STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROCYCLES: NOVEL SYNTHESES OF PYRIDO[4,3-*d*]PYRIDAZINES AND OF PYRIDO[3,4-*d*]PYRIDAZINES

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As a part of our programme aimed at developing efficient syntheses of polyfunctionally substituted azines and condensed azines, we have in the past reported[1,2] efficient syntheses of compounds *I* – *III*. In conjuction of this work we report results of our further studies aimed at exploring the synthetic potentialities of *I* – *III*.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on Shimadzu 200-91506 spectrophotometer. ^{1}H NMR spectra were obtained in $(CD_3)_2SO$ with Varian GE 60 MHz spectrometer with TMS as internal standard, chemical shifts are expressed in δ ppm. Microanalytical data were performed by the Microanalytical Center at Cairo University.

Ethyl 5-Amino-3,4-dihydro-3,7-diphenyl-4-oxopyrido[3,4-*d*]pyridazine-1-carboxylate (*IV*)

Method A: A solution of *I* (0.01 mol, 2.83 g) was treated with benzaldehyde (0.01 mol, 1.0 ml), then with concentrated ammonia (30 ml of 30% solution). The reaction mixture was refluxed for 1 h and then evaporated in vacuo. The remaining solid product was triturated with water and the solid product, so formed, was collected by filtration and crystallized from methanol.

Pyridazine *IV*: m.p. 155 – 158 °C; yield 57%. IR spectrum: 3 200, 2 900 (NH_2); 1 720, 1 680 (CO). ^{1}H NMR spectrum: 1.3 t, 3 H (CH_3, J = 7); 4.1 q, 2 H (CH_2, J = 7); 7.2 – 7.7 m, 11 H (aromatic protons); 9.0 br, 2 H (NH_2). For $C_{22}H_{18}N_4O_3$ (386.4) calculated: 68.3% C, 4.6% H, 14.5% N; found: 68.60% C, 4.80% H, 15.00% N.

Method B: A solution of *II* (0.01 mol, 3.71 g) was treated with concentrated ammonia (30 ml of 30% solution). The reaction mixture was refluxed for 1 h and then evaporated in vacuo. The remaining product was triturated with water and the solid product, so formed, was collected by filtration, crystallized from methanol and identified (m.p. and mixed m.p.) as *IV*.

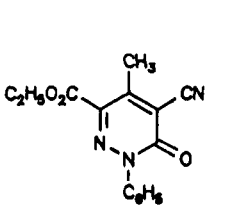
Ethyl 3,7-Diphenyl-3,4,5,6-tetrahydro-4,5-dioxopyrido[3,4-*d*]pyridazine-1-carboxylate (*V*)

A solution of *II* (0.01 mol, 3.71 g) in acetic acid (30 ml) was treated with concentrated hydrochloric acid (3.0 ml). The reaction mixture was refluxed for 3 h and then evaporated in vacuo. The remaining product was triturated with water. The solid product, so formed, was collected by filtration and crystallized from dioxane.

Compound *V*: m.p. 188 – 190 °C, yield 78%. IR spectrum: 3 300 (NH); 1 740, 1 670 (CO). ^{1}H NMR spectrum: 1.2 t, 3 H (CH_3, J = 7); 3.5 br, 1 H (NH); 4.1 q, 2 H (CH_2, J = 7); 7.4 – 7.8 m, 11 H (aromatic protons). For $C_{22}H_{17}N_3O_4$ (387.4) calculated: 68.2% C, 4.4% H, 10.8% N; found: 68.4% C, 4.4% H, 10.6% N.

3,7-Diphenyl-4,5-dioxo-3,4,5,6-tetrahydropyrido[3,4-*c*]pyridazine-1-carboxylic Acid (*VI*)

Method A: A suspension of *II* (0.01 mol, 3.71 g) in ethanol (30 ml) was treated with sodium hydroxide (0.01 mol, 0.4 g). The reaction mixture was refluxed for 5 h and then evaporated in vacuo. The remaining solid was then triturated with water and acidified with concentrated hydrochloric acid. The solid product, so formed, was collected by filtration and crystallized from methanol.



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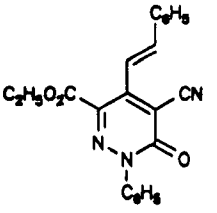

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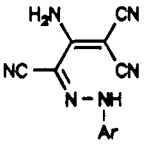

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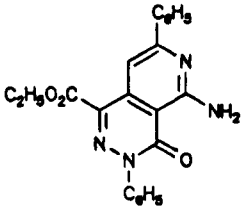

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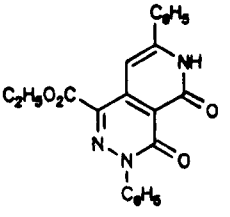

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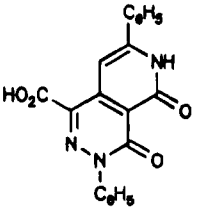

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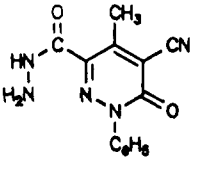

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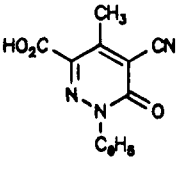
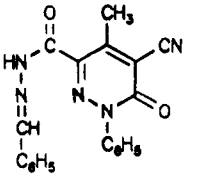


VIII



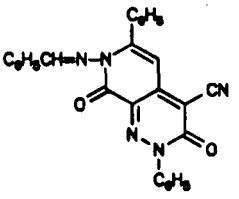
IX

Compound *VI*: m.p. 255 – 260 °C; yield 70%. IR spectrum: 3 500 – 2 800 (OH, NH); 1 740, 1 680 (CO). ^{1}H NMR spectrum: 4.4 br, 1 H (NH); 7.0 – 7.6 m, 11 H (aromatic protons). For $C_{20}H_{13}N_3O_4$ (359.3) calculated: 66.8% C, 3.6% H, 11.6% N; found: 66.6% C, 4.4% H, 10.6% N.

Method B: A solution of *V* (0.01 mol, 3.87 g) in ethanol (30 ml) was treated with sodium hydroxide (0.01 mol, 0.4 g). The reaction mixture was refluxed for 2 h and then evaporated in vacuo. The remaining product was treated as described above and the solid product isolated was identified (m.p. and mixed m.p.) as *VI*.

5-Cyano-4-methyl-1-phenyl-1,6-dihydro-6-oxopyridazine-3-carboxylic Acid Hydrazide (*VII*)

A suspension of *I* (0.01 mol, 2.83 g) in ethanol (50 ml) was treated with hydrazine hydrate (0.02 mol, 1.0 ml). The reaction mixture was refluxed for 4 h and then left to cool. The solid product, separated on standing, was collected by filtration and recrystallized from methanol.



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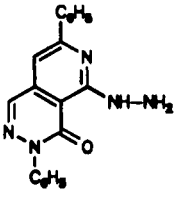

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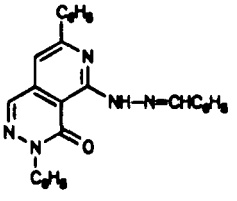

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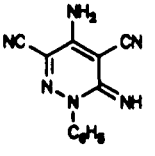

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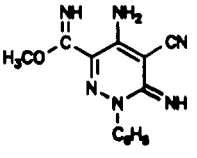

XIV

In formulae *III*, *XIII*, *XIV*: a, Ar = C_6H_5
b, Ar = p-CH_3-C_6H_4
c, Ar = p-Cl-C_6H_4

Compound *VII*: m.p. 230 – 233 °C; yield 70%. IR spectrum: 3 500 – 3 400 (NH, NH_2); 2 210 (CN); 1 620 (CO). For $C_{13}H_{11}N_5O_2$ (269.2) calculated: 57.9% C, 4.1% H, 26.0% N; found: 57.80% C, 4.20% H, 26.20% N.

5-Cyano-4-methyl-1-phenyl-1,6-dihydro-6-oxopyridazine-3-carboxylic Acid (*VIII*)

A solution of *VII* (0.01 mol, 2.69 g) in acetic acid (50 ml) was treated with hydrochloric acid (5 ml, 35%). The reaction mixture was refluxed for 3 h and then evaporated in vacuo. The remaining product was triturated with water. The solid product, so formed, was collected by filtration and identified (m.p. and mixed m.p.) as *VIII*.

Compound *VIII* was also formed in 65% yield when *IX* was similarly treated with the mixture of acetic acid and hydrochloric acid.

5-Cyano-1,6-dihydro-4-methyl-1-phenyl-6-oxopyridazine-3-carboxylic Acid Benzylidenehydrazide (*IX*)

A suspension of *VII* (0.01 mol, 2.69 g) in ethanol (50 ml) was treated with benzaldehyde (0.01 mol, 1.0 ml) piperidine (2 drops) was added. The reaction mixture was refluxed for 3 h and then left to stand at room temperature for 24 h. The solid product, so formed, was collected by filtration and crystallized from chloroform–petroleum ether (1 : 1).

Compound *IX*: m.p. 190 – 194 °C; yield 80%. IR spectrum: 3 300 (NH); 2 210 (CN); 1 740, 1 680 (CO). ^{1}H NMR spectrum: 2.4 s, 3 H (CH_3); 7.4 – 7.8 m, 10 H (aromatic protons); 8.3 s, 1 H (C=NH); 11.8 br, 1 H (NH). For $C_{20}H_{15}N_5O_2$ (357.3) calculated: 67.2% C, 4.2% H, 19.5% N; found: 67.5% C, 4.6% H, 19.2% N.

7-Benzylideneamino-2,6-diphenyl-3,8-dioxo-2,3,7,8-tetrahydropyrido[3,4-c]pyridazine (*X*)

A suspension of *IX* (0.01 mol, 3.57 g) in pyridine (20 ml) was treated with benzaldehyde (0.01 mol, 1.0 ml). The reaction mixture was refluxed for 3 h and then poured into ice cold water and neutralized by hydrochloric acid. The solid product, so formed, was collected by filtration and crystallized from dioxane.

Compound *X*: m.p. 245 – 248 °C; yield 80%. IR spectrum: 2 210 (CN); 1 700, 1 680 (CO). ^{1}H NMR spectrum: 5.90 s, 1 H (pyridine H-3); 7.4 – 7.8 m, 15 H (aromatic protons); 8.6 br, 1 H (C=NH). For $C_{27}H_{17}N_5O_2$ (443.4) calculated: 73.1% C, 3.8% H, 15.7% N; found: 72.9% C, 4.0% H, 15.5% N.

3,4-Dihydro-3,7-diphenyl-4-oxopyrido[3,4-*d*]pyridazine-5-yl Hydrazine (*XI*)

A suspension of *II* (0.01 mol, 3.71 g) in ethanol (50 ml) was treated with hydrazine hydrate (0.02 mol, 1.0 ml). The reaction mixture was refluxed for 4 h and then left to cool. The solid product, separated on standing, was collected by filtration and crystallized from $(CD_3)_2SO$.

Compound *XI*: m.p. > 305 °C; yield 79%. IR spectrum: 3 400, 3 200 (NH, NH_2); 1 680 (CO). ^{1}H NMR spectrum: 6.5 s, 1 H (pyridine H-3); 7.4 – 7.8 m, 10 H (aromatic protons); 7.9 br, 2 H (NH_2); 12.1 br, 1 H (NH). For $C_{19}H_{15}N_5O$ (329.3) calculated: 69.2% C, 4.5% H, 21.2% N; found: 69.3%C, 4.6% H, 21.2% N.

Reaction of *XI* with Benzaldehyde

A suspension of *XI* (0.01 mol, 3.29 g) in ethanol (50 ml) and piperidine (2 drops) was treated with benzaldehyde (0.01 mol, 1.0 ml). The reaction mixture was refluxed for 4 h and then evaporated in vacuo. The solid product, so formed, was collected by filtration and crystallized from methanol.

Compound *XII*: m.p. 95 °C; yield 80%. IR spectrum: 3 000 (NH); 1 650 (CO). ^{1}H NMR spectrum: 7.2 – 8.1 m, 17 H (aromatic protons); 8.2 s, 1 H (NH); 8.6 s, 1 H (C=NH). For $C_{26}H_{19}N_5O$ (417.4) calculated: 74.8% C, 4.5% H, 16.7% N; found: 74.6% C, 5.0% H, 16.6% N.

4-Amino-6-imino-1-aryl-1,6-dihydropyridazine-3,5-dicarbonitrile (*XIIIa*)

A solution of *IIIa* was heated under reflux in dioxane for 1 h and then evaporated in vacuo. The remaining product was triturated with water. The solid product, so formed, was collected by filtration and crystallized from dioxane.

Compound *XIIIa*: m.p. 220 – 223 °C; yield 90%. IR spectrum: 3 420, 3 303 (NH, NH_2); 2 220 (CN). For $C_{12}H_8N_6$ (236.2) calculated: 61.00% C, 3.4% H, 35.5% N; found: 60.6% C, 3.6% H, 35.6% N.

Cyclization of *IIIa* – *IIIc*: Formation of *XIVa* – *XIVc*

A suspension of *IIIa*, *IIIb* or *IIIc* (0.01 mol) in methanol (50 ml) was treated with sodium (0.25 g). After complete dissolution of sodium the reaction mixture was refluxed for 8 h and then evaporated. The remaining product was triturated with water. The solid product, so formed, was collected by filtration and crystallized from dioxane.

Compound *XIVa* was also formed when *XIIIa* was treated with sodium methoxide solution.

Compound *XIVa*: m.p. 205 – 207 °C; yield 90%. IR spectrum: 3 420, 3 300 (NH, NH_2); 2 210 (CN); 1 680 (CO). For $C_{13}H_{12}N_6O$ (268.2) calculated: 58.1% C, 4.5% H, 31.3% N; found: 57.6% C, 4.2% H, 31.5% N.

Compound *XIVb*: m.p. 195 – 196 °C; yield 70%. IR spectrum: 3 460, 3 310 (NH, NH_2); 2 210 (CN); 1 640 (CO). For $C_{14}H_{14}N_6O$ (282.3) calculated: 59.5% C, 4.9% H, 29.7% N; found: 59.61% C, 4.85% H, 29.82% N.

Compound *XIVc*: m.p. 200 – 201 °C; yield 77%. IR spectrum: 3 400, 3 310 (NH, NH_2); 2 210 (CN). ^1H NMR spectrum: 3.8 s, 3 H (CH_3), 7.4 – 8.1 m, 6 H (aromatic and NH_2 protons); 9.2 br, 1 H (NH). For $C_{13}H_{11}ClN_6O$ (302.7) calculated: 51.5% C, 3.6% H, 27.7% N; found: 52.00% C, 3.9% H, 27.6% N.

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2. Elnagdi M. H., Sadek K. U., Taha N. S., Yassein Y. S.: Collect. Czech. Chem. Commun. *55*, 734 (1990).