Synthesis of a New Pyrrolo[1,3]diazepine: 4*H*-Pyrrolo[1,2-*a*]thieno[2,3-*e*][1,3]diazepine

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The 4*H*-pyrrolo[1,2-*a*]thieno[2,3-*e*][1,3]diazepine (**20**) was synthesized by the one-pot intramolecular cyclization of the appropriate nitroaldehyde **13**. This key intermediate **13** was obtained by two pathways from methyl 3-bromomethylthiophene-2-carboxylate (**6**).

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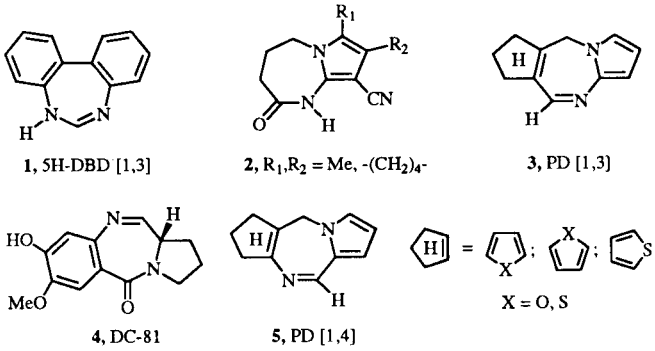
Benzo[1,3]diazepines, as compound **1** [1] or pyrrolo-[1,3]diazepines, such as compound **2** [2] are little explored in the literature and to our knowledge no structure with the pyrrolothieno[1,3]diazepine moiety as in structure **3** is reported in contrast to the well known benzo[1,4]diazepines. Derivatives of benzo[1,4]diazepines annelated to a heterocyclic ring have remarkable tranquilizing, hypnotic, and central nervous system (CNS) activities like the DC-81 **4** [3]. This latter belongs to a novel antibiotic-antitumor class. Just now, no biological activity concerning benzo[1,3]diazepines has been mentioned so it appears interesting to study and to evaluate the pyrrolo[1,3]diazepine system.

Scheme I



In connection with our studies on nitrogen and sulfur or oxygen heterocyclic systems [4a-f] structurally related to antibiotics possessing antitumor activity, we were interested in the synthesis of the first thienopyrrolo[1,3]-diazepine **20** analogue to the thieno(or furo)pyrrolo-[1,4]diazepine **5** described by us in previous publications [4a-f]. Our strategy consisted of the synthesis the nitroaldehyde **13** which is the key intermediate by two pathways, as it is shown in Scheme II.

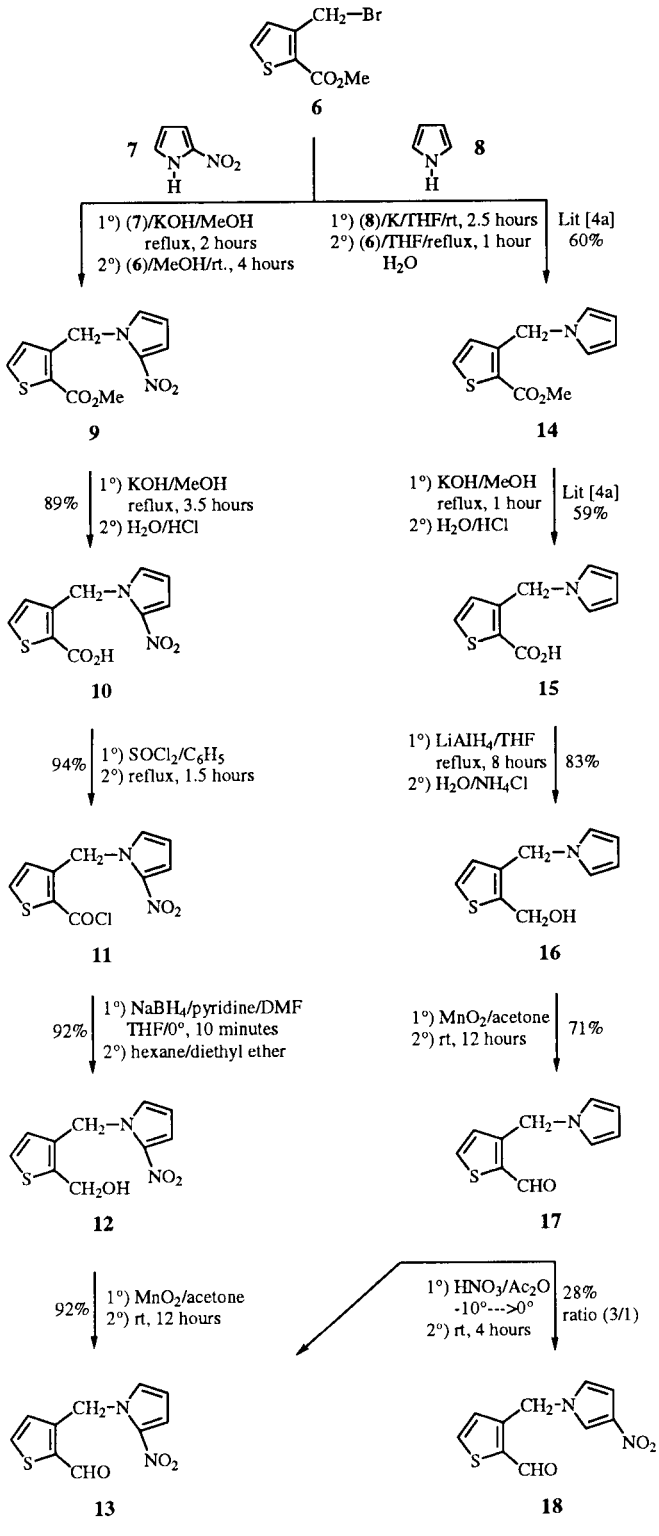
In fact, the methyl 3-bromomethylthiophene-2-carboxylate (**6**) [5] treated with the potassium salt of 2-nitropyrrole (**7**) [6] in anhydrous methanol at room temperature for 4 hours furnished the nitroester **9** in high yield (88%). An alkaline hydrolysis of **9** under reflux in methanol followed by acidic treatment afforded the 3-(2-nitropyrrol-1-ylmethyl)thiophene-2-carboxylic acid (**10**) in 89% yield. This compound was then transformed into the acid chloride **11** quantitatively by reaction with freshly distilled thionyl chloride in a large quantity of benzene as the solvent. In the absence of solvent under stoechiometric conditions or in the presence of a large excess of thionyl chloride, the carboxylic acid **10** did not give the acid chloride **11** and the starting material was generally not recovered.

A selective reduction of the nitroacid chloride compound **11** to the corresponding nitroalcohol **12** was accomplished in high yield (92%) by using sodium borohydride in *N,N*-dimethylformamide solution containing tetrahydrofuran and a molar excess of pyridine as a borane scavenger. This result, is in contrast to these reported by Babler [7], since both aromatic and aliphatic acid chlorides lead exclusively to the corresponding aldehydes not contaminated with alcohols under the same conditions. In our case, no trace of the nitroaldehyde **13** was detected. Therefore, compound **13** was obtained easily by oxidation of the nitroalcohol **12** with activated manganese dioxide [8] in dry acetone at room temperature for 12 hours.

Another method for the preparation of the key product **13** started from carboxylic acid **15** previously reported by us [4a]. Thus, lithium aluminium hydride (LAH) reduction of 3-(1-pyrrolylmethyl)thiophene-2-carboxylic acid (**15**) in anhydrous tetrahydrofuran by refluxing for 8 hours followed by a hydrolysis with an ammonium chloride solution led to the expected alcohol **16** (83%) which was oxidized in a manner similar to that for **12** to the formyl compound **17** in satisfactory yield (71%).

Functionalization of the pyrrole ring of product **17** was accomplished using the nitration reaction by nitric acid in the presence of acetic anhydride at -10° for 4 hours. Under these conditions the nitration occured on the 2- and 3-positions of the pyrrole ring and afforded a mixture of 3-(2-nitro-1-pyrrolylmethyl)thiophene-2-carboxaldehyde (**13**) and 3-(3-nitro-1-pyrrolylmethyl)thiophene-2-carboxaldehyde (**18**) in a ratio of about 3:1 which was determined by ^{1}H nmr analysis of the crude product. These results are in accordance with those observed during the nitration of the

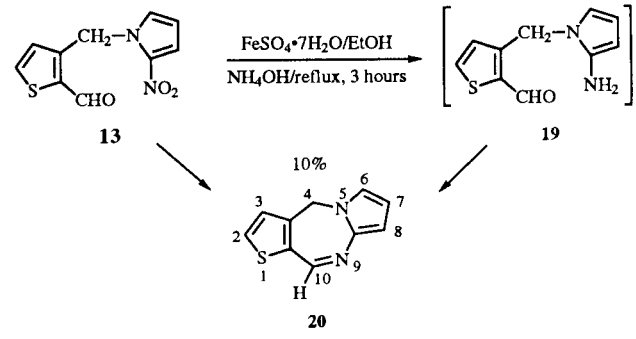
Scheme II



known 1-methylpyrrole [6] and 1-(2- or 3-thienylmethyl)-pyrrole [4a], unfortunately compounds **13** and **18** could not be separated, whatever the conditions (chromatography on florisil or silica gel, or recrystallization).

Finally as it is shown in Scheme III, reduction of the nitro group of the nitroaldehyde **13** was carried out with iron (II) sulfate in aqueous ammonia solution at the boiling point of ethanol for 3 hours.

Scheme III



The expected aminoaldehyde that formed **19** [4f,9] was not isolated, since intramolecular nucleophilic attack of the carbonyl function at the 2-position of the thiophene ring with displacement of water, occurred with the formation of the title tricyclic product **20** in 10% yield associated with considerable resinification. It is also interesting to note that the instability of this diazepine which was decomposed in a few hours and the poor yield obtained in the preparation of this product, could be explained by the high fragility of the 2-aminopyrrole moiety cited in the literature [10] and which is incorporated into the intermediate 3-(2-amino-1-pyrrolylmethyl)thiophene-2-carboxaldehyde (**19**).

Nevertheless, the structure of product **20** was characterized by the imine absorption (CH=N) at 1608 cm^{-1} in the ir spectrum and the signal at δ = 7.94 ppm (CH=N) in the ^1H nmr spectrum. These values are similar to these observed for all the known thieno (or furo)pyrrolo[1,4]-diazepines [4a-f] analogous to the tricyclic system described here. On the other hand, we observe a deshielding of +0.30 ppm of the H_6 and H_8 protons of the pyrrole ring compared to those of the corresponding 4*H*-pyrrolo-[1,2-*a*]thieno[2,3-*e*][1,4]diazepine isomer [4a]. Details of spectroscopic data of this final compound and those of the all intermediates are reported in the experimental.

EXPERIMENTAL

All Melting points were determined by using a Leitz hot plate apparatus and are uncorrected. Infrared spectra were recorded on a Hewlett-packard FT-IR spectrometer. The nuclear magnetic resonance spectra (^1H nmr and ^{13}C nmr) were taken on a Bruker AC-200 (200 MHz) instrument in the solvent indicated (deuteriochloroform or DMSO-d_6). Chemical shifts values are reported in ppm from tetramethylsilane (TMS) as an internal ref-

erence and are given in δ units (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet). Elemental analyses were obtained in the microanalysis laboratory of the Institut National des Sciences Appliquées, place Emile Blondel, 76131 Mont Saint-Aignan cedex, France.

Methyl 3-(2-Nitro-1-pyrrolylmethyl)thiophene-2-carboxylate (**9**).

To a well stirred suspension of methyl 3-bromomethylthiophene-2-carboxylate (**6**) [5] (2.5 g, 10.6 mmoles) dissolved in 30 ml of dry methanol was added dropwise at room temperature a solution of the potassium salt of 2-nitropyrrole (**7**) [prepared from 2-nitropyrrole (**7**) [6] (1.2 g, 10.7 mmoles) and potassium hydroxide (0.6 g, 10.7 mmoles) in 20 ml of dry methanol at reflux for 2 hours]. After 4 hours reaction time at the same temperature, the formed precipitate was collected by filtration and washed with a cold mixture of methanol-water (7/3) to give the desired product **9** in 88% yield (2.48 g). An analytical sample was obtained by recrystallization from a mixture of methanol-water (3/2) and gave white needles, mp 159-160°; ir (potassium bromide): ν cm^{-1} 1708 (C=O), 1530 (NO_2); ^1H nmr (deuteriochloroform): δ ppm 3.81 (s, 3H, CH_3 (methyl ester)), 5.92 (s, 2H, CH_2-N), 6.18 (dd, 1H, H_4-pyrrole), 6.52 (d, 1H, J = 4.93 Hz, H_4-thiophene), 6.90 (t, 1H, H_3-pyrrole), 7.22 (dd, 1H, H_5-pyrrole), 7.39 (d, 1H, J = 4.93 Hz, H_5-thiophene).

Anal. Calcd. for $C_{11}H_{10}N_2O_4S$: C, 49.61; H, 3.78; N, 10.52. Found: C, 49.52; H, 3.76; N, 10.39.

3-(2-Nitro-1-pyrrolylmethyl)thiophene-2-carboxylic Acid (**10**).

A mixture of 2.1 g (7.9 mmoles) of the nitroester **9**, 0.62 g (11 mmoles) of potassium hydroxide pellets in a mixture of 25 ml of methanol and 20 ml of water was refluxed for 3.5 hours. After cooling, the reaction mixture was extracted twice with 25 ml of diethyl ether. The water layer was treated with charcoal, filtered and acidified cautiously with hydrochloric acid (6*N*). The precipitate was removed by filtration, washed twice with 40 ml of cold water and air dried. The desired carboxylic acid **10** (1.77 g, 89%) was obtained after crystallization from a mixture of ethanol-water (1/1) and melted at 190-191°; ir (potassium bromide): ν cm^{-1} 3350-2260 (OH), 1695 (C=O), 1515 (NO_2); ^1H nmr (DMSO-d_6): δ ppm 5.90 (s, 2H, CH_2-N), 6.22 (m, 2H, H_4-thiophene and H_4-pyrrole), 6.30 (broad, 1H, O-H acid), 7.41 (m, 2H, H_5-thiophene and H_3-pyrrole), 7.85 (dd, 1H, H_5-pyrrole).

Anal. Calcd. for $C_{10}H_8N_2O_4S$: C, 47.61; H, 3.19; N, 11.10. Found: C, 47.53; H, 2.97; N, 10.92.

3-(2-Nitro-1-pyrrolylmethyl)thiophene-2-acid Chloride (**11**).

To a well stirred solution of 3 g (11.9 mmoles) of 3-(2-nitro-1-pyrrolylmethyl)thiophene-2-carboxylic acid (**10**) in 120 ml of anhydrous benzene was added cautiously dropwise 1.43 g (12 mmoles) of thionyl chloride dissolved in 80 ml of the same solvent. After 15 minutes at room temperature, the solution was refluxed for 1.5 hours. After cooling, the solvent was evaporated *in vacuo* and the crude acid chloride was purified by recrystallization from ligroin to give the suitable product **11** (3.1 g, 94%), mp 90-91°, ir (potassium bromide): ν cm^{-1} 1707 (C=O), 1520 (NO_2); ^1H nmr (deuteriochloroform): δ ppm 5.76 (s, 2H, CH_2-N), 6.27 (dd, 1H, H_4-pyrrole), 6.49 (d, 1H, J = 5.36 Hz, H_4-thiophene), 6.94 (m, 1H, H_3-pyrrole), 7.26 (dd, 1H, H_5-pyrrole), 7.63 (d, 1H, J = 5.36 Hz, H_5-thiophene).

Anal. Calcd. for $C_{10}H_7ClN_2O_3S$: C, 44.36; H, 2.60; N, 10.35. Found: C, 44.24; H, 2.51; N, 10.22.

3-(2-Nitro-1-pyrrolylmethyl)thiophene-2-methanol (**12**).

To a stirred solution of 0.31 g (8 mmoles) of sodium borohydride and 4 ml of dry pyridine in 8 ml of dry *N,N*-dimethylformamide and 6 ml of anhydrous tetrahydrofuran cooled to approximately 0°, was added rapidly 1.08 g (4 mmoles) of the acid chloride **11** in 5 ml of anhydrous tetrahydrofuran. This mixture was subsequently stirred at the same temperature for 10 minutes before 10 ml of water was added. After another 10 minutes of stirring, 30 ml of a mixture of hexane-diethyl ether (3/2), was introduced quickly into the solution followed by rapid filtration through a small column of silica gel. An additional 40 ml of the same mixture of solvents was used to rinse out the column. The eluates were combined and washed successively with brine, 2*N* aqueous hydrochloric acid, 1*N* aqueous potassium hydroxide and finally water. After drying over anhydrous magnesium sulfate, the organic phase was concentrated *in vacuo* to give pure **12** (0.88 g, 92%) as an oily material, ir (neat); ν cm^{-1} 3340-2960 (OH), 1515 (NO_2); ^1H nmr (deuteriochloroform): δ ppm 3.10 (broad, 1H, OH exchanged with deuterium oxide), 4.78 (s, 2H, CH_2-OH), 5.54 (s, 2H, CH_2-N), 6.13 (dd, 1H, H_4-pyrrole), 6.61 (d, 1H, J = 5.15 Hz, H_4-thiophene), 6.97 (dd, 1H, H_3-pyrrole), 7.05 (d, 1H, J = 5.15 Hz, H_5-thiophene), 7.15 (dd, 1H, H_5-pyrrole). This product was used for the next reaction without further purification.

3-(1-Pyrrolylmethyl)thiophene-2-methanol (**16**).

A solution of 4.14 g (20 mmoles) of 3-(1-pyrrolylmethyl)-thiophene-2-carboxylic acid (**15**) [4a] in 60 ml of anhydrous tetrahydrofuran was dropped into a well stirred suspension of 1.52 g (40 mmoles) of lithium aluminum hydride in 80 ml of the same solvent. After completion of the addition, the mixture was heated at reflux for 8 hours, then cooled to room temperature and treated successively with 100 ml of 4*N* ammonium chloride solution and 50 g of crushed ice. Filtration of the precipitate on celite followed by decantation of the filtrate gave a solution, which was dried on anhydrous sodium sulfate. Removal of the solvant *in vacuo* furnished a crude solid which was recrystallized from a mixture of hexane-ligroin to give the suitable alcohol **16** in 83% yield (3.21 g) as white crystals, mp 58-60°; ir (potassium bromide): ν cm^{-1} 3330-2930 (OH); ^1H nmr (deuteriochloroform): δ ppm 1.82 (broad, 1H, OH exchanged with deuterium oxide), 4.61 (s, 2H, CH_2-OH), 4.96 (s, 2H, CH_2-N), 6.03 (t, 2H, H_3 and H_4-pyrrole), 6.58 (t, 2H, H_2 and H_5-pyrrole), 6.74 (d, 1H, J = 5.18 Hz, H_4-thiophene), 7.05 (d, 1H, J = 5.18 Hz, H_5-thiophene).

Anal. Calcd. for $C_{10}H_{11}NOS$: C, 62.14; H, 5.73; N, 7.25. Found: C, 62.01; H, 5.61; N, 7.19.

3-(1-Pyrrolylmethyl)thiophene-2-carboxaldehyde (**17**).

To a solution of 0.965 g (5 mmoles) of 3-(1-pyrrolylmethyl) thiophene-2-methanol (**16**) in 100 ml of dry acetone was added in 4 portions 6 g of manganese dioxide. The mixture was stirred at room temperature overnight and then filtered. The filtrate was evaporated on a steam bath under reduced pressure to afford pure carboxaldehyde **17** as an oily material in 71% yield (0.678 g); ir (neat): ν cm^{-1} 1695 (C=O); ^1H nmr (deuteriochloroform): δ ppm 5.41 (s, 2H, CH_2-N), 6.29 (dd, 2H, H_3 and H_4-pyrrole), 6.78 (m, 3H, H_2 and H_5-pyrrole, H_4-thiophene), 7.65 (d, 1H, J = 5.12 Hz, H_5-thiophene), 9.71 (s, 1H, CHO).

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.72; N, 7.32. Found: C, 62.48; H, 4.48; N, 7.12.

3-(2-Nitro-1-pyrrolylmethyl)thiophene-2-carboxaldehyde (**13**).

Method A: Oxidization of the Nitroalcohol **12**.

In a similar manner as described for the synthesis of aldehyde **17**, the above nitroalcohol **12** (2.1 g, 8.82 mmoles) with 10 g of manganese dioxide in 150 ml of dry acetone was converted to the corresponding nitroaldehyde **13** (1.42 g, 68%) after 12 hours at room temperature. Recrystallization for analysis from diethyl ether-hexane gave colourless needles with mp 89-102°; ir (potassium bromide): ν cm^{-1} 1685 (C=O), 1525 (NO_2); ^1H nmr (deuteriochloroform): δ ppm 5.86 (s, 2H, CH_2-N), 6.18 (dd, 1H, H_4-pyrrole), 6.65 (d, 1H, J = 4.91 Hz, H_4-thiophene), 6.96 (dd, 1H, H_3-pyrrole), 7.21 (dd, 1H, H_5-pyrrole), 7.58 (d, 1H, J = 4.91 Hz, H_5-thiophene), 9.83 (s, 1H, CHO).

Anal. Calcd. for $C_{10}H_8N_2O_3S$: C, 50.83; H, 3.41; N, 11.86. Found: C, 50.59; H, 3.11; N, 11.46.

Method B: Nitration of the Carboxaldehyde **17**.

A solution of 3-(1-pyrrolylmethyl)thiophene-2-carboxaldehyde (**17**) (1.25 g, 6.54 mmoles) in 10 ml of acetic anhydride was treated with a cold solution of 1 g of 70% nitric acid in 5 ml of acetic anhydride at -10°. After 1 hour at this temperature the mixture was allowed to warm to room temperature for about 3 hours, poured onto crushed ice and extracted with diethyl ether. The organic layer washed with 1*N* potassium hydroxide solution, was treated with charcoal and dried over anhydrous sodium sulfate. After evaporation of the solvent, the solution led to the mixture of the nitroaldehyde **13** (25%) identical with the sample prepared above as described in method A, and the nitroaldehyde **18** (2.8%), the nmr spectra of this minor product was deducted from the one of the mixture; ^1H nmr (deuteriochloroform): δ ppm 5.51 (s, 2H, CH_2-N), 6.23 (m, 1H, H_4-pyrrole), 6.70 (d, 1H, J = 4.98 Hz, H_4-thiophene), 6.99 (m, 1H, H_2-pyrrole), 7.24 (m, 1H, H_5-pyrrole), 7.62 (d, 1H, J = 4.98 Hz, H_5-thiophene), 9.55 (s, 1H, CHO).

4*H*-Pyrrolo[1,2-*a*]thieno[2,3-*e*][1,3]diazepine (**20**).

A solution of the nitroaldehyde **13** (1.05 g, 4.45 mmoles) in 80 ml of hot ethanol was added to a suspension of ferrous(II) sulfate heptahydrate (12.45 g, 44.5 mmoles) in 40 ml of water and 6 ml of concentrated aqueous ammonia. The mixture was heated cautiously at 80-90° for 2.5 hours with stirring while 10 ml of concentrated aqueous ammonia was added dropwise. The black solid was filtered off and washed with ethanol and discarded. The filtrate was extracted with chloroform and the organic phase was dried over sodium sulfate and concentrated to give an orange solid which turned swiftly to brown. An analytical sample was recrystallized from diethyl ether-heptane and gave the title compound **20** (0.084 g, 10%) as colourless crystals, mp 115-116° (decomposition); ir (potassium bromide): ν cm^{-1} 1608 (CH=N); ^1H nmr (DMSO-d_6): δ ppm 5.21 (s, 2H, CH_2-N), 6.02 (dd, 1H, $J_{H4',H3'}$ = 3.76 Hz, $J_{H4',H5'}$ = 2.42 Hz, $H_{4'}$-pyrrole), 6.7 (d, 1H, J = 5.28 Hz, H_4-thiophene), 6.91 (dd, 1H, $J_{H3',H4'}$ = 3.76 Hz, $J_{H3',H5'}$ = 1.62 Hz, H3'-pyrrole), 7.11 (dd, 1H, $J_{H5',H4'}$ = 2.42 Hz, $J_{H5',H3'}$= 1.62 Hz, $H_{5'}$-pyrrole) 7.36 (d, 1H, J = 5.28 Hz, H_5-thiophene), 7.94 (s, 1H, CH =N); ^{13}C nmr (DMSO-d_6): δ ppm 46.6 (CH_2), 110 (CH), 118 (CH), 123 (CH), 126 (CH), 130.6 (C_q), 130.9 (C_q), 131 (C_q), 146 (CH), 167 (CH=N).

Anal. Calcd. for $C_{10}H_8N_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 63.71; H, 4.20; N, 14.75.

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