# The Synthesis of Derivatives of New Tetracyclic Heterocyclic Systems Pyrazolo-bis-azolopyridazines



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The synthesis of new tetracyclic systems and new stable tautomers of known systems 11*H*- **13** and 10*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]-*s*-triazolo[3,4-*f*]pyridazine **16**, 9*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:5′,1′-*f*]-pyridazine **15**, 10*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:3′,4′-*f*]pyridazine **17**, and 10*H*-pyrazolo[4,3-*d*]bis-*s*-triazolo[4,3-*b*:5′,1′-*f*]pyridazine **18** is described.

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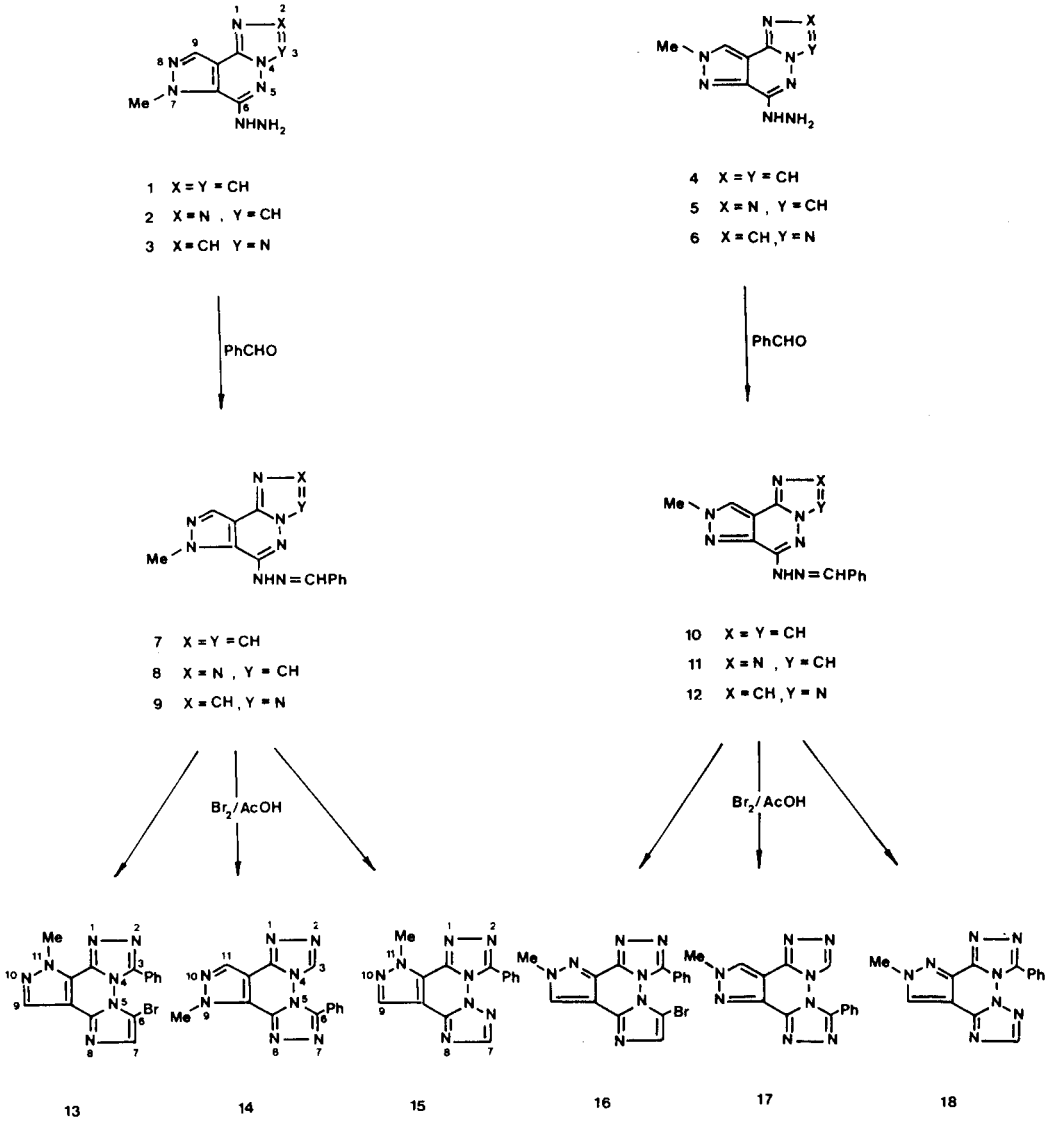
Recently, we have described the synthesis of derivatives of new tetracyclic systems 11*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:3′,4′-*f*]pyridazine [1] 9*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:5′,1′-*f*]pyridazine and 11*H*-pyrazolo[3,4-*d*]-bis-*s*-triazolo[1,5-*b*:3′,4′-*f*]pyridazine [2] by 1,3-dipolar cycloaddition of 2-diazopropane to isomeric bis-*s*-triazolo-pyridazines, and by independent syntheses starting from suitably substituted 9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]-pyridazines and 9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyrida-zines. On the other hand, cyclization of 6-benzylidene-

Scheme 1



hydrazino substituted 7-methyl-7*H*- and 8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazines taking place at nitrogen at position 5 followed by azido-tetrazolo isomerization has produced derivatives of pyrazolo[3,4-*d*]azolopyridazines [3].

In continuation of our studies in this area, we report now the synthesis of derivatives of the following new tetracyclic systems or new stable tautomers of previously described tetracyclic systems: 11*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]-*s*-triazolo[3,4-*f*]pyridazine **13**, 9*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:3′,4′-*f*]pyridazine **14**, 11*H*-pyrazolo[3,4-*d*]-bis-*s*-triazolo[4,3-*b*:5′,1′-*f*]pyridazine **15**, 10*H*-imidazo-[1,2-*b*]pyrazolo[4,3-*d*]-*s*-triazolo[3,4-*f*]pyridazine **16**, 10*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:3′,4′-*f*]pyridazine **17**, and 10*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:5′,1′-*f*]pyridazine **18** [4]. These systems were prepared in the following reaction sequence, starting from 6-hydrazino-7-methyl-7*H*-pyrazolo[4,3-*d*]azolopyridazines **1-3** and 8-methyl-8*H*-pyrazolo[4,3-*d*]azolopyridazines **4-6**. The hydrazino compounds **1-6** were converted with benzaldehyde into the corresponding hydrazones **7-12** and further cyclized with bromine in glacial acetic acid, according to the procedure previously described for the preparation of bicyclic *s*-triazolo[4,3-*b*]pyridazines [5], affording the derivatives of tetracyclic systems **13-18**. (Scheme 1). By cyclization of hydrazones **9** and **12** containing the imidazole ring bromination in the imidazole ring of the fused system at position 6 of **13** and **16** occurred, similarly as previously observed in the preparation of derivatives of the tricyclic system imidazo[1,2-*b*]-*s*-triazolo[4,3-*d*]pyridazine [6] (Scheme 1).

The structure determination of **13-18** is based on microanalytical data and on $^1$H nmr spectral characteristics. In $^1$H nmr spectra the *N*-methyl groups at position 11 ($\delta$ = 4.33 ppm) in **13**, position 9 ($\delta$ = 4.40 ppm) in **14** and position 11 ($\delta$ = 4.33 ppm) in **15** are shifted downfield, due to the ring current effect of the adjacent azole ring, in comparison to the *N*-groups in the corresponding tautomeric forms at position 10 ($\delta$ = 4.22 ppm) in **16**, position 10 ($\delta$ = 4.14 ppm) in **17** and position 10 ($\delta$ = 4.12 ppm) in **18**. This observation, on the basis of which it can be easily differentiated between isomeric structures, is in agreement with results observed previously [3].

## EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage, $^1$H nmr spectra were obtained on a JEOL JNM C 60 HL spectrometer, mass spectra on a Hitachi-Perkin-Elmer mass spectrometer RMU-6L, and micro analyses for C, H, and N on a Perkin-Elmer Analyser 240 C.

The following compounds were prepared according to the procedures described earlier: 6-hydrazino-7-methyl-7*H*- (**1**) and 6-hydrazino-8-methyl-8*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**4**) [3], 6-hydrazino-7-methyl-7*H*- (**2**) and 6-hydrazino-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**5**) [3], and 6-hydrazino-7-methyl-7*H*- (**3**) and 6-hydrazino-8-methyl-8*H*-pyrazolo-[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**6**) [3].

6-Benzylidenehydrazino-7-methyl-7*H*-imidazo[1,2-*b*]pyrazolo-[4,3-*d*]pyridazine (**7**).

A solution of **1** (200 mg) and benzaldehyde (0.5 ml) in ethanol (20 ml) was heated under reflux for two hours. Ethanol was evaporated *in vacuo* and the solid residue was recrystallized from acetone to give 185 mg (61%) of **7**, mp 230°; dec; $^1$H nmr (DMSO-$d_6$): $\delta$ 4.20 (s, 7-Me), 7.19 (d, $H_2$), 7.29-7.73 (m, Ph), 7.78 (d, $H_3$), 8.47 (s, CH), 8.67 (s, $H_9$), 11.35 (br s, NH), $J_{H_2,H_3}$ = 1.8 Hz.

*Anal.* Calcd. for $C_{15}H_{13}N_7$: C, 61.84; H, 4.50; N, 33.66. Found: C, 62.17; H, 4.53; N, 33.69.

In the same manner the following compounds were prepared:

6-Benzylidenehydrazino-8-methyl-8*H*-imidazo[1,2-*b*]pyrazolo-[3,4-*d*]pyridazine (**10**).

This compound was prepared from **4** in 80% yield, mp 235° dec; $^1$H nmr (DMSO-$d_6$): $\delta$ 4.35 (s, 8-Me), 7.38-7.82 (m, $H_2$, Ph), 7.92 (d, $H_3$), 8.38 (s, $H_9$, CH), 10.56 (br s, NH).

*Anal.* Calcd. for $C_{15}H_{13}N_7$: C, 61.84; H, 4.50; N, 33.66. Found: C, 61.51; H, 4.45; N, 33.36.

6-Benzylidenehydrazino-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo-[4,3-*b*]pyridazine (**11**).

This compound was prepared from **2** in 65% yield, mp 270° dec (from a mixture of 2-propanol and water); ms: 292 ($M^+$); $^1$H nmr (DMSO-$d_6$): $\delta$ 4.20 (s, 7-Me), 7.28-7.77 (m, Ph), 8.47 (s, CH), 8.80 (s, $H_9$), 9.07 (s, $H_3$), 11.45 (br s, NH).

*Anal.* Calcd. for $C_{14}H_{12}N_8$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.61; H, 4.31; N, 38.27.

6-Benzylidenehydrazino-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo-[4,3-*b*]pyridazine (**11**).

This compound was prepared from **5** in 58% yield, mp 250° dec (from a mixture of ethanol and water); $^1$H nmr (DMSO-$d_6$): $\delta$ 4.38 (s, 8-Me), 7.30-7.80 (m, Ph), 8.37 (s, CH), 8.43 (s, $H_9$), 9.25 (s, $H_3$), 11.55 (br s, NH).

*Anal.* Calcd. for $C_{14}H_{12}N_8$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.24; H, 4.11; N, 38.44.

6-Benzylidenehydrazino-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo-[1,5-*b*]pyridazine (**9**).

This compound was prepared from **3** in 52% yield, mp 285-287° (from a mixture of benzene and ethanol); $^1$H nmr (DMSO-$d_6$): $\delta$ 4.23 (s, 7-Me), 7.26-8.03 (m, Ph), 8.45 (s, CH), 8.70 (s, $H_9$), 10.9 (br s, NH).

*Anal.* Calcd. for $C_{14}H_{12}N_8$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.59; H, 4.30; N, 38.03.

6-Benzylidenehydrazino-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo-[1,5-*b*]pyridazine (**12**).

This compound was prepared from **6** in 50% yield, mp 276° dec (from ethanol); $^1$H nmr (DMSO-$d_6$): $\delta$ 4.33 (s, 8-Me), 7.24-7.77 (m, Ph), 8.18 (s, $H_2$), 8.38 (s, $H_9$, CH), 9.68 (br s, NH).

*Anal.* Calcd. for $C_{14}H_{12}N_8$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.55; H, 4.28; N, 38.56.

6-Bromo-11-methyl-3-phenyl-11*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]-*s*-triazolo[3,4-*f*]pyridazine (**13**).

To a solution of **7** (200 mg) and sodium acetate (200 mg) in

glacial acetic acid a solution of bromine (0.5 ml) in glacial acetic acid (2 ml) was added dropwise at room temperature. The solution was then heated under reflux for 5 minutes. The volatile components were evaporated *in vacuo* and the solid residue recrystallized from ethanol to give **13** (80 mg, 32%), mp 230° dec; $^1$H nmr (DMSO-$d_6$): δ 4.33 (s, 11-Me), 7.30 (s, $H_7$), 2.40 (br s, Ph), 8.22 (s, $H_9$).

*Anal.* Calcd. for $C_{15}H_{10}BrN_7$: C, 48.93; H, 2.74; N, 26.63. Found: C, 49.06; H, 3.04; N, 26.27.

In the same manner the following compounds were prepared:

6-Bromo-10-methyl-3-phenyl-10*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]-*s*-triazolo[3,4-*f*]pyridazine (**16**).

This compound was prepared from **10** in 50% yield, mp 265° (from ethanol); $^1$H nmr (DMSO-$d_6$): δ 4.22 (s, 10-Me), 7.24 (s, $H_7$), 7.30-7.83 (m, Ph), 8.58 (s, $H_9$).

*Anal.* Calcd. for $C_{15}H_{10}BrN_7$: C, 48.93; H, 2.74; N, 26.63. Found: C, 48.63; H, 3.07; N, 26.86.

9-Methyl-6-phenyl-9*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:3′,4′-*f*]-pyridazine Hydrobromide (**14**).

This compound was prepared from **8** in 36% yield, mp 275° dec (from a mixture of ethanol and water; $^1$H nmr (DMSO-$d_6$): δ 4.40 (s, 9-Me), 7.58 (s, $H_{11}$), 7.48-7.77 (m, Ph), 8.27 (s, $H_3$).

*Anal.* Calcd. for $C_{14}H_{10}N_8$.HBr: C, 45.30; H, 2.99; N, 30.19. Found: C, 45.34; H, 2.84; N, 30.39.

10-Methyl-6-phenyl-10*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:3′,4′-*f*]-pyridazine Hydrobromide (**17**).

This compound was prepared from **11** in 71% yield, mp 280° dec (from a mixture of ethanol and water); $^1$H nmr (DMSO-$d_6$): δ 4.14 (s, 10-Me), 7.58 (s, $H_{11}$), 7.53-7.73 (m, Ph), 8.77 (s, $H_3$).

*Anal.* Calcd. for $C_{14}H_{10}N_8$.HBr: C, 45.30; H, 2.99; N, 30.19. Found: C, 45.56; H, 2.88; N, 30.53.

11-Methyl-3-phenyl-11*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:5′,1′-*f*]-pyridazine (**15**).

This compound was prepared from **9** in 60% yield, mp 220-222° (from ethanol); $^1$H nmr (DMSO-$d_6$): δ 4.46 (s, 11-Me), 7.41-7.94 (m, Ph), 8.26 (s, $H_7$), 8.44 (s, $H_9$).

*Anal.* Calcd. for $C_{14}H_{10}N_8$: C, 57.92; H, 3.47; N, 38.60. Found: C, 57.76; H, 3.51; N, 38.45.

10-Methyl-3-phenyl-10*H*-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:5′,1′-*f*]-pyridazine (**18**).

This compound was prepared from **12** in 67% yield, mp 273-275° (from a mixture of ethanol and water); $^1$H nmr (DMSO-$d_6$): δ 4.12 (s, 10-Me), 7.45-7.98 (m, Ph), 8.23 (s, $H_7$), 8.92 (s, $H_9$).

*Anal.* Calcd. for $C_{14}H_{10}N_8$: C, 57.92; H, 3.47; N, 38.60. Found: C, 57.99; H, 3.62; N, 38.72.

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