Synthesis and Biological Activities of Some Pyrrolopyrazoles and 2-Pyrazolines

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Cycloaddition reactions of the nitrilimines **4-6** with *N*-arylmaleimides **7** and acrylamide (**11**) yield the pyrrolopyrazole derivatives **8-10** and 2-pyrazolines **12**, respectively, in excellent yield. The regioselectivity and biological activities of some of the new compounds were investigated.

Synthese und biologische Aktivität einiger Pyrrolopyrazole und 2-Pyrazoline

Cycloadditionen der Nitrilimine **4-6** mit den Maleinimiden **7** und Acrylamid (**11**) führt in sehr guten Ausbeuten zu den Pyrrolopyrazolen **8-10** bzw. zu den 2-Pyrazolinen **12**. Regioselektivität und biologische Aktivität der neuen Verbindungen wurden untersucht.

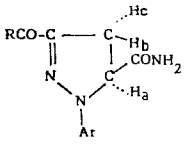
The hydrazonyl halides **1-3** undergo 1,3-base catalyzed elimination to give the nitrilimines **4-6** (Scheme 1)[1,2]. The latter are versatile intermediates for 1,3-dipolar cycloaddition reactions and have been employed in the syntheses of numerous heterocycles[1-3].

In continuation of our research directed towards exploring the synthetic potentials of the hydrazonyl halides **1-3**, we report on the cycloaddition reaction of **1-3** with the *N*-arylmaleimides **7a-d** and acrylamide **11** aiming to synthesize the pyrrolopyrazoles **8-10** and 2-pyrazoline **12** and to study their biological activity.

The cycloaddition reactions of the *C*-phenylaminocarbonyl-*N*-arylnitrilimines **4A,B**, generated *in situ* by treatment of the corresponding *C*-phenylaminocarbonyl-*N*-arylmethanohydrazonyl chlorides **1A,B** with triethylamine, with *N*-arylmaleimides **7a-d** gave, in each case, one product as evidenced by tlc, in almost quantitative yield. The assigned structures of the cycloadducts **8Aa-d** and **8Ba-d** isolated were supported by analytical and spectral data. The ^{1}H nmr spectra of the cycloadducts **8Aa-d** and **8Ba-d** are characterized by two doublets (J = 9 Hz) near δ 5.0 and 5.8 ppm assignable to 3a H and 6a H, respectively. On the basis of J = 9 Hz the adducts **8Aa-d**, **8Ba-d** were assigned cis configuration[4]. Similarly, nitrilimines **5A,B** and **6B** derived from the corresponding hydrazonyl chlorides **2A,B** and **3B**, respectively, react with *N*-arylmaleimides to give the cycloadducts **9Aa-d**, **9Ba-d**, and **10Ba-d**. Their structures were assigned on the basis of elemental analysis and spectral data.

The reaction of the nitrilimines **2B-D**, generated *in situ* by treatment of the corresponding hydrazonyl chlorides **1B-D** with triethylamine, with acrylamide afforded exclusively the 5-carboxamido-2-pyrazoline derivatives **12B-D**. The regiochemistry of **12B-D** was assigned on the basis of the similarity of the chemical shifts of the 4-CH_2 and 5-CH protons with those reported for 3-substituted 2-pyrazoline-5-carboxamides (Table 1)[5]. The data show that the 3-phenylaminocarbonyl group slightly deshields the 4-CH_2 protons more than the 3-ethoxycarbonyl and the 3-acetyl analogs.

Table 1: Characteristic ^{1}H-NMR data of some 3-substituted 2-pyrazoline-5-carboxamides



R	H_a	H_b	H_c
C_6H_5NHCO	4.90 (dd)	3.70 (dd)	3.10 (dd)
C_2H_5OCO	4.90 (dd)	3.54 (dd)	2.97 (dd)
CH_3CO	4.87 (dd)	3.68 (dd)	2.89 (dd)

Biological Results

Results of antibacterial tests are shown in Table 2, it reveals that only **8Bc** and **10Ba** have significant activity. The

Table 2: Antibacterial activities *in vitro*

Organism	8Bc	8Bd	9Ac	10a	10c	10d
Bacillus cereus	++	++	-	++	-	-
Bacillus lichereforrnis	++	-	-	++	-	-
Bacillus subtilis	++	-	-	++	++	++
Micrococcus luteus	-	-	-	++	-	-
Mycobacterium phlei	+++	-	++	++++	-	-
Proteus vulqaris	++	-	-	++	-	-

Inhibition zone around the disc (each disc contains 10 μg):
- = negative result + = 9 mm ++ = 10-12 mm +++ = 13-14 mm ++++ = 18 mm.
Compounds not listed do not show any effects.

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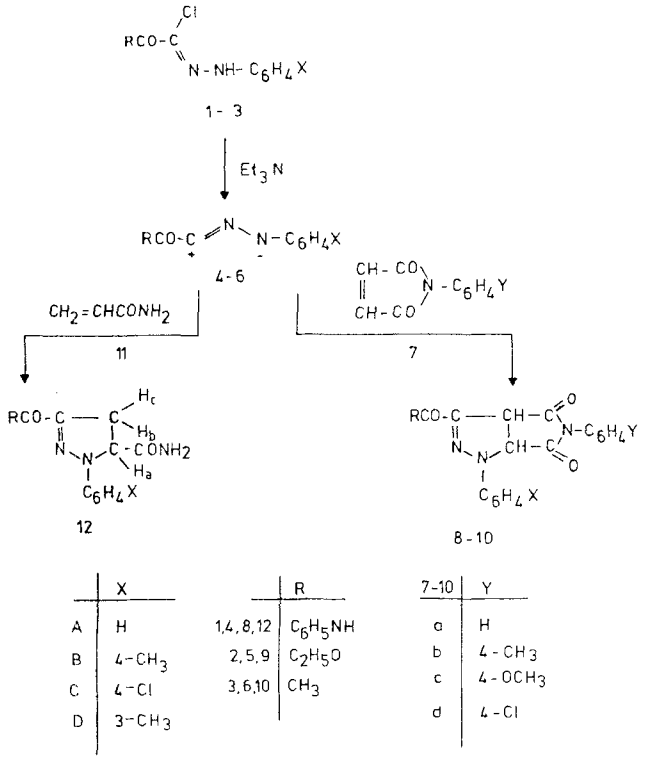

following bacterial species showed negative results against all tested compounds: *Erwinia carotovora, Var. carotovora*; *Erwinia carotovora*; *Var. citrullis*; *Erwinia toxica*; *Pseudomonas lachrymans*; *E. coli*; and *Serratia marescence*.

Experimental Part

Melting points: uncorrected.- IR spectra: Pye Unicam SP-1100, KBr discs.- ^{1}H-NMR spectra: Varian EM 390, 90 MHz, DMSO-d_6, TMS as int. standard; Chemical shifts in ppm units.- Microanalysis: microanalytical center at Cairo University.- Hydrazonyl chlorides[6-8] and N-arylmaleimides[9] were prepared using literature procedure.- Temp. in °C.

Pyrrolopyrazole Derivatives **8-10**; *General Procedure*

To a solution of the appropriate hydrazonyl chlorides **1-3** (5 mmoles) and the appropriate N-arylmaleimide **7a-d** (5 mmoles) in chloroform (30 ml) was added triethylamine (0.7 ml, 5 mmoles), the mixture was refluxed for 8 h and then cooled. The solvent was evaporated in vacuo and the residue triturated with a little methanol, whereupon it solidified. The crude solid was crystallized from the suitable solvent. Compounds **8Aa-d, 8Ba-d, 9Aa-d**, and **10Ba-d** are listed below.

3a,4,6,6a-Tetrahydro-1,5-diphenyl-3-phenylaminocarbonyl-1H,5H-pyrrolo-[3,4-c]pyrazole-4,6-dione (**8Aa**)

95%; m.p. 239°.- $C_{24}H_{18}N_4O_3$ (410.2) Calc. C 70.2 H 4.42 N 13.6 Found C 70.0 H 4.39 N 13.5.- IR: 3380 (NH); 1700 (C=O); 1660 (C=O).- ^{1}H-NMR: 10.2 (s, 1H, NH); 7.0-7.8 (m, 15H); 5.65 (d, J = 9 Hz, 1H); 5.15 (d, J = 9 Hz, 1H).

3a,4,6,6a-Tetrahydro-1-phenyl-3-phenylaminocarbonyl-5-(p-tolyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**8Ab**)

90%; m.p. 260°.- $C_{25}H_{20}N_4O_3$ (424.2) Calc. C 70.7 H 4.75 N 13.2 Found C 70.5 H 4.7 N 13.0.- IR: 3385 (NH); 1720 (C=O); 1655 (C=O).- ^{1}H-NMR: 10.25 (s, 1H); 7.05-7.8 (m, 14H); 5.65 (d, J = 9 Hz, 1H), 5.15 (d, J = 9 Hz, 1H); 2.35 (s, 3H).

3a,4,6,6a-Tetrahydro-1-phenyl-3-phenylaminocarbonyl-5-(p-methoxyphenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**8Ac**)

90%; m.p. 238°.- $C_{25}H_{20}N_4O_4$ (440.3) Calc. C 68.2 H 4.58 N 12.7 Found C 68.0 H 4.42 N 12.5.- IR: 3380 (NH); 1700 (C=O); 1660 (C=O).- ^{1}H-NMR: 10.2 (s, 1H); 7.0-7.8 (m, 14H); 5.65 (d, J = 9 Hz, 1H); 5.15 (d, J = 9 Hz, 1H); 3.75 (s, 3H).

3a,4,6,6a-Tetrahydro-1-phenyl-3-phenylaminocarbonyl-5-(p-chlorophenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**8Ad**)

95%; m.p. 126°.- $C_{24}H_{17}ClN_4O_3$ (444.5) Calc. C 64.7 H 3.82 N 12.6 Found C 64.9 H 3.75 N 12.5.- IR: 3300 (NH); 1700 (C=O); 1650 (C=O).

3a,4,6,6a-Tetrahydro-1-(p-tolyl)-5-phenyl-3-phenylaminocarbonyl-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**8Ba**)

85%; m.p. 231°.- $C_{25}H_{20}N_4O_3$ (424.2) calc. C 70.7 H 4.75 N 13.2 Found C 70.5 H 4.70 N 13.1.- IR: 3380 (NH); 1700 (C=O); 1660 (C=O).- ^{1}H-NMR: 10.2 (s, 1H); 7.0-7.8 (m, 14H); 5.65 (d, J = 9 Hz, 1H); 5.15 (d, J = 9 Hz, 1H); 2.25 (s, 3H).

3a,4,6,6a-Tetrahydro-1,5-di-(p-tolyl)-3-phenylaminocarbonyl-1H,5H-pyrrolo-[3,4-c]pyrazole-4,6-dione (**8Bb**)

90%; m.p. 265°.- $C_{26}H_{22}N_4O_3$ (438.3) Calc. C 71.2 H 5.06 N 12.8 Found C 71.0 H 5.0 N 12.6.- IR: 3380 (NH); 1710 (C=O); 1670 (C=O).

3a,4,6,6a-Tetrahydro-1-(p-tolyl)-3-phenylaminocarbonyl-5-(p-methoxyphenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**8Bc**)

85%; m.p. 214°.- $C_{26}H_{22}N_4O_4$ (454.3) Calc. C 68.7 H 4.88 N 12.3 Found C 68.5 H 4.8 N 12.1.- IR: 3400 (NH); 1700 (C=O); 1660 (C=O).

3a,4,6,6a-Tetrahydro-1-(p-tolyl)-3-phenylaminocarbonyl-5-(p-chlorophenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**8Bd**)

95%; m.p. 243°.- $C_{25}H_{19}ClN_4O_3$ (458.5) Calc. C 65.4 H 4.14 N 12.2 Found C 65.2 H 4.0 N 12.1.- IR: 3380 (NH); 1720 (C=O) and 1655 (C=O).- ^{1}H-NMR: 10.1 (s, 1H); 7.0-7.75 (m, 13H); 5.55 (d, J = 9 Hz, 1H); 5.1 (d, J = 9 Hz, 1H); 2.25 (s, 3H).

3a,4,6,6a-Tetrahydro-1,5-diphenyl-3-ethoxycarbonyl-1H,5H-pyrrolo-[3,4-c]pyrazole-4,6-dione (**9Aa**)

90%; m.p. 163°.- $C_{20}H_{17}N_3O_4$ (363.2) Calc. C 66.1 H 4.72 N 11.6 Found C 65.9 H 4.68 N 11.7.- IR: 1730 (C=O) and 1710 (C=O).- ^{1}H-NMR: 7.0-7.8 (m, 10H); 5.5 (d, J = 9 Hz, 1H); 5.1 (d, J = 9 Hz, 1H); 4.3 (q, J = 7 Hz, 2H); 1.3 (t, J = 7 Hz, 3H).

3a,4,6,6a-Tetrahydro-1-phenyl-3-ethoxycarbonyl-5-(p-tolyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**9Ab**)

95%; m.p. 203°.- $C_{21}H_{19}N_3O_4$ (377.2) Calc. C 66.8 H 5.07 N H11.1 Found C 66.6 H 5.0 N 10.9.

3a,4,6,6a-Tetrahydro-1-phenyl-3-ethoxycarbonyl-5-(p-methoxyphenyl)-1H-5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**9Ac**)

85%; m.p. 170°.- $C_{21}H_{19}N_3O_5$ (393.3) Calc. C 64.1 H 4.87 N 10.7 Found C 63.9 H 4.7 N 10.6.

3a,4,6,6a-Tetrahydro-1-phenyl-3-ethoxycarbonyl-5-(p-chlorophenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione (**9Ad**)

80%; m.p. 175°.- $C_{20}H_{16}ClN_3O_4$ (397.5) Calc. C 60.4 H 4.03 N 10.6 Found C 60.2 H 4.0 N 10.5.

3a,4,6,6a-Tetrahydro-1-(p-tolyl)-3-ethoxycarbonyl-5-phenyl-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione **(9Ba)**

90%; m.p. 230°.- $C_{21}H_{19}N_3O_4$ (377.3) Calc. C 66.8 H 5.07 N 11.1 Found C 66.7 H 5.0 N 10.9.- IR: 1730 (C=O) and 1710 (C=O).- ^{1}H-NMR: 7.1-7.9 (m, 9H); 5.4 (d, J = 9 Hz, 1H); 5.1 (d, J = 9 Hz, 1H); 4.2 (q, J = 7 Hz, 2H), 2.4 (s, 3H); 1.3 (t, J = 7 Hz, 3H).

3a,4,6,6a-Tetrahydro-1,5-di(p-tolyl)-3-ethoxycarbonyl-1H,5H-pyrrolo-[3,4-c]pyrazole-4,6-dione **(9Bb)**

90%; m.p. 205°.- $C_{22}H_{21}N_3O_4$ (391.2) Calc. C 67.5 H 5.41 N 10.7 Found C 67.4 H 5.3 N 10.5.

3a,4,6,6a-Tetrahydro-1-(p-tolyl)-3-ethoxycarbonyl-5(p-methoxyphenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione **(9Bc)**

85%; m.p. 169°.- $C_{22}H_{21}N_3O_5$ (407.3) Calc. C 64.8 H 5.2 N 10.3 Found C 64.6 H 5.1 N 10.1.

3a,4,6,6a-Tetrahydro-1-(p-tolyl)-3-ethoxycarbonyl-5(p-chlorophenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione **(9Bd)**

80%; m.p. 199°.- $C_{21}H_{18}ClN_3O_4$ (411.6) Calc. C 61.2 H 4.37 N 10.2 Found C 61.1 H 4.2 N 10.1.

3a,4,6,6a-Tetrahydro-1-(p-tolyl)-3-acetyl-5-phenyl-1H,5H-pyrrolo-[3,4-c]pyrazole-4,6-dione **(10Ba)**

80%; m.p. 219°.- $C_{20}H_{17}N_3O_3$ (347.2) Calc. C 63.3 H 4.52 N 11.1 Found C 63.2 H 4.42 N 10.9.- IR: 1715 (C=O) and 1710 (C=O).- ^{1}H-NMR: 7.0-7.9 (m, 9H); 5.4 (d, J = 9 Hz, 1H); 5.1 (d, J = 9 Hz, 1H); 2.5 (s, 3H); 2.4 (s, 3H).

3a,4,6,6a-Tetrahydro-1,5-di-(p-tolyl)-3-acetyl-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione **(10Bb)**

85%; m.p. 217°.- $C_{21}H_{19}N_3O_3$ (261.2) Calc. C 69.7 H 5.3 N 11.6 Found C 69.5 H 5.22 N 11.5.

3a,4,6,6a-Tetrahydro-1-(p-tolyl)-3-acetyl-5-(p-methoxyphenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione **(10Bc)**

90%; m.p. 214°.- $C_{21}H_{19}N_3O_4$ (377.2) Calc. C 66.8 H 5.07 N 11.1 Found C 66.7 H 4.93 N 11.0.

3a,4,6,6a-Tetrahydro-1-(p-tolyl)-3-acetyl-5-(p-chlorophenyl)-1H,5H-pyrrolo[3,4-c]pyrazole-4,6-dione **(10Bd)**

80%; m.p. 179°.- $C_{20}H_{16}ClN_3O_3$ (381.5) Calc. C 62.9 H 4.19 N 11.0 Found C 62.8 H 4.09 N 10.9.

Preparation of 5-Carboxamido-2-pyrazoline Derivatives **12B-D**

Triethylamine (0.7 ml, 5 mmole) was added to a mixture of acrylamide (0.4 gm, 5 mmoles) and of the appropriate hydrazonyl chloride **1B-D** (5 mmoles) in benzene (40 ml). The mixture was refluxed for 10 h and filtered to remove the triethylamine hydrochloride. The excess solvent was evaporated under reduced pressure and the residue was triturated with a little methanol when it solidified. The crude solid was crystallized from the suitable solvent. Compounds **12B-D** are listed below.

1-(p-Tolyl)-3-phenylaminocarbonyl-5-carboxamido-2-pyrazoline **(12B)**

80%; $C_{18}H_{18}N_4O_2$ (322.2) Calc. C 67.0 H 5.58 N 17.4 Found C 66.8 H 5.5 N 17.2.- IR: 1680 (C=O) and 1640 (C=O).- ^{1}H-NMR: 10.2 (s, 1H); 7.0-8.0 (m, 9H); 4.9 (dd, J = 8;12 Hz, $1H_a$); 3.7 (dd, J = 12;18 Hz, $1H_b$); 3.1 (dd, J = 8;18 Hz, H_c), 2.4 (s, 3H).

1-(p-Chlorophenyl)-3-phenylaminocarbonyl-5-carboxamido-2-pyrazoline **(12C)**

85%; m.p. 269°.- $C_{17}H_{15}ClN_4O_2$ (342.6) Calc. C 59.6 H 4.37 N 16.4 Found C 59.4 H 4.75 N 16.5.

1-(m-Tolyl)-3-phenylaminocarbonyl-5-carboxamido-2-pyrazoline **(12D)**

90%; m.p. 253°.- $C_{18}H_{18}N_4O_2$ (322.2) Calc. C 67.0 H 5.58 N 17.4 Found C 66.7 H 5.43 N 17.0.

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