), 6.10 (s, 1H), 7.2-8.1 (m, 5H); ir: (potassium bromide): 3510, 3395, 3015, 2960, 1690, 1625, 1530 cm^{-1}; ms: 383 (MH^+).

Anal. Calcd. for $C_{16}H_{18}N_2O_7S$: C, 50.26; H, 4.74; N, 7.33. Found: C, 49.95; H, 4.91; N, 7.26.

Methyl 2,3,4,5-Tetrahydro-5-methyl-7-(2-nitrophenyl)-1,1-dioxothieno[3,2-*b*]pyridine-6-carboxylate (**1a**) (R = CH_3, n = 2, X = 2-NO_2).

A mixture of methyl 2,3,3a,4,7,7a-hexahydro-3a-hydroxy-5-methyl-7-(2-nitrophenyl)-1,1-dioxothieno[3,2-*b*]pyridine-6-carboxylate (**5a**) (2.5 g, 6.5 mmoles) and toluene (60 ml) was refluxed for 24 hours. The solvent was removed *in vacuo* and the resulting solid was filtered and dried at 65° under high vacuum for 48 hours. This gave 1.78 g product; mp 215-217°; ^{1}H nmr: δ 2.16 (s, 3H), 2.7-3.4 (m, 4H), 3.4 (s, 3H), 5.57 (s, 1H), 7.1-7.9 (m, 4H), 9.35 (s, 1H); ir: (potassium bromide): 3325, 1710, 1690, 1500 cm^{-1}; ms: 365 (MH^+).

Anal. Calcd. for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 52.66; H, 4.55; N, 7.63.

General Procedure for the Synthesis of **1b**.

Methyl 3,4,5,8-Tetrahydro-6-methyl-8-(3-nitrophenyl)-1,1-dioxo-2*H*-thiopyrano[3,2-*b*]pyridine-7-carboxylate (**1b**) (R = CH_3, n = 3, X = 3-NO_2).

A mixture of tetrahydrothiopyran-3-one 1,1-dioxide (**4b**) (0.83 g, 5.6 mmoles), 3-nitrobenzaldehyde (0.846 g, 0.0056 moles) and methyl 3-aminocrotonate (0.70 g, 5.6 mmoles in methanol (20 ml) was refluxed for 16 hours. After cooling, the resulting solid was isolated by filtration and washed with diethyl ether. This solid was dried at 40° for 4 hours under vacuum to give 0.620 g product; mp 236-238°; ^{1}H nmr: 1.9-2.9 (m, 4H), 2.31 (s, 3H), 2.9-3.4 (m, 2H), 3.58 (s, 3H), 5.10 (s, 1H), 7.2-8.2 (m, 4H), 9.12 (s, 1H); ir (potassium bromide): 3300, 1705, 1655, 1575 cm^{-1}; ms: 379 (MH^+).

Anal. Calcd. for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.40. Found: C, 53.66; H, 4.59; N, 7.43.

General Procedure for the Tin Tetrachloride Catalyzed Ring Expansion of *beta* Keto Sulfones **4b,c,d** to **4c,d,e**.

Thiacycloheptan-3-one 1,1-dioxide (**4c**).

To a mechanically stirred solution of dry diethyl ether (250 ml) under nitrogen cooled to 0° was slowly added tin tetrachloride (48.8 ml, 0.415 mole). After the exotherm had ceased and a white precipitate had formed tetrahydrothiopyran-3-one 1,1-dioxide **4b** (43.2 g, 0.292 mole) was added in one portion. Ethyl diazoacetate (100 g, 0.877 mole) was diluted with 50 ml of diethyl ether and added dropwise over a 90 minute period. Most of the nitrogen evolution was completed within 4 hours but the reaction was allowed to stir overnight. The ether was removed by evaporation at room temperature to afford a brown viscous residue. To this mechanically stirred oil was added methylene chloride (200 ml) followed by slow addition of saturated aqueous tartartic acid. The saturated tartaric acid solution was added until the exothermic reaction ends and two layers were formed. The methylene chloride layer (which in this case is the upper layer) is isolated and the remaining aqueous layer was extracted 2x with methylene chloride (50 ml). The combined organic extracts were washed once with distilled water (50 ml) and dried over magnesium sulfate and evaporated *in vacuo*. The resulting light yellow oil was distilled (0.5 torr, 35°) to remove ethyl ethoxyacetate which is a biproduct of the reaction. The remaining residue was recrystallized using absolute ethanol affording 20.5 g of ethyl thiacyclohepten-3-one-4-carboxylate 1,1-dioxide. The remaining mother liquor was chromatographed on silica gel with 1:1:1 ethyl acetate/hexane/dichloromethane to afford an additional 12.5 g of ester.

The 33 g of ester was heated to reflux with 100 ml of 10% of sulfuric acid in a 1:1 mixture of water and methanol for 16 hours. After cooling to room temperature the reaction was diluted with 100 ml of water and extracted with methylene chloride (4 x 50 ml). The organic phases were dried with magnesium sulfate, filtered and concentrated *in vacuo*. The resulting solid was triturated with ether and filtered to give 21.0 g of **4d** (45% yield) identical to material obtained by the method of Eistert.

General Procedure for the Synthesis of **1c** Where X is Not a Bulky *ortho* substitutent.

Ethyl 2,3,4,5,6,9-Hexahydro-7-methyl-9-(3-nitrophenyl)-1,1-dioxothiacycloheptenо[3,2-*b*]pyridine-7-carboxylate (**1c**) (R = CH_2CH_3, n = 4, X = 3-NO_2).

A mixture of thiacycloheptan-3-one 1,1-dioxide (**4c**) (1.3 g, 8.0 mmoles) 3-nitrobenzaldehyde (1.2 g, 8.0 mmoles) and ethyl 3-aminocrotonate (1.0 g, 8.0 mmoles) in 20 ml absolute ethanol was refluxed overnight. After evaporation of the solvent *in vacuo* the crude reaction mixture was chromatographed on 250 g silica gel using a 4:1 mixture of ethyl acetate/hexane. The enriched fractions were combined to give 1.5 g of product; mp 211-213°; ^{1}H nmr: δ 1.23 (t, J = 7.4 Hz, 3H), 1.4-2.4 (m, 4H), 2.38 (s, 3H), 2.5-3.2 (m, 4H), 4.08 (q, J = 7.4 Hz, 2H), 4.06 (s, 1H), 5.15 (s, 1H), 7.5-8.2 (m, 4H); ir (potassium bromide): 3390, 2950, 1690, 1570 cm^{-1}; ms: 393 (MH^+).

Anal. Calcd. for $C_{19}H_{22}N_2O_6S$: C, 56.15; H, 5.46; N, 6.89. Found: C, 55.79; H, 5.56; N, 6.70.

General Procedure for the Synthesis of **1c** where X is a Bulky *ortho* Substituent.

Methyl 2,3,4,5,9,9a-Hexahydro-7-methyl-9-(2-nitrophenyl)-1,1-dioxothiacycloheptenо[3,2-*b*]pyridine-8-carboxylate (**6c**) (R = CH_3, n = 3, X = 2-NO_2).

A solution of thiacycloheptan-3-one 1,1-dioxide (**4c**) (0.45 g, 2.8 mmoles), 2-nitrobenzaldehyde (0.42 g, 2.8 mmoles) and methyl 3-aminocrotonate (0.32 g, 2.8 mmoles) was refluxed in 40 ml of methanol overnight. After cooling, the solid was isolated by filtration and washed with ether and dried under high vacuum overnight resulting in 407 mg of product, mp 208-210°; ^{1}H nmr: 400 MHz δ 1.8-2.6 (m, 5H), 2.31 (s, 3H), 3.31 (s, 3H), 3.56 (t, J = 9.7 Hz, 1H), 4.84 (d, J = 0.8 Hz, 1H), 5.20 (d, J = 0.8 Hz, 1H), 5.67 (t, J = 5.8 Hz, 1H), 7.12 (d, J = 6.2 Hz, 1H), 7.43 (t, J = 6.2 Hz, 1H), 7.59 (t, J = 6.2 Hz, 1H), 7.83 (d, J = 6.2 Hz, 1H), 9.30 (s, 1H); ^{13}C nmr: δ 19.5, 22.8, 28.3, 28.8, 50.1, 58.9, 59.1, 93.3, 111.7, 123.6, 127.7, 128.6, 130.7, 133.4, 138.2, 148.6, 149.6, 166.0; ir (potassium bromide): 3370, 1685, 1595, 1560 cm^{-1}; ms: 393 (MH^+).

Anal. Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 55.06; H, 5.34; N, 7.05.

Methyl 2,3,4,5,6,9-Hexahydro-7-methyl-9-(2-nitrophenyl)-1,1-dioxothiacycloheptenо[3,2-*b*]pyridine-8-carboxylate (**1c**) (R = CH_3, n = 3, X = 2-NO_2).

A mixture of **6c** (0.390 g, 1.0 mmoles) and 20 ml of toluene was refluxed for 5 hours. After cooling a crystalline solid formed and was isolated by filtration affording 210 mg of product, mp 211-213°; ^{1}H nmr: δ 1.4-2.2 (m, 4H), 2.21 (s, 3H), 2.5-3.1 (m, 4H), 3.44 (s, 3H), 5.69 (s, 1H), 7.2-7.8 (m, 4H), 9.10 (s, 1H); ^{13}C nmr: δ 18.1, 23.4, 25.1, 30.3, 33.7, 50.6, 56.1, 101.7, 124.0, 127.7, 130.9, 133.3, 140.8, 146.0, 147.0, 148.1, 166.5; ir (potassium bromide): 3290, 1695, 1640, 1535, 1480 cm^{-1}; ms: 393 (MH^+).

Anal. Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 55.14; H, 5.04; N, 7.11.

General Procedure for Synthesis of **1d,e**.

Ethyl 3,4,5,6,10-Hexahydro-8-methyl-10-(3-nitrophenyl)-1,1-dioxo-2*H*-thiacycloocteno[3,2-*b*]pyridine-9-carboxylate (**6d**) (R = Et, n = 4, X = 3-NO_2).

A solution of thiacyclooctan-3-one 1,1-dioxide (**4d**) (0.35 g, 2.0 mmoles), 3-nitrobenzaldehyde (0.30 g, 2.0 mmoles) and ethyl 3-aminocrotonate (0.26 g, 2.0 mmoles) was refluxed in 30 ml of ethanol overnight. After cooling a yellow solid was obtained which was isolated by filtration and washed with ether and dried under vaccum overnight resulting in 556 mg of product, mp 211-214°; ^{1}H nmr: δ 1.02 (t, J = 7.2 Hz, 3H), 1.3-2.6 (m, 6H), 2.30 (s, 3H), 3.1-3.4 (m, 1H), 3.25 (s, 1H), 3.91 (q, J = 7.2 Hz, 2H), 4.54 (s, 1H), 4.83 (s, 1H), 5.23 (t, J = 8.6 Hz, 1H), 7.4-8.3 (m, 4H), 9.12 (s, 1H); ir (potassium bromide): 3340, 1605, 1522 cm^{-1}; ms: 421 (MH^+).

Anal. Calcd. for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 57.17; H, 5.85; N, 6.62.

Ethyl 3,4,5,7,10,10a-Hexahydro-8-methyl-10-(3-nitrophenyl)-1,1-dioxo-2*H*-thiacycloocteno[3,2-*b*]pyridine-9-carboxylate (**1d**) (R = Et, n = 4), X = 3-NO_2).

A mixture of **6d** and 20 ml of toluene was refluxed for 24 hours. After removal of the solvent *in vacuo* the residue was triturated with ethanol and filtered to give 357 mg of product, mp 234-235°; ^{1}H nmr: δ 1.14 (t, J = 7.0 Hz, 3H), 1.1-1.2 (m, 6H), 2.36 (s, 3H), 2.6-3.4 (m, 4H), 4.11 (q, J = 7.0 Hz, 2H), 5.08 (s, 1H), 7.5-8.3 (m, 4H), 9.24 (s, 1H); ir (potassium bromide): 3330, 1713, 1521, 1499 cm^{-1}; ms: 421 (MH^+).

Anal. Calcd. for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.68. Found: C, 57.47; H, 5.91; N, 6.57.

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