1,3-Dipolar Cycloaddition of Diazomethane to Azolopyridazines. The Synthesis of Isomeric 7-Methyl-7*H*- and 8-Methyl-8*H*-pyrazolo[4,3-*d*]azolopyridazines

Marjo Merslavič, Andrej Petrič, Damjana Rozman, Branko Stanovnik*, and Miha Tišler

Department of Chemistry, Edvard Kardelj University
61000 Ljubljana, Yugoslavia

Received September 30, 1988

1,3-Dipolar cycloaddition of diazomethane to 6-chloro substituted azolopyridazines **1-4** produces isomeric pairs of 7-methyl-7*H*- **9-12** and 8-methyl-8*H*-pyrazolo[4,3-*d*]azolopyridazines **13-16**. The nucleophilic substitution of chlorine at position 6 affords the corresponding 6-amino **17**, **20**, **23**, **26**, **29**, **32**, **35** and **38**, 6-methoxy **18**, **21**, **24**, **27**, **30**, **33**, **36**, and **39** and 6-hydrazino derivatives **19**, **22**, **25**, **28**, **31**, **34**, **37**, and **40** of these tricyclic systems.

J. Heterocyclic Chem., **26**, 445 (1989).

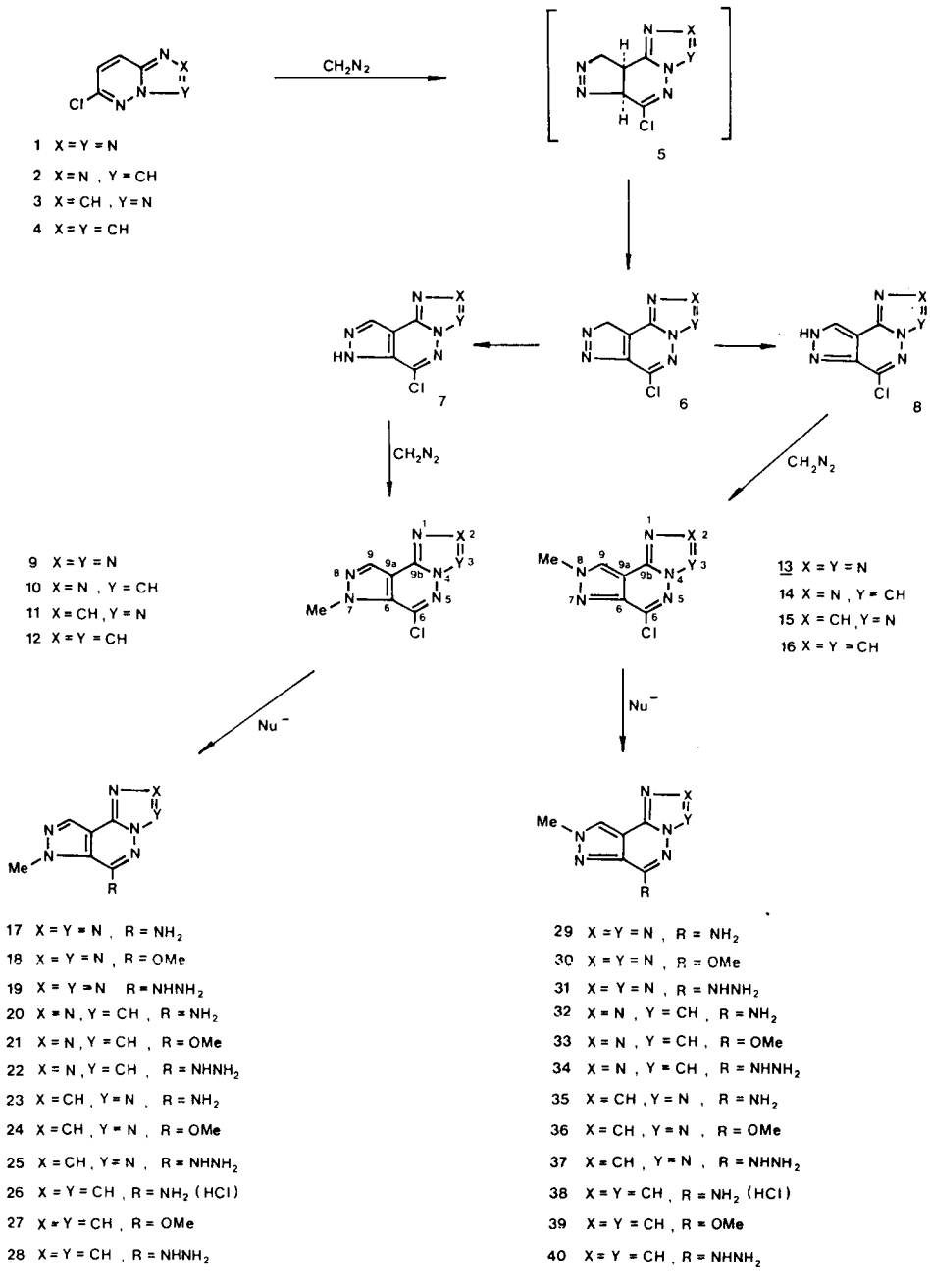
Recently, we have reported on the 1,3-dipolar cycloadditions of 2-diazopropane to derivatives of bicyclic 10π-electron systems, such as imidazo[1,2-*b*]pyridazine, *s*-triazolo[4,3-*b*]pyridazine, *s*-triazolo[1,5-*b*]pyridazine and tetrazolo[1,5-*b*]pyridazine to give the corresponding 9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]azolopyridazines in high yields [1-4]. The structures of these new heterocyclic systems have been established by photochemical elimination of nitrogen to give 8-substituted azolopyridazines [2,5-7] and for two examples also by X-ray analyses [8,9]. The reactions are highly regiospecific and proceed in opposite manner in comparison to that found in α,β-unsaturated carbonyl compounds [10].

In this communication we report on the preparation of derivatives of isomeric 7-methyl-7*H*- and 8-methyl-8*H*-pyrazolo[4,3-*d*]azolopyridazines by 1,3-dipolar cycloaddition of diazomethane to 6-chloro substituted tetrazolo[1,5-*b*]pyridazine (**1**), *s*-triazolo[4,3-*b*]pyridazine (**2**), *s*-triazolo[1,5-*b*]pyridazine (**3**) and imidazo[1,2-*b*]pyridazine (**4**). The reaction is assumed to proceed regiospecifically to the C_7-C_8 partially localized and polarized double bond in pyridazine nucleus to give primary cycloadducts of the type **5**, followed by oxidative transformation into intermediates **6**, 1,3- and/or 1,5-sigmatropic rearrangement of one of the hydrogen atoms of the methylene group to give the tautomeric intermediates **7** and **8**, and further methylation with an excess of diazomethane to produce mixtures of the corresponding isomeric pairs of 7-methyl-7*H*- **9-12** and 8-methyl-8*H*-pyrazolo[4,3-*d*]azolopyridazines **13-16** (Scheme 1).

The structure determination of the compounds **9-16** is based on the elemental analyses, mass spectral data and ^{1}H and ^{13}C nmr spectra. Namely, the position of the methyl group attached at either of nitrogen atoms in pyrazole ring can be determined on the basis of chemical shifts of the *N*-methyl groups and of the protons H_9. In all four isomeric pairs the protons at position 9 for 7-methyl-7*H*-isomers **9-12** appear at δ = 8.83-9.18 ppm and are shifted downfield in comparison to those in the corresponding 8-methyl-8*H*- isomers **13-16**, which appear at δ = 8.40-8.80 ppm. On the other hand, the methyl groups at position 7 in 7-methyl-7*H*- isomers **9-12** appear at δ = 4.18-4.33 ppm, while the methyl groups at position 8 in 8-methyl-8*H*-isomers **13-16** are shifted downfield and appear at δ = 4.33-4.42 ppm. This observation is also supported by ^{13}C nmr spectral data. The carbon atoms $^{13}C_9$ in 7-methyl-7*H*- isomers **9-12** appear as doublets at δ = 131.4-132.5 ppm with the coupling constants $^1J_{^{13}C\text{-}H}$ = 198.6-200.1 Hz, due to the coupling with H_9, while the carbons $^{13}C_9$ in 8-methyl-8*H*- isomers **13-16** appear as quartets of a doublet at δ = 125.1-129.9.ppm with the coupling constants $^1J_{^{13}C\text{-}H}$ = 197.1-202.9 Hz, due to the coupling with H_9, and $^4J_{^{13}C\text{-}N\text{-}Me}$ = 2.4-2.9 Hz, due to the coupling with the protons of the adjacent *N*-methyl group. Furthermore, the orientation of the pyrazole ring against pyridazine ring is also supported by the following long-range coupling constants between carbon-13 and protons. The atoms $^{13}C_{6a}$ in 7-methyl-7*H*- isomers **9-12** appear as multiplets at δ = 128.6-130.7 ppm, due to the coupling with H_9 on one side, and the coupling with the protons of the 7-methyl group on the other side, while the carbon atoms $^{13}C_{6a}$ in the 8-methyl-8*H*- isomers **13-16** appear only as doublets at δ = 137.8-139.6 ppm with coupling constants $^3J_{^{13}C_{6a}\text{-}C_{9a}\text{-}C_9\text{-}H}$ = 7.1-7.4 Hz. The carbon atoms $^{13}C_{9a}$ appear in both sets of isomers as doublets at δ = 108.4-116.7 ppm with coupling constants $^2J_{^{13}C_{9a}\text{-}C_9\text{-}H}$ = 7.9-11.0 Hz.

Since these compounds are new isomers of the pyrazolo[4,3-*d*]azolopyridazines, some nucleophilic substitutions of the chlorine at position 6 were studied in order to prepare intermediates suitable for further cyclizations. When the

Scheme 1



compounds **9-16** were heated in ethanolic ammonia in an autoclave at 100° for 10 hours, the corresponding 6-amino-7-methyl-7*H*- **17, 20, 23,** and **26,** and 6-amino-8-methyl-8*H*-pyrazolo[4,3-*d*]azolopyridazines **29, 32, 35,** and **38** were obtained. Similarly, when the compounds **9-16** were heated with lithium methoxide in methanol under reflux for four hours, the corresponding 6-methoxy derivatives **18, 21, 24, 27** and **30, 33, 36,** and **39** were formed, and when heated with hydrazine hydrate (80%) in ethanol under reflux for three hours, the corresponding 6-hydrazino derivatives **19, 22, 25, 28** and **31, 34, 37** and **40** were isolated. (Scheme 1).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. All ^{1}H nmr spectra were obtained on a JEOL JNM C60-HL spectrometer, mass spectra on a Hitachi-Perkin-Elmer mass spectrometer RMU-6L, and microanalyses for C, H, and N on a Perkin-Elmer Analyser 240C.

The following compounds were prepared according to the procedure described in literature: 6-chlorotetrazolo[1,5-*b*]pyridazine (**1**) [11], 6-chloro-*s*-triazolo[4,3-*b*]pyridazine (**2**) [12], 6-chloro-*s*-triazolo[1,5-*b*]pyridazine (**3**) [13], 6-chloroimidazo[1,2-*b*]pyridazine (**4**) [14], and diazomethane [15].

6-Chloro-7-methyl-7*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**9**) and 6-Chloro-8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**13**).

To a solution of **1** (5 g, 0.032 mole) in tetrahydrofuran (400 ml) a solution of diazomethane (6 g, 0.142 mole) in diethyl ether (300 ml) was added dropwise, and the mixture was left at room temperature until all the starting material was consumed (approximately 24 hours). Acetic acid was then added dropwise to the solution, in order to destroy the excess of diazomethane, until the evolution of nitrogen ceased. The volatile components were evaporated *in vacuo*, water (20 ml) was added to the solid residue and the precipitate was collected by filtration to give the crude mixture (4.2 g) of **9** and **13** in 1:1 ratio determined by ^{1}H nmr technique. The mixture was suspended in hot tetrahydrofuran (70 ml), the solid was collected by filtration and recrystallization from ethanol to give **9** (1.4 g, 43%), mp 230° dec; ms: 209 (M^+); ^{1}H nmr (DMSO-d_6): δ 4.27 (s, 7-Me), 9.18 (s, H_9).

Anal. Calcd. for $C_6H_4ClN_7$: C, 34.38; H, 1.92; N 46.78. Found: C, 34.42; H, 1.96; N, 46.92.

The filtrate, obtained above, was evaporated *in vacuo* and the solid residue was purified by column chromatography (silicagel 0.063-0.200 mm, chloroform, 20:1, as eluent) followed by recrystallization from ethanol to give **13** (1.5 g, 45%), mp 195° dec; ms: 209 (M^+); ^{1}H nmr (DMSO-d_6): δ 4.42 (s, 8-Me), 8.80 (s, H_9); ^{13}C nmr (DMSO-d_6): δ 144.4 (s, C_6), 140.3 (s, C_{9b}), 139.6 (d, C_{6a}), 129.9 (dq, C_9), 108.4 (d, C_{9a}), 40.5 (q, 8-CH_3), $J_{C_{6a}\text{-}H_9}$ = 7.1 Hz, $J_{C_9\text{-}H_9}$ = 202.9 Hz, $J_{C_9\text{-}N_8\text{-}Me}$ = 2.9 Hz, $J_{C_{9a}\text{-}C_9\text{-}H_9}$ = 8.7 Hz, J_{M^+} = 144.3 Hz.

Anal. Calcd. for $C_6H_4ClN_7$: C, 34.38; H, 1.92; N, 46.78. Found: C, 34.33; H, 1.86; N, 46.59.

Analogously the following compounds were prepared:

6-Chloro-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**10**) and 6-Chloro-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**14**).

These two compounds were prepared from **2**. The separation of both isomers, as described above, gave a solid insoluble material in hot tetrahydrofuran, identified as **10** (1.2 g, 36%), mp >300° (from a mixture of ethanol and water); ms: 208 (M^+); ^{1}H nmr (DMSO-d_6): δ 4.22 (s, 7-Me), 8.80 (s, H_9); ^{13}C nmr (DMSO-d_6): δ 138.9 (s, C_6), 137.8 (s, C_3), 131.4 (d, C_9), 128.6 (dq, C_{6a}), 136.1 (s, C_{9b}), 112.2 (d, C_{9a}), 39.0 (q, 7-Me), $J_{C_3\text{-}H_3}$ = 219.0 Hz, $J_{C_9\text{-}H_9}$ = 199.0 Hz, J_{M^+} = 142.4 Hz, $J_{C_{6a}\text{-}N_7\text{-}Me}$ = 7.4 Hz, $J_{C_{9a}\text{-}C_9\text{-}H_9}$ = 9.5 Hz.

Anal. Calcd. for $C_7H_5ClN_6$: C, 40.29; H, 2.42; N, 40.29. Found: C, 40.64; H, 2.40; N, 40.35.

Evaporation of the filtrate *in vacuo* and purification of the dry residue by column chromatography as above gave **14** (1.4 g, 41%), mp 225° dec (from ethanol); ms: 208 (M^+); ^{1}H nmr (DMSO-d_6): δ 4.33 (s, 8-Me), 8.43 (s, H_9), 9.30 (s, H_3); ^{13}C nmr (DMSO-d_6): δ 142.2 (s, C_6), 139.2 (d, C_{9b}), 138.4 (d, C_3), 137.8 (d, C_{6a}), 127.5 (dq, C_9), 109.1 (d, C_{9a}), 38.7 (q, 8-Me), $J_{C_3\text{-}H_3}$ = 220.3 H z, $J_{C_9\text{-}H_9}$ = 200.1 Hz, $J_{C_9\text{-}N_8\text{-}Me}$ = 2.6 Hz, $J_{C_{9a}\text{-}C_9\text{-}H_9}$ = 8.6 Hz, $J_{C_{6a}\text{-}C_{9a}\text{-}C_9\text{-}H_9}$ = 7.4 Hz, $J_{C_{9a}\text{-}C_{9a}\text{-}C_9\text{-}H_9}$ = 3.6 Hz, J_{M^+} = 143 Hz.

Anal. Calcd. for $C_7H_5ClN_6$: C, 40.29; H, 2.42; N, 40.29. Found: C, 40.25; H, 2.36; N, 40.28.

6-Chloro-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**11**) and 6-Chloro-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**15**).

These two compounds were prepared from **3**. The mixture was suspended in ethanol (50 ml). The solid was collected by filtration and recrystallized from a mixture of ethanol and chloroform (10:1) to give **11** (1.8 g, 52%), mp 280° dec; ^{1}H nmr (DMSO-d_6): δ 4.23 (s, 7-Me), 8.21 (s, H_9), 8.84 (s, H_2); ^{13}C nmr (DMSO-d_6): δ 151.7 (d, C_2), 140.2 (d, C_{9b}), 133.3 (s, C_6), 132.5 (d, C_9), 130.7 (m, C_{6a}), 115.8 (d, C_{9a}), 39.9 (q, 7-Me), $J_{C_2\text{-}H_2}$ = 212.2 Hz, $J_{C_9\text{-}H_9}$ = 200.0 Hz, J_{M^+} = 142.0 Hz, $J_{C_{9a}\text{-}C_9\text{-}H_9}$ = 11.3 Hz, $J_{C_{9a}\text{-}C_{9a}\text{-}H_9}$ = 7.9 Hz.

Anal. Calcd. for $C_7H_5ClN_6$: C, 40.29: H, 2.42; N, 40.29. Found: C, 40.26; H, 2.26; N, 40.18.

Evaporation of the filtrate and purification of the solid residue by column chromatography as above gave **15** (1.5 g, 44%), mp 195-196°; ^{1}H nmr (DMSO-d_6): δ 4.41 (s, 8-Me), 8.36 (s, H_2), 8.44 (s, H_9); ^{13}C nmr (DMSO-d_6): δ 149.7 (d, C_2), 139.8 (d, C_{9b}), 139.4 (s, C_6), 138.7 (d, C_{6a}), 126.8 (dq, C_9), 111.3 (d, C_{9a}), 40.3 (q, 8-Me), $J_{C_2\text{-}H_2}$ = 212.3 Hz, $J_{C_9\text{-}H_9}$ = 201.7 Hz, $J_{C_9\text{-}N_8\text{-}Me}$ = 2.4 Hz, $J_{C_{9a}\text{-}C_9\text{-}H_9}$ = 8.6 Hz, $J_{C_{9a}\text{-}C_{9a}\text{-}C_9\text{-}H_9}$ = 7.4 Hz, $J_{C_{6a}\text{-}C_{9a}\text{-}C_9\text{-}H_9}$ = 7.4 Hz, J_{M^+} = 142.5 Hz.

Anal. Calcd. for $C_7H_5ClN_6$: C, 40.29; H, 2.42; N, 40.29. Found: C, 40.13; H, 2.28; N, 40.15.

6-Chloro-7-methyl-7*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**12**) and 6-Chloro-8-methyl-8*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**16**).

To a solution of **4** (5 g, 0.0325 mole) in a mixture of DMF (100 ml) and chloroform (200 ml) a solution of diazomethane (6 g, 0.142 mole) in ether (300 ml) was added dropwise. Every second day a fresh solution of diazomethane was added to the reaction mixture. The volume of the reaction mixture was reduced to one-half, before a new solution of diazomethane was added, and this was continued for one month until all the starting compound was consumed. The evaporation of the volatile components gave a mixture of two isomers, which were separated by column chromatography (silica gel 0.063-0.200 mm, a mixture of chloroform and ethanol, 10:1, as eluent). The first component eluted from the column gave **16** (1.4 g, 41%), mp 141° dec (from ethanol), ^{1}H nmr (DMSO-d_6): δ 4.32 (s, 8-Me), 7.52 (d, H_2), 8.13 (d, H_3), 8.45 (s, H_9), J_{H_2,H_3} = 1.4 Hz; ^{13}C nmr (deuteriochloroform): δ 134.1 (dd, C_{9b}), 131.5 (d, C_9), 133.0 (s, C_6), 130.9 (dd, C_2), 128.7 (br C_{6a}), 116.7 (d, C_{9a}), 116.2 (dd, C_3), 39.6 (q, 7-Me), $J_{C_2\text{-}H_2}$ = 193.6 Hz, $J_{C_3\text{-}H_3}$ = 198.4 Hz, $J_{C_9\text{-}H_9}$ = 198.6 Hz, J_{M^+} = 142.7 Hz, $J_{C_2\text{-}C_3\text{-}H_2}$ = 10 Hz, $J_{C_3\text{-}C_2\text{-}H_2}$ = 15.9 Hz, $J_{C_{9a}\text{-}C_9\text{-}H_9}$ = 11 Hz, $J_{C_{9a}\text{-}C_{9a}\text{-}C_9\text{-}H_9}$ = 6.0 Hz, $J_{C_{9b}\text{-}N_4\text{-}C_2\text{-}N_2}$ = 10.7 Hz.

Anal. Calcd. for $C_6H_6ClN_5$: C, 46.27; H, 2.91; N, 33.73. Found: C, 45.94; H, 2.86; N, 33.61.

The second component eluted from the column gave **12** (1.5 g, 44%), mp 232° dec (from ethanol); ^{1}H nmr (DMSO-d_6): δ 4.22 (s, 7-Me), 7.38 (d, H_2), 8.00 (d, H_3), 8.83 (s, H_9), J_{H_2,H_3} = 1.4 Hz; ^{13}C nmr (deuteriochloroform): δ 140.3 (s, C_6), 139.0 (d, C_{6a}), 133.8 (s, C_{9b}), 129.3 (dd, C_2), 125.1 (dq, C_9), 117.0 (dd, C_3), 113.9 (d, C_{9a}), 41.0 (q, 8-Me), $J_{C_2\text{-}H_2}$ = 1.92 Hz, $J_{C_3\text{-}H_3}$ = 198.3 Hz, $J_{C_9\text{-}H_9}$ = 197.1 Hz, $J_{8\text{-}Me}$ = 143.6 Hz, $J_{C_3\text{-}H_3}$ = 9.9 Hz, $J_{C_3\text{-}C_2\text{-}H_2}$ = 16.0 Hz, $J_{C_{6a}\text{-}C_{9a}\text{-}C_9\text{-}H_9}$ = 7.3 Hz, $J_{C_9\text{-}N_8\text{-}Me}$ = 2.9 Hz, $J_{C_{9a}\text{-}C_9\text{-}H_9}$ = 7.9 Hz.

Anal. Calcd. for $C_6H_6ClN_5$: C, 46.27; H, 2.91; N, 33.73. Found: C, 46.20; H, 2.87; N, 33.83.

6-Amino-7-methyl-7*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**17**).

A suspension of **9** (170 mg, 0.008 mole) in a mixture of ethanol (5 ml) and liquid ammonia (60 ml) was heated in an autoclave at 100° for 10 hours. Ammonia was, after cooling, evaporated *in vacuo* and the solid residue recrystallized from a mixture of glacial acetic acid and water to give **17** (120 mg, 77%), mp >300°; ^{1}H nmr (DMSO-d_6): δ 4.23 (s, 7-Me), 6.90 (br s, NH_2), 8.83 (s, H_9).

Anal. Calcd. for $C_6H_6N_8$: C, 37.89; H, 3.18; N, 58.93. Found: C, 37.68; H, 3.16; N, 58.58.

The following compound were prepared in the same manner:

6-Amino-8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**29**).

This compound was prepared from **13** in 71% yield, mp >300° (from a mixture of glacial acetic and water); ^{1}H nmr (DMSO-d_6): 140°, δ 4.40 (s, 8-Me), 6.86 (br s, NH_2), 8.50 (s, H_9).

Anal. Calcd. for $C_6H_6N_8$: C, 37.89; H, 3.18; N, 58.93. Found: C, 37.78; H, 3.17; N, 58.89.

6-Amino-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**20**).

This compound was prepared from **10** in 71% yield, mp >310° (from water); ^{1}H nmr (DMSO-d_6): 150°, δ 4.18 (s, 7-Me), 6.38 (br s, NH_2), 8.65 (s, H_9), 8.78 (s, H_3).

Anal. Calcd. for $C_7H_7N_7$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.61; H, 3.84; N, 51.97.

6-Amino-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**32**).

This compound was prepared from **14** in 70% yield, mp >315° (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): δ 4.32 (s, 8-Me), 6.20 (br s, NH_2), 8.22 (s, H_9), 8.87 (s, H_3).

Anal. Calcd. for $C_7H_7N_7$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.12; H, 3.76; N, 51.51.

6-Amino-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**23**).

This compound was prepared from **11** in 60% yield, mp >300°C (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): 150°, δ 4.15 (s, 7-Me), 6.21 (br s, NH_2), 7.85 (s, H_2), 8.85 (s, H_9).

Anal. Calcd. for $C_7H_7N_7$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.46; H, 3.77; N, 52.05.

6-Amino-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**35**).

This compound was prepared from **15** in 66% yield, mp 282° dec (from ethanol); ^{1}H nmr (DMSO-d_6): δ 4.22 (s, 8-Me), 6.80 (br s, NH_2), 8.17 (s, H_2), 8.40 (s, H_9).

Anal. Calcd. for $C_7H_7N_7$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.57; H, 3.91; N, 52.07.

6-Amino-7-methyl-7*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine hydrochloride (**26**).

This compound was prepared from **12** in 71% yield as hydrochloride salt, mp >300° (from 2-propanol); ^{1}H nmr (DMSO-d_6): 145°, δ 4.28 (s, 7-Me), 4.08 (br s, NH_2), 7.62 (d, H_2), 7.80 (d, H_3), 8.87 (s, H_9), J_{H_2,H_3} = 2.0 Hz.

Anal. Calcd. for $C_8H_9ClN_6$: C, 42.77; H, 4.04; N, 37.41. Found: C, 42.75; H, 4.13; N, 37.16.

6-Amino-8-methyl-8*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine hydrochloride (**38**).

This compound was prepared from **16** in 54% yield, mp >300° (from 2-propanol); ^{1}H nmr (DMSO-d_6): 150°, δ 4.35 (s, 8-Me), 5.57 (br s, NH_2), 7.68 (d, H_2), 7.87 (d, H_3), 8.53 (s, H_9), J_{H_2,H_3} = 2.0 Hz.

Anal. Calcd. for $C_8H_9ClN_6$: C, 42.77; H, 4.04; N, 37.41. Found: C, 42.39; H, 4.17; N, 37.63.

6-Methoxy-7-methyl-7*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**18**).

A mixture of **9** (130 mg, 0.0006 mole) and lithium methoxide (30 mg) in methanol (15 ml) was heated under reflux for four hours. The precipitate was after cooling, collected by filtration and recrystallized from a mixture of ethanol and water to give **18** (75 mg, 59%), mp 265° dec; ms: 205 (M^+); ^{1}H nmr (DMSO-d_6): 150°, δ 4.07 (s, OMe), 4.20 (s, 7-Me), 8.86 (s, H_9).

Anal. Calcd. for $C_7H_7N_7O$: C, 40.97; H, 3.44; N, 47.79. Found: C, 40.94; H, 3.47; N, 48.00.

In an analogous manner the following compounds were prepared:

6-Methoxy-8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**30**).

This compound was prepared from **13** in 61% yield, mp 215° dec (from ethanol); ^{1}H nmr (DMSO-d_6): 118°, δ 4.21 (s, OMe), 4.27 (s, 8-Me), 8.50 (s, H_9).

Anal. Calcd. for $C_7H_7N_7O$: C, 40.97; H, 3.44; N, 47.79. Found: C, 40.76; H, 3.38; N, 47.41.

6-Methoxy-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**21**).

This compound was prepared from **10** in 48% yield, mp 255° dec (from methanol); ms: 204 (M^+): ^{1}H nmr (DMSO-d_6): 130°, δ 4.05 (s, OMe), 4.13 (s, 7-Me), 8.63 (s, H_9), 8.92 (s, H_3).

Anal. Calcd. for $C_8H_8N_6O$: C, 47.05; H, 3.95; N, 41.16. Found: C, 47.02; H, 3.94; N, 41.04.

6-Methoxy-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**33**).

This compound was prepared from **14** in 82% yield, mp >310° (from water); ^{1}H nmr (DMSO-d_6): δ 4.12 (s, OMe), 4.23 (s, 8-Me), 8.43 (s, H_9), 9.25 (s, H_3).

Anal. Calcd. for $C_8H_8N_6O$: C, 47.05; H, 3.95; N, 41.16. Found: C, 46.79; H, 4.21; N, 40.77.

6-Methoxy-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**24**).

This compound was prepared from **11** in 61% yield, mp 283°; ^{1}H nmr (DMSO-d_6): δ 4.13 (s, OMe), 4.22 (s, 7-Me), 8.14 (s, H_2), 8.71 (s, H_9).

Anal. Calcd. for $C_8H_8N_6O$: C, 47.05; H, 3.95; N, 41.16. Found: C, 47.27; H, 4.02; N, 41.36.

6-Methoxy-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**36**).

This compound was prepared from **15** in 75% yield, mp 200° dec (from water); ^{1}H nmr (DMSO-d_6): δ 4.13 (s, OMe), 4.22 (s, 8-Me), 8.12 (s, H_2), 8.25 (s, H_9).

Anal. Calcd. for $C_8H_8N_6O$: C, 47.05; H, 3.95; N, 41.16. Found: C, 47.29; H, 4.01; N, 41.06.

6-Methoxy-7-methyl-7*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**27**).

This compound was prepared from **12** in 47% yield, mp 235° dec (from water); ^{1}H nmr (DMSO-d_6): δ 4.06 (s, OMe), 4.14 (s, 7-Me), 7.18 (d, H_2), 7.62 (d, H_3), 8.47 (s,H_9), J_{H_2,H_3} = 1.2 Hz.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.19; H, 4.46; N, 34.47. Found: C, 53.31; H, 4.43; N, 34.35.

6-Methoxy-8-methyl-8*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**39**).

This compound was prepared from **16** in 54% yield, mp 175° dec (from water); ^{1}H nmr (DMSO-d_6): δ 4.09 (s, OMe), 4.20 (s, 8-Me), 7.31 (d, H_2), 7.85 (d, H_3), 8.24 (s, H_9), J_{H_2,H_3} = 1.2 Hz.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.19; H, 4.46; N, 34.47. Found: C, 53.19; H, 4.45; N, 34.36.

6-Hydrazino-7-methyl-7*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**19**).

A mixture of **9** (836 mg, 0.004 mole) and hydrazine hydrate (80%, 0.8 ml) in ethanol (30 ml) was heated under reflux for three hours. The precipitate was after cooling collected by filtration and recrystallized from water to give **19** (500 mg, 64%), mp 270° dec; ^{1}H nmr (DMSO-d_6): 150°, δ 4.17 (s, 7-Me), 8.73 (s, H_9).

Anal. Calcd. for $C_6H_7N_9$: C, 35.12; H, 3.44; N, 61.44. Found: C, 34.93; H, 3.36; N, 61.66.

In an analogous manner the following compouds were prepared:

6-Hydrazino-8-methyl-8*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**31**).

This compound was prepared from **13** in 76% yield, mp 280° dec (from water); ^{1}H nmr (DMSO-d_6): δ 4.30 (s, 8-Me), 8.36 (s, H_9).

Anal. Calcd. for $C_6H_7N_9$: C, 35.12; H, 3.44; N, 61.44. Found: C, 35.21; H, 3.53; N, 61.52.

6-Hydrazino-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**22**).

This compound was prepared from **10** in 69% yield, mp >305° dec (from water); ms: 204 (M^+); ^{1}H nmr (DMSO-d_6): 150°, δ 4.08 (s, 7-Me), 8.47 (s, H_9), 8.65 (s, H_3).

Anal. Calcd. for $C_7H_8N_8$: C, 41.17; H, 3.95; N, 54.88. Found: C, 40.94; H, 4.04; N, 54.94.

6-Hydrazino-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**34**).

This compound was prepared from **14** in 87% yield, mp >300° (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): 146°, δ 4.28 (s, 8-Me), 8.25 (s, H_9), 9.92 (s, H_3).

Anal. Calcd. for $C_7H_8N_8$: C, 41.17; H, 3.95; N, 54.88. Found: C, 40.90; H, 3.87; N, 54.92.

6-Hydrazino-7-methyl-7*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**25**).

This compound was prepared from **11** in 85% yield, mp >300° (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): 150°, δ 4.16 (s, 7-Me), 7.98 (s, H_2), 8.60 (s, H_9).

Anal. Calcd. for $C_7H_8N_8$: C, 41.17; H, 3.95; N, 54.88. Found: C, 41.18; H, 4.03; N, 54.59.

6-Hydrazino-8-methyl-8*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**37**).

This compound was prepared from **15** in 82% yield, mp >310° (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): 130°, δ 4.32 (s,

8-Me), 8.11 (s, H_2), 8.28 (s, H_9).

Anal. Calcd. for $C_7H_8N_8$: C, 41.17; H, 3.95; N, 54.88. Found: C, 41.22; H, 4.02; N, 54.73.

6-Hydrazino-7-methyl-7*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**28**).

This compound was prepared from **12** in 59% yield, mp 280° dec (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): 122°, 4.11 (s, 7-Me), 7.08 (d, H_2), 7.51 (d, H_3), 8.35 (s, H_9), J_{H_2,H_3} = 1.8 Hz.

Anal. Calcd. for $C_8H_9N_7$: C, 47.28; H, 4.46; N, 48.26. Found: C, 47.34; H, 4.48; N, 47.92.

6-Hydrazino-8-methyl-8*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**40**).

This compound was prepared from **16** in 82% yield, mp 275° dec (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): δ 4.31 (s, 7-Me), 7.25 (d, H_2), 7.77 (d, H_3), 8.20 (s, H_9), J_{H_2,H_3} = 1.8 Hz.

Anal. Calcd. for $C_8H_9N_7$: C, 47.28; H, 4.46; N, 48.26. Found: C, 47.26; H, 4.44; N, 48.17.

Acknowledgements.

The authors wish to express their gratitude to the Research Council of Slovenia, Ljubljana, and to the KRKA Pharmaceutical and Chemical Works, Novo mesto, for partial financial support of this investigation.

REFERENCES AND NOTES

[1] B. Stanovnik, M. Kupper, M. Tišler, I. Leban, and L. Golič, *J. Chem. Soc., Chem. Commun.*, 268 (1984).

[2] B. Stanovnik, B. Furlan, A. Sarka, M. Tišler, and M. Žličar, *Heterocycles*, **22**, 2479 (1984).

[3] B. Furlan, B. Stanovnik, and M. Tišler, *Synthesis*, 78 (1986).

[4] B. Stanovnik, B. Furlan, M. Kupper, L. Malež, A. Štimac, M. Tišler, and M. Žličar, *J. Heterocyclic Chem.*, **25**, 393 (1988).

[5] S. J. Buckland, B. Halton, and B. Stanovnik, *Tetrahedron Letters*, **27**, 1309 (1986).

[6] S. J. Buckland, B. Halton, and B. Stanovnik, *Aust. J. Chem.*, **40**, 2037 (1987).

[7] B. Stanovnik, M. Arnšek, B. Furlan, M. Šereg, M. Tišler, and M. Žličar, *Vestn. Slov. Kem. Drus.*, **35**, 63 (1988).

[8] I. Leban, L. Golič, B. Stanovnik, and M. Tišler, *Acta Cryst.*, **C43**, 1814 (1987).

[9] I. Leban, L. Golič, B. Stanovnik, and M. Tišler, *Acta Cryst.*, **C44**, 193 (1988).

[10] For a recent review see: M. Regitz and H. Heydt, "Diazoalkanes", in "1,3-Dipolar Cycloaddition Chemistry", A. Padwa, ed, John Wiley and Sons, New York, 1984, pp 393-558.

[11] N. Takahayashi, *J. Pharm. Soc. Japan*, **75**, 1242 (1955); *Chem. Abstr.*, **50**, 8655 (1956).

[12] A. Pollak and M. Tišler, *Tetrahedron*, **22**, 2073 (1966).

[13] S. Polanc, B. Verček, B. Šek, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, **39**, 2143 (1974).

[14] B. Stanovnik and M. Tišler, *Tetrahedron*, **23**, 387 (1967).

[15] Th. J. De Boer and H. J. Backer, *Org. Synth., Coll. Vol.*, **4**, p 250.