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[Ph 260]

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Polyfunctionally Substituted Pyridines from Cyanoacetamide and Cyanoacetanilide

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The polyfunctionally substituted pyridines **3a, b** obtained from cyanoacetamide and cyanoacetanilide are reactive reagents. They cyclize under acidic and basic conditions and react with electrophiles to yield a variety of compounds (Scheme 2).

Pyridine mit mehreren funktionellen Gruppen aus Cyanoacetamid und Cyanoacetanilid

Aus den im Titel genannten Verbindungen entstehen die sechsfach substituierte Pyridine **3a, b**, die sauer und basisch cyclisiert und mit Electrophilen umgesetzt werden (Schema 2).

In the course of a programme designed to investigate the efficiency of pyridine derivatives as antiulcer agents[1–4], we needed a simple synthesis of polyfunctionally substituted pyridines. This report concerns with the synthesis of such pyridine derivatives.

Cyanoacetamide **(1a)** and cyanoacetanilide **(1b)** reacted with malononitrile **(2)** in a molar ratio 1:2 to give pyridinyl acetamide and acetanilide derivatives **3a** and **3b**, respectively. Structures of **3a, b** were established based on IR- and ^{1}H-NMR spectra (see Experimental part). A logical mechanism for this reaction was based on dimerisation of malononitrile in basic medium to give **4**[5,6], followed by its reaction with **1a** and **1b** to give **3a** and **3b**, respectively. This sequence was confirmed via fusion of equimolar

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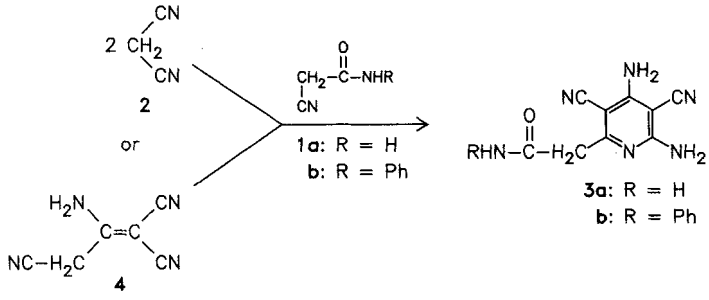
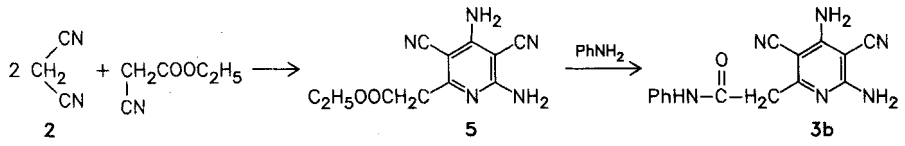
amounts of malononitrile dimer **(4)** with **1a** and **1b** and a catalytic amount of piperidine when **3a, b** respectively, were obtained. On the other hand, fusion of malononitrile and ethyl cyanoacetate in a molar ratio 2:1 gave ethyl α-(2,4-diamino-3,5-dicyano-6-pyridinyl)-acetate **(5)**. The structure of **5** was assigned on the basis of its analytical and spectral data. **5** was fused with aniline at 120° where the anilide **3b** was obtained.



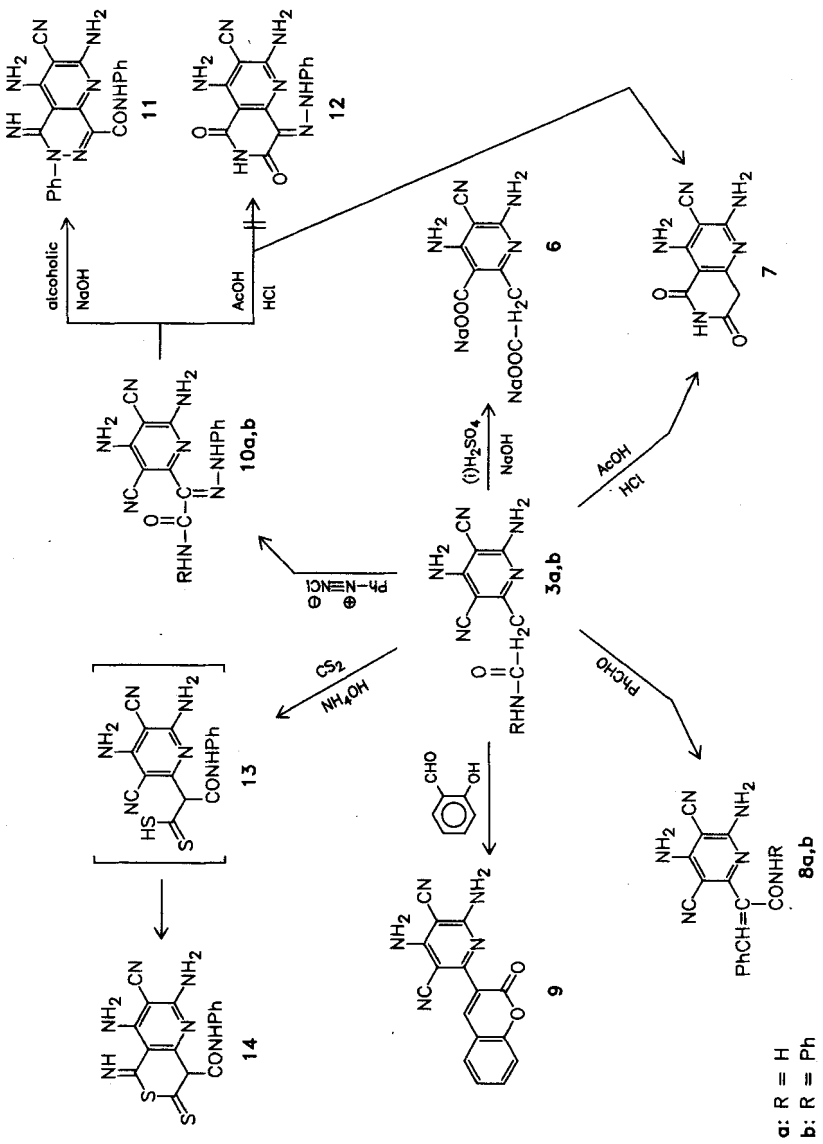


Heating of **3a, b** with conc. H_2SO_4 followed by NaOH till pH 10 gives the disodium salt **6**. Formation of **6** proves the reactivity of C-5 CN and the stability of C-3 CN in the pyridine ring which may be caused by the presence of two flanking amino groups. This different reactivity of the two CN functions was further observed in an acid medium: refluxing **3a, b** in acetic acid/HCl a product $C_9H_7N_5O_2$ was obtained. Structure **7** was proposed for the reaction product based on analytical and spectral data.

Compounds **3a, b** condens with aromatic aldehydes, thus, with benzaldehyde the benzylidine derivatives **8a, b**, respectively, were obtained. On the other hand, **3a, b** with salicylaldehyde gave the coumarine **9**. Such formation of a coumarine derivative finds parallism to that reported[7, 8].

3a and **3b** are coupled with benzenediazonium chloride in the presence of OH^- to the phenylhydrazones **10a** and **10b**, respectively. **10b** shows two pathways of cyclisation in different media. Thus refluxing **10b** in alcoholic NaOH gave the pyrido [2,3-d]pyridazine derivative **11**[9]. On the other hand, refluxing **10b** in acetic acid/HCl did not give the expected cyclized hydrazo derivative **12** but a colourless product $C_9H_7N_5O_2$ was obtained via elimination of the phenylazogroup[10]. The product was identified to be **7** by m.p. and mixed m.p.

3b reacts with CS_2 in basic medium to give the cyclized adduct **14** which is formed via the intermediate **13**. Compounds **3a, b–14** are tested for gastric antisecretory and cytoprotective properties, the results will be published in a forthcoming paper.



Experimental Part

M.P.s are uncorrected. – IR spectra (KBr): Pye Unicam SP-1000 Spectrophotometer. – ^{1}H-NMR spectra (DMSO): EM-90 MHZ Spectrometer, TMS as int. standard; chemical shifts in δ values (ppm). – Microanalytical data: Microanalytical Data Unit at Cairo University.

α-(2,4-Diamino-3,5-dicyano-6-pyridinyl)-acetamide (3a) and α-(2,4-Diamino-3,5-dicyano-6-pyridinyl)-acetanilide **(3b)**

Method A: A mixture of malononitrile **(2)** (0.5 mol) and cyanoacetamide or cyanoacetanilide (0.25 mol) containing piperidine (½ ml) was fused in an oil bath at 140° for ½ h, then left to cool. The solid product was washed with EtOH.

Method B: The procedure described above was carried out but using 3-amino-2,4-dicyano-crotononitrile **(4)** instead of **2** with equivalent amounts of **1a** or **1b**.

3a: pale yellow crystals from dioxan; yield 70 %; m.p. > 300°. - IR: 3500–3300 (NH_2); 2985 (CH_2); 2225 (C-3 CN); 2220 (C-5 CN); 1680 (C=O) and 1630 cm^{-1} (NH_2 deformation). - ^{1}H-NMR: δ (ppm) 4.35 (s, 2H, CH_2); 4.68 (s, 2H, NH_2 and 6.58–6.71 (m, 4H, $2NH_2$). $C_9H_8N_6O$ (216.2) Calc. C 50.0 H 3.73 N 38.9 Found C 50.4 H 3.41 N 39.0.

3b: colourless crystals from dioxan; yield 73 %; m.p. > 300°. - IR: 3450–3300 (NH_2); 3050 (CH aromatic); 2980 (CH_2); 2225 (C-3 CN); 2220 (C-5 CN); 1690 (C=O) and 1630 cm^{-1} (NH_2, deformation). - ^{1}H-NMR: δ (ppm) 4.31 (s, 2H, CH_2); 4.68; 6.81 (2s, 4H, 2 NH_2); 7.35 (m, 5H, C_6H_5) and 10.11 (s, br, 1H, NH). - $C_{15}H_{12}N_6O$ (292.3) Calc. C 61.6 H 4.14 N 28.8 Found C 61.5 H 4.00 N 29.1.

Ethyl α-(2,4-diamino-3,5-dicyano-6-pyridinyl)-acetate **(5)**

2 (0.1 mol), ethyl cyanoacetate (0.05 mol) and ½ ml of piperidine are heated in an oil bath at 140° for 40 min then left to cool. The product was heated in EtOH (100 ml), bhen collected by filtration. **5** forms yellow crystals from DMF; yield 65 %; **5** darkens at 295°. - IR: 3350, 3200 (NH_2); 2950 (CH_2, CH_3); 2225 (C-3 CN); 2220 (C-5 CN); 1710 (C=O) and 1650 cm^{-1} (NH_2, deformation). - ^{1}H-NMR: δ (ppm) 1.68 (t, 3H, CH_3); 3.85 (s, 2H, CH_2); 4.58 (q, 2H, CH_2); 5.70 (s, 2H, NH_2); 7.23 (s, 2H, NH_2). - $C_{11}H_{11}N_5O_2$ (245.2) Calc. C 53.9 H 4.48 N 28.6 Found C 54.1 H 4.33 N8.6.

Sodium α-(2,4-diamino-3-cyano-5-sodiumoxy carbonyl-6-pyridinyl)-acetate **(6)**

3a, 3b (0.01 mol) and H_2SO_4 (70 %, 15 ml) were heated in a boiling water bath for 2 h, then poured onto ice/water. The product was precipitated by adding NaOH (25 %) till pH 10, then collected by filtration. **6** forms colourless crystals from EtOH/H_2O; yield 65 %; m.p. > 300°. - IR: 3450–3250 (NH_2); 2980 (CH_2); 1680 (C=O) and 1630 (NH_2, deformation). - $C_9H_6O_4N_4Na_2$ (280.1) Calc. C 38.6 H 2.14 N 20.0 Found C 38.4 H 2.09 N 19.6.

2,4-Diamino-3-cyano-5,7-dioxo-8H-pyrido[4,3-b]-pyridine **(7)**

Method: A solution of **3a** or **3b** in a mixture of acetic acid (25 ml) and HCl (5 ml) was heated under reflux for 4 h then poured onto ice/water, the solid precipitated by neutralisation with NaOH (25 % was collected by filtration.

Method B: A solution of **10b** (0.01 mol) in acetic acid (30ml) and HCl) (10 ml) was heated under reflux for 5 h then poured onto ice/water. The resulting product was precipitated by adding NaOH till neutralization and collected by filtration.

7 forms red crystals from DMF; yield 59 %; m.p. > 300°. - IR: 3450–3310 (NH_2, NH); 2980 (CH_2); 2220 (CN); 1680, 1700 (two C=O) and 1630 cm^{-1} (NH_2 deformation). - ^{1}H-NMR: δ (ppm) 4.57 (s, 2H, CH_2); 5.75 (s, 2H, NH_2); 6.89 (s, 2H, NH_2) and 10.10 (s, br, 1H, NH). $C_9H_7O_2N_5$ (217.2) Calc. C 49.8 H 33.25 N 32.3 Found C 49.7 H 3.01 N 32.7.

α-(2,4-Diamino-3,5-dicyano-6-pyridinyl)-benzalacetamide **(8a)** *and α-(2,4-Diamino-3,5-dicyano-6-pyridinyl)-benzalacetanilide* **(8b)**

General procedure: To a solution of **3a** or **3b** (0.01 mol) in DMF (30 ml) containing ½ ml of piperidine, benzaldehyde (0.01 mol) was added. The mixture was heated under reflux for 2 h then evapourated i. vac. The solid product was triturated with EtOH and collected by filtration. **8a** forms yellow crystals from EtOH; yield 65 %; m.p. 245–247°. - IR: 3450, 3300 (NH_2); 3050 (CH aromatic); 2225 (C-3 CN); 2220

(C-5 CN); 1690 (C=O) and 1635 cm^{-1} (NH_2 deformation). – ^{1}H-NMR: δ (ppm) = 4.60 (s, 2H, NH_2); 5.98 (s, 2H, NH_2); 6.76 (s, 2H, NH_2) and 7.29–7.35 (m, 6H, CH, C_6H_5). – $C_{16}H_{12}ON_6$ (304.) Calc. C 63.2 H 3.98 N 27.6 Found C 62.9 H 3.54 N 27.7.

8b forms orange crystals from EtOH; yield 69 %; m.p. > 300 °. – IR: 3450–3330 (NH_2); 3045 (CH aromatic); 2225 (C-3 CN); 2220 (C-5 CN); 1685 (C=O) and 1630 cm^{-1} (NH_2 deformation). – ^{1}H-NMR: δ (ppm)= 4.58 (s, 2H, NH_2); 6.12 (s, 2H, NH_2); 6.17 (s, 2H, NH_2); 7.30–7.34 (m, 11H, CH, $2C_6H_5$); and 10.34 (s, br, 1H, NH). – $C_{22}H_{16}ON_6$ (380.4) Calc. C 69.5 H 4.21 N 22.1 Found C 69.2 H 4.01 N 21.8.

3-(2',4'-Diamino-3',5'-dicyano-6'-pyridinyl)-coumarin-2-one **(9)**

The same procedure as described for **8a, b** was carried out using salicylaldehyde instead of benzaldehyde. **9** forms orange crystals from EtOH; yield 78 %; m.p. 222–226°. – IR: 3450–3300 (NH_2); 3050 (CH aromatic); 2225 (C-3 CN); 2220 (C-5 CN); 1685 (C=O) and 1630 cm^{-1} (deformation). – ^{1}H-NMR: = 4.65 (s, 2H, NH_2); 6.57 (s, 2H, NH_2); 7.35–7.55 (m, 5H, C_6H_4 and pyrane CH). – $C_{16}H_9O_2N_5$ (303.3) Calc. C 63.4 H 2.99 N 23.1 Found C 63.6 H 3.35 N 23.4.

α-(2,4-Diamino-3,5-dicyano-6-pyridinyl)-phenylhydrazo acetamide **(10a)** *and α-(2,4-Diamino-3,5-dicyano-6-pyridinyl)-phenylhydrazo acetanilide* **(10b)**

General procedure: To a solution of **3a** or **3b** (0.01 mol) in EtOH (30 ml) containing NaOH (10 ml, 5 %) benzenediazonium chloride (obtained by adding $NaNO_2$ solution to the equivalent amount of aniline in HCl with cooling and stirring) was added. The reaction was stirred for 1h and the solid product was collected by filtration. **10a** forms yellow crystals from EtOH; yield 70 %; m.p. 168°. – IR: 3450–3300 (NH_2, NH); 3050 (CH aromatic); 2225 (C-3 CN), 2220 (C-5 CN); 1680 (C=O) and 1630 cm^{-1} (NH_2 deformation). – ^{1}H-NMR: δ (ppm) = 4.15 (s, 2H, NH_2); 5.67, 6.34 (2s, 4H, $2NH_2$); 7.29 (s, 5H, C_6H_5); 10.23 (s, br, 1H, NH). – $C_{15}H_{12}N_8O$ (320.3) Calc. C 56.3 H 3.75 N 35.0 Found C 56.7 H 3.45 N 35.0.

10b forms orange-red crystals from EtOH; yield 76 %; m.p. 190–192°. – IR: 3450–3300 (NH_2, NH); 3050 (CH aromatic); 2220 (C-3 CN); 2210 (C-5 CN); 1690 (C=O) and 1630 cm^{-1} (NH_2 deformation). – ^{1}H NMR: δ (ppm) = 4.36 (s, 2H, NH_2); 6.15 (s, 2H, NH_2); 7.28–7.37 (m, 10H, $2C_6H_5$); 10.12, 10.45 (2s, br, 2H, 2NH). – $C_{21}H_{16}ON_8$ (396.4) Calc. C 63.6 H 4.04 N 28.3 Found C 63.5 H 4.26 N 28.0.

5,7-Diamino-6-cyano-1-phenyl-8-oxo-3-carbanilido-pyrido[2,3-d] pyridazine **(11)**

A solution of **10b** (0.01 mol) in EtOH (30 ml) containing 3 pellets of NaOH was heated under reflux for 3 h then poured onto ice/water containing a few drops of HCl. The solid product was collected by filtration. **11** forms colourless crystals from dioxan; yield 70 %; m.p. 285–287. – IR: 3450–3300 (NH_2); 3050 (CH aromatic); 2220 (CN); 1700, 1695 (two C=O) and 1630 cm^{-1} (NH_2 deformation). –^{1}H NMR: δ (ppm) = 4.67 (s, 2H, NH_2); 6.45 (s, 2H, NH_2); 7.35–7.41 (m, 10H, $2C_6H_5$); 10.31 (s, br, 1H, NH). $C_{21}H_{15}O_2N_7$ (397.4) Calc. C 63.5 H 3.77 N 24.7 found C 63.3 H 3.59 N 24.4.

6-Cyano-5,7-diamino-8-imino-2-thioxo-3-carboanilido-thiopyrano [4.3-b] pyridine **(14)**

To a suspension of **3b** (0.01 mol) in NH_4OH (50 ml) CS_2 (0.02 mol) was added. The mixture was left at room temp. overnight with stirring then the product was precipitated by adding HCl till pH 5 and collected by filtration. **14** forms reddish brown crystals from DMF; yield 62 %; m.p. > 300°. – IR: 3470–3330 (NH_2, NH); 3040 (CH aromatic); 2220 (CN); 1695 (C=O); 1630 (NH_2 deformation) and 1190 cm^{-1} (C=S). – ^{1}H NMR: δ (ppm) = 4.67 (s, 2H, NH_2); 5.99 (s, 1H, CH); 6.51 (s, 2H, NH_2); 7.41 (s, 5H, C_6H_5); 10.11, 11.25 (2s, br, 2H, 2NH). $C_{16}H_{12}ON_6S_2$ (368.4) Calc. C 52.2 H 3.26 N 22.8 Found C 52.0 H 2.99 N 22.6.

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Reaktionen mit Aziridinen, 40. Mitt.[1]

Nucleophile Ringöffnung von 2,2-Dimethylaziridinen durch die Anionen von Fluoren und Carbazol: Regioselektivitätssteuerung durch die Art der Aziridin-Aktivierung

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Eingegangen am 28. August 1986

Fluorenyl-Anion öffnet den Ring von sulfonyl-aktiviertem Dimethylaziridin **3** am unsubstituierten C-Atom. Fluorenyl- und Carbazol-Anion öffnen den Ring von acyl-aktiviertem **3** dagegen am tertiären C-Atom.

Reactions with Aziridines, XL:[1]
Nucleophilic Ring Opening of 2,2-Dimethylaziridines by the Anions of Fluorene and Carbazole. Control of Regioselectivity by the Kind of Aziridine Activation

The anion of fluorene opens the ring of sulfonylactivated 2,2-dimethylaziridine **3** at the unsubstituted carbon atom. In contrast, the anions of fluorene and carbazole open the ring of acyl-activated **3** at the tertiary carbon atom.

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