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6-Methoxy-2-methylpyridazin-3(2*H*)-one (**1**) gave with 2-diazopropane (**8**) a mixture of 3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one derivative **12**, as the main product, and -7(6*H*)-one derivative **10**, as the minor product. On the other hand, 4-substituted pyridazin-3(2*H*)-ones **2**, **3**, and **4** gave 3*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one **10**, exclusively, while 5-substituted pyridazin-3(2*H*)-ones **5**, **6**, and **7** produced only the isomeric 3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one **12**. The 5-phenylsulfonyl derivative **13** gave with **8** by elimination of a molecule of nitrogen, followed by rearrangement, 1,2-diazepine derivative **15** and with an excess of **8** 3*H*-pyrazolo[3,4-*d*][1,2]diazepine derivative **16**. 1,2-Dimethylpyridazine-3,6-(1*H*,2*H*)-dione (**17**) and its derivatives **18** and **19** produced 3*H*-pyrazolo[3,4-*d*]pyridazine-4,7(5*H*,6*H*)-dione derivative **23**, while from **17** and 1-diazoinane (**24**) the spiro compound **27** was obtained. The 1,2-dihydro and 3*a*,7*a*-dihydro intermediates **21** and **25** were isolated.

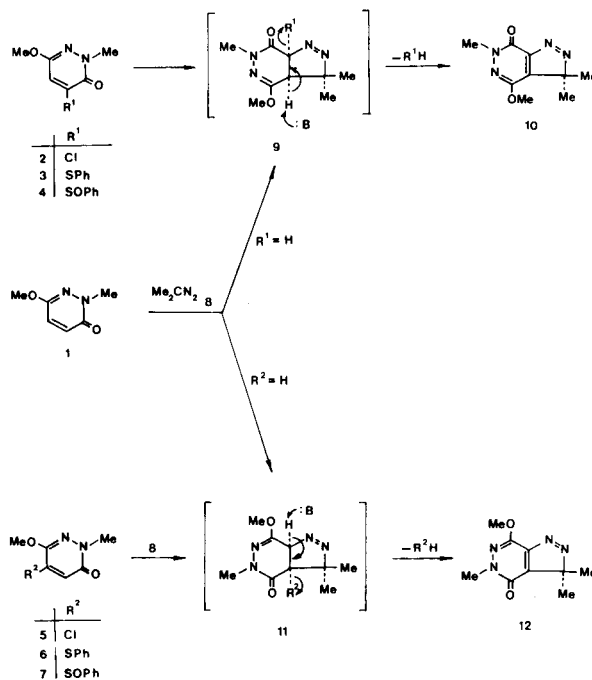
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It has been reported that 1,3-dipolar cycloadditions of diazoalkanes to 4- and 5-unsubstituted pyridazin-3(2*H*)-ones is regiospecific producing in most cases derivatives of pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones [1,2]. Recently, we have found some examples, in which also derivatives of the isomeric pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones are formed in minor extend [3]. These results prompted us to study the factors influencing the regiospecificity of this type of cycloadditions.

In this connection we prepared a series of pyridazin-3(2*H*)-ones with substituents at position 4 or 5, in order to study their influence on the regiospecificity of cycloaddition in more detail. The following isomeric pairs of compounds were prepared: 4-chloro- (**2**) and 5-chloro-6-methoxy-2-methylpyridazin-3(2*H*)-one (**5**), 6-methoxy-2-methyl-4-phenylthio- (**3**) and 6-methoxy-2-methyl-5-phenylthio-pyridazin-3(2*H*)-one (**6**), 6-methoxy-2-methyl-4-phenyl sulfinyl (**4**) and 6-methoxy-2-methyl-5-phenylsulfonylpyridazin-3(2*H*)-one (**7**), and 6-methoxy-2-methyl-5-phenylsulfonylpyridazin-3(2*H*)-one (**13**). When we treated 4-substituted derivatives **2**, **3**, and **4** with 2-diazopropane (**8**) in a mixture of chloroform and diethyl ether in the presence of triethylamine, we obtained 4-methoxy-3,3,6-trimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one (**10**) in 65%, 9%, and 70% yield, respectively, as the only product, although

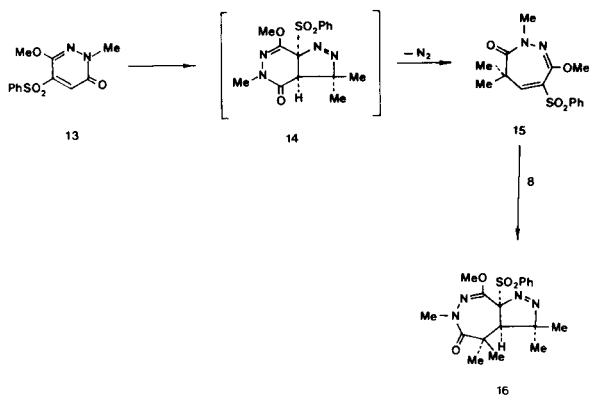
from **3** only in a low yield. On the other hand, from 5-substituted derivatives **5**, **6** and **7** the isomeric 7-methoxy-3,3,5-trimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**12**) was formed as the only product in 70%, 11%, and 83% yield, respectively. Here again, the 5-phenylthio derivative **6** gave the lowest yield. These examples show that cycloaddition is regiospecific, dependent on the position of substituent, in contrast to 6-methoxy-2-methylpyridazin-3(2*H*)-one (**1**) which, as we have found recently, gives a mixture of **12** as the major product (82%) and **10** as the minor product (5.3%) [3]. The cycloaddition of 5-phenyl-

Scheme 1

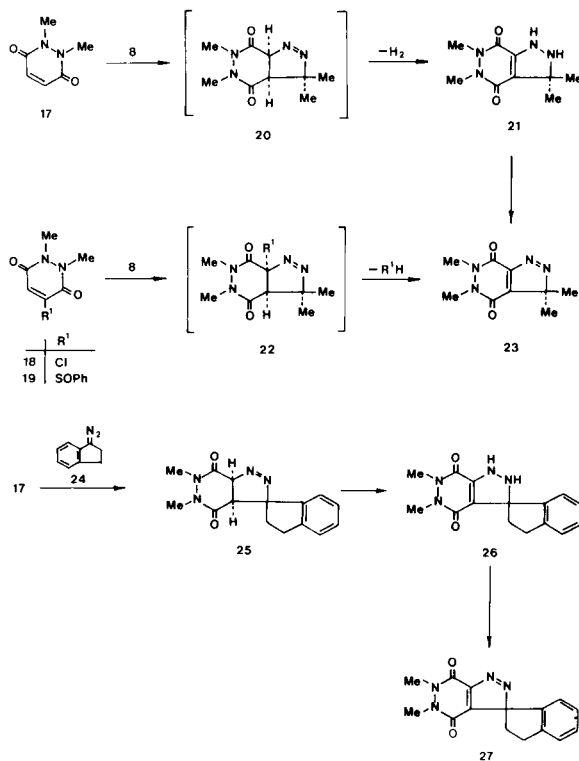


sulfonyl derivative **13** took a different course. In this example, the corresponding primary cycloadduct **14** was not transformed into pyrazolopyridazine derivative by elimination of phenylsulfonic acid, instead, a molecule of nitrogen was eliminated and the rest of the molecule was rearranged into the 1,2-diazepine derivative **15**, similarly, as observed earlier by cycloaddition of **8** to 2-methyl-6-phenylpyridazin-3(2*H*)-one [2] and 8-phenylsulfonyl-6-methyl-*s*-triazolo[4,3-*b*]pyridazine [4]. The diazepine derivative **15** reacted further with **8** to give pyrazolo[3,4-*d*][1,2]diazepine derivative **16**.

Scheme 2



Scheme 3



We extended this reaction to 1,2-dimethylpyridazine-3,6-(1*H*,2*H*)-dione (**17**) and its 4-chloro- (**18**) and 4-phenylsulfinyl (**19**) derivatives, which are more reactive than pyridazin-3(2*H*)-ones. The compound **17** gave with **8** at 5° in a mixture of chloroform and diethyl ether 1,2-dihydro derivative **21**, which was transformed by oxidation into **23**, obtained also directly from 4-substituted derivatives **18** and **19** in high yields.

The high reactivity of **17** is also demonstrated in the reaction with 1-diazoindane (**24**). While with pyridazin-3(2*H*)-ones only spiro cyclopropane compounds have been isolated [3], **17** gave in a mixture of chloroform and diethyl

ether at 5° the primary 3a,7a-dihydro cycloadduct **25**, which was transformed in the presence of an acid into 1,2-dihydro derivative **26** and further dihydrogenated into **27**.

## EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. All  $^1H$  nmr spectra were obtained on a JEOL C-60 HL spectrometer 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 in the literature: 2-diazopropane (**8**) [5], 1-diazoindane (**24**) [6], 6-methoxy-2-methylpyridazin-3(2*H*)-one (**1**) [7], 4-chloro-6-methoxy-2-methylpyridazin-3(2*H*)-one (**2**) [8], 5-chloro-6-methoxy-2-methylpyridazin-3(2*H*)-one (**5**) [8], 4-chloro-1,2-dimethylpyridazine-3,6(1*H*,2*H*)-dione (**18**) [8].

### 6-Methoxy-2-methyl-4-phenylthiopyridazin-3(2*H*)-one (**3**).

A mixture of **2** (2.6 g), thiophenol (1.5 ml) and triethylamine (2 ml) in chloroform (20 ml) was stirred at room temperature for 30 minutes. The solvent was evaporated *in vacuo* and the residue was recrystallized from diisopropyl ether to give **3** (2.8 g, 75%), mp 131-132°;  $^1H$  nmr (deuteriochloroform):  $\delta$  3.62 (s, 2-Me and 6-OMe), 5.90 (s,  $H_5$ ), 7.35 (br s, 4-SPh).

*Anal.* Calcd. for  $C_{12}H_{12}N_2O_2S$ : C, 58.05; H, 4.89; N, 11.28. Found: C, 58.02; H, 4.83; N, 11.24.

In analogous manner the following compounds were prepared:

### 6-Methoxy-2-methyl-5-phenylthiopyridazin-3(2*H*)-one (**6**).

This compound was prepared from **5** in 70% yield, mp 147-148° (from diisopropyl ether);  $^1H$  nmr (deuteriochloroform):  $\delta$  3.48 (s) and 3.82 (s) (2-Me and 6-OMe), 5.87 (s,  $H_4$ ), 7.35 (br s, 5-SPh).

*Anal.* Calcd. for  $C_{12}H_{12}N_2O_2S$ : C, 58.05; H, 4.89; N, 11.28. Found: C, 58.02; H, 4.98; N, 11.15.

### 1,2-Dimethyl-4-phenylthiopyridazine-3,6-(1*H*,2*H*)-dione. (The starting compound for **19**).

This compound was prepared from **18** in 80% yield, mp 128-129° (from a mixture of ethanol and diisopropyl ether);  $^1H$  nmr (deuteriochloroform):  $\delta$  3.50 (s) and 3.68 (s) (1-Me and 2-Me), 5.99 (s,  $H_5$ ), 7.50 (br s, 4-SPh).

*Anal.* Calcd. for  $C_{12}H_{12}N_2O_2S$ : C, 58.05; H, 4.87; N, 11.20. Found: C, 58.16; H, 4.97; N, 11.57.

### 6-Methoxy-2-methyl-4-phenylsulfinylpyridazin-3(2*H*)-one (**4**)

To a solution of **3** (2.5 g) in acetic acid (20 ml) a solution of hydrogen peroxide (70%, 0.6 ml) was added and the mixture was heated at 50° for 3 hours. The volatile components were evaporated *in vacuo*, a saturated aqueous solution of sodium hydrogen carbonate (50 ml) was added to the residue and the mixture was extracted with chloroform (3 times, 50 ml each time). The combined extracts were dried with anhydrous sodium sulphate. Evaporation of chloroform *in vacuo* gave **4** (2.5 g, 95%), mp 162-167° (from a mixture of toluene and *n*-heptane);  $^1H$  nmr (deuteriochloroform):  $\delta$  3.52 (s) and 3.75 (s) (2-Me and 6-OMe), 7.30-7.45 (m) and 7.60-7.70 (m) (4-SOPh), 7.45 (s,  $H_5$ ).

*Anal.* Calcd. for  $C_{12}H_{12}N_2O_3S$ : C, 54.53; H, 4.58; N, 10.59. Found: C, 54.90; H, 4.64; N, 10.39.

In the same manner the following compounds were prepared:

## 6-methoxy-2-methyl-5-phenylsulfinylpyridazin-3(2H)-one (7).

This compound was prepared from **6** in 94% yield, mp 140-142° (from a mixture of toluene and *n*-heptane); <sup>1</sup>H nmr (deuteriochloroform): δ 3.52 (s) and 3.70 (s) (2-Me and 6-OMe), 7.25-7.65 (m, H<sub>4</sub> and 5-SOPh).

Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S: C, 54.53; H, 4.58; N, 10.59. Found: C, 54.57; H, 4.63; N, 10.40.

## 1,2-Dimethyl-4-phenylsulfinylpyridazine-3,6-(1H,2H)-dione (19).

This compound was prepared from 1,2-dimethyl-4-phenylthio-pyridazine-3,6-(1H,2H)-dione in 85% yield, mp 150-151° (from ethanol); <sup>1</sup>H nmr (deuteriochloroform): δ 3.61 (s) and 3.65 (s) (1-Me and 2-Me), 7.50-7.58 (m) and 7.80-7.92 (m) (4-SOPh).

Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S: C, 54.53; H, 4.58; N, 10.59. Found: C, 54.11; H, 4.40; N, 10.58.

## 6-Methoxy-2-methyl-5-phenylsulfonylpyridazin-3(2H)-one (13).

A mixture of **6** (2.6 g) and hydrogen peroxide (70%, 15 ml) in acetic acid (10 ml) was heated at 60° for 3 hours. The volatile components were evaporated *in vacuo* and the residue separated by flash chromatography (Kieselgel 60, 0.040-0.063 mm, E. Merck, and diethyl ether as eluent). The second component gave, after evaporation of the solvent, **13** in 53% yield, mp 167-169° (from a mixture of ethanol and 2-propanol).

Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>S: C, 51.42; H, 4.31; N, 9.99. Found: C, 51.67; H, 4.52; N, 9.93.

## 4-Methoxy-3,3,6-trimethyl-3H-pyrazolo[3,4-d]pyridazin-7(6H)-one (10).

To a solution of **2** (176 mg, 0.001 mole) in chloroform (10 ml) and triethylamine (1 ml) a solution of **8** in diethyl ether (2M, 20 ml) was added and the mixture was left in refrigerator for 12 hours at 0°. The volatile components were evaporated *in vacuo* and the dry residue was recrystallized from diisopropyl ether to give **10** in 65% yield, mp 172-173°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.60 (s, 6H, 3,3-diMe), 3.80 (s, 3H, 6-Me), 4.05 (s, 3H, 4-Me).

Anal. Calcd. for C<sub>9</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>: C, 51.92; H, 5.81; N, 26.91. Found: C, 52.05; H, 6.06; N, 27.15.

The compound **10** was obtained also from **3** in 9% yield, or from **4** in 70% yield in essentially the manner as described above.

In the same manner the following compound was prepared:

## 7-Methoxy-3,3,5-trimethyl-3H-pyrazolo[3,4-d]pyridazin-4(5H)-one (12).

This compound was prepared from **5** in 70% yield, mp 154-155° (from a mixture of ethanol and diisopropyl ether); <sup>1</sup>H nmr (deuteriochloroform): δ 1.68 (s, 6H, 3,3-diMe), 3.77 (s, 3H, 5-Me), 4.10 (s, 3H, 7-OMe).

Anal. Calcd. for C<sub>9</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>: C, 51.92; H, 5.81; N, 26.91. Found: C, 51.78; H, 5.85; N, 27.18.

Compound **12** was also obtained from **6** in 11% yield, or from **7** in 83% yield, in essentially the same manner.

## 7-Methoxy-6-phenylsulphonyl-2,4,4-trimethyl-4H-1,2-diazepin-3(2H)-one (15).

To a solution of **13** (1.4 g, 0.005 mole) in chloroform (15 ml) a solution of **8** in diethyl ether (2M, 20 ml) was added at 0° and the mixture was left for 24 hours in the refrigerator. Evaporation of

solvents *in vacuo* gave **15** (1.3 g, 77%), mp 173° (from a mixture of ethanol and 2-propanol); <sup>1</sup>H nmr (deuteriochloroform): δ 1.25 (s, 6H, 4,4-diMe), 3.23 (s, 3H) and 3.58 (s, 3H) (2-Me and 7-Me), 7.13 (s, 1H, H<sub>3</sub>), 7.25-7.85 (m, 5H, Ph).

Anal. Calcd. for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S: C, 55.88; H, 5.63; N, 8.69. Found: C, 55.74; H, 5.65; N, 8.57.

## 8-Methoxy-3,3,4,4,6-pentamethyl-8a-phenylsulphonyl-3a,8a-dihydropyrazolo[3,4-d][1,2]diazepin-5(6H)-one (16).

To a solution of **15** (465 mg, 0.002 mole) in chloroform (15 ml) a solution of **8** in diethyl ether (2M, 10 ml) was added and the mixture was left for 12 hours at room temperature. The solvent was evaporated *in vacuo* and the solid residue recrystallized from a mixture of ethanol and diisopropyl ether to give **16** (487 mg, 62%), mp 111-113°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.27 (s, 3H), 1.45 (s, 3H), 1.49 (s, 3H), 1.65 (s, 3H) (3,3-diMe, 4,4-diMe), 2.91 (s, 1H, H<sub>3a</sub>), 3.22 (s, 3H) and 3.42 (s, 3H) N-Me and OMe), 7.4-7.9 (m, 5H, Ph).

Anal. Calcd. for C<sub>18</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub>S: C, 55.08; H, 6.16; N, 14.27. Found: C, 55.39; H, 6.35; N, 13.93.

## 3,3,5,6-Tetramethyl-1,2-dihydro-3H-pyrazolo[3,4-d]pyridazine-4,7(5H,6H)-dione (21).

To a solution of **17** (1.4 g, 0.010 mole) in chloroform (10 ml) a solution of **8** in diethyl ether (2M, 40 ml) was added at 5° and the mixture was left for 10 hours in refrigerator. The precipitate was collected by filtration, washed with diethyl ether and *n*-heptane to give analytically pure **21** (1.83 g, 87%), mp 175-177° dec; <sup>1</sup>H nmr (deuteriochloroform): δ 1.60 (s, 6H, 3,3-diMe), 3.70 (s, 3H) and 3.78 (s, 3H) (5-Me and 6-Me), 10.0 (br s, 1H, NH).

Anal. Calcd. for C<sub>9</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>: C, 51.42; H, 6.71; N, 26.64. Found: C, 51.44; H, 6.76; N, 26.34.

## 3,3,5,6-Tetramethyl-3H-pyrazolo[3,4-d]pyridazine-4,7(5H,6H)-dione (23).

A: To a stirred solution of **21** (420 mg, 0.002 mole) in acetic acid (5 ml) a solution of bromine (320 mg) in acetic acid (2 ml) was added dropwise and the mixture was stirred for 30 minutes at room temperature. The mixture was evaporated to one half, water (2 ml) was added and the mixture was neutralized with ammonia (aqueous solution, 28%). The precipitate was collected by filtration and recrystallized from a mixture of ethanol and 2-propanol to give **23** (260 mg, 63%), mp 152°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.65 (s, 6H, 3,3-diMe), 3.73 (s, 3H) and 3.79 (s, 3H) (5-Me, 6-Me).

Anal. Calcd. for C<sub>9</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>: C, 51.92; H, 5.81; N, 26.91. Found: C, 51.69; H, 6.05; N, 26.80.

B: To a stirred solution of **18** (872 mg, 0.005 mole) in chloroform (8 ml) a solution of **8** in diethyl ether (2M, 20 ml) was added and the mixture was left for 12 hours at room temperature. The solvent was evaporated to one third, cooled to 0° and the crystalline material was collected by filtration to give **23** in 55% yield, mp 152° (from a mixture of ethanol and diisopropyl ether).

The same compound was obtained also from **19** in essentially the same manner in 85% yield.

## 3a,7a-Dihydrospiro Compound 25.

To a stirred solution of **17** (4.0 g, 0.028 mole) in chloroform (50 ml) a solution of **24**, prepared from 1-indanone hydrazone (8.5 g), in diethyl ether (100 ml) was added in small portions at 0°. The mixture was stirred at 5° for several hours until all the starting

compound was consumed. The product, formed during this time, was collected by filtration and recrystallized from a mixture of benzene and hexane to give **25** (6.2 g, 78%), mp 92-95° dec; <sup>1</sup>H nmr (deuteriochloroform): δ 2.98 (s) and 3.05 (s) (N-Me, N-Me), 3.00 (t, CH<sub>2</sub>), 3.25 (t, CH<sub>2</sub>), 3.50 (d, H<sub>3a</sub>), 6.15 (d, H<sub>7a</sub>), 6.60-7.30 (m, arom.), J<sub>CH<sub>1</sub>CH<sub>2</sub></sub> = 4.5 Hz, J<sub>H<sub>3a</sub>H<sub>7a</sub></sub> = 6.0 Hz.

*Anal.* Calcd. for C<sub>15</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>: C, 63.37; H, 5.67; N, 19.70. Found: C, 63.69; H, 5.45; N, 19.74.

#### Spiro Compound **27**.

A solution of **25** (284 mg, 0.001 mole) in ethanol (5 ml) and triethylamine (1.5 ml) was stirred for 20 minutes at room temperature. The product was precipitated by addition of diethyl ether and, after cooling to 0° collected by filtration to give **27** (231 mg, 82%), mp 140-141° (from ethanol); <sup>1</sup>H nmr (deuteriochloroform): δ 2.68 (t, 2H, CH<sub>2</sub>), 3.55 (t, 2H, CH<sub>2</sub>), 3.55 (s, 3H, N-Me), 3.60 (s, 3H, N-Me), 6.15-6.35 (m) and 6.80-7.40 (m) (4H, Ph), J<sub>CH<sub>1</sub>CH<sub>2</sub></sub> = 7.0 Hz.

*Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>: C, 63.82; H, 4.99; N, 19.85. Found: C, 63.59; H, 5.02; N, 19.24.

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