PREPARATION OF SOME 6-SUBSTITUTED N-PYRAZINYL-2-PYRAZINECARBOXAMIDES

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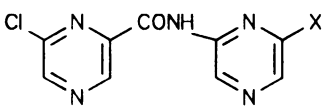
In connection with our research into antimycobacterial pyrazine derivatives[1] we were interested in binuclear analogues with –CONH– bridge.

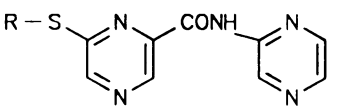
The prepared compounds *Ia*, *Ib*, *IIa* – *IIc* were tested in the form of dimethyl sulfoxide solutions for their activity against *Mycobacterium tuberculosis* $H_{37}Rv$, *M. kansasii* PKG 8, *M. avium* 80/72 and *M. fortuitum* 1021 on a liquid Sula medium (pH 5.4). None of the compounds studied was particularly effective compared with pyrazinecarboxamide as the reference.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. Samples for elemental analysis were dried in vacuo of about 100 Pa over phosphorus pentoxide at room temperature. Infrared spectra were recorded on a Perkin–Elmer model 577 spectrometer in KBr pellets, unless otherwise noted; wavenumbers are given in cm^{-1}. ^1H NMR spectra were determined for solutions in hexadeuteriodimethyl sulfoxide with tetramethylsilane as the internal standard with a BS 497 (Tesla Brno) 100 MHz apparatus; chemical shifts are given in ppm, coupling constants (J) in Hz.



Ia, X = H
Ib, X = Cl



IIa, R = C_6H_5
IIb, R = $CH_2C_6H_5$
IIc, R = 2-pyrazinyl

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The starting compounds were prepared according to the described methods: 6-chloro-2-pyrazine carboxylic acid[2] (m.p. 156 – 157 °C, ref.[2] gives 154 – 155 °C), 2-pyrazinamine[3], 6-chloro-2-pyrazinamine[4], phenylmethanethiol[5], 2-pyrazinethiol[6] (m.p. 208 – 212 °C, ref.[6] gives 210 – 215 °C). Benzenethiol was purchased from Fluka.

6-Chloro-2-pyrazinecarbonyl Chloride

A mixture of 6-chloro-2-pyrazinecarboxylic acid (4.9 g, 31 mmol), thionyl chloride (16 ml, 220 mmol), and benzene (25 ml) was refluxed for 1.5 h. The solvent and excess thionyl chloride were then removed under reduced pressure and the crude product was distilled in vacuo yielding 4.1 g (73%) of the title compound, b.p. 96 – 97 °C/1.99 kPa. IR spectrum ($CHCl_3$): 2 985 (CH arom.); 1 737 (COCl); 1 537, 1 505, 1 388, 1 372, 1 328, 1 238, 1 167, 1 140, 1 012 (pyrazine ring); 805 (CH pyrazine ring).

N-(2-Pyrazinyl)-6-chloro-2-pyrazinecarboxamide (*Ia*)

To a mixture of 2-pyrazinamine (0.2 g, 2 mmol) and 6-chloro-2-pyrazinecarbonyl chloride (0.35 g, 2 mmol) in benzene (10 ml) was added triethylamine (1 ml) and the mixture was kept at 20 °C for 0.5 h. Then the benzene was distilled off under reduced pressure, the solid residue was washed thoroughly with water and the crude product was recrystallized from ethanol. Yield 85%, m.p. 204.5 – 205.5 °C. For $C_9H_6ClN_5O$ (235.6) calculated: 45.88% C, 2.57% H, 15.05% Cl, 29.72% N; found: 45.82% C, 2.53% H, 15.34% Cl, 29.69% N. IR spectrum: 3 380, 3 180, (NH amide); 3 042 (CH arom.); 1 670 (CO amide); 1 495, 1 450, 1 400, 1 375, 1305, 1 298, 1 280, 1 258, 1 172, 1 148, 1 122, 1 060, 1 015 (pyrazine nucleus); 1 565, 1 530 (NH amide); 855, 805 (CH arom.). ^{1}H NMR spectrum: 8.52 AB part of ABX system, 2 H (H-5', H-6'); 9.11 d, 1 H (H-5, $J < 0.5$); 9.28 d, 1 H (H-3, $J < 0.5$); 9.42 part X of ABX system, 1 H (H-3', $J \approx 1.1$); 10.7 bs, 1 H (CONH).

N-(6-Chloro-2-pyrazinyl)-6-chloro-2-pyrazinecarboxamide (*Ib*)

Using the same procedure as for *Ia*, the following quantities were combined: 6-chloro-2-pyrazinamine (0.55 g, 4 mmol), 6-chloro-2-pyrazinecarbonyl chloride (0.7 g, 4 mmol), benzene (20 ml), and triethylamine (1 ml), and the mixture was kept at 20 °C for 1 h. Yield 61%, m.p. 174.5 – 175.5 °C. For $C_9H_5Cl_2N_5O$ (270.1) calculated: 40.02% C, 1.87% H, 26.25% Cl, 25.93% N; found: 39.92% C, 1.83% H, 25.99% Cl, 26.12% N. IR spectrum: 3 340, 3 180 (NH amide); 3 120, 3 020 (CH arom.); 1 678 (CO amide); 1 400, 1 372, 1 332, 1 265, 1 155, 1 112, 1 010, 1 005 (pyrazine nucleus); 1 528 (NH amide); 885, 858, 812 (CH arom.). ^{1}H NMR spectrum: 8.62 d, 1 H (H-5', $J < 0.5$); 9.11 d, 1 H (H-3, $J < 0.5$); 9.27 d, 1 H (H-5, $J < 0.5$); 9.38 d, 1 H (H-3', $J < 0.5$); 11.18 bs, 1 H (CONH).

General Procedure for Preparation of N-(2-Pyrazinyl)-6-arylthio-2-pyrazinecarboxamides *IIa – IIc*

An appropriate arenethiol (9 mmol) was added to dioxane (20 ml). Sodium (0.21 g, 9 mmol) was dissolved in the resulting mixture by heating under reflux. Then *Ia* (2.0 g, 9 mmol) was added and the mixture was refluxed for 3 h. The dioxane was removed under reduced pressure. The crude product was washed with water and recrystallized from ethanol.

N-(2-Pyrazinyl)-6-phenylthio-2-pyrazinecarboxamide (IIa): Benzenethiol afforded *IIa* in 42% yield, m.p. 145.5 – 146.5 °C. For $C_{15}H_{11}N_5OS$ (309.4) calculated: 58.24% C, 3.58% H, 22.64% N, 10.36% S; found: 58.36% C, 3.49% H, 22.40% N, 10.51% S. IR spectrum: 3 320 (NH amide); 3 035 (CH arom.); 1 672 (CO amide); 1 470, 1 442, 1 410, 1 300, 1 250, 1 172, 1 155, 1 140, 1 155, 1 060, 1 010 (pyrazine nucleus); 1 555, 1 515 (NH amide); 890, 855, 820 (CH arom.). ^{1}H NMR spectrum: 7.66 m, 5 H (C_6H_5); 8.48 s, 2 H (H-5', H-6'); 8.63 d, 1 H (H-5, $J < 0.5$); 9.01 d, 1 H (H-3, $J < 0.5$); 9.44 s, 1 H (H-3'); 10.07 bs, 1 H (CONH).

N-(2-Pyrazinyl)-6-phenylmethylthio-2-pyrazinecarboxamide (IIb): Phenylmethanethiol gave *IIb* in 45% yield, m.p. 156.5 – 158.5 °C. For $C_{16}H_{13}N_5OS$ (323.4) calculated: 59.43% C, 4.05% H, 21.66% N, 9.91% S; found: 59.28% C, 4.16%H, 21.47% N, 10.17% S. IR spectrum: 3 400, 3 200 (NH amide); 3 045 (CH arom.); 2 950 (CH aliph.); 1 670 (CO amide); 1 495, 1 456, 1 395, 1 370, 1 300, 1 270, 1 225, 1 172, 1 148, 1 125, 1 055, 1 010 (pyrazine nucleus); 1 570, 1 535 (NH amide); 855, 800 (CH arom.). ^{1}H NMR spectrum: 4.68 s, 2 H (CH_2); 7.2 – 7.6 m, 5 H (C_6H_5); 8.50 d, 1 H (H-5', J = 2.6); 8.56 dd, 1 H (H-6', J(5,6) = 2.6, J(3,6) = 1.4); 8.89 d, 1 H (H-3 or H-5, J < 0.5); 8.97 d, 1 H (H-5 or H-3, J < 0.5); 9.48 d, 1 H (H-3', J = 1.4); 10.68 bs, 1 H (CONH).

N-(2-Pyrazinyl)-6-(2-pyrazinylthio)-2-pyrazinecarboxamide (IIc): 2-Pyrazinethiol gave *IIc* in 41% yield, m.p. 153 – 155 °C. For $C_{13}H_{11}N_7OS$ (311.3) calculated: 50.15% C, 2.91% H, 31.50% N, 10.30% S; found: 49.95% C, 2.63% H, 31.35% N, 10.40% S. IR spectrum: 3 390, 3 280 (NH amide); 3 022 (CH arom.); 1 670 (CO amide); 1 440, 1 405, 1 300, 1 255, 1 172, 1 152, 1 132, 1 112, 1 060, 1 048, 1 015 (pyrazine nucleus); 1 565, 1 525 (NH amide); 865, 805 (CH arom.). ^{1}H NMR spectrum: 8.49 s, 2 H (H-5', H-6'); 8.66 s, 2 H (H-5", H-6"); 8.95 s, 1 H (H-3"); 9.08 d, 1 H (H-5, J < 0.5); 9.20 d, 1 H (H-3, J < 0.5); 9.44 s, 1 H (H-3'); 10.35 bs, 1 H (CONH).

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