Synthesis of 1-Hydrazinopyridazino[4,5-*b*]quinoxaline and Related Compounds

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This paper describes the synthesis of 1-hydrazinopyridazino[4,5-*b*]quinoxaline (**10**), tetrazolo[4,3-*b*]pyridazino[4,5-*b*]quinoxaline (**11**) and some 1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]quinoxalines **13**. Starting with 2-ethoxycarbonyl-3-methylquinoxaline 1,4-dioxide (**1**), 1,2-dihydro-1-oxopyridazino[4,5-*b*]quinoxaline (**5**) was prepared by three different ways: (a) chlorination of **1** in acetic acid gave 2-ethoxycarbonyl-3-dichloromethylquinoxaline 1,4-dioxide, which reacts with an excess of hydrazine to give about 60% of **5**; (b) oxidation of **1** with selenium dioxide gave 90% of 2-ethoxycarbonyl-3-formylquinoxaline 1,4-dioxide (**3**), which reacts with hydrazine to give **5** (63%); (c) compound **3** was treated with hydrazine to give 1,2-dihydro-1-oxopyridazino-[4,5-*b*]quinoxaline 1,4-dioxide (**4**) (70%), which by reduction with sodium dithionite gave **5** (80%). Compound **5** reacts with phosphorus pentasulfide or the Lawesson reagent to give 1,2-dihydro-1-thiocarbonylpyridazino[4,5-*b*]quinoxaline (**9**), which treated with hydrazine gave **5** (80%). This last compound reacts with nitrous acid to give **11**. Some hydrazones **12** from **10** are described. Heating the aldehyde hydrazones **12a,c,d** with dimethylsulfoxide some 1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]quinoxalines **13** were obtained. Compound **13a** was also obtained in the reaction of **10** with benzoyl chloride. Reaction of **3** with phenylhydrazine gave 1,2-dihydro-1-oxo-2-phenylpyridazino[4,5-*b*]quinoxaline (**6**). Reactions of **5** with acetic anhydride and dimethylsulfate gave, respectively, 1-acetoxypyridazino[4,5-*b*]quinoxaline (**8**) and 1,2-dihydro-1-oxo-2-methylpyridazino-[4,5-*b*]quinoxaline (**7**). All the compounds were characterized by elemental analysis and ^{1}H-nmr spectra. Compounds **5** and **10** showed antihypertensive activity in rats.

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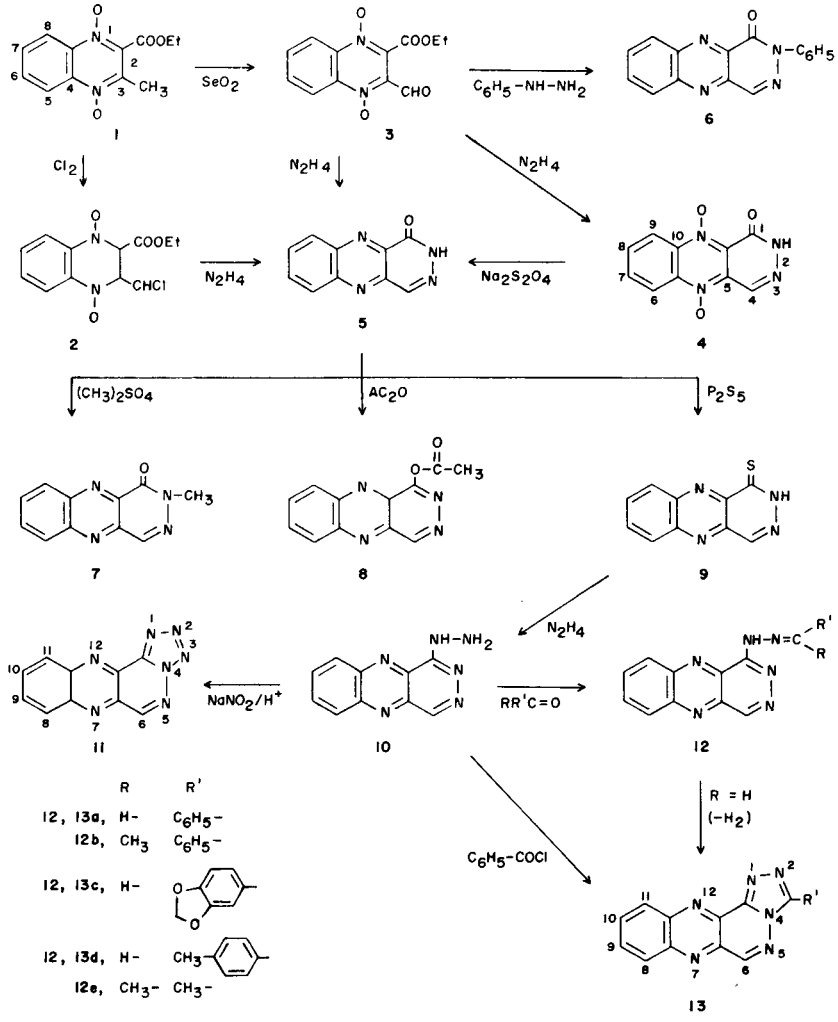
As a continuation of our previous work [1-4] about the synthesis and properties as potential antihypertensive agents of new structural analogs of the well known antihypertensive agent Hydralazine (Apresoline, 1-hydrazinophthalazine) [5], we report in this paper the synthesis of 1-hydrazinopyridazino[4,5-*b*]quinoxaline (**10**) and some related compounds.

The chemistry of pyridazines [6,7], pyrazines [8] and condensed pyrazines [9], including quinoxalines and ring fused quinoxalines with a series of heterocyclic systems (pyrrole, pyrazole, pyridine, *etc.*) is very well documented [9]. However, the information about pyridazinoquinoxalines is comparatively very limited. In an exhaustive review through Chemical Abstracts we have found references to pyridazino[4,5-*b*]quinoxalines [10,11], pyridazino[3,4-*b*]-quinoxalines [12], pyridazino[4,5-*f*]quinoxalines [13], pyridazino[2,3-*a*]quinoxalines [14] and pyridazino[2,3-*g*]quinoxalines [15].

Compound **10** and related pyridazino[4,5-*b*]quinoxalines reported in this paper were prepared according to Scheme 1, starting with 2-ethoxycarbonyl-3-methylquinoxaline-1,4-dioxide (**1**). The preparation of this compound from benzofuroxan [16] by the Beirut reaction [16] has been now substantially improved (from 22% to 82% yield) by the use of morpholine as the catalyst. Conversion of **1** in the intermediary **5** was carried out in three ways: (a) Chlorination of **1** in acetic acid at about 80-85° gave about 90% of **2**; this compound has been previously reported by us [17]. Reaction of **2** with excess of hydrazine gave 60% of **5**. (b) Compound **1** was oxidized with selenium dioxide to give **3** [18] and this compound was boiled with hydrazine hydrate in ethanol to obtain about 63% of **5**. On the other hand, when **3** was boiled with phenylhydrazine in ethanol, **6**, previously reported by a different method [11], was obtained. (c) Compound **3** was treated with hydrazine hydrate and the reaction just stopped when the characteristic ir-bands at about 1690 cm^{-1} and 1730 cm^{-1} for **3** had disappeared. Compound **4** was obtained in about 70% yield and its further reduction [16,19] with sodium dithionite (or hydrazine) gave **5**.

Compound **9** was prepared from **5** by two procedures: (a) Treating **5** with phosphorus pentasulfide in boiling pyridine; although this reaction works well, substantial loss of the product took place through the purification, and the pure product was obtained in about 60% yield. (b) Treating **5** with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) [21] in boiling toluene; this reaction was slower and the crude reaction product was more difficult to purify. Boiling **9** with hydrazine in ethanol gave about 80% of **10**, as garnet coloured crystals, which when treated in the usual fashion with sodium nitrite in acid medium gave **11**. The ir spectra of this compound does not show any of the characteristic bands for an azido group at about 2000-2200 cm^{-1} and 1300

SCHEME I



cm^{-1}; thus, it seems that in the solid state **11** has essentially the represented tetrazolic structure, without any estimable contribution of the possible azido form.

Starting with **10** in the usual way with several aldehydes and ketones, the hydrazones **12** were obtained in perhaps quantitative yields. On the other hand, when **12d** was heated in air, it changes at about 200° to a new compound, which was identified as **13d**. The same compound **13d** from **12d** and also **13c** and **13d** respectively, from **12c** and **12d** were obtained when the corresponding compounds **12** were heated in dimethylsulfoxide. These reactions may be explained according to the mechanism illustrated in Scheme 2. An equilibrium is proposed between the two tautomeric forms **12** and **12'** for the hydrazone, the formation of **12'** being thermally initiated. An easy dehydrogenation (oxidation) of **12'** (R = H) will give **13**. The attempted isolation of **12'b** or **12'e** or further transformation products, heating **12b** and **12e**, respectively, in boiling dimethylsulfoxide, was unsuccessful, and only the starting compound **12** was recovered.

The structure of compounds **12** was further confirmed through the preparation of **13a** by a different way: **10** was heated with benzoyl chloride and the N^2-benzoylhydrazine thermally cyclized to give **13a** (Scheme 2).

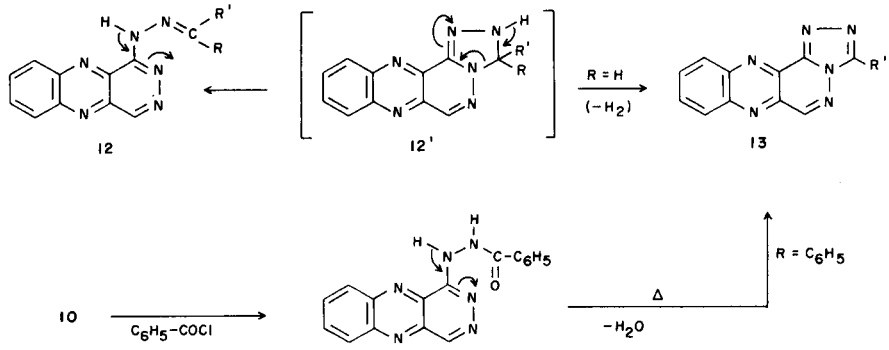
All the compounds reported in this paper gave satisfactory elemental analysis and the expected ir and ^{1}H-nmr spectra which are detailed in the experimental section.

Compounds **5** and **10**, in preliminary experiments with spontaneously hypertensive rats (S.H.R.), showed an interesting antihypertensive activity after oral or intraperitoneal administration at doses from 5 mg/kg to 25 mg/kg. Details of these and other pharmacologic experiments will be published.

EXPERIMENTAL

Melting points were determined in a Kofler and they are uncorrected.

SCHEME 2



Elemental analysis were obtained from vacuum-dried samples (over phosphorus pentoxide at 1-2 mm Hg, 2-3 hours, at about 60-70°). The ir spectra were recorded on a Perkin-Elmer 608 apparatus, using potassium bromide tablets; the frequencies are expressed in cm^{-1}. The ^1H-nmr spectra were obtained on Hitachi-Perkin-Elmer R-24 A (60 MHz) and/or R-32 (90 MHz) instruments, with TMS as the internal reference at a concentration of about 0.1 g/ml and solvents as indicated; the chemical shifts are reported in ppm from TMS and are given in δ units; the abbreviations (s, m, t...) are the usual.

The thin layer chromatographies (tlc) were carried out on silicagel (HF, 254-366, Merck or DSF-S Cammaga) plates with about 0.3 mm thickness, with benzene:dioxane:acetic acid 90:25:4 (v/v) as solvent, and the plates were scanned under ultraviolet light, λ = 254 and 366 nm.

2-Ethoxycarbonyl-3-methylquinoxaline 1,4-Dioxide (**1**).

This compound was prepared by modification of a previously reported method [16]. To a stirred mixture of benzofuroxane [20] (13.6 g, 0.1 mole) and ethyl acetoacetate (13.0 g, 0.1 mole), cooled in an ice-water bath, morpholine (18.0 g, 0.2 mole) was drop by drop slowly added. the ice water was removed and the mixture stirred for 10 hours. The precipitate was collected by filtration, washed with cold ethanol, and recrystallized as yellow coloured crystals, mp 132-133° (ethanol), yield about 82%, reported [16] mp 132-133°; ir (potassium bromide): 1740 (s, C=O), 1600 (m, C=N), 1290 (s), 1335 ((s), N-O); ^1H-nmr (DMSO-d_6): 1.40 (t, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.55 (c, 2H, CH_2), 7.80-8.10 (m, 2H, H-6, H-7), 8.20-8.50 (m, 2H, H-5, H-8).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.23; H, 4.55; N, 11.20.

2-Ethoxycarbonyl-3-dichloromethylquinoxaline 1,4-Dioxide (**2**).

In a 250 ml three-neck flask, provided with 1 reflux-condenser, thermometer and a gas inlet, **1** (5.0 g, 20 mmoles) was dissolved in acetic acid (120 ml) at about 70°. Chlorine was bubbled into the solution at an appropriate rate, so that the temperature rose to about 80-85° and it was maintained within this interval. The course of the reaction is followed by tlc and it was completed in about one hour. Most of the acetic acid was removed by azeotropic distillation with cyclohexane in vacuum using a rotovapor and the residual material cooled and neutralized with a saturated solution of sodium bicarbonate. The yellow precipitate was collected by filtration and recrystallized from ethanol as yellow coloured crystals with mp 150-152° (yield about 90%) reported [17] mp 150-152°; ir (potassium bromide): 1730 (s, C=O), 1600 (m, C=N), 1280 (s), 1350 ((s), N-O); ^1H-nmr (DMSO-d_6): 1.32 (t, 3H, CH_3), 4.46 (c, 2H, CH_2), 7.74-7.80 (m, 2H, H-6, H-7), 8.30-8.60 (m, 2H, H-5, H-8), 7.52 (s, 1H, $CHCl_2$).

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2O_4$: C, 45.40; H, 3.15; N, 8.83; Cl, 22.44. Found: C, 45.6; H, 3.03; N, 8.87; Cl, 22.66.

2-Ethoxycarbonyl-3-formylquinoxaline 1,4-Dioxide (**3**).

A mixture of **1** (5.0 g, 20 mmoles), selenium dioxide (2.3 g, 20 mmoles) and ethyl acetate (150 ml) was boiled. The colour of the reaction mixture changed progressively from yellow to dark red and tlc showed the progress of the reaction, which was practically complete in about 3-4 hours. Solvent was removed in vacuum and the black-red residual solid extracted with several portions of warm chloroform. Solvent was removed from the collected extracts, mp 176° (ethanol), yield about 90%, reported [18], mp 176°; ir (potassium bromide): 1730 (s, C=O ester), 1690 (s, C=O, aldehyde), 1600 (m, C=N), 1280 (s), 1350 ((s), N-O); ^1H-nmr (DMSO-d_6): 1.30 (t, 3H, CH_3), 4.55 (c, 2H, CH_2), 7.90-8.20 (m, 2H, H-6, H-7), 8.30-8.60 (m, 2H, H-5, H-8), 10.25 (s, 1H, -CH=O).

Anal. Calcd. for $C_{12}H_8N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 55.01; H, 3.91; N, 10.46.

1,2-Dihydro-1-oxopyridazino[4,5-*b*]quinoxaline 5,10-Dioxide (**4**).

To a stirred and boiling solution of **3** (2.62 g, 10 mmoles) in absolute ethanol (100 ml), a solution of 100% hydrazine hydrate (1.0 ml) in ethanol (10 ml) was added drop by drop. An orange coloured precipitate of the respective hydrazone was instantly formed, which progressively changed to a brown coloured precipitate. The course of the reaction was followed by the ir spectra of the precipitate. First, the 1690 cm^{-1} band (formyl group) of the starting material and then slowly the 1730 cm^{-1} (CO ester) band disappeared and a new one at about 1670 cm^{-1} (CO amide) formed. The reaction was complete in about three hours. The cold reaction mixture was filtered and the solid material washed with several portions of water and then with ethanol and recrystallized from ethanol-DMF as a brown coloured powder with mp 300° (yield about 70%); ir (potassium bromide): 3180 (m, NH), 1670 (s, CO), 1350 (s), 1280 ((s), N-O); ^1H-nmr (DMSO-d_6): 7.90-8.30 (m, 2H, H-7, H-8), 8.40-8.50 (m, 2H, H-5, H-9), 9.20 (s, 1H, CH=N).

Anal. Calcd. for $C_{10}H_6N_4O_3$: C, 52.18; H, 2.63; N, 24.34. Found: C, 51.75; H, 2.26; N, 24.26.

1,2-Dihydro-1-oxopyridazino[4,5-*b*]quinoxaline (**5**). Method A [16].

Into a boiling and stirred suspension of **4** (2.62 g, 10 mmoles) in ethanol-water (3:1, 50 ml) a solution of disodium dithionite (1.74 g, 10 mmoles) in a minimum amount of water was slowly added dropwise. After two hours of boiling, the solvent was removed in vacuum and the solid material washed with water and recrystallized from ethanol-DMF, as a yellow coloured powder with mp 330-331° (yield about 80%); ir (potassium bromide): 3200 (w, NH), 1680 (s, CO); ^1H-nmr (DMSO-d_6): 8.0-8.20 (m, 2H, H-7, H-8), 8.20-8.40 (m, 2H, H-6, H-9), 8.55 (s, 1H, CH=N).

Anal. Calcd. for $C_{10}H_6N_4O$: C, 60.61; H, 3.05; N, 28.27. Found: C, 60.68; H, 2.98; N, 27.99.

Method B.

To a stirred ice-cold solution of **2** (3.17 g, 10 mmoles) in ethanol (50 ml) 90% hydrazine hydrate (2.68 g, 30 mmoles) was added dropwise. The reaction mixture was maintained for 24 hours at room temperature and the precipitate collected by filtration and recrystallized from ethanol-DMF, mp 330-331° (yield about 60%).

Method C [19].

To a boiling and stirred solution of **3** (2.62 g, 10 mmoles) in absolute ethanol (50 ml) a solution of 100% hydrazine hydrate (2.5 g) in ethanol (10 ml) was added dropwise. In about three hours all of the starting compound **2** had been transformed into compound **4** (see above preparation of **4**; ir spectroscopy). The reaction mixture was boiled for 6 additional hours and the ir spectra showed the disappearance of the characteristic bands (N-O) of **4** at about 1280 and 1350 cm^{-1}. The cold suspension was filtered, the solid washed with water and then with ethanol and recrystallized (ethanol-DMF), mp 330-332° (yield about 70%).

1,2-Dihydro-1-oxo-2-phenylpyridazino[4,5-*b*]quinoxaline (**6**).

Into a boiling solution of **3** (3.0 g, 11 mmoles) in ethanol (10 ml), a solution of phenylhydrazine (2.16 g, 20 mmoles) in ethanol (10 ml) was added dropwise. The reaction mixture took on a progressively dark red colour. After two hours of boiling, the solvent was removed in vacuum, the residue washed with ethanol and recrystallized from ethyl acetate to give orange crystals, mp 280° (yield about 80%), reported [11] mp 283°; ir: 3020 (w, NH), 1680 (s, C=O), 1620 (w, C=N); ^{1}H-nmr (DMSO-d_6): 7.60 (s, 5H, C_6H_5-), 8.20-8.40 (m, 2H, H-7, H-8), 8.45-8.70 (m, 2H, H-6, H-9), 9.20 (s, 1H, CH=N).

Anal. Calcd. for $C_{16}H_{10}N_4O$: C, 70.07; H, 3.67; N, 20.43. Found: C, 70.08; H, 3.83; N, 20.04.

1,2-Dihydro-1-oxo-2-methylpyridazino[4,5-*b*]quinoxaline (**7**).

A mixture of **5** (1.0 g, 5 mmols), anhydrous potassium carbonate (14 g), dimethyl sulphate (1.90 g, 15 mmoles) and dried acetone (50 ml) was boiled for 5 hours under vigorous stirring and protected with a tube of anhydrous calcium chloride. Most of the acetone was removed in vacuum in a rotavapor and water was added to the residual material in order to dissolve the potassium carbonate. The aqueous mixture was extracted with chloroform, the organic solution dried with anhydrous sodium sulphate, filtered, and the solvent once again removed by vacuum. The residual solid was recrystallized from ethanol as yellow coloured crystals, mp 212-214° (yield about 90%); ir: 1680 (s, C=O), 1610 (w, C=N), 770 (s, aromatic 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): 3.85 (s, 3H, CH_3), 8.10-8.50 (m, 4H, H-6, H-7, H-8, H-9), 8.65 (s, 1H, CH=N).

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.60; N, 26.40. Found: C, 61.84; H, 3.67; N, 26.27.

1-Acetoxypyridazino[4,5-*b*]quinoxaline (**8**).

A mixture of **5** (2.0 g, 10 mmoles) and acetic anhydride (30 ml) was boiled for 4 hours. Solvent was removed in vacuum in a rotavapor and the residual material recrystallized from ethanol-DMF as a yellow coloured cotton-like solid, mp 235-236° (yield about 85%); ir: 1760 (s, C=O), 1690 (s, C=N), 760 (s, aromatic 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): 2.70 (s, 3H, CH_3), 8.10-8.50 (m, 4H, H-6, H-7, H-8, H-9), 8.70 (s, 1H, CH=N).

Anal. Calcd. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32. Found: C, 59.67; H, 3.28; N, 23.12.

1,2-Dihydro-1-thiocarbonylpyridazino[4,5-*b*]quinoxaline (**9**). Method A.

A mixture of **5** (6.0 g, 30 mmoles), phosphorus pentasulfide (3.0 g) and dried pyridine (150 ml) was boiled for 6 hours, the reaction mixture being protected with a tube of anhydrous calcium chloride. Solvent was removed *in vacuo* in a rotavapor and a tar-like residue was obtained. This material was extracted with dioxane (3 × 100 ml), the solvent removed from the collected extracts and the residual material washed with carbon disulfide and the insoluble material recrystallized from absolute ethanol to give orange coloured crystals, mp 227-229° (yield about 60%); ir: 3120 (w, NH), 1600 (w, C=N), 1350 (s, N-C=S), 760 (s, aromatic 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): 7.90-8.10 (m, 2H, H-7, H-8), 8.10-8.40 (m, 2H, H-6, H-9), 8.80 (s, 1H, CH=N).

Anal. Calcd. for $C_{10}H_6N_4S$: C, 56.08; H, 2.82; N, 26.16. Found: C, 56.10; H, 2.79; N, 26.33.

Method B [6].

The preparation of this compound was also attempted starting with **5** (3.0 g) and the Lawesson reagent [21] (6.0 g) in boiling toluene (150 ml). A slow reaction took place, and the reaction was completed in about 15 hours. Solvent was removed *in vacuo* and the residual material repeatedly washed with carbon disulfide, and the extracts discarded. The crude compound **9** obtained (yield about 75%) was difficult to purify and it was directly used occasionally in the preparation of **10**.

1-Hydrazinopyridazino[4,5-*b*]quinoxaline (**10**).

To a warm solution of **9** (1.0 g, 4 mmoles) in absolute ethanol (50 ml) anhydrous hydrazine (3.0 ml) was added. The reaction mixture was protected with a tube of anhydrous calcium chloride and boiled for 4 hours. Solvent was removed *in vacuo* in a rotavapor and the solid residue recrystallized from absolute ethanol, to give garnet coloured crystals, mp 271-273° (yield about 80%). This compound is unstable in light, air and humidity and it is best stored in vacuum in a dessicator; ir: 3200-3360 (m, NH), 1600 (s, C=N), 750 (s, aromatic 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): 3.60 (bs, NH), 7.60-8.00 (m, 5H, aromatic protons).

Anal. Calcd. for $C_{10}H_8N_6$: C, 56.60; H, 3.77; N, 39.62. Found: C, 56.79; H, 3.32; N, 39.33.

Tetrazolo[4,3-*b*]pyridazino[4,5-*b*]quinoxaline (**11**).

On a stirred mixture of **10** (1.06 g, 5 mmoles) and powdered sodium nitrite (1.5 g, 21 mmoles) hydrochloric acid (1*N*, 50 ml) was dropped and the mixture stirred for 10 hours at room temperature. The precipitate was collected by filtration, washed with water and recrystallized from ethanol-DMF to give green-coloured crystals, mp 260-265° dec (yield about 90%); ir: 1670 (s, C=N); ^{1}H-nmr (DMSO-d_6): 8.30-8.50 (m, 2H, H-9, H-10), 8.60-8.80 (m, 2H, H-8, H-11), 9.45 (s, 1H, H-6).

Anal. Calcd. for $C_{10}H_5N_7$: C, 53.79; H, 2.24; N, 43.92. Found: C, 53.82; H, 2.35; N, 44.01.

Hydrazones of 1-Hydrazinopyridazino[4,5-*b*]quinoxaline (**12**).

Compound **12a**.

A solution of **10** (1.0 g, 5 mmoles) and benzaldehyde (2 ml) in absolute ethanol (50 ml) was boiled for 1 hour. Solvent was removed *in vacuo* and the residual material recrystallized from absolute ethanol to give red coloured crystals, mp 231° (yield about 95%); ir: 3300 (m, NH), 1615 (m, C=N, hydrazone), 1580 (s), 1590 ((m) C=N rings), 750 (s, aromatic 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): 7.50-7.65 (m, 3H, H-3′, H-4′, H-5′ of C_6H_5-), 8.00-8.40 (m, 7H, H-4, H-6, H-7, H-8, H-9 and H-2′, H-6′ of C_6H_5-), 8.70 (s, 1H, N=CH-Ph), 12.40 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{12}N_6$: C, 68.00; H, 4.00; N, 28.00. Found: C, 67.86; H, 3.95; N, 28.33.

Compound **12b**.

From **10** (1.0 g, 5 mmoles), acetophenone (1.2 g) and ethanol (50 ml) were used in a similar manner as described above for **12a**. The product was recrystallized from ethanol as a dark red coloured powder, mp 219-221° (yield about 90%); ir: 3300 (m, NH), 1600 (s, C=N hydrazone), 1580 (m, C=N ring), 760 (s, aromatic 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): 7.40-7.60 (m, 3H, H-3′, H-4′, H-5′), 7.90-8.40 (m, 7H, H-4, H-6, H-7, H-8, H-9, H-2′, H-6′), 12.10 (s, 1H, NH), 2.60 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{14}N_6$: C, 68.80; H, 4.45; N, 26.73. Found: C, 68.79; H, 4.39; N, 26.75.

Compound **12c**.

This compound was prepared in a similar manner as described above for **12a** from **10** (1.0 g, 5 mmoles), piperonal (1.0 g) in ethanol (30 ml), mp 272-273° (2-propanol), red coloured powder (yield about 95%); ir: 3300 (m, NH), 1620 (s, C=N, hydrazone), 1600 (s), 1580 (m, C=N rings), 750 (s, aromatic 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): 6.90-8.30 (m, 8 aromatic protons), 8.50 (s, 1H, N=CH-aryl), 12.4 (s, 1H, NH), 6.10 (s, 2H, CH_2O_2).

Anal. Calcd. for $C_{18}H_{12}N_6O_2$: C, 62.87; H, 3.48; N, 24.40. Found: C, 62.79; H, 3.45; N, 24.42.

Compound **12d**.

This compound was prepared in a similar manner as described above for **12a** from **10** (0.5 g), tolualdehyde (0.6 g) in ethanol (25 ml). The reaction was completed in 10 minutes; dark red coloured powder (yield about 90%). No mp can be determined; on heating the compound changes at

about 200° to a new yellow coloured compound, which was identified as compound **13d** with mp > 300°; for **12d**: ir: 3300 (m, NH), 1610 (s, C=N hydrazone), 1570 (m), 1580 (m, C=N rings), 870 (m), and 750 (s), respectively, aromatic 1,2-disubstitutions; ^{1}H-nmr (DMSO-d_6): 7.20-7.40 (m, 2H, H-3', H-5'), 7.85-8.20 (m, 7H, H-4, H-6, H-7, H-8, H-9, H-2', H-6'), 8.50 (s, 1H, -N=CH-aryl), 2.35 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{14}N_6$: C, 68.80; H, 4.45; N, 26.73. Found: C, 68.82; H, 4.52; N, 26.74.

Compound **12e**.

This compound was prepared in a similar manner as described above for **12a** from **10** (1.0 g) acetone (3.0 ml) in ethanol (50 ml); 20 minutes at about 40-50°, dark red coloured powder, mp 140-143° (yield about 90%); ir: 3250 (m, NH), 1630 (s, C=N hydrazone), 1580 (m, C=N, rings), 760 (s, aromatic 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): 7.30-8.40 (m, 5 aromatic protons), 2.20 (s, 3H) and 2.30 (s, 3H, for $2CH_3$).

Anal. Calcd. for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.21. Found: C, 61.80; H, 4.83; N, 33.35.

1,2,4-Triazolo[4,3-*b*]pyridazino[4,5-*b*]quinoxaline (**13**).

Compound **13a**. Method A.

A mixture of **10** (1.0 g, 5 mmoles), dried dioxane (50 ml) and benzoyl chloride (20 drops) was boiled for 0.5 hours. The warm solution was filtered in order to remove some dark-insoluble material, and the solvent from the filtrate removed *in vacuo*, yellow coloured crystals from dioxane, mp 274-275° (yield about 70%); ir: 1620 (w), 1590 (w, C=N), 770 (s, aromatic 1,2-disubstitution), 760 (s), 690 (s, aromatic monosubstitution); ^{1}H-nmr (deuteriochloroform + trifluoroacetic acid): 7.5-7.70 (m, 3H, H-3', H-4', H-5'), 8.00-8.60 (m, 6H, H-8, to H-11, H-2', H-6'), 9.30 (s, 1H, H-6).

Anal. Calcd. for $C_{17}H_{10}N_6$: C, 68.44; H, 3.37; N, 28.17. Found: C, 68.42; H, 3.28; N, 28.09.

Method B.

Compound **12a** (0.5 g) in dimethylsulfoxide (10 ml) was warmed without boiling for 5 minutes. The initial red coloured solution changed quickly to a deep yellow. To the cold reaction mixture water was added and the precipitate collected by filtration and recrystallized, mp 274-275° (dioxane), yield about 98%.

Compound **13c**.

This compound was prepared in a similar way to that above described for **13a** (Method B) from **12c** (0.5 g) and dimethylsulfoxide (10 ml), but the reaction mixture was boiled for 30 minutes. Orange coloured cottony crystals (dioxane), mp 273-275° (yield about 97%); ir: 1620 (w), 1590 (w, C=N),m 870 (s, aromatic 1,2,4-trisubstitution), 760 (s, aromatic 1,2-disubstitution), 1250 (s, C-O); ^{1}H-nmr (DMSO-d_6): 7.20-8.50 (m, 7H, H-8 to H-11, H-2', H-5', H-6'), 9.30 (s, 1H, H-6), 6.10 (s, 2H, CH_2O_2).

Anal. Calcd. for $C_{18}H_{10}N_6O_2$: C, 63.15; H, 2.94; N, 24.55. Found: C, 63.09; H, 2.87; N, 24.48.

Compound **13d**.

This compound was prepared as described above for **13a** (Method B) from **12d** (0.5 g) and dimethylsulfoxide (10 ml), but the reaction mixture was boiled for 10 minutes, yellow-coloured crystals (dioxane), mp > 300° (yield about 98%); ir: 1615 (w), 1590 (w, C=N), 820 (s, aromatic 1,4-disubstitution), 760 (s, aromatic 1,2-disubstitution); ^{1}H-nmr (trifluoroacetic acid): 7.50-7.70 (m, 2H, H-3', H-5'), 8.20-8.70 (m, 6H, H-8 to H-11, H-2', H-6'), 9.60 (s, 1H, H-6), 2.55 (s, 1H, CH_3).

This compound was also produced by heating compound **12d** at about 200° in air (see **12d** above).

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