1,3-Dipolar Cycloaddition of Diazomethane to Azolopyridazines. The Synthesis of 8-Methyl-8*H*- and 9-Methyl-9*H*-pyrazolo[3,4-*d*]-*s*-triazolo[4,3-*b*]pyridazine and 1-Methyl-1*H*- and 2-Methyl-2*H*-imidazo[1,2-*b*]pyrazolo[3,4-*d*]pyridazine Derivatives.

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The transformations of 7-methyl-7*H*- and 8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazines **1, 2, 9** and **10** into 8-methyl-8*H*- and 9-methyl-9*H*-pyrazolo[3,4-*d*]-*s*-triazolo[4,3-*b*]pyridazines **7** and **8**, and 1-methyl-1*H*- and 2-methyl-2*H*-imidazo[1,2-*b*]pyrazolo[3,4-*d*]pyridazines **13** and **14** are described.

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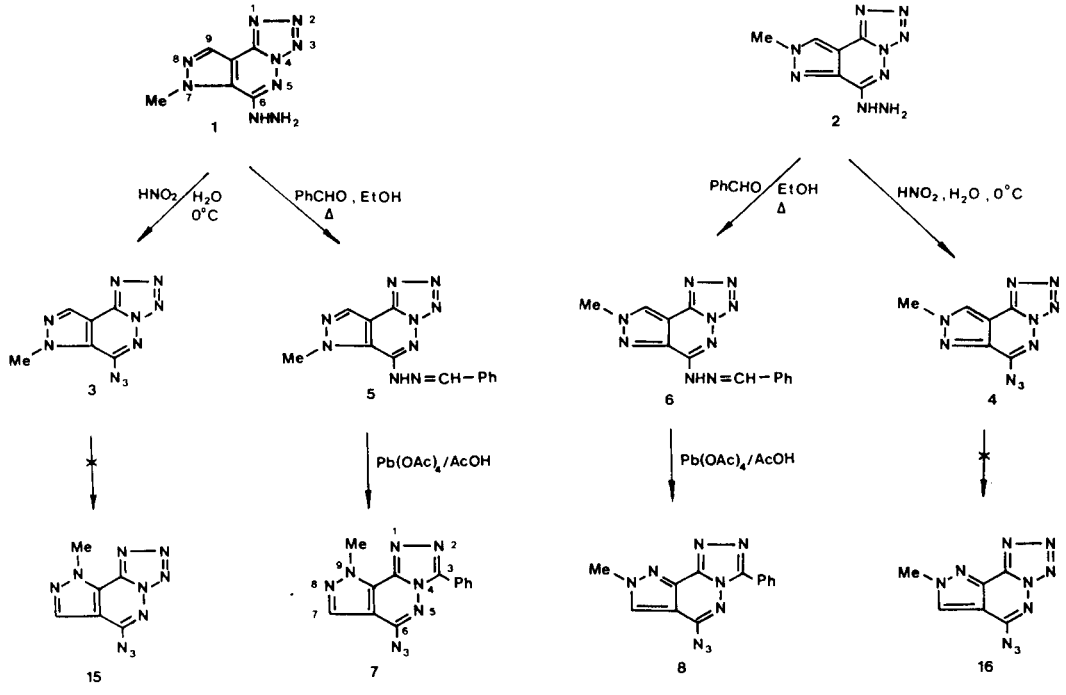
The 1,3-dipolar cycloaddition of diazoalkanes to heteroaromatic azolopyridazines has been found to be highly regiospecific to give pyrazolo[4,3-*d*]azolopyridazines [1,2]. The isomeric pyrazolo[3,4-*d*]azolopyridazines have been prepared only by azido-tetrazolo valence isomerization from the corresponding 9,9-dimethyl-6-hydrazino-9*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine, which has been transformed into 6-azido-9,9-dimethyl-9*H*-pyrazolo[3,4-*d*]tetrazolo[1,5-*b*]pyridazine and 6-azido-9,9-dimethyl-9*H*-pyrazolo[3,4-*d*]-*s*-triazolo[4,3-*b*]pyridazine [3].

In this communication we report on the preparation of 8-methyl-8*H*- and 9-methyl-9*H*-pyrazolo[3,4-*d*]-*s*-triazolo[4,3-*b*]pyridazines and 1-methyl-1*H*- and 2-methyl-2*H*-imidazo[1,2-*b*]pyrazolo[3,4-*d*]pyridazines. When the compounds **1** and **2** were treated with sodium nitrite in acetic acid at low temperature (0-5°) and the product washed only with ice-cold water the corresponding derivatives **3** and **4** were isolated. No azido-tetrazolo isomerization of the pyrazolo[4,3-*d*]-fused ring system into pyrazolo[3,4-*d*]-fused system was observed in these two examples. On the other hand, the compounds **1** and **2** were converted with benzaldehyde into the isomeric hydrazones **5** and **6**. By oxidation of the compounds **5** and **6** with bromine in glacial acetic acid the cyclization to nitrogen at position **5** was taking place followed by ring opening of the tetrazole ring according to the procedure known in the bicyclic *s*-triazolo[4,3-*b*]pyridazines [4], to give the isomeric 6-azido-9-methyl-3-phenyl-9*H*- (**7**) and 6-azido-8-methyl-3-phenyl-8*H*-pyrazolo[3,4-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8**) (Scheme 1).

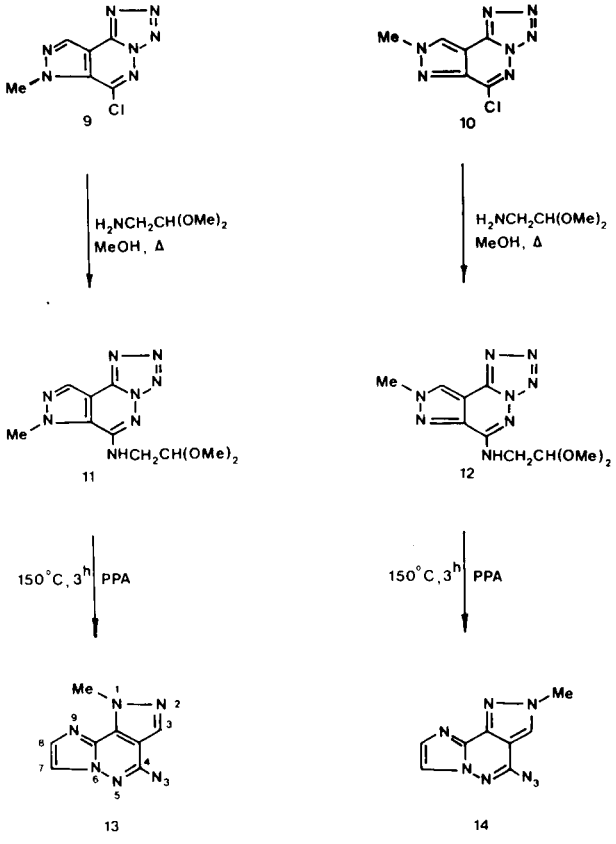
Since the transformation of 6-substituted 9,9-dimethyl-

Scheme 1



9*H*-pyrazolo[4,3-*b*]tetrazolo[1,5-*b*]pyridazines into imidazo[1,2-*b*]pyrazolo[3,4-*d*]pyridazines in PPA has not been successful [1], due to the decomposition, analogous procedure was undertaken starting from 6-chloro-7-methyl-7*H*- (**9**) and 6-chloro-8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo-[1,5-*b*]pyridazine (**10**) in the following way. The nucleophilic substitution of chlorine in the compounds **9** and **10** with aminoacetaldehyde dimethylacetal by heating under reflux in methanol for one hour afforded the corresponding 6-(2,2-dimethoxyethylamino) derivatives **11** and **12**. When these two intermediates were heated in PPA at 150° for three hours, cyclization of the 6-(2,2-dimethoxyethylamino) group occurred to nitrogen at position **5** in the pyridazine ring, followed by the valence isomerization of the tetrazole ring into the azido group to give 4-azido-1-methyl-1*H*- (**13**) and 4-azido-2-methyl-2*H*-imidazo[1,2-*b*]pyrazolo[3,4-*d*]pyridazine (**14**) [5], respectively (Scheme 2).

Scheme 2



The structures of the new systems are supported by ^{1}H nmr data. We observed earlier, that the N-Me groups at position 7 in pyrazolo[4,3-*d*]-fused systems are shifted upfield in comparison to the N-Me groups at position 8 [2]. During the transformation of these systems into pyrazolo-[3,4-*d*]-fused systems, described here, the 7-Me group in **1** becomes 9-Me group (δ = 4.38 ppm) in **7** and 7-Me group in **9** becomes 1-Me group (δ = 4.28 ppm) in **11**. They are shifted downfield in comparison to the 8-Me group (δ = 4.15 ppm) in **8** and 2-Me group (δ = 4.09 ppm) in **14**. On the other hand, the chemical shifts for 7-methyl group (δ = 4.24 ppm) in **3** and for 8-Me group (δ = 4.42 ppm) in **4** indicate that no azidotetrazolo isomerization into **15** and **16** took place during the preparation and work-up procedure of these two compounds.

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 240C.

The following starting compounds were prepared according to the procedures described in literature: 6-hydrazino-7-methyl-7*H*- (**1**) [2], 6-hydazino-8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**2**) [2], 6-chloro-7-methyl-7*H*- (**9**) [2] and 6-chloro-8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[[1,5-*b*]pyridazine (**10**) [2].

6-Azido-7-methyl-7*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**3**).

To a stirred ice-cold suspenson of **1** (102 mg, 0.005 mole) in acetic acid (12%, 10 ml) an ice-cold solution of sodium nitrite (100 mg) in water (5 ml) was added dropwise. The stirring was continued for another two hours at 0-5°. The precipitate was then collected by filtration, and washed with ice-cold water to give 70 mg (67%) of **3**, mp 170° dec; ^{1}H nmr (DMSO-d_6): δ 4.24 (s, 7-Me), 8.88 (s, H_9).

Anal. Calcd. for $C_6H_4N_{10}$: C, 33.33; H, 1.86; N, 64.80. Found: C, 33.23; H, 1.85; N, 65.19.

In analogous manner the following compound was prepared:

6-Azido-8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**4**).

This compound was prepared from **2** in 48% yield, mp 185° dec; ^{1}H nmr (DMSO-d_6): δ 4.42 (s, 8-Me), 8.42 (s, H_9).

Anal. Calcd. for $C_6H_4N_{10}$: C, 33.33; H, 1.86; N, 64.80. Found: C, 33.38; H, 1.83; N, 64.95.

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

To a suspension of **1** (410 mg, 0.002 mole) in ethanol (30 ml) benzaldehyde (0.6 ml) was added and the mixture was heated under reflux for two hours. The precipitate was, after cooling, collected by filtration and recrystallized from a mixture of ethanol and water to give **5** in 67% yield; mp >300°; ms: 293 (M^+); ^{1}H nmr (DMSO-d_6): 150°, δ 4.23 (s, 7-Me), 7.25-7.87 (m, Ph), 8.47 (s, CH), 8.83 (s, H_9).

Anal. Calcd. for $C_{13}H_{11}N_9$: C, 53.23; H, 3.78; N, 42.98. Found: C, 53.43; H, 3.78; N, 43.10.

In the same manner the following compound was prepared:

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

This compound was prepared from **2** in 65% yield, mp 260° dec (from water); ^{1}H nmr (DMSO-d_6): 60°, δ 4.48 (s, 8-Me), 7.37-7.89 (m, Ph), 8.52 (s, CH), 8.68 (s, H_9), 9.05 (br s, NH).

Anal. Calcd. for $C_{13}H_{11}N_9$: C, 53.23; H, 3.78; N, 42.98. Found: C, 53.01; H, 3.60; N, 42.92.

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

To a mixture of **5** (293 mg, 0.001 mole) and sodium acetate (300 mg) in glacial acetic acid (10 ml) a solution of bromine (0.5 ml) in glacial acetic acid (2 ml) was added dropwise, and the mixture was heated under reflux for 5 minutes. The solution was, after cooling, poured on crushed ice (20 g) and the precipitate was collected by filtration and recrystallized from a mixture of ethanol and water to give **7** in 76% yield, mp 180° dec; ms: 291 (M^+); ^1H nmr (DMSO-d_6): δ 4.38 (s, 9-Me), 7.40-7.63 (m) and 8.17-8.40 (m) (Ph), 8.07 (s, H_7).

Anal. Calcd. for $C_{13}H_9N_9$: C, 53.60; H, 3.11; N, 43.28. Found: C, 53.60; H, 3.09; N, 43.09.

In analogous manner the following compound was prepared:

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

This compound was prepared from **6** in 60% yield, mp 217° (from ethanol); ^1H nmr (DMSO-d_6): 150°, δ 4.15 (s, 8-Me), 7.37-7.58 (m) and 8.38-8.51 (m) (Ph), 8.51 (s, H_7).

Anal. Calcd. for $C_{13}H_9N_9$: C, 53.60; H, 3.11; N, 43.28. Found: C, 53.48; H, 3.14; N, 43.25.

6-(2,2-Dimethoxyethylamino)-7-methyl-7*H*-pyrazolo[4,3-*b*]tetrazolo[1,5-*b*]pyridazine (**11**).

A mixture of **9** (209 mg, 0.001 mole) and aminoacetaldehyde dimethyl acetal (0.5 ml) in methanol (10 ml) was heated under reflux for one hour. The volatile components were evaporated *in vacuo* and the solid residue was recrystallized from ethanol to give 160 mg (60%) of **11**, mp 170-172°; ^1H nmr (DMSO-d_6): δ 3.33 (s, OMe), 3.73 (dd, CH_2), 4.25 (s, 7-Me), 4.77 (t, CH), 7.75 (t, NH), 8.98 (s, H_9), $J_{CH_2,CH}$ = 5.0 Hz, $J_{CH_2,NH}$ = 6.0 Hz.

Anal. Calcd. for $C_{10}H_{14}N_8O_2$: C, 43.16; H, 5.07; N, 40.27. Found: C, 43.09; H, 5.19; N, 39.98.

In the same manner the following compound was prepared:

6-(2,2-Dimethoxyethylamino)-8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**12**).

This compound was prepared from **10** in 66% yield, mp 180° dec (from a mixture of ethanol and water); ^1H nmr (DMSO-d_6): δ 3.37 (s, OMe), 3.60 (d, CH_2), 4.35 (s, 8-Me), 4.75 (t, CH), 8.55 (s, H_9), $J_{CH,CH}$ = 5.0 Hz.

Anal. Calcd. for $C_{10}H_{14}N_8O_2$: C, 43.16; H, 5.07; N, 40.27. Found: C, 43.16; H, 5.19; N, 39.92.

4-Azido-1-methyl-1*H*-imidazo[1,2-*b*]pyrazolo[3,4-*d*]pyridazine (**13**) [5].

A mixture of **11** (350 mg, 0.00125 mole) and PPA (5 g) was heated at 150° until all the starting material was transformed (approximately 3 hours). The mixture was, after cooling, poured on crushed ice (20 g) and neutralized with solid sodium hydrogen carbonate. The precipitate wsa collected by filtration and recrystallized from water to give 100 mg (68%) of **13**, mp 165° dec; ^1H nmr (DMSO-d_6): 125°, δ 4.28 (s, 1-Me), 7.47 (d, H_8), 7.75 (s, H_3), 8.00 (d, H_7), J_{H_7,H_8} = 2.0 Hz.

Anal. Calcd. for $C_8H_6N_6$: C, 44.86; H, 2.82; N, 52.32. Found: C, 44.98; H, 2.86; N, 52.57.

In analogous manner the following compound ws prepared:

4-Azido-2-methyl-2*H*-imidazo[1,2-*b*]pyrazolo[3,4-*d*]pyridazine (**14**) [5].

This compound was prepared from **12** in 37% yield, mp 220° dec (from ethanol); ^1H nmr (DMSO-d_6): 120°, δ 4.09 (s, 2-Me), 7.33 (d, H_8), 7.83 (s, H_3), 8.40 (d, H_7), J_{H_7,H_8} = 2.0 Hz.

Anal. Calcd. for $C_8H_6N_6$: C, 44.86; H, 2.82; N, 52.32. Found: C, 44.85; H, 2.83; N, 52.32.

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[5] We thank Dr.K. Loening, Nomenclature Director, Chemical Abstracts Service, for helping to correctly name, number and orient this new heterocyclic system.