The Synthesis of 11*H*-1,2,4-Triazolo[4,3-*b*]pyridazino[4,5-*b*]indoles, 11*H*-Tetrazolo[4,5-*b*]pyridazino[4,5-*b*]indoles and 1,2,4-Triazolo[3,4-*f*]-1,2,4-triazino[4,5-*a*]indoles

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This paper describes the synthesis of the previously unknown 11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indoles (**2**) and 11*H*-tetrazolo[4,5-*b*]pyridazino[4,5-*b*]indoles (**3**) from 4-hydrazino-5*H*-pyridazino[4,5-*b*]indoles (**1**), as well as the synthesis of 1,2,4-triazolo[3,4-*f*]-1,2,4-triazino-[4,5-*a*]indoles (**10**) from 2-indolecarbohydrazide (**4**). Compounds **2** were obtained by acylation of compounds **1**, followed of thermal cyclization and compounds **3** by treating compounds **1** with nitrous acid. The reactions of compound **4** with formic acid or ethyl orthoformiate gave 1,2-dihydro-1-oxo-1,2,4-triazino[4,5-*a*]indole (**6**). Treating this last compound with phosphorus oxychloride or phosphorus pentasulfide, followed by hydrazine, gave 1-hydrazino-1,2,4-triazino-[4,5-*a*]indole (**9**). Acylation of this last compound, followed of cyclization gave compounds **10**. All the compounds were characterized by elemental analysis and ir and ^{1}H-nmr spectra.

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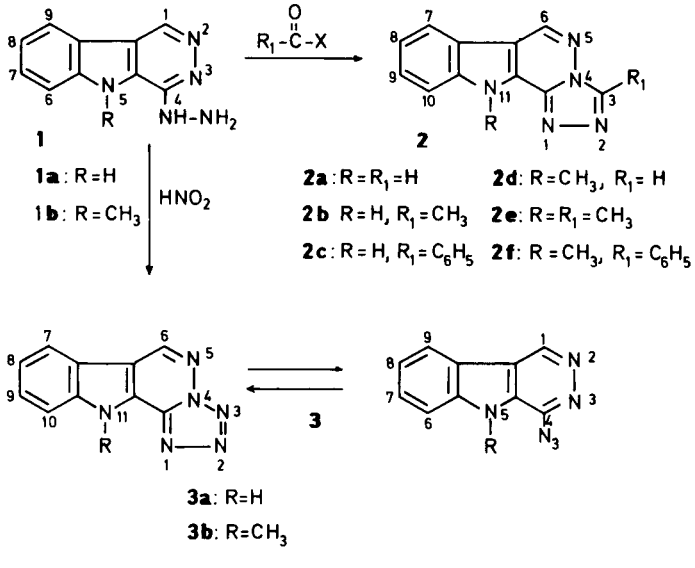
In the last few years, considerable attention has been drawn to the synthesis of several condensed heterocyclic systems, specially derived from triazole (1-4), tetrazole (1-6) and triazine (7-11). Recently we have described (12) the synthesis of 4-hydrazino-5*H*-pyridazino[4,5-*b*]indole (**1a**), a structural analog of the Hydralazine (1-hydrazinophthalazine), which also shows interesting antihypertensive properties (12). The well-known metabolism of Hydralazine and related compounds (13,14) suggests to us that the metabolites of compound **1a** would be related to derivatives of 11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]-indoles (**2**).

This paper describes the synthesis of the previously unknown 11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indoles (**2**) and 11*H*tetrazolo[4,5-*b*]pyridazino[4,5-*b*]indoles (**3**) from 4-hydrazino-5*H*-pyridazino[4,5-*b*]indoles (**1**), as well as the synthesis of 1,2,4-triazolo[3,4-*f*]-1,2,4-triazino[4,5-*a*]-indoles (**10**) from 2-indole carbohydrazide (**4**) (Scheme 1 and Scheme 2).

Scheme 1



Compounds **2** were prepared in the usual manner (1-4), (Scheme 1), through N^2-acylation of the compounds **1** with formic or acetic acids or benzoyl chloride, respectively, and thermal cyclization to the corresponding triazoles.

Treating the compounds **1** with nitrous acid gave, in nearly quantitative yield, the corresponding tetrazole derivatives (**3**). The chemistry of the tetrazole-azide equilibrium for a series of condensed systems derived from tetrazole is well documented (5,6,15,16). Generally, in the solid state only the most stable tetrazole form is present whereas in solution an equilibrium is often detected with the percent of each form depending on the system, the solvent, and the temperature (5,6,15,16). The ir spectra (potassium bromide) of compounds **3** does not show the characteristic band of the azido group at about 4.6 μ. This suggests that in the crystalline state, the compounds **3** have the tetrazole structure. However, the ^{1}H-nmr spectra (trifluoroacetic acid) of the compounds **3** show that both forms are present in solution. Compound **3a** shows two signals at about δ 9.77 (s, 0.8 H) and 9.87 (s, 0.2 H), assigned to H_1 of the pyridazino[4,5-*b*]indole system in the tetrazole and azido forms, respectively. Similarly, the compound **3b** shows two signals for this proton at about δ 9.55 (s, 0.8 H) and 9.76 (s, 0.2 H) and two signals for the methyl group at about δ 4.56 (s, 0.8 CH_3) and 4.50 (s, 0.2 CH_3). These assignments take into consideration the well known fact (5) that the tetrazole system shifts the protons on the

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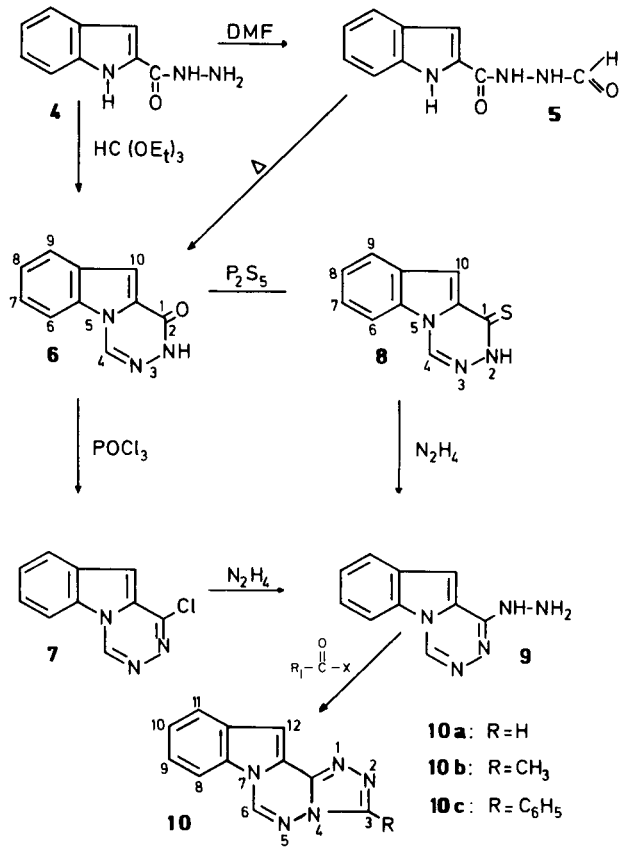
ring condensed with it to higher δ values than for the azido group. We conclude that in the crystalline form, the compounds **3** have the tetrazole structure, whereas the trifluoroacetic acid solution this form is present in about 90% for the compound **3a** and 80% for the compound **3b**. These results are also in agreement with the observation (17) that the introduction of electron-donor groups shift the equilibrium to the azide form.

The compounds **10** were prepared from 2-indolecarbohydrazide (**4**) (Scheme 2). Boiling compound **4** with ethyl orthoformiate in DMF, or thermal cyclodehydration of compound **5** gave compound **6** in 80% and 70% yields, respectively. Treating compound **6** with phosphorus oxychloride or phosphorus pentasulfide gave **7** and **8**, respectively, in nearly quantitative yields. Both compounds (**7** and **8**) react with hydrazine to give 1-hydrazino-1,2,4-triazino[4,5-*a*]indole (**9**), which was transformed into compounds **10** by similar reactions to those reported for the preparation of compounds **2**.

Scheme 2



EXPERIMENTAL

Melting points were determined in a Kofler apparatus and they are uncorrected. Elemental analysis were obtained on vacuum-dried samples (over phosphorus pentoxide at 3-5 mm Hg, 2-3 hours, at about 60-70°); where a molecular formula is given, analytical results were obtained within ± 0.4% of the theoretical values. Ir spectra were recorded on a Perkin-Elmer 237 apparatus, in potassium bromide tablets and the frequencies are expressed in cm^{-1}. ^{1}H-nmr spectra were obtained on a Perkin-Elmer R-24A or R-12 (60 MHz) instruments, with TMS as the internal reference, to a concentration of about 0.1 g./ml. and the solvent indicated in each case: s,d,t... for singulet, doublet, triplet....., dd = double deformed doublet; sb = broad signal.

4-Hydrazino-5*H*-pyridazino[4,5-*b*]indoles (**1**).

Compound **1b** was prepared from 3,4-dihydro-5-methyl-5*H*-*pyridazino-[4,5-b]*indole (18) in a manner similar to that previously reported for compound **1a** (12), yield, 85%, m.p. 178-180° dec. (ethanol); ir (potassium bromide): ν = 3200 (sb, NH); 1625 (m, C=N); 755 (s, arom. 1,2-disubst); ^{1}H-nmr (DMSO-d_6): δ = 3.40 (sb, 2H, NH_2); 4.25 (s, 3H, CH_3); 7.10-7.90 (m, 3H, H_{6-8}); 7.95-8.30 (dd, 1 H_9); 8.50 (sb, 1H, NH) 9.95 (s, 1 H_1).

Anal. Calcd. for $C_{11}H_{11}N_5$: C, 61.97; H, 5.16; N, 32.86. Found: C, 62.34; H, 5.27; N, 32.80.

11*H*-1,2,4-Triazolo[4,3-*b*]pyridazino[4,5-*b*]indoles (**2**).

A solution of compounds **1a** or **1b** (1.0 mmole) in 10 ml. of formic acid (or acetic acid, benzoyl chloride, according to the compound to be prepared) was refluxed during 5 hours. The excess reagent was removed in vacuum and water was added to the residual meterial. The precipitate was collected and recrystallized from DMF. The following compounds were obtained in this way:

Compound **2a**.

From **1a** and formic acid **2a** was obtained in a yield of 90%, white crystals m.p. 320° dec.; ir (potassium bromide): ν = 2500-3100 (sb, NH) 1650 (s, C=N); 750 (s, arom. 1,2-disubst); ^{1}H-nmr (trifluoroacetic acid): δ = 7.60-8.15 (m, 3H, H_{8-10}); 8.30-8.65 (dd, 1 H_7); 9.74 (s, 1 H_3); 9.78 (s, 1 H_6).

Anal. Calcd. for $C_{11}H_7N_5$: C, 63.15; H, 3.34; N, 33.47. Found: C, 62.75; H, 3.37; N, 33.12.

Compound **2b**.

From **1a** and acetic acid, **2b** was obtained in a yield of 95%, yellow needles, m.p. 320° (DMF); ir (potassium bromide): ν = 2500-3100 (sb, NH); 1645 (s, C=N); 750 (s, arom. 1,2-disubst); ^{1}H-nmr (trifluoroacetic acid): δ = 3.22 (s, 3H, CH_3); 7.60-8.15 (m, 3H, H_{8-10}); 8.30-8.60 (dd, 1 H_7); 9.80 (s, 1 H_6).

Anal. Calcd. for $C_{12}H_9N_5$: C, 64.52; H, 4.03; N, 31.39. Found: C, 64.68; H, 3.84; N, 30.98.

Compound **2c**.

From **1b** and benzoyl chloride **2c** was obtained in a yield of 95%, white crystals, m.p. 320° (DMF); ir (potassium bromide): ν = 2500-3100 (sb, NH); 1650 (s, C=N); 740 (s, arom, 1,2-disubst); 690 (s) and 770 (s) (arom. mono subst); ^{1}H-nmr (trifluoroacetic acid): δ = 7.60-8.10 (m, 6H, C_{8-10} + $H_{3'}$ + $H_{5'}$); 8.35-8.75 (m, 3H, H_7 + $H_{2'}$ + $H_{6'}$); 9.78 (s, 1 H_6).

Anal. Calcd. for $C_{17}H_{11}N_5$: C, 71.57; H, 3.86; N, 24.56. Found: C, 71.27; H, 3.94; N, 24.95.

Compound **2d**.

From **1b** and formic acid **2d** was obtained in a yield of 97%, white crystals, m.p. 253-255° (DMF); ir (potassium bromide): ν = 1640 (s, C=N); 750 (s, arom. 1,2-disubst); ^{1}H-nmr (trifluoroacetic acid): δ = 4.50 (s, 3H, CH_3); 7.50-8.10 (m, 3H, H_{8-10}); 8.15-8.50 (dd, 1 H_7); 9.50 (s, 1 H_6); 10.1 (s, 1 H_3).

Anal. Calcd. for $C_{12}H_9N_5$: C, 64.57; H, 4.03; N, 31.39. Found: C, 64.55; H, 4.04; N, 31.64.

Compound **2e**.

From **1b** and acetic acid **2e** was obtained in a yield of 95%, white crystals, m.p. 235-237° (DMF); ir (potassium bromide): ν = 1640 (s, C=N); 755 (s, arom. 1,2-disubst); ^{1}H-nmr (trifluoroacetic acid): δ = 3.25 (s, 3H, CH_3); 4.50 (s, 3H, N-CH_3); 7.30-8.15 (m, 3H, H_{8-10}); 8.15-8.57 (dd, 1 H_7); 9.40 (s, 1 H_6).

Anal. Calcd. for $C_{13}H_{11}N_5$: C, 65.82; H, 4.64; N, 29.53. Found: C, 65.72; H, 4.44; N, 29.40.

Compound **2f**.

From **1b** and benzoyl chloride **2f** was obtained in a yield of 95%, white crystals, m.p. 265-267° (DMF); ir (potassium bromide): ν = 1640 (s, C=N); 750 (s, arom. 1,2-disubst); 690 (s) and 760 (s) (arom. monosubst); ^{1}H-nmr (trifluoroacetic acid): δ = 4.51 (s, 3H, CH_3); 7.50-8.10 (m, 6H, C_{8-10} + $H_{3'}$ + $H_{5'}$); 8.10-8.70 (m, 3H, H_7 + $H_{2'}$ + $H_{6'}$); 9.50 (s, 1 H_6).

Anal. Calcd. for $C_{18}H_{13}N_5$: C, 72.24; H, 4.35; N, 23.41. Found: C, 72.52; H, 4.46; N, 23.52.

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

Into an ice-cold solution of compounds **1a** or **1b** (25 mmoles) in 1.25*N* hydrochloric acid (20 ml.), a solution of sodium nitrite (25 mmoles) in water (10 ml.) was slowly dropped, so that the temperature remains below 5°. Afterwards the mixture was stirred for 12 hours at room temperature. The precipitate was collected and recrystallized from ethanol/DMF. The following compounds were prepared in this manner.

Compound **3a**.

From **1a**, **3a** was obtained in a yield of 90%, white crystals, m.p. 250-290°; ir (potassium bromide): ν = 2600-3200 (sb, NH); 1650 (s, C=N); 760 (s, arom. 1,2-disubst); ^{1}H-nmr (trifluoroacetic acid): δ = 7.60-8.15 (m, 3H, C_{8-10}); 8.30-8.60 (m, 1 H_7); 9.77 (s, 0.9 H, H_6); 9.87 (s, 0.1 H, H_6).

Anal. Calcd. for $C_{10}H_6N_6$: C, 57.14; H, 2.84; N, 40.00. Found: C, 57.56; H, 2.74; N, 39.83.

Compound **3b**.

From **1b**, **3b** was obtained as white crystals, m.p. 262-267° dec., yield, 95%; ir (potassium bromide): ν = 1640 (s, C=N); 740 (m, arom. 1,2-disubst); ^{1}H-nmr (trifluoroacetic acid): δ = 4.50 (s, 0.2 CH_3); 4.56 (s, 0.8 CH_3); 7.65-8.10 (m, 3H, C_{8-10}); 8.10-8.50 (m, 1 H_7); 9.55 (s, 0.8 H_6) and 9.76 (s, 0.2 H_6).

Anal. Calcd. for $C_{11}H_8N_6$: C, 58.92; H, 3.57; N, 37.5. Found: C, 59.1; H, 3.92; N, 37.2.

1-Formyl-2-(2-indolecarbonyl)hydrazine (**5**).

A solution of 2-indolecarbohydrazide **4** (10 mmoles) (19) in DMF (10 ml.) was refluxed for 17 hours and the reaction mixture was protected with a calcium chloride tube. The excess reagent was removed in vacuum and the crude product was triturated with 2-propanol (25 ml.), filtered and washed with the same solvent (4 × 25 ml.), yield 83%, m.p. 240° (lit (9) m.p. 230°); ir (potassium bromide): ν = 3337 (s), 3260 (s) (NH); 1675 (s), 1640 (s), (C=O); 750 (s, arom. 1,2-disubstitution); ^{1}H-nmr (DMSO-d_6): δ = 6.90-8.50 (m, 4H, H_{4-7}); 8.22 (s, 1H, CH=O); 10.2 (s, 1 H_4) 10.4 (s, 1H, CONH), 11.60 (sb 1H, NH, indole).

1,2-Dihydro-1-oxo-1,2,4-triazino[4,5-*a*]indole (**6**).

Method A.

A solution of 2-indolecarbohydrazide (2.0 g., 11 mmoles) (19) and ethyl orthoformiate (2.0 g., 14 mmoles) in DMF (10 ml.) was refluxed for 2.5 hours while the reaction mixture was protected with a calcium chloride tube. Solvent was removed in vacuum an the residual oil recrystallized, m.p. 275° (dioxan), yield 1.52 g. (80%). (Lit. (6), m.p. 275°).

Method B.

A solution of compound **5** (2.0 g., 12 mmoles) in DMF (10 ml.) was refluxed for 8 days while the reaction mixture was protected with a calcium chloride tube. Solvent was removed in vacuum and the residual oil recrystallized, m.p. 275° (dioxan), yield, 1.45 g., (70%).

1-Chloro-1,2,4-triazino[4,5-*a*]indole (**7**).

A mixture of compound **6** (1.85 g., 10 mmoles) and phosphorus oxychloride (10 ml.) was refluxed for 2 hours while the reaction mixture was protected with a calcium chloride tube. To the cold reaction mixture, dried ether (50 ml.) was added. The hydrochloride of compound **7** crystallized, yield, 98% yellow crystals, m.p. 300° dec. (dioxan); ir (potassium bromide): ν = 2620 (m, sb, NH^+); 1600 (s, C=N); 755 (m, arom. 1,2-disubst); ^{1}H-nmr (DMSO-d_6): δ = 7.30-8.20 (m, 5H indole); 10.2 (s, 1 H_4).

Anal. Calcd. for $C_{10}H_6ClN_3$·HCl: C, 50.0; H, 2.91; N, 17.5; Cl, 29.58. Found: C, 50.3; H, 3.29; N, 17.7; Cl, 29.8.

1,2-Dihydro-1,2,4-triazino[4,5-*a*]indole-1-thione (**8**).

To a suspension of **6** (1.85 g., 2 mmoles) in dioxan (60 ml.), phosphorus pentasulfide (1 g., 4.5 mmoles) was added. The mixture was refluxed for 2.5 hours. The product crystallized on cooling and it was collected by filtration and successively washed with carbon disulfide, dioxan and ethanol, yield 1.80 g. (90%) m.p. 300° (dioxan); ir (potassium bromide): ν = 3190 (sb, NH); 1620 (m, C=N) 1554 (m, C=S) 745 (s, arom. 1,2-disubst); ^{1}H-nmr (DMSO-d_6): δ = 7.20-8.40 (m, 5H, H_{6-10}); 9.50 (s, 1 H_4); 13.40 (sb, 1H, NH).

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.70; H, 3.48; N, 20.89; S, 15.92. Found: C, 59.51; H, 3.42; N, 20.65; S, 15.63.

1-Hydrazino-1,2,4-triazino[4,5-*a*]indole (**9**).

Method A.

A mixture of compound **8** (2.0 g., 10 mmoles) and 90% hydrazine hydrate (10 ml.) was stirred at room temperature for 20 minutes. The solid material was collected by filtration and recrystallized from dioxan, yield, 98%, m.p. 210-250° dec., white crystals.

Method B.

A mixture of compound **9** (2.0 g., 10 mmoles and 90% hydrazine hydrate (10 ml.) was stirred at room temperature for 12 hours. The solid material was treated as above, yield, 95%, m.p. 210-250° dec. (dioxan); ir (potassium bromide): ν 3300 (s) 3190 (s) (NH); 1640 (s), 1620 (s) (C=N); 735 (s, arom. 1,2-disubst); ^{1}H-nmr (DMSO-d_6): δ = 7.20-8.10 (m, 5H, H_{6-10}); 8.60 (s, 1 H_4).

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.29; H, 4.55; N, 35.15. Found: C, 60.14; H, 4.50; N, 35.38.

1,2,4-Triazolo[3,4-*f*]-1,2,4-triazino[4,5-*a*]indoles (**10**).

From compound **9** (1.0 mmole) in the same way described above for the preparation of compounds **2** from compounds **1**, the following compounds were prepared:

Compound **10a**.

From **9** and formic acid, yellow crystals of **10a** were obtained, m.p. 210-270° dec. (DMF), yield, 80%; ir (potassium bromide): ν = 1670 (m), 1650 (m), (C=N); 760 (s, arom. 1,2-disubst); ^{1}H-nmr (trifluoroacetic acid): δ = 7.51-8.05 (m, 5H indole), 9.05 (s, 1 H_6); 9.55 (s, 1 H_3).

Anal. Calcd. for $C_{11}H_7N_5$: C, 63.15; H, 3.34; N, 33.47. Found: C, 62.95; H, 3.46; N, 32.70.

Compound **10b**.

From **9** and acetic acid, yellow crystals of **10b** were obtained, m.p. 265-285° dec. (DMF), yield, 85%; ir (potassium bromide): ν = 1670 (m), 1650 (m), (C=N); 750 (s, arom. 1,2-disubst); ^{1}H-nmr (trifluoroacetic acid): δ = 3.00 (s, 3H, CH_3); 7.50-8.05 (m, 5H, indole); 8.90 (s, 1 H_6).

Anal. Calcd. for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.37. Found: C, 64.53; H, 4.10; N, 31.01.

Compound **10c**.

From **9** and benzoyl chloride, yellow crystals of **10c** were obtained, m.p. = 260-270° dec. (DMF-2-propanol), yield, 80%; ir (potassium bromide): ν = 1680 (m), 1650 (m) (C=N); 760 (s, arom. 1,2-disubst); 695 (s), 780 (s), (arom. monosubst); ^{1}H-nmr (trifluoroacetic acid): δ = 7.50-8.10 (m, 10H, 5H indole + C_6H_5); 9.10 (s, 1 H_6).

Anal. Calcd. for $C_{17}H_{11}N_5$: C, 71.57; H, 3.85; N, 24.55. Found: C, 71.57; H, 4.13; N, 24.23.

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