A New Procedure for the Synthesis of 4*H*-Pyrazolo[1,5-*c*][1,3,5]thiadiazine-4-thiones

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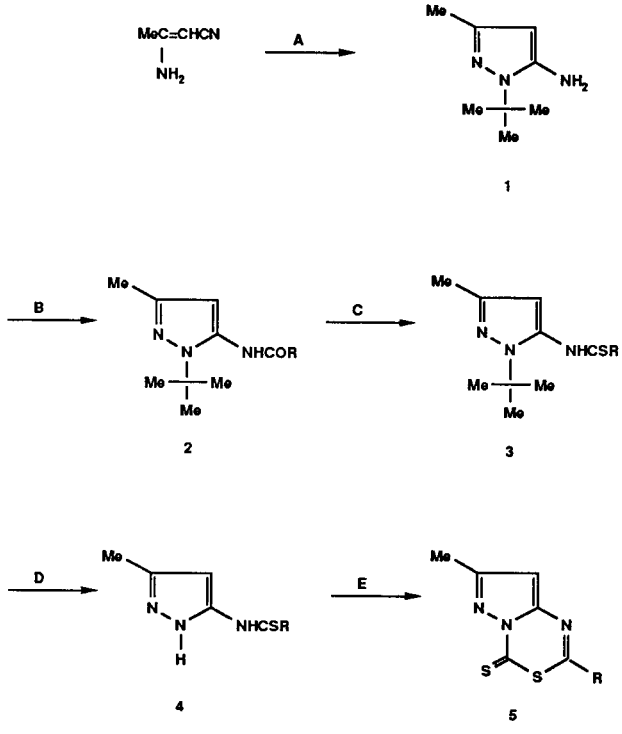
Received April 20, 1994

Thiation of *N*-(1-*tert*-butyl-3-methylpyrazol-5-yl)carboxamides **2** with the Lawesson reagent afforded the corresponding thiocarboxamides **3**. Heating of **3** in formic acid gave the *N*-dealkylated thiocarboxamides **4** which were cyclized into 4*H*-pyrazolo[1,5-*c*][1,3,5]thiadiazine-4-thiones **5** by treatment with thiophosgene.

J. Heterocyclic Chem., **31**, 1477 (1994).

A large number of thiadiazines has been investigated for biological activity. Among the six possible isomers, most work has been expended on the study of 1,3,5-thiadiazine derivatives because of their application in medicine as diuretics [1] and in agriculture as fungicides [2]. Continuing a previous program aimed at the synthesis and pharmacological evaluation of annulated thiadiazines [3], our interest was focused on the synthesis of pyrazolo[1,5-*c*]-[1,3,5]thiadiazine-4-thiones. The literature on this subject is very limited, the only reported synthetic routes being: i) the cyclization of 5-amino-1-thiocarbamoylpyrazole with thiophosgene [4] and ii) the reaction of carbon disulfide with 5-amino-1-benzoylpyrazole in the presence of a strong base [5]. Both these procedures have applications limited only to specific derivatives and cannot be utilized to prepare series of homologues useful for activity modulation. Therefore we decided to seek a new general method based on the use of 5-amino-1-*tert*-butylpyrazole as the starting material. This choice was supported by the knowledge that the *tert*-butyl group is cleavable from ring nitrogen atom and therefore it could be utilized as a protecting group. It is well known that alkyl groups can be cleaved from aromatic rings as well as from secondary and tertiary aromatic amines by proton and Lewis acids [6,7]. Tertiary groups are the most easily cleaved; for this reason the *tert*-butyl group can be introduced into an aromatic ring in order to direct a successive electrophilic substitution and then removed under controlled conditions [7]. Moreover, recent experiments in our laboratories have shown that nitrogen heterocycles *N*-substituted with a *tert*-butyl group can be promptly dealkylated under heating in formic acid [8]. Therefore the synthesis of the target system was planned as shown in the Scheme.

Scheme



a: R= Me, **b**: R= Et, **c**: R= *n*-Pr, **d**: R= *p*-BrPh, **e**: R= *p*-ClPh

Reagents: A: *t*-BuNHNH$_2$; B: RCOX (X= Cl, OCOR); C: Lawesson reagent; D: HCOOH, reflux; E: CSCl$_2$.

The amine **1** was prepared by reacting 3-amino-2-butenenitrile with *tert*-butylhydrazine. Acylation of **1** with activated aliphatic and aromatic carboxylic acids gave the corresponding amides **2**. Thiation of **2** with the Lawesson reagent afforded the thioamides **3**. Heating of **3** in formic acid provided the dealkylated thioamides **4**. Finally, treatment of **4** with thiophosgene gave the target pyrazolothiadiazinethiones **5**. The assigned structures are unambiguously supported by analytical and spectral data (see Experimental).

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded from po-

tassium bromide discs on a Perkin-Elmer 299B spectrophotometer. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard and coupling constants are in Hz. For column chromatography, silica gel (Kieselgel 60 Merck, 70-230 mesh ASTM) was used. Compounds **2a** and **3a** were prepared according to the reported procedure [8].

5-Amino-1-*tert*-butyl-3-methylpyrazole (**1**).

Triethylamine (12.26 ml, 88 mmoles) was added to a solution of *tert*-butylhydrazine hydrochloride (10.96 g, 88 mmoles) in ethanol (500 ml). After stirring at room temperature for 15 minutes, 3-amino-2-butenenitrile (6.56 g, 80 mmoles) was added and the mixture was heated under reflux for 6 hours. The solvent was removed, the residue was dissolved in water (250 ml) and extracted with ethyl ether (3 x 200 ml). Removal of the solvent gave a solid which was recrystallized from hexane, white crystals, yield 11.65 g, 95%, mp 66-67°; ir: 3450 (br), 3350 (br), 1630 (br), 1560 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 1.47 (s, 9H, $C(CH_3)_3$), 1.93 (s, 3H, CH_3), 4.71 (s, 2H, NH_2), 5.16 (s, 1H, CH).

Anal. Calcd. for $C_8H_{15}N_3$: C, 62.71; H, 9.87; N, 27.42. Found: C, 62.70; H, 9.77; N, 27.38.

Procedure for *N*-(Pyrazol-5-yl)carboxamides **2b,c**.

The amine **1** (1.53 g, 10 mmoles) was dissolved in the appropriate anhydride (20 ml) and stirred at room temperature until no more of the starting material could be detected by tlc. The solvent was removed and the resulting solid was collected, washed with hexane and recrystallized. By using this procedure the following compounds were obtained:

N-(1-*tert*-Butyl-3-methylpyrazol-5-yl)propionamide (**2b**).

This compound was obtained by reacting **1** with propionic anhydride for 8 hours, white crystals, yield 73%, mp 122-123° (toluene); ir: 3260, 2980, 1620, 1560 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 1.05 (t, J = 7.5 Hz, 3H, CH_3), 1.47 (s, 9H, $C(CH_3)_3$), 2.08 (s, 3H, CH_3), 2.57 (q, J = 7.5 Hz, 2H, CH_2), 5.79 (s, 1H, CH), 9.33 (br, 1H, NH).

Anal. Calcd. for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.52; H, 9.22; N, 20.08.

N-(1-*tert*-Butyl-3-methylpyrazol-5-yl)butyramide (**2c**).

This compound was obtained by reacting **1** with butyric anhydride for 24 hours, white crystals, yield 78%, mp 96-97° (hexane); ir: 3220, 3160, 2960, 1660, 1560 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 0.90 (t, J = 7.3 Hz, 3H, CH_3), 1.47 (s, 9H, $C(CH_3)_3$), 1.57 (m, 2H, CH_2), 2.07 (s, 3H, CH_3), 2.24 (t, J = 7.4 Hz, 2H, CH_2), 5.78 (s, 1H, CH), 9.35 (br, 1H, NH).

Anal. Calcd. for $C_{12}H_{21}N_3O$: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.80; H, 9.60; N, 19.02.

Procedure for *N*-(Pyrazol-5-yl)carboxamides **2d,e**.

A solution of the required acyl chloride (20 mmoles) in methylene chloride (15 ml) was added dropwise to a mixture of **1** (3.06 g, 20 mmoles) in methylene chloride (100 ml) and sodium hydrogen carbonate (1.68 g, 20 mmoles) in water (50 ml). After 24 hours stirring at room temperature, a first crop of product was collected; the organic phase of the filtrate was separated and concentrated to give a second crop of product. After being anhydrified *in vacuo* over phosphorus pentoxide, the two crops were pooled and recrystallized. By using this procedure the following compounds were obtained:

N-(1-*tert*-Butyl-3-methylpyrazol-5-yl)-4-bromobenzamide (**2d**).

This compound was obtained by reacting **1** with 4-bromobenzoyl chloride, colorless crystals, yield 55%, mp 247-248° (ethyl acetate); ir: 3310, 3000, 1670, 1570 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 1.50 (s, 9H, $C(CH_3)_3$), 2.13 (s, 3H, CH_3), 5.93 (s, 1H, CH), 7.75 (d, J = 8.5 Hz, 2H, aromatic), 7.90 (d, J = 8.5 Hz, 2H, aromatic), 10.09 (br, 1H, NH).

Anal. Calcd. for $C_{15}H_{18}BrN_3O$: C, 53.58; H, 5.40; N, 12.50. Found: C, 53.34; H, 5.28; N, 12.26.

N-(1-*tert*-Butyl-3-methylpyrazol-5-yl)-4-chlorobenzamide (**2e**).

This compound was obtained by reacting **1** with 4-chlorobenzoyl chloride, colorless crystals, yield 56%, mp 233-234° (ethyl acetate); ir: 3280, 2980, 1660, 1550 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 1.50 (s, 9H, $C(CH_3)_3$), 2.13 (s, 3H, CH_3), 5.93 (s, 1H, CH), 7.62 (d, J = 8.4 Hz, 2H, aromatic), 7.96 (d, J = 8.4 Hz, 2H, aromatic), 10.10 (br, 1H, NH).

Anal. Calcd. for $C_{15}H_{18}ClN_3O$: C, 61.75; H, 6.22; N, 14.40. Found: C, 61.44; H, 6.42; N, 14.62.

General Procedure for *N*-(Pyrazol-5-yl)thiocarboxamides **3**.

The Lawesson reagent (1.01 g, 2.5 mmoles) was added to a solution of each carboxamide **2** (5 mmoles) in anhydrous toluene (90 ml) at 80°. The mixture was kept under stirring at 80° for 5 hours and then extracted with 1*N* sodium hydroxide (3 x 50 ml). The aqueous layer was acidified to *p*H 6 with hydrochloric acid and extracted with ethyl acetate (3 x 50 ml). After drying over anhydrous magnesium sulfate, the solvent was removed and the residue was purified by column chromatography (eluent:ethyl acetate/light petroleum ether 8:2 v/v). By using this procedure the following compounds were prepared:

N-(1-*tert*-Butyl-3-methylpyrazol-5-yl)thiopropionamide (**3b**).

This compound was obtained as colorless crystals, yield 77%, mp 92-93° (methanol-water); ir: 3380 (br), 3180 (br), 2950 (br) 1570, 1380 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 1.23 (t, J = 7.3 Hz, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$), 2.10 (s, 3H, CH_3), 3.70 (q, J = 7.3 Hz, 2H, CH_2), 5.62 (s, 1H, CH), 11.00 (br, 1H, NH).

Anal. Calcd. for $C_{11}H_{19}N_3S$: C, 58.63; H, 8.50; N, 18.65; S, 14.23. Found: C, 58.80; H, 8.48; N, 18.42; S, 14.14.

N-(1-*tert*-Butyl-3-methylpyrazol-5-yl)thiobutyramide (**3c**).

This compound was obtained as colorless crystals, yield 73%, mp 91-92° (hexane); ir: 3160, 2980, 1560, 1380 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 0.93 (t, J = 7.5 Hz, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$), 1.80 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.65 (t, J = 7.3 Hz, 2H, CH_2), 5.85 (s, 1H, CH), 11.15 (br, 1H, NH).

Anal. Calcd. for $C_{12}H_{21}N_3S$: C, 60.21; H, 8.84; N, 17.55; S, 13.39. Found: C, 60.00; H, 8.64; N, 17.68; S, 13.00.

N-(1-*tert*-Butyl-3-methylpyrazol-5-yl)-4-bromothiobenzamide (**3d**).

This compound was obtained as yellow crystals, yield 70%, mp 139° (hexane); ir: 3240, 1590, 1560, 1390 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 1.53 (s, 9H, $C(CH_3)_3$), 2.15 (s, 3H, CH_3), 5.95 (s, 1H, CH), 7.70 (d, J = 8.6 Hz, 2H, aromatic), 7.80 (d, J = 8.6 Hz, 2H aromatic), 11.50 (br, 1H, NH).

Anal. Calcd. for $C_{15}H_{18}BrN_3S$: C, 51.14; H, 5.15; N, 11.93; S, 9.10. Found: C, 50.88; H, 5.24; N, 11.76; S, 9.20.

N-(1-*tert*-Butyl-3-methylpyrazol-5-yl)-4-chlorothiobenzamide (**3e**).

This compound was obtained as yellow crystals, yield 60%, mp 162-163° (hexane); ir: 3180, 2980, 1590, 1550, 1390 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 1.52 (s, 9H, $C(CH_3)_3$), 2.14 (s, 3H, CH_3), 5.95 (s, 1H, CH), 7.57 (d, J = 8.5 Hz, 2H, aromatic), 7.88 (d, J = 8.5 Hz, 2H, aromatic), 11.50 (br, 1H, NH).

Anal. Calcd. for $C_{15}H_{18}ClN_3S$: C, 58.53; H, 5.89; N, 13.65; S, 10.41. Found: C, 58.90; H, 5.70; N, 13.44; S, 10.32.

Cleavage of the *tert*-Butyl Group from **3**.

N-(3-Methylpyrazol-5-yl)thiocarboxamides **4**.

A solution of each **3** (6 mmoles) in formic acid (30 ml) was heated under reflux until dealkylation was completed (45-60 minutes, tlc control). The solution was diluted with water (50 ml), neutralized with 2*N* sodium hydroxide and extracted with ethyl acetate (2 x 50 ml). After drying over anhydrous magnesium sulfate, the solvent was removed and the resulting solid was recrystallized. By using this procedure the following compounds were prepared:

N-(3-Methylpyrazol-5-yl)thioacetamide (**4a**).

This compound was obtained as white crystals, yield 70%, mp 193-194° (ethyl acetate); ir: 3260, 2880 (br), 1600, 1380 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 2.22 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.93 (s, 1H, CH), 11.94 (br, 1H, NH), 12.36 (br, 1H, NH).

Anal. Calcd. for $C_6H_9N_3S$: C, 46.43; H, 5.84; N, 27.07; S, 20.65. Found: C, 46.75; H, 5.66; N, 27.27; S, 20.46.

N-(3-Methylpyrazol-5-yl)thiopropionamide (**4b**).

This compound was obtained as white crystals, yield 74%, mp 179-180° (methanol); ir: 3240 (br), 2900 (br), 1600, 1400 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 1.19 (t, J = 7.4 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.68 (q, J = 7.4 Hz, 2H, CH_2), 6.94 (s, 1H, CH), 11.89 (s, 1H, NH), 12.36 (s, 1H, NH).

Anal. Calcd. for $C_7H_{11}N_3S$: C, 49.68; H, 6.55; N, 24.83; S, 18.94. Found: C, 49.36; H, 6.35; N, 24.52; S, 18.68.

N-(3-Methylpyrazol-5-yl)thiobutyramide (**4c**).

This compound was obtained as white crystals, yield 88%, mp 144-145° (toluene); ir: 3200-2900 (br), 1600, 1400 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 0.87 (t, J = 7.1 Hz, 3H, CH_3), 1.70 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 2.67 (t, J = 7.2 Hz, 2H, CH_2), 6.97 (s, 1H, CH), 11.88 (br, 1H, NH), 12.36 (br, 1H, NH).

Anal. Calcd. for $C_8H_{13}N_3S$: C, 52.43; H, 7.15; N, 22.93; S, 17.49. Found: C, 52.22; H, 7.34; N, 22.75; S, 17.06.

N-(3-Methylpyrazol-5-yl)-4-bromothiobenzamide (**4d**).

This compound was obtained as yellow crystals, yield 70%, mp 148-149° (toluene); ir: 3200, 1580, 1400 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 2.26 (br, 3H, CH_3), 6.90 (s, 1H, CH), 7.60-7.68 (m, 4H, aromatic), 12.18 (br, 1H, NH), 12.49 (br, 1H, NH).

Anal. Calcd. for $C_{11}H_{10}BrN_3S$: C, 44.61; H, 3.40; N, 14.19; S, 10.82. Found: C, 44.32; H, 3.26; N, 14.18; S, 10.80.

N-(3-Methylpyrazol-5-yl)-4-chlorothiobenzamide (**4e**).

This compound was obtained as yellow crystals, yield 86%, mp 151-152° (toluene); ir: 3250 (br), 1580, 1350 cm^{-1}; ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ 2.28 (s, 3H, CH_3), 6.90 (s, 1H, CH), 7.47 (d, J = 8.5 Hz, 2H, aromatic), 7.78 (d, J = 8.5 Hz, 2H, aromatic), 12.17 (br, 1H, NH), 12.49 (br, 1H, NH).

Anal. Calcd. for $C_{11}H_{10}ClN_3S$: C, 52.48; H, 4.00; N, 16.69; S, 12.74. Found: C, 52.15; H, 4.14; N, 16.50; S, 12.48.

General Procedure for 4*H*-Pyrazolo[1,5-*c*][1,3,5]thiadiazine-4-thiones **5**.

Thiophosgene (0.60 ml, 6 mmoles) was added dropwise to a heterogeneous mixture of each dealkylated thioamide **4** (6 mmoles) in water (45 ml) with vigorous stirring [9]. The red color gradually disappeared and a yellow-green precipitate formed. After 3 hours stirring at room temperature, the precipitate was collected, washed with water and dissolved in ethyl acetate. After drying over anhydrous magnesium sulfate, the solvent was removed to give a solid which was purified by column chromatography (eluent:ethyl acetate/light petroleum ether 8:2 v:v). By using this procedure the following compounds were obtained:

2,7-Dimethylpyrazolo[1,5-*c*][1,3,5]thiadiazine-4-thione (**5a**).

This compound was obtained as yellow crystals, yield 60%, mp 123-123.5° (methanol); ir: 1600, 1350 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.48 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 6.55 (s, 1H, CH); ^{13}C-nmr (deuteriochloroform): δ 14.7 (CH_3), 25.2 (CH_3), 106.8 (C-8), 144.2 (C-8a), 158.0 (C-7), 162.8 (C-2), 180.4 (C-4).

Anal. Calcd. for $C_7H_7N_3S_2$: C, 42.62; H, 3.58; N, 21.30; S, 32.50. Found: C, 42.80; H, 3.42; N, 21.56; S, 32.38.

2-Ethyl-7-methylpyrazolo[1,5-*c*][1,3,5]thiadiazine-4-thione (**5b**).

This compound was obtained as yellow crystals, yield 69%, mp 82-83.5° (hexane); ir: 1600, 1350 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.36 (t, J = 7.5 Hz, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.75 (q, J = 7.5 Hz, 2H, CH_2), 6.56 (s, 1H, CH); ^{13}C-nmr (deuteriochloroform): δ 11.5 (CH_3), 14.6 (CH_3), 32.2 (CH_2), 106.7 (C-8), 144.2 (C-8a), 157.9 (C-7), 167.8 (C-2), 180.7 (C-4).

Anal. Calcd. for $C_8H_9N_3S_2$: C, 45.48; H, 4.29; N, 19.89; S, 30.35. Found: C, 45.24; H, 4.38; N, 19.60; S, 30.22.

7-Methyl-2-propylpyrazolo[1,5-*c*][1,3,5]thiadiazine-4-thione (**5c**).

This compound was obtained as yellow crystals, yield 60%, mp 48-49° (methanol/water); ir: 1600, 1380, 1350 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.03 (t, J = 7.3 Hz, 3H, CH_3), 1.64 (m, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.69 (t, J = 7.7 Hz, 2H, CH_2), 6.56 (s, 1H, CH); ^{13}C-nmr (deuteriochloroform): δ 13.47 (CH_3), 14.7 (CH_3), 21.1 (CH_2), 40.7 (CH_2), 106.8 (C-8), 144.3 (C-8a), 158.0 (C-7), 167.0 (C-2), 180.9 (C-4).

Anal. Calcd. for $C_9H_{11}N_3S_2$: C, 47.97; H, 4.92; N, 18.65; S, 28.46. Found: C, 47.80; H, 4.72; N, 18.38; S, 28.30.

2-(4-Bromophenyl)-7-methylpyrazolo[1,5-*c*][1,3,5]thiadiazine-4-thione (**5d**).

This compound was obtained as yellow-green crystals, yield 56%, mp 206-208° (methanol/water); ir: 1580, 1380 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 6.67 (s, 1H, CH), 7.65 (d, J = 8.7 Hz, 2H, aromatic), 7.83 (d, J = 8.6 Hz, 2H, aromatic); ^{13}C-nmr (deuteriochloroform): δ 14.8 (q, J = 128.0 Hz, CH_3), 108.0 (d, J = 179.9 Hz, C-8), 128.4 (d, J = 163.2 Hz, aromatic), 128.4 (s, aromatic), 132.6 (d, J = 168.3 Hz, aromatic), 132.8 (s, aromatic), 144.5 (s, C-8a), 158.5 (s, C-7), 159.7 (s, C-2), 179.0 (s, C-4).

Anal. Calcd. for $C_{12}H_8BrN_3S_2$: C, 42.61; H, 2.38; N, 12.42; S, 18.96. Found: C, 42.38; H, 2.30; N, 12.60; S, 18.78.

2-(4-Chlorophenyl)-7-methylpyrazolo[1,5-*c*][1,3,5]thiadiazine-4-thione (**5e**).

This compound was obtained as yellow-green crystals, yield

50%, mp 203-204° (methanol/water); ir: 1580, 1380 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 6.64 (s, 1H, CH), 7.47 (d, J = 8.3 Hz, 2H, aromatic), 7.89 (d, J = 8.3 Hz, 2H, aromatic); ^{13}C-nmr (deuteriochloroform): δ 14.8 (CH_3), 107.9 (C-8), 128.0 (aromatic), 129.5 (aromatic), 132.3 (aromatic), 139.5 (aromatic), 144.4 (C-8a), 158.4 (C-7), 159.4 (C-2), 179.2 (C-4).

Anal. Calcd. for $C_{12}H_8ClN_3S_2$: C, 49.06; H, 2.74; N, 14.30; S, 21.83. Found: C, 49.28; H, 2.62; N, 14.46; S, 21.80.

Acknowledgements.

The Authors are grateful to Dr. A. Casolari and to P. Orlandini for carrying out nmr spectra. Research work supported by grants of MURST, Italy (Research Fund 40%).

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