Synthesis and characterization of chloromaleimidobenzenesulfonylhydrazones

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Abstract
This paper describes the synthesis of a new series of imidosulfonylhydrazones in a search for antibactericidal and/or antinociceptive lead compounds. Cyclic imides comprise an important family of organic compounds with therapeutic potential, including the sulfonylhydrazones. 3,4-Dichloro-1-phenyl-1H-pyrrole-2,5-dione (1) was obtained from the reaction between aniline and dichloromaleic anhydride in acetic acid. Reaction of (1) with pyrrolidine gave 3-chloro-1-phenyl-4-pyrrolidin-1-yl-1H-pyrrole-2,5-dione (2). 4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1H-pyrrol-1-yl)benzenesulfonyl chloride (3) was obtained from the chlorosulfonation of compound (2). The reaction of (3) with hydrazine hydrate produced 4-(3-chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1H-pyrrol-1-yl)benzenesulfonylhydrazide (4), which was characterized through condensation with aldehydes to yield the imidosulfonylhydrazones (5-12).

Keywords: Chloromaleimidobenzenesulfonylhydrazones, sulfonylhydrazones, synthesis

Introduction
The synthesis of sulfonylhydrazones is of great interest since these compounds have shown anti-inflammatory, analgesic1-5, anti-pyretic4, and antibacterial activities5. The antineoplastic activity of some sulfonylhydrazones has also been reported6. Studies carried out by Barreiro et al. have shown that sulfonylhydrazone derivatives of safrole have potent analgesic action, exceeding and/or equalling the potency observed under the same conditions for either dypirone or indomethacin7. This paper describes the synthesis of chloromaleimidobenzenesulfonylhydrazones, in a search for antibactericidal and/or antinociceptive lead compounds.

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Results and Discussion

The cyclic imide (1) was obtained from the reaction between aniline and dichloromaleic anhydride with acetic acid under reflux, as previously described\(^8\) (Scheme 1). Compound (2) was obtained from the reaction of compound (1) (1 mol) and pyrrolidine (2 mol) in dichloromethane at room temperature\(^9\). Compound (3) was prepared by the reaction of compound (2) (1 mol) with chlorosulfonic acid (6 mol)\(^9\). The reaction of the sulfonylchloride with hydrazine hydrate gave the sulfonylhydrazide (4), which was characterized by condensation with aldehydes to yield the sulfonylhydrazones (5-12) (Scheme 1).

Scheme 1
The configuration of the imino double bonds of (5-12) could not be determined by NMR data, where only one imino hydrogen was observed. However, a study of the relative stability of the $E/Z$ diastereomers involved, employing the Hamiltonian PM3 molecular model and the work of Barreiro et al.\textsuperscript{10}, indicated that the $E$ isomers may be preferentially formed. The structures were confirmed through $^1$H NMR and $^{13}$C NMR spectroscopic analysis and CNH elemental analysis.

**Experimental Section**

**General Procedures.** All compounds were characterised by $^1$H NMR, $^{13}$C NMR, IR, and microanalysis. The purity of these compounds was determined by thin layer chromatography (TLC). Infrared spectra were obtained with a Perkin Elmer 16PC spectrophotometer (Perkin Elmer, Wellesley, MA, USA). $^1$H NMR and $^{13}$C NMR spectra were recorded with a Bruker AC-200F spectrometer (Rheinstetten, Germany) (at 200 MHz and 50 MHz, respectively). CDCl$_3$ and DMSO were used as solvents with tetramethylsilane (TMS) as the internal standard; chemical shifts ($\delta$) are reported in parts per million. For the CHN analysis, a CHN elemental analyser PERKIN ELMER 2400 (Boston, MA, USA) was used. In the TLC, aluminium sheets with 60 F-254 silica gel and 0.2 mm thickness were utilised.

**3,4-Dichloro-1-phenyl-1$H$-pyrrole-2,5-dione (1).** Imide (1) was obtained as describe in the literature\textsuperscript{8}. Yield: 82 %. mp 206-207 °C (Lit\textsuperscript{8} m.p. 204-206°C).

**3-Chloro-1-phenyl-4-pyrrolidin-1-yl-1$H$-pyrrole-2,5-dione (2).** Imide (2) was obtained as describe in the literature\textsuperscript{9}. Yield: 80 %. mp 134-135 °C (Lit\textsuperscript{9} m.p. 135-136°C).

**4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1$H$-pyrrol-1-yl)benzenesulfonyl chloride (3).** Chloride (3) was obtained as described in the literature\textsuperscript{9}. Yield: 89 %. mp 121-123 °C (Lit\textsuperscript{9} m.p. 122-123°C).

**4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1$H$-pyrrol-1-yl)benzenesulfonohydrazide (4).** Hydrazine hydrate (51.3 mg, 1.60 mmol) was added to a mixture of 4-(3-chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1$H$-pyrrol-1-yl)benzenesulfonyl chloride (3) (0.3 g, 0.80 mmol) in methanol (30 mL) at 0 °C. The mixture was allowed to warm to room temperature for 30 minutes and was then poured onto ice-water. The solid formed was obtained through filtration with suction. The product was crystallized from hexane-chloroform (1:2). Yield: 89 %. mp 178.1-179.0 °C. $IR$(KBr) $\nu$\textsubscript{Max}: 3383, 3192, 2963, 1777, 1708, 1387, 1193, 1173, 837.

**4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1$H$-pyrrol-1-yl)-N'-(1$E$)phenylmethylene]benzenesulfonylhydrazide (5).** Benzaldehyde (28.6 mg, 0.27 mmol) was added to a mixture of 4-(3-chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1$H$-pyrrol-1-yl)benzenesulfonyl hydrazide (4) (0.10 g, 0.27 mmol) in ethanol (10 mL), along with a drop of hydrochloric acid as the catalyst. The reaction was left under stirring at room temperature for 1 ½ hours. The solid formed was obtained through filtration with suction. The product was crystallized from ethanol-ethyl acetate (2:1) as light yellow colored crystals. Yield: 73 %. mp
189.2-190.5 °C. *IR*(KBr)ν\textsubscript{Max} 3210, 2970, 1770, 1704, 1635, 1493, 1386, 1232. Anal. Calcd. for C\textsubscript{21} H\textsubscript{19} Cl N\textsubscript{4} O\textsubscript{4} S: C, 54.96; H, 4.17; Cl, 7.73; N, 12.21; S, 6.99. Found: C, 54.49; H, 4.30; N, 12.10; S, 6.94. \(^1\)H NMR δ ppm, DMSO-\textsubscript{d}\textsubscript{6}: 11.58 (s, 1H: -NH-N=); 7.93 (s, 1H: -N=CH-); 7.98 and 7.94 (2d, 2H: ArH; J= 8.2 Hz); 7.91 (m, 5H: ArH); 3.88-  (s, 4H: CH\textsubscript{2}-N-CH\textsubscript{2}); 1.87 (s, 4H: CH\textsubscript{2}-CH\textsubscript{2}). \(^{13}\)C NMR δ ppm, DMSO-\textsubscript{d}\textsubscript{6}: 25.31 (CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-N); 51.11(CH\textsubscript{2}-N-CH\textsubscript{2}−); 89.87 (Cl-C=); 127.23, 127.54; 128.57; 129.50; 130.88; 134.25 (CH Ar); 136.39 (-Cl-C=Cl−); 137.81 (-C Ar-SO\textsubscript{2}); 141.72 (-C Ar-N-); 148.20 (-N=C-); 163.45 (C=O), 165.57 (C=O).

Using this procedure the following sulfonylhydrazones were prepared:

**4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1\textsubscript{H}-pyrrol-1-yl)-N\textsuperscript{′}-(1\textsuperscript{E})-(4-hydroxyphenyl)methylene]benzenesulfonohydrazide (6).** Yield: 71 %. Dec.: 200 °C. *IR*(KBr)ν\textsubscript{Max}: 3452, 3156, 2995, 1759, 1706, 1499, 1389, 1174, 1232. Anal. Calcd. for C\textsubscript{21} H\textsubscript{19} Cl N\textsubscript{4} O\textsubscript{5} S: C, 53.11; H, 4.03; Cl, 7.47; N, 11.80; S, 6.75. Found: C, 52.87; H, 4.18; N, 11.74; S, 6.71. \(^1\)H NMR δ ppm, DMSO-\textsubscript{d}\textsubscript{6}: 11.27 (s, 1H: -NH-N=); 9.91 (s, 1H: OH); 7.95 and 7.91 (2d, 2H: ArH; J= 8.0 Hz); 7.82 (s, 1H: -N=CH-); 7.60 and 7.56 (2d, 2H: ArH; J= 8.0 Hz); 7.42 and 7.38 (2d, 2H: ArH; J= 8.0 Hz); 6.78 and 6.74 (2d, 2H: ArH; J= 8.0 Hz); 3.88 (s, 4H: -CH\textsubscript{2}-N-CH\textsubscript{2}); 1.87 (s, 4H: -CH\textsubscript{2}-CH\textsubscript{2}). \(^{13}\)C NMR δ ppm, DMSO-\textsubscript{d}\textsubscript{6}: 24.70 (CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-N); 50.51 (CH\textsubscript{2}-N-CH\textsubscript{2}); 109.26 (Cl-C=Cl−); 115.71; 124.66; 126.61; 127.96; 128.72 (CH Ar); 135.65 (-Cl-C=Cl−); 137.29 (-C Ar-SO\textsubscript{2}); 141.12 (-C Ar-N); 148.14 (-N=C-); 159.51 (-HC-OH Ar); 162.86 (C=O); 165.00 (C=O).

**4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1\textsubscript{H}-pyrrol-1-yl)-N\textsuperscript{′}-(1\textsuperscript{E})-(4-nitrophenyl)methylene]benzenesulfonohydrazide (7).** Yield: 80 %. mp 201.0-202.7 °C. *IR*(KBr)ν\textsubscript{Max}: 3240, 3156, 2995, 1759, 1706, 1630, 1495, 1522, 1348, 1385, 1168, 1226, 852. Anal. Calcd. for C\textsubscript{21} H\textsubscript{18} Cl N\textsubscript{5} O\textsubscript{6} S: C, 50.05; H, 3.60; Cl, 7.04; N, 13.90; S, 6.36. Found: C, 49.76; H, 3.83; N, 13.85; S, 6.22. \(^1\)H NMR δ ppm, DMSO-\textsubscript{d}\textsubscript{6}: 11.96 (s, 1H: -NH-N=); 8.26 and 8.22 (2d, 2H: ArH; J= 8.2 Hz); 7.99 (s, 1H: -N=CH-); 7.96 (m, 4H: ArH); 7.59 (m, 2H: ArH); 3.89 (s, 4H: -CH\textsubscript{2}-N-CH\textsubscript{2}); 1.87 (s, 4H: -CH\textsubscript{2}-CH\textsubscript{2}). \(^{13}\)C NMR δ ppm, DMSO-\textsubscript{d}\textsubscript{6}: 24.70 (CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-N); 50.51 (CH\textsubscript{2}-N-CH\textsubscript{2}); 109.26 (Cl-C=Cl−); 115.71; 124.66; 126.61; 127.96; 128.72 (CH Ar); 136.56 (-Cl-C=Cl−); 137.29 (-C Ar-SO\textsubscript{2}); 141.12 (-C Ar-N); 148.14 (-N=C-); 159.51 (-HC-OH Ar); 162.86 (C=O); 165.00 (C=O).

**4-(3-Chloro-2,5-dioxo-4-pyrrolidin-1-yl-2,5-dihydro-1\textsubscript{H}-pyrrol-1-yl)-N\textsuperscript{′}-(1\textsuperscript{E})-(3-nitrophenyl)methylene]benzenesulfonohydrazide (8).** Yield: 88 %. mp 199.6-201.4 °C. *IR*(KBr)ν\textsubscript{Max}: 3208, 2985, 1764, 1706, 1633, 1500, 1543, 1348, 1372, 1166, 1241, 869. Anal. Calcd. for C\textsubscript{21} H\textsubscript{18} Cl N\textsubscript{5} O\textsubscript{6} S: C, 50.05; H, 3.60; Cl, 7.04; N, 13.90; S, 6.36. Found: C, 49.96; H, 3.74; N, 13.77; S, 6.24. \(^1\)H NMR δ ppm, DMSO-\textsubscript{d}\textsubscript{6}: 11.96 (s, 1H: -NH-N=); 8.38 (2m, 2H: ArH; J= 8.0 Hz); 8.24 and 8.20 (2d, 2H: ArH; J= 8.0 Hz); 8.15 (s, 1H: -N=CH-); 7.80 (m, 4H: ArH); 7.61 (2d, 2H: ArH; J= 8.1); 3.90 (s, 4H: -CH\textsubscript{2}-N-CH\textsubscript{2}); 1.87 (s, 4H: -CH\textsubscript{2}-CH\textsubscript{2}). \(^{13}\)C NMR δ ppm, DMSO-\textsubscript{d}\textsubscript{6}: 25.30 (CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-N); 51.11 (CH\textsubscript{2}-N-CH\textsubscript{2}); 88.98 (Cl-C=Cl−); 121.91, 125.12; 127.30, 128.53, 131.13, 133.41, 136.05 (CH Ar); 136.52 (-Cl-C=Cl−); 137.70 (-C Ar-SO\textsubscript{2}); 141.72 (-C Ar-N); 145.84 (-C Ar-NO\textsubscript{2}); 146.80 (C=O); 163.43 (C=O); 165.54 (C=O).
4-(3-Chloro-2,5-dioxo-4-pyrrolin-1-yl-2,5-dihydro-1H-pyrrol-1-yl)-N''-[1(E)-4-(dimethylamino)phenyl]methylene]benzenesulfonohydrazide (9). Yield: 71 %. Dec. 170 °C. IR(KBr) \( \nu_{\text{Max}} \): 3126, 2978, 1770, 1717, 1634, 1495, 1365, 1232. Found: C, 54.83; H, 4.98; N, 13.82; S, 6.26. ¹H NMR \( \delta \) ppm, DMSO-\( d_6 \): 11.32 (s, 1H: -NH-N=); 7.97 and 7.93 (2d, 2H: ArH, J= 8.0 Hz); 7.45 and 7.41 (2d, 2H: ArH, J= 8.0 Hz); 6.91 and 6.87 (2d, 2H: ArH, J= 8.0 Hz); 3.89 (s, 4H: -CH2-N-CH2-); 2.97 (s, 6H: -N-(CH3)2); 1.88 (s, 4H -CH2-CH2-). ¹³C NMR \( \delta \) ppm, DMSO-\( d_6 \): 24.68 (CH2=CH2-CH2-N); 50.47 (CH2-N-CH2-); 110.53 (Cl-C=C); 114.09, 126.55, 128.26 (CH Ar); 135.61 (-Cl-C=C); 137.29 (-C Ar-SO2); 141.07 (-C Ar-N); 148.09 (-CH(N(CH3)2)), 149.86 (-N=C=-); 162.81 (C=O), 164.96 (C=O).

4-(3-Chloro-2,5-dioxo-4-pyrrolin-1-yl-2,5-dihydro-1H-pyrrol-1-yl)-N''-[(1E)-1,3-benzodioxol-5-ylmethylene]benzenesulfonohydrazide (10). Yield: 69 %. mp 217.5 – 218.1 °C. IR(KBr) \( \nu_{\text{Max}} \): 3157, 2976, 1764, 1706, 1632, 1500, 1372, 1163, 1258. Found: C, 52.54; H, 3.81; Cl, 7.05; N, 11.14; S, 6.15. ¹H NMR \( \delta \) ppm, DMSO-\( d_6 \): 11.36 (s, 1H: -NH-N=); 7.98 and 7.94 (2d, 2H: ArH, J= 8.4 Hz); 7.83 (s, 1H: -N=CH-); 7.61 and 7.57 (2d, 2H: ArH, J= 8.4 Hz); 7.03 (m, 3H: ArH); 6.05 (s, 2H: O-CH2-O); 3.90 (s, 4H: -CH2-N-CH2-); 1.89 (s, 4H: -CH2-CH2-). ¹³C NMR \( \delta \) ppm, DMSO-\( d_6 \): 24.68 (CH2=CH2-CH2-N); 50.47 (CH2-N-CH2-); 101.60 (O-CH2-O); 104.98 (Cl-C=CH); 108.45, 123.24, 126.58, 127.97, 147.45, 147.99 (CH Ar); 135.70 (-Cl-C=CH); 137.11 (-C Ar-SO2); 141.08 (-C Ar-N); 149.18 (-CH(N(CH3)2)), 149.86 (-N=C=-); 162.81 (C=O), 164.96 (C=O).

4-(3-Chloro-2,5-dioxo-4-pyrrolin-1-yl-2,5-dihydro-1H-pyrrol-1-yl)-N''-[(1E)-2-furylmethylene]benzenesulfonohydrazide (11). Yield: 64 %. Dec.: 195.0 oC. IR(KBr) \( \nu_{\text{Max}} \): 3147, 2995, 1759, 1701, 1638, 1506, 1378, 1168, 1240. Found: C, 50.84; H, 3.82; Cl, 7.90; N, 12.48; S, 7.14. ¹H NMR \( \delta \) ppm, DMSO-\( d_6 \): 11.57 (s, 1H: -NH-N=); 7.95 (s, 1H: -N=CH-); 7.85 (m, 2H: ArH); 7.60 (m, 2H: ArH); 6.81 (m, 2H: O-CH=CH-CH); 6.56 (s, 1H: O-CH=CH); 6.50 (m, 3H: ArH); 6.05 (s, 2H: O-CH2-O); 3.90 (s, 4H: -CH2-N-CH2-); 1.87 (s, 4H: -CH2-CH2-). ¹³C NMR \( \delta \) ppm, DMSO-\( d_6 \): 24.68 (CH2=CH2-CH2-N); 50.47 (CH2-N-CH2-); 101.60 (O-CH2-O); 104.98 (Cl-C=C); 108.45, 123.24, 126.58, 127.97, 147.45, 147.99 (CH Ar); 135.70 (-Cl-C=C); 137.11 (-C Ar-SO2); 141.08 (-C Ar-N); 149.18 (-N=C=-); 162.81 (C=O), 164.96 (C=O).

4-(3-Chloro-2,5-dioxo-4-pyrrolin-1-yl-2,5-dihydro-1H-pyrrol-1-yl)-N''-[1(E)-1,3-benzodioxol-5-ylmethylene]benzenesulfonohydrazide (10). Yield: 69 % mp 217.5 – 218.1 °C. IR(KBr) \( \nu_{\text{Max}} \): 3157, 2976, 1764, 1706, 1632, 1500, 1372, 1163, 1258. Anal. Calcd. for C22 H24 Cl N5 O4 S: C, 55.03; H, 4.82; Cl, 7.06; N, 13.95; S, 6.39. Found: C, 54.83; H, 4.98; N, 13.82; S, 6.26. ¹H NMR \( \delta \) ppm, DMSO-\( d_6 \): 11.32 (s, 1H: -NH-N=); 7.97 and 7.93 (2d, 2H: ArH, J= 8.0 Hz); 7.83 (s, 1H: -N=CH-); 7.59 and 7.55 (2d, 2H: ArH, J= 8.0 Hz); 7.45 and 7.41 (2d, 2H: ArH, J= 8.0 Hz); 6.91 and 6.87 (2d, 2H: ArH, J= 8.0 Hz); 3.89 (s, 4H: -CH2-N-CH2-); 2.97 (s, 6H: -N-(CH3)2); 1.88 (s, 4H -CH2-CH2-). ¹³C NMR \( \delta \) ppm, DMSO-\( d_6 \): 24.68 (CH2=CH2-CH2-N); 50.47 (CH2-N-CH2-); 110.53 (Cl-C=C); 114.09, 126.55, 128.26 (CH Ar); 135.61 (-Cl-C=C); 137.29 (-C Ar-SO2); 141.07 (-C Ar-N); 148.09 (-CH(N(CH3)2)), 149.86 (-N=C=-); 162.81 (C=O), 164.96 (C=O).
Cl-C=\(-\); 135.75 (-C Ar-N), 137.49 (-S-\(-\)\ CH=CH\(-\)); 145.28 (-N=C-), 151.96 (HC=C-S-); 161.89 (C=O); 163.91 (C=O).

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References