PREPARATION OF SOME *N*-SUBSTITUTED 3-AMINO-5-CYANO-2-PYRAZINECARBOXAMIDES

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Received June 30, 1994
Accepted August 21, 1994

During the course of a search for new antimycotic agents a series of 3-amino-5-cyano-2-pyrazinecarboxamides *I – XI* have been synthesized; after the method of Foks[1]. The prepared compounds were tested for their antimycotic activity. The MIC of these in the form of dimethyl sulfoxide solutions was measured against *Candida albicans ATCC 44859, Candida tropicalis 156, Candida krusei E28, Candida glabrata 20/I, Trichosporon beigelii 1188, Trichophyton mentagrophytes 445, Aspergillus fumigatus 231,* and *Absidia corymbifera 272*. None of the compounds studied was particularly effective.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. All the compounds were checked for purity by TLC on Silufol UV 254 plates (Kavalier, Votice). Samples for elemental analysis were dried in vacuo of about 100 Pa over phosphorus pentoxide at room temperature. IR spectra were recorded on a Perkin–Elmer model 577 spectrometer in KBr pellets; wavenumbers are given in cm^{-1}. ^1H NMR spectra were determined for solutions in deuteriochloroform (unless stated otherwise) with tetramethylsilane as the internal standard with a BS 494 (Tesla, Brno) 100 MHz apparatus; chemical shifts are given in ppm (δ-scale), coupling constant (*J*) in Hz.

General Procedure for Preparation of 3-Amino-5-cyano-2-pyrazinecarboxamides *I – XI*

3-Chloro-5-cyano-2-pyrazinecarboxamide[2] (1.82 g, 10 mmol) was dissolved in dry benzene (50 ml). To this solution an appropriate amine (25 mmol) was added. This mixture was refluxed for 1 h. After cooling, the mixture was filtered, the solvent was then removed under reduced pressure, and the crude product was recrystallized from water.

5-Cyano-3-diethylamino-2-pyrazinecarboxamide (I). Diethylamine (1.83 g) afforded *I* in 74% yield, m.p. 186 – 188 °C. For $C_{10}H_{13}N_5O$ (219.2) calculated: 54.78% C, 5.98% H, 31.94% N; found: 54.86% C, 6.09% H, 31.69% N. IR spectrum: 3 380 (NH amide); 2 280 (CN); 1 660 (CO amide); 1 440, 1 390, 1 270, 1 180, 1 050 (pyrazine nucleus); 1 550 (NH amide). ^1H NMR spectrum (CD_3SOCD_3): 1.14 (t, J = 7, 6 H, 2 × CH_3); 3.50 (q, J = 7, 4 H, 2 × CH_2); 7.82 (bs, 1 H, CONH); 8.22 (bs, 1 H, CONH); 8.24 (s, 1 H, H-pyrazine).

5-Cyano-3-propylamino-2-pyrazinecarboxamide (II). Propylamine (1.48 g) gave *II* in 82% yield, m.p. 147 – 150 °C. For $C_9H_{11}N_5O$ (205.2) calculated: 52.68% C, 5.40% H, 34.13% N; found: 52.50% C, 5.58% H, 34.37% N. IR spectrum: 3 410 (NH amide); 2 290 (CN); 1 685 (CO amide);

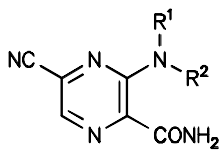
1 395, 1 290, 1 210, 1 160, 1 110, 1 060 (pyrazine nucleus); 1 580 (NH amide). ^{1}H NMR spectrum: 1.00 (t, J = 7, 3 H, CH_3); 1.68 (m, 2 H, CH_2); 3.45 (m, 2 H, NCH_2); 5.70 (bs, 1 H, CONH); 7.67 (bs, 1 H, CONH); 7.93 (s, 1 H, H-pyrazine); 8.83 (bs, 1 H, NH).

5-Cyano-3-dipropylamino-2-pyrazinecarboxamide (III). Dipropylamine (2.52 g) gave *III* in 83% yield, m.p. 125 – 127 °C. For $C_{12}H_{17}N_5O$ (247.3) calculated: 58.28% C, 6.93% H, 28.32% N; found: 58.25% C, 7.04% H, 28.20% N. IR spectrum: 3 390 (NH amide); 2 275 (CN); 1 650 (CO amide); 1 395, 1 270, 1 180, 1 020 (pyrazine nucleus); 1 555 (NH amide). ^{1}H NMR spectrum: 0.88 (t, J = 7, 6 H, 2 × CH_3); 1.64 (m, 4 H, 2 × CH_2); 3.46 (t, J = 7, 4 H, 2 × NCH_2); 5.72 (bs, 1 H, CONH); 7.09 (bs, 1 H, CONH); 7.99 (s, 1 H, H-pyrazine).

3-Allylamino-5-cyano-2-pyrazinecarboxamide (IV). Allylamine (1.43 g) afforded *IV* in 78% yield, m.p. 148 – 150 °C. For $C_9H_9N_5O$ (203.2) calculated: 53.20% C, 4.46% H, 34.46% N; found: 53.47% C, 4.10% H, 34.66% N. IR spectrum: 3 420 (NH amide); 2 280 (CN); 1 660 (CO amide); 1 460, 1 360, 1 280, 1 210, 1 010 (pyrazine nucleus); 1 560 (NH amide). ^{1}H NMR spectrum: 4.12 (m, 2 H, CH_2N); 5.18 (m, 1 H, *trans*-CH); 5.35 (m, 1 H, *cis*-CH); 5.92 (m, 2 H, =CH– and CONH); 7.67 (bs, 1 H, CONH); 7.97 (s, 1 H, H-pyrazine); 8.91 (bs, 1 H, NH).

5-Cyano-3-diallylamino-2-pyrazinecarboxamide (V). Diallylamine (2.43 g) afforded *V* in 81% yield, m.p. 158 – 159 °C. For $C_{12}H_{13}N_5O$ (243.3) calculated: 59.25% C, 5.39% H, 28.79% N; found: 59.06% C, 5.24% H, 28.54% N. IR spectrum: 3 360 (NH amide); 2 280 (CN); 1 660 (CO amide); 1 460, 1 300, 1 260, 1 150, 1 020 (pyrazine nucleus); 1 550 (NH amide). ^{1}H NMR spectrum: 4.14 (qd, 4 H, $(CH_2)_2N$); 5.17 (m, 2 H, 2 × *trans*-CH); 5.30 (m, 2 H, 2 × *cis*-CH); 5.76 (m, 2 H, 2 × =CH–); 8.06 (s, 1 H, H-pyrazine).

3-Butylamino-5-cyano-2-pyrazinecarboxamide (VI). Butylamine (0.90 g) gave *VI* in 65% yield, m.p. 126 – 127 °C. For $C_{10}H_{13}N_5O$ (219.2) calculated: 54.78% C, 5.98% H, 31.94% N; found: 54.92% C, 5.76% H, 31.84% N. IR spectrum: 3 430 (NH amide); 2 275 (CN); 1 685 (CO amide); 1 420, 1 395, 1 310, 1 210 (pyrazine nucleus); 1 580 (NH amide). ^{1}H NMR spectrum: 0.97 (t, J = 7, 3 H, CH_3); 1.23 – 1.79 (m, 4 H, $(CH_2)_2$); 3.43 (m, 2 H, CH_2N); 5.70 (bs, 1 H, CONH); 7.65 (bs, 1 H, CONH); 7.93 (s, 1 H, H-pyrazine); 8.80 (bs, 1 H, NH).



	R^1	R^2
I	C_2H_5	C_2H_5
II	H	$CH_3(CH_2)_2$
III	$CH_3(CH_2)_2$	$CH_3(CH_2)_2$
IV	H	CH_2=CH–CH_2
V	CH_2=CH–CH_2	CH_2=CH–CH_2
VI	H	$CH_3(CH_2)_3$

	R^1	R^2
VII	H	$(CH_3)_2CHCH_2$
VIII	$CH_3(CH_2)_3$	$CH_3(CH_2)_3$
IX	$-(CH_2)_4-$	
X	$-(CH_2)_5-$	
XI	$-(CH_2)_2O(CH_2)_2-$	

5-Cyano-3-isobutylamino-2-pyrazinecarboxamide (VII). Isobutylamine (0.90 g) afforded *VII* in 69% yield, m.p. 147 – 148 °C. For $C_{10}H_{13}N_5O$ (219.2) calculated: 54.78% C, 5.98% H, 31.94% N; found: 54.69% C, 5.72% H, 32.09% N. IR spectrum: 3 410 (NH amide); 2 290 (CN); 1 685 (CO amide); 1 395, 1 290, 1 210, 1 160, 1 110, 1 060 (pyrazine nucleus); 1 580 (NH amide). ^{1}H NMR spectrum: 0.95 (d, J = 6.5, 6 H, 2 × CH_3); 1.70 (m, 1 H, CH); 3.45 (m, 2 H, CH_2N); 5.70 (bs, 1 H, CONH); 7.67 (bs, 1 H, CONH); 7.93 (s, 1 H, H-pyrazine); 8.81 (bs, 1 H, NH).

5-Cyano-3-dibutylamino-2-pyrazinecarboxamide (VIII). Dibutylamine (2.31 g) gave *VIII* in 78% yield, m.p. 99 – 101 °C. For $C_{14}H_{21}N_5O$ (275.4) calculated: 61.07% C, 7.69% H, 25.43% N; found: 60.96% C, 7.60% H, 25.26% N. IR spectrum: 3 380 (NH amide); 2 280 (CN); 1 660 (CO amide); 1 440, 1 395, 1 310, 1 190, 1 130 (pyrazine nucleus); 1 580 (NH amide). ^{1}H NMR spectrum: 0.92 (t, J = 7, 6 H, 2 × CH_3); 1.13 – 1.76 (m, 8 H, 2 × $(CH_2)_2$); 3.50 (m, 4 H, 2 × CH_2N); 7.98 (s, 1 H, H-pyrazine).

5-Cyano-3-pyrrolidino-2-pyrazinecarboxamide (IX). Pyrrolidine (1.77 g) afforded *IX* in 73% yield, m.p. 250 – 253 °C. For $C_{10}H_{11}N_5O$ (217.2) calculated: 55.29% C, 5.10% H, 32.24% N; found: 55.28% C, 4.98% H, 32.14% N. IR spectrum: 3 360 (NH amide); 2 280 (CN); 1 660 (CO amide); 1 395, 1 360, 1 310, 1 275, 1 250, 1 220, 1 170, 1 135 (pyrazine nucleus); 1 550 (NH amide). ^{1}H NMR spectrum: 1.98 (m, 4 H, CH_2CH_2); 3.51 (m, 4 H, $(CH_2)_2N$); 5.65 (bs, 1 H, CONH); 7.06 (bs, 1 H, CONH); 8.01 (s, 1 H, H-pyrazine).

5-Cyano-3-piperidino-2-pyrazinecarboxamide (X). Piperidine (2.13 g) gave *X* in 80% yield, m.p. 200 – 202 °C. For $C_{11}H_{13}N_5O$ (231.3) calculated: 57.13% C, 5.67% H, 30.28% N; found: 56.91% C, 5.72% H, 30.27% N. IR spectrum: 3 370 (NH amide); 2 275 (CN); 1 660 (CO amide); 1 440, 1 390, 1 300, 1 270, 1 210, 1 050 (pyrazine nucleus); 1 550 (NH amide). ^{1}H NMR spectrum: 1.69 (m, 6 H, $(CH_2)_3$); 3.56 (m, 4 H, $(CH_2)_2N$); 5.78 (bs, 1 H, CONH); 7.20 (bs, 1 H, CONH); 8.02 (s, 1 H, H-pyrazine).

5-Cyano-3-morpholino-2-pyrazinecarboxamide (XI). Morpholine (2.18 g) afforded *XI* in 92% yield, m.p. 236 – 238 °C. For $C_{10}H_{11}N_5O_2$ (233.2) calculated: 51.50% C, 4.75% H, 30.03% N; found: 51.56% C, 4.50% H, 29.88% N. IR spectrum: 3 380 (NH amide); 2 280 (CN); 1 650 (CO amide); 1 315, 1 300, 1 265, 1 220, 1 140, 1 090, 1 020 (pyrazine nucleus); 1 555 (NH amide). ^{1}H NMR spectrum: 3.49 (AA′ part of AA′XX′ system, 4 H, $(CH_2)_2O$), 3.70 (XX′ part of AA′XX′ system, 4 H, $(CH_2)_2N$), 7.86 (bs, 1 H, CONH), 8.23 (bs, 1 H, CONH), 8.39 (s, 1 H, H-pyrazine).

This study was supported by the Internal Grant Agency of Charles University (Regist. No. 40/93). The authors thank Dr V. Buchta for providing antimycotic data. They also thank Mrs D. Karlickova and Mrs J. Zizkova for performing the elemental analyses and recording the IR spectra.

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Translated by the author (M. D.).