Tetrahedron Vol. 46, No. 19, pp. 6915-6930, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

1,3-DIPOLAR CYCLOADDITION OF 2-DIAZOPROPANE TO 2-METHYL-6-PHENYLPYRIDAZIN-3(2H)-ONE. THE FORMATION OF PYRAZOLO/3,4-D/PYRIDAZINE DERIVATIVES

Anton Štimac, Branko Stanovnik*, Miha Tišler, and Ljubo Golič

Department of Chemistry, Edvard Kardelj University,
61000 Ljubljana, Yugoslavia

(*Received in UK* 19 *April* 1990)

Abstract

In a regiospecific 1,3-dipolar cycloaddition of 2-diazopropane (2) to 2-methyl-6-phenylpyridazin-3(2H)-one (1) the primary cycloadduct 3 and rearranged NH,NH-dihydro cycloadduct 4 were isolated. They were transformed, dependent on the reaction conditions into 1,2-diazepine derivative 5, 4-isopropyl substituted pyridazine derivative 6, diazabicyclo/4.1.0/heptenone derivative 7, and pyrazolo/3,4-d/pyridazine derivative 8. 1,5-Sigmatropic rearrangements were observed, when 8 was heated in PPA or concentrated sulphuric acid to give pyrazolo/3,4-d/pyridazine derivatives 10 and 11, and a pyrazole derivative 13.

It has been reported that a regiospecific 1,3-dipolar cycloaddition of 2-diazopropane (2) to 2-methyl-6-phenylpyridazin-3(2H)-one (1) results in the formation of the primary cycloadduct 3, which is unstable and thermally decomposes into a mixture of three products, 1,2-diazepine derivative 5, 4-isopropyl substituted pyridazine derivative 6 and diazabicyclo /4.1.0/heptenone derivative 7. The primary cycloadduct has been apparently isolated, however, no spectroscopic and analytical data are given in the paper.[1]

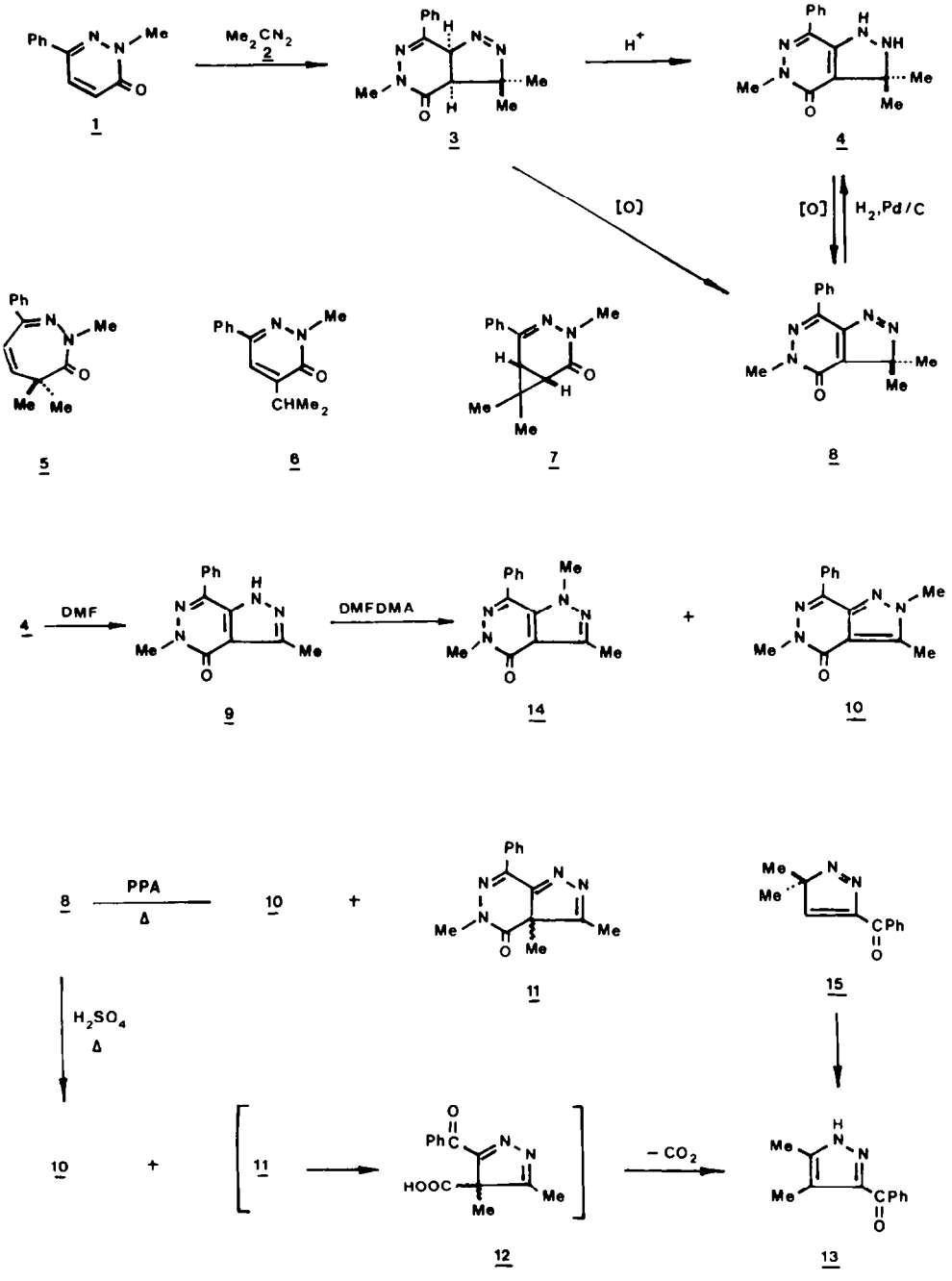
We found this report surprising in view of some other studies and our experiences in the field of 1,3-dipolar cycloadditions of diazoalkanes to pyridazines and bicyclic azolo- and azinopyridazines. Namely, in most

cases the corresponding pyrazolo/3,4-d/pyridazines are the major, if not the only products[2-8], and their structures have been in some instances confirmed by X-ray analyses[9,10]. According to this, we decided to reinvestigate the reaction mentioned above in order to find the reaction conditions for formation of pyrazolo/3,4-d/pyridazine derivative 8.

We repeated the 1,3-dipolar cycloaddition of 2-diazopropane (2) to 2-methyl-6-phenylpyridazin-3(2H)-one (1) under esentially the same conditions as described in lit.[1], and found that the same products are formed. However, in different solvents and at various temperatures the distribution of the products was strongly dependent on the solvent. The primary cycloadduct (3) could be isolated in analytically pure form at temperatures below 0°C due to its relatively low solubility in diethyl ether. At room temperature, the secondary reactions were observed in which 3 transformed in three different ways. In the presence of an acid, the isomerization of 3 into NH,NH-dihydro species 4 took place, dehydrogenation (oxidation) in the presence of oxygen from the air produced 3H-pyrazolo/3,4-d/pyridazine derivative 8, while elimination of a molecule of nitrogen from the pyrazole part of the molecule, followed by rearrangement, gave a mixture of 5, 6 and 7. This latter transformation was carried out in different solvents at 18°C under essentially the same reaction conditions. In more polar solvents, such as DMF, methanol and ethanol, in the presence of air 3 was dehydrogenated quantitatively into 8, in propanol a mixture of 4 and 8 was formed, while in less polar solvents the yields of 5, 6, and 7 were increased. In hydroxylic solvents also some starting material was recovered unchanged due to faster decomposition of 2-diazopropane (2). For example, in methanol 2-diazopropane was decomposed in 10 minutes. At 18°C the reactions were finished in 70 - 85 minutes, while at -30°C in diethyl ether the reaction was finished in 24 hours. The formation and ratios among products are summarized in Table 1. According to these experiments 4 was isolated in analytically pure form from acetone in 54 % yield, while 8 was the only product in DMF.

Both dihydro intermediates 3 and 4 are thermally unstable. They decompose vigorously at temperatures above 90°C. In chloroform at room temperature the decomposition of 3 required two days, while in refluxing toluene, it took only two minutes. We studied this decomposition in more detail. The results are summarized in Table 2. In general, one can conclude that in most cases a mixture of 5, 6, and 7 was formed, while in hydroxylic solvents also 4 and 8 were formed. By transformation of 3 in the solid state by heating above its melting point 5, 6, and 7 were formed in approximately equimolar amounts, in nonpolar solvents, such as

Scheme 1


Ph
Me
O
1
Me_2CN_2
2
3
H^+
4
[O]
H_2,Pd/C
5
6
$CHMe_2$
7
8
DMF
9
DMFDMA
14
10
PPA
Δ
11
15
H_2SO_4
Δ
12
$-CO_2$
13

benzene, toluene and dioxane, 5 was the main product, in more polar solvents, such as DMF and DMSO, 6 was the major product, while the formation of 7 was in thermal transformations always only the minor product. 1,2-Dihydro derivative 4 thermally more stable. It can be purified by crystallization. However, by heating in DMF elimination of methane, which was observed, when the reaction was followed by ^{1}H nmr technique, took place to afford 9.

Oxidation of 3 and 4 could be achieved with a variety of oxidizing agents, such as oxygen from air and bromine. The simplest method is oxidation by air in the presence of a base. Under these conditions the transformation is practically quantitative to give 8 as the only product. On the other hand, catalytic hydrogenation of 8 over Pd/C produced 4 as the only dihydro product.

When 8 was heated in PPA or in concentrated sulfuric acid at 100°C, the 1,5-sigmatropic rearrangement of one of the methyl groups was observed. In PPA two products 10 and 11 were isolated in 41 % and 43 % yield, respectively. In concentrated sulfuric acid 10 and 13 were formed in 12 % and 88 % yield, respectively. The compounds 10 and 11 are formed in 1,5-sigmatropic rearrangements of one of the methyl groups taking place either in clockwise or anticlockwise direction around the pyrazole part of the molecule, analogous to the rearrangement observed in the 3H-pyrazole series[11]. The formation of 13 can be explained in the following way. Namely, the compound 11 can be regarded as a cyclic hydrazide-hydrazone, which is hydrolyzed to give the intermediate 12, followed by decarboxylation to give 13, the structure of which was confirmed by an independent synthesis from 15. In these processes only one i.e. 10, of the two possible N-methyl substituted isomers is formed. The structure of this compound was determined in the following manner. Methylation of 9 with DMFDMA gave a mixture of 14 and 10. The phenyl group of 14 appears in the ^{1}H nmr spectrum as a broad singlet at δ = 7.44 ppm, due to the steric hindrance, while the phenyl group in 10 shows two multiplets at δ = 7.20 - 7.50 ppm and δ = 8.10-8.35 ppm, indicating the coplanarity of the phenyl group with the rest of the molecule. This is further supported by coupling constants in ^{13}C nmr spectra. Namely, the C_{7a} in 14 appears as a quartet, $J_{C_{7a}-N_1-CH_3}$ = 7.0 Hz, while for the C_{7a} in 10 only a singlet was observed.

Since the bicyclic pyrazolo/3,4-d/pyridazine derivative 8 in a new compound isolated in this reaction, its structure was confirmed by X-ray analysis (Fig. 1, Table 6). Since this compound is formed from the cycloadducts 3 or 4, their structures must be as shown on the Scheme 1, and consequently, it confirms also the structures of 5, 6 and 7.

Table 1. The formation of products in the reaction of 1 with 2 in various solvents.

Solvent	Products [%][a]					
	1	4	5	6	7	8
DMF	-	-	-	-	-	100
MeOH[b]	65	-	-	-	-	35
EtOH	14	-	-	-	-	86
1-propanol	10	13	-	-	-	77
2-propanol	7	16	-	-	-	62
acetone	-	60	-	15	-	34
acetonitrile	-	-	13	17	8	62
dioxane	-	-	45	31	12	11
dioxane/water (4:1)	20	24	13	7	2	35
ethyl acetate	-	-	48	35	12	6
methylene chloride	-	-	69	22	9	-
benzene	-	-	61	27	12	-

a) determined by ^{1}H nmr technique
b) decomposition of 2 in this solvent is very fast (∿ 10 min).

Table 2 The formation of products of by thermal decomposition of 3

Solvent	Reaction conditions	Products[a]				
		4	5	6	7	8
-	Δ (∿ 90°C)	-	37	35	28	-
benzene	reflux, 30 min.	-	58	24	18	-
toluene	reflux, 10 min.	-	52	27	21	-
dioxane	reflux, 10 min.	-	52	32	16	-
DMF	reflux, 15 min.	-	26	62	12	-
DMSO	115°C, 5 min.	9	17	68	6	-
DMF/H_2O (1:1)	reflux, 5 min.	31	25	35	6	3
MeOH	reflux, 30 min.	36	21	23	6	13

a) determined by ^{1}H nmr technique

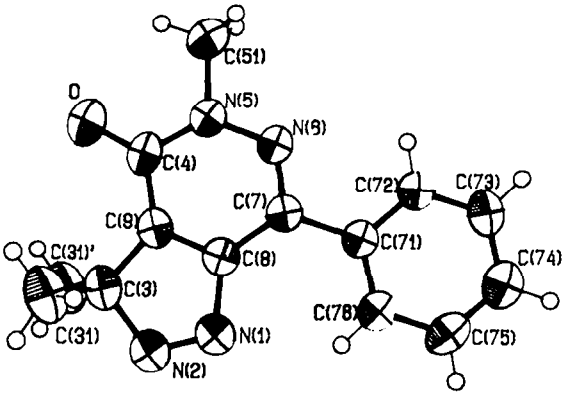


Fig. 1

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope. ^{1}H and ^{13}C nmr spectra were recorded on a JEOL FX 90Q FT spectrometer with TMS as internal standard. Elemental analyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 240 C. The reactions were followed by tlc (DC Fertigplatten Kieselgel 60 F_{254}, E. Merck, and a mixture of chloroform/methanol, 10:1, as solvent). The following compounds were prepared according to the procedures described in literature: 2-methyl-6-phenylpyridazin-3(2H)-one (1)[12] and 2-diazopropane (2)[13].

Reaction of 1 with 2 in diethyl ether at room temperature. The formation of 7-phenyl-2,4,4-trimethyl-2,4-dihydro-3H-1,2-diazepin-3-one (5), 4-isopropyl-2-methyl-6-phenyl-pyridazin-3(2H)-one (6), and 3,7,7-trimethyl-5-phenyl-3,4-diazabicyclo/4.1.0/hept-4-en-2-one (7).

To a solution of 1 (931 mg, 0.005 mole) in diethyl ether (20 ml) a solution of 2-diazopropane (2) prepared from acetone hydrazone (3 g) in diethyl ether (10 ml) was added. The mixture was left at room temperature until the excess of diazopropane decomposed (approx. 12 hours). The reaction mixture was evaporated in vacuo and the oily residue was separated by flash chromatography (Kieselgel 60, 0.40-0.063 mm, E.Merck, and benzene/diethyl ether, 50:1, as solvent) to give, after evaporation of the solvent, 5 (615 mg, 54 %) as the first component, mp 57-58°C, lit.[1] mp 53°C, lit.[14] 56-57°C, ^{1}H nmr ($CDCl_3$): δ 1.19 (s, 6H, 4,4-diMe), 3.58 (s, 3H, 2-Me), 5.98

(d, 1H) and 6.34 (d, 1H) (H_5,H_6), 7.20-7.85 (m, 5H, 7-Ph), J_{H_5,H_6} = 10.5 Hz.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.43; H, 7.34; N, 12.21.

The second component was the compound 6 (400 mg, 35 %), liquid; ^{1}H nmr ($CDCl_3$): δ 1.27 (d, 6H, $CH\underline{Me}_2$), 3.29 (h, 1H, $C\underline{H}Me_2$), 3.85 (s, 3H, 2-Me), 7.25-7.90 (m, 6H, H_5 and 6-Ph), J_{CHMe_2} = 7.1 Hz.

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.42; H, 7.12; N, 12.29.

Further elution of the colomn with diethyl ether gave, after evaporation of the solvent, 7 contaminated with traces of 6. The compound (160 mg, 14 %) was obtained in pure form by flash chromatography (Kieselgel 60, 0.40-0.63 mm, E.Merck, and mixture of diethyl ether/petroleum ether/diethylamine 72:24:1, as solvent), mp 140-141°C (ethanol/water), lit.[1] mp 131°C, lit.[14] mp 140-141°C; ^{1}H nmr ($CDCl_3$): δ 0.92 (s, 3H, 7-Me_{exo}), 1.44 (s, 3H, 7-Me_{endo}), 2.07 (d, 1H) and 2.30 (d, 1H), (H_1, H_6), 3.44 (s, 3H, 3-Me), 7.20-7.80 (m, 5H, 5-Ph), J_{H_1,H_6} = 7.5 Hz.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.59; H, 7.20; N, 12.33.

Reaction of 1 with 2 in diethyl ether at -30°C.

7-Phenyl-3,3,5-trimethyl-3a-7a-dihydro-3H-pyrazolo/3,4-d/pyridazin-4(5H)-one (3).

To a solution of 1 (931 mg, 0.005 mole) in methylene chloride (5 ml) a solution of diazopropane, prepared from acetone hydrazone (6 g) in diethyl ether (20 ml) was added at -30°C and the mixture was left at this temperature in refrigerator for 24 hours. The precipitate was then collected by filtration and washed with cold diethyl ether to give 3 (870 mg, 68 %), analytically pure, mp 90-92°C; MS m/e 256 (M^+, 1.2 %), 288 (24.1 %), 200 (63.8 %), 187 (100 %). ^{1}H nmr ($CDCl_3$): δ 1.13 (s, 3H, 3-Me_{endo}), 1.72 (s, 3H, 3-Me_{exo}), 3.45 (s, 3H, 5-Me), 2.66 (d, 1H, H_{3a}), 6.11 (d, 1H, H_{7a}), 7.20-7.55 (m, 3H, H_3, H_4,, H_5,), 7.90-8.30 (m, 2H, H_2,, H_6,), $J_{3a,7a}$= 12.o Hz.

Anal. Calcd. for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.58; H, 6.29; N, 21.81.

7-Phenyl-3,3,5-trimethyl-1,2-dihydro-3H-pyrazolo/3,4-d/pyridazin-4(5H)-one (4).

Method A: To a suspension of 3)512 mg, o.002 mole) in methanol (20 ml) concentrated hydrochloric acid (37 %, 1 ml) was added dropwise at 0°C. After 2-3 minutes a clear solution resulted and the isomerization

was finished after 15 minutes by stirring at room temperature. The reaction mixture was evaporated in vacuo. The dry residue was dissolved in water (10 ml) and adjusted to pH=7 with aqueous sodium hydrogen carbonate solution (5 %) to give 4 (486 mg, 95 %), mp 173-177°C (from toluene); MS m/e 256 (M^+, 11.5 %), 241 (M - Me, 100 %); ^{1}H nmr ($CDCl_3$): δ 1.53 (s, 6H, 3,3-diMe), 3.81 (s, 3H, 5-Me), 5.0 (br s, 2H, NH, NH), 7.30-7.90 (m, 5H, Ph).

Anal. Calcd. for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.61; H, 6.27; N, 21.80.

Method B: To a solution of 1 (931 mg, 0.005 mole) in acetone (25 ml) a solution of 2, prepared from acetone hydrazone (3 g) in diethyl ether (20 ml) was added, and the reaction mixture was left in the refrigerator at -30°C for 12 hours. The precipitate was collected by filtration to give 4 (680 mg, 54 %), mp 173-177°C (from toluene).

Method C: To a solution of 8 (1014 mg, 0.004 mole) in methanol (30 ml) Pd/C (5 %, 150 mg) was added and the mixture was hydrogenated at normal pressure for 3 hours. The filtrate was evaporated in vacuo, the dry residue was dissolved in water and adjusted to pH=7 with sodium hydrogen carbonate (5 %). The precipitate was collected by filtration to give 4 (656 mg, 64 %) mp 173-177°C (from toluene).

7-Phenyl-3,3,5-trimethyl-3H-pyrazolo/3,4-d/pyridazin-4(5H)-one (8).

To a solution of 1 (931 mg, 0.005 mole) in DMF (10 ml) a solution of 2, prepared from acetone hydrazone (3.0 g) in diethyl ether (20 ml), was added and the mixture was left for 12 hours at room temperature. The solvent was evaporated in vacuo and the solid residue was washed with water to give 8 (1.27 g, quant.), mp 151-153°C (ethanol); MS m/e 254 (M^+); ^{1}H nmr ($CDCl_3$): δ 1.68 (s, 6H, 3,3-diMe), 3.91 (s, 3 H, 5-Me), 7.30-7.60 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 8.10-8.40 (m, 2H, $H_{2'}$, $H_{6'}$).

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.25; H, 5.61; N, 22.22.

Thermal decomposition of 3. General procedure.

The solid sample of 3 (512 mg, 0.002 mole) was heated in a glass tube in an oil bath at the temperature above its mp (∿ 95°C), or in an apropriate solvent under reflux for 5-30 minutes. The solvent was evaporated in vacuo and the composition of the products was determined by ^{1}H nmr technique. The results are summarized in the Table 2.

Thermal decomposition of 4. 3,5-dimethyl-7-phenyl-1H-pyrazolo/3,4-d/pyridazin-4(5H)-one (9).

A solution of 4 (512 mg, 0.002 mole) in DMF (3 ml) was heated under reflux for 30 minutes. To the cold solution water (10 ml) was added and the precipitate was collected by filtration and washed with cold water (3 ml) to give 9 (345 mg, 72 %), mp 281-282 °C (methanol); MS m/e 240 M^+, 100 %); ^1H nmr (DMSO-d_6): δ 2.71 (s, 3H, 3-Me), 3.76 (s, 3H, 5-Me), 7.40-7.70 (m, 3H, H_3,, H_4,, H_5,), 8.10-8.45 (m, 2H, H_2,, H_6,).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.00; H, 5.05; N, 23.13.

Oxidation of 3 into 8

a) With oxygen in the presence of a base.

To a stirred suspension of 3 (256 mg, 0.001 mole) in methanol (5 ml) a solution of sodium hydroxide (1 M, 1 ml) was added. From the resulting orange-red solution the product 8 started to crystallize after 5 minutes. The stirring was continued for 30 minutes, during this time the solution became greenish. Water (5 ml) was added to the mixture and the precipitate was collected by filtration to give 8 (242 mg, 95 %).

b) A degassed solution of 3 (128 mg, 0.0005 mole) in methanol (5 ml and a degassed solution of potassium hydroxide in methanol (1M, 1 ml) were mixed under vacuum in a closed system. The solution immediately turned red, and this colour persisted under exclusion of oxygen at least for 24 hours at room temperature. When the air was introduced into the reaction flask, the solution turned greenish and after 10 minutes the colorless crystals started to precipitate. Water (5 ml) was added to the mixture and the precipitate was collected by filtration to give 8 (115 mg, 90 %).

c) with bromine

To a solution of 3 (256 mg, 0.001 mole) in methylene chloride (2 ml) a solution of bromine (160 mg) in methylene chloride (2 ml) was added dropwise and the mixture was stirred at room temperature for 30 minutes. The volatile components were evaporated in vacuo, water (10 ml) was added to the residue, followed by addition of ammonia (conc.aqueous solution, 3 ml). The precipitate was collected by filtration to give 8 (185 mg, 73 %).

Oxidation of 4 into 8.

a) with oxygen in the presence of a base

To a stirred solution of 4 (256 mg, 0.001 mole) in methanol (5 ml) a

solution of potassium hydroxide (1 M, 1 ml) was added and the stirring was continued at room temperature. The colour changed from orange-red into greenish in approximately 15 minutes. Water (5 ml) was added and the crystals were collected by filtration to give 8 (242 mg, 95 %).

b) with bromine

To a stirred solution of 4 (256 mg, 0.001 mole) in acetic acid (2 ml) a solution of bromine (160 mg) in acetic acid (2 ml) was added dropwise. The stirring was continued for 30 minutes at room temperature. The volatile components were evaporated in vacuo. Water (10 ml) was added to dry residue followed by addition of ammonia (conc. aqueous solution, 3 ml) and the precipitate was collected by filtration to give 8 240 mg, 95 %).

Reaction of 8 in polyphosphoric acid. 7-Phenyl-2,3,5-trimethyl-2H-pyrazolo/3,4-d/pyridazin-4(5H)-one (10) and 7-Phenyl-3,3a,5-trimethyl-3aH-pyrazolo/3,4-d/pyridazin-4(5H)-one (11).

A mixture of 8 (508 mg, 0.002 mole) and polyphosphoric acid (5 g) was heated at 100°C for 30 minutes. After cooling, water (20 ml) was added and the mixture was neutralized with aqueous solution of potassium hydroxide (5 %). Red precipitate (470 mg) was collected by filtration to give a mixture of two components, separated by flash chromatography (Kieselgel 60, 0.40-0.063 mm, E.Merck). The first component was eluted with diethyl ether and gave, after evaporation of the solvent in vacuo, 11 (220 mg, 43 %), mp 171-176°C (n-heptane); MS m/e 254 (M^+, 100 %); ^{1}H nmr ($CDCl_3$): δ 1.83 (s, 3H, 3a-Me), 2.40 (s, 3H, 3-Me), 3.84 (s, 3H, 5-Me), 7.48 (br s, 5H, Ph).

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 65.94; H, 5.60; N, 22.07.

Further elution with diethyl ether gave, after evaporation of the solvent in vacuo, 10 (210 mg, 41 %), mp 143-144°C (n-heptane). The ir spectrum of the compound is identical with the spectrum of the compound prepared from 9 and DMFDMA.

Reaction of 8 in concentrated sulphuric acid. 7-Phenyl-2,3,5-trimethyl-2H-pyrazolo/3,4-d/pyridazin-4(5H)-one (10) and 3-Benzoyl-4,5-dimethyl-1H-pyrazole (13).

A mixture of 8 (508 mg, 0.002 mole) and concentrated sulphuric acid (2 ml) was heated for 5 minutes at 100°C. During this time the colour of the solution changed from red to yellow. After cooling, crushed ice (20 g)

was added to the reaction mixture and the solution was neutralized with aqueous solution of potassium hydroxide (5 %). The precipitate was collected by filtration and washed with ice-cold water to give 415 mg of the mixture of 13 (88 %) and 10 (12 %). The compounds were identified by ^{1}H nmr technique by addition of samples of authentic compounds.

7-Phenyl-2,3,5-trimethyl-2H-pyrazolo/3,4-d/pyridazin-4(5H)-one (10) and 7-Phenyl-1,3,5-trimethyl-1H-pyrazolo/3,4-d/pyridazin-4(5H)-one (14).

A mixture of 9 (240 mg, 0.001 mole) and DMFDMA (0.25 ml) in toluene (2.5 ml) was heated under reflux for 15 minutes. The volatile components were evaporated in vacuo, to give a mixture of two compounds separated by flash chromatography (Kieselgel 60, 0.40-0.063 mm, E.Merck). The first component was eluted with diethyl ether, which gave, after evaporation of the solvent in vacuo, 14 (58 mg, 23 %), mp 180-184°C (n-heptane); MS m/e 154 (M^{+}, 100 %); ^{1}H nmr ($CDCl_3$): δ 2.65 (s, 3H, 3-Me), 3.53 (s, 3H, 1-Me), 3.79 (s, 3H, 5-Me), 7.44 (br s, 5H, Ph). ^{13}C nmr ($CDCl_3$): δ 158.4 (C_4, br s), 147.0 (C_{7a}, q, $^{3}J_{CMe(1)}$ = 7 Hz), 137.7 (C_{3a}, br s), 136.1 (C_7, m), 134.0, 129.7, 129.2, 128.8 (Ph), 114.6 (C_3, q, $^{2}J_{CMe(3)}$ = 3 Hz), 38.6 (2- or 5-Me, q, $^{1}J_{CH}$ = 141 Hz), 38.4 (5- or 2-Me, q, $^{1}J_{CH}$ = 141 Hz), 12.7 (3-Me, q, $^{1}J_{CH}$ = 128 Hz).

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.30; H, 5.64; N, 22.24.

The second component was eluted with methanol, which gave, after evaporation of the solvent in vacuo 10 (195 mg, 77 %), mp 143-144°C (cyclohexane); MS m/e 254 (M^{+}, 100 %); ^{1}H nmr ($CDCl_3$): δ 2.67 (s, 3H, 3-Me), 3.76 (s, 3H) and 3.87 (s, 3H) (2-Me and 5-Me), 7.20-7.50 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 8.10-8.35 (m, 2H, $H_{2'}$, $H_{6'}$). ^{13}C nmr ($CDCl_3$): δ 158.9 (C_4, q, $^{1}J_{CMe(5)}$ = 2 Hz), 143.9 (C_{7a}, s), 139.9 (C_{3a}, m), 138.9 (C_7, t, $^{1}J_{CH(1')}$ = 3 Hz), 134.2, 129.2, 128.3, 127.9 (Ph), 113.3 (C_3, q, $^{2}J_{CMe(3)}$ = 3 Hz), 38.2 (2-Me, q, $^{1}J_{CH}$ = 14 Hz), 37.1 (5-Me, q, $^{1}J_{CH}$ = 142 Hz), 10.4 (3-Me, q, $^{1}J_{CH}$ = 130.5 Hz).

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.01; H, 5.75; N, 22.21.

3-Benzoyl-4,5-dimethyl-1H-pyrazole (13).

A mixture of 15 [15] (400 mg, 0.002 mole) and concentrated sulphuric acid (2 ml) was heated for two minutes at 100°C. After cooling, crushed ice (20 g) was added and the resulting solution neutralized with aqueous solution of potassium hydroxide (5 %). The precipitate was collected by

filtration to give 13 (360 mg, 90 %), mp 131-134°C (n-heptane); MS m/e 200 (M^+, 96 %); ^{1}H nmr ($CDCl_3$): δ 2.08 (s, 3H) and 2.15 (s, 3H) (4-Me, 5-Me), 7.15-7.50 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$) 7.75-8.10 (m, 2H, $H_{2'}$, $H_{6'}$), 10.7 (br s, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.90; H, 6.23; N, 13.84.

X-Ray Analysis

The molecular structure was determined by single crystal structure analysis. Enraf-Nonius CAD-4 diffractometer and graphite-monochromated MoKα radiation (λ = 0.71069 Å) were used. Precise unit-cell dimension were obtained by least squares from the θ values of 104 moderately high-order reflections centered with diffractometer in the range $10^\circ < \theta < 15^\circ$ using $MoK\alpha_1$ value λ = 0.70926 Å at 293(1) K. Integrated intensities were measured in the reciprocal hemisphere k<0 up to θ_{max} 25°. Crystal stability was monitored by periodically measuring three standard reflections every 240 reflections; there was no evidence of crystal deterioration. The space group was determined from systematic absences. σ(I) based on counting statistics, intensities greater than 2.5 σ(I) were considered as observed. A summary of the crystal data and data collection parameters is given in Table 3. Intensities were corrected for background and change in the standards, and converted to structure amplitudes after applying Lorentz and polarization corrections. No absorption correction was made.

The structure was solved in a routine way by direct method with MULTAN80[16]. E map with the highest combined figure of merit, using 232 phase (|E|>1.20) resulted in initial coordinates for all nonhydrogen atoms. Positions of hydrogen atoms were partly calculated partly were got from difference map. Atomic scattering factors for neutral O, N anc C atoms were taken from [17], for H atoms from [18]. Dispersion correction for O, N and C[19] was used. A full-matrix least squares refinement with anisotropic temperature factors for nonhydrogen atoms and isotropic ones for hydrogen atoms using empirical weighting function proceeded to R = 0.045. A summary of refinement parameters is presented in Table 4.

All calculations were performed on the DEC-10 computer at RCU Ljubljana with the XRAY-76[20] system of crystallographic programs.

A view of the molecule with the numbering of atoms is shown in Fig.1, final atomic coordinates and equivalent isotropic thermal parameters for nonhydrogen atoms are given in Table 5 and interatomic bond lenghts and angles are given in Table 6.[21] All nonhydrogen atoms but C(31) are in 4c special position on a mirror plane resulting a planar molecule. The cry-

stal consists of a van der Waals packing of monomeric units without significantly short intermolecular contacts.

The mean C - C bond of 1.377(8) Å and C - C - C angle of 120(1)° in the phenyl ring correspond to usual data. The N - C bond lengths are in the range from 1.480(4) to 1.304(3) Å, from single- to double-bond length. N(1) - C(8) of 1.445(4) Å and N(5) - C(4) of 1.381(4) Å are intermediate between single- and double-bond. N(1) - N(2) of 1.257(4) Å is a perfect double-bond distance[22], while N(5) - N(6) of 1.349(3) Å is again an intermediate between single- and double-bond lengths.

Table 3. Crystal and data collection summary

Empirical formula	$C_{14}H_{14}N_4O$
Formula weight	254.29
Crystal system	orthorhombic
Space group	Pnma No.: 62
Temperature (K)	293(1)
Unit cell	
a (Å)	20.699(4)
b	6.961(1)
c	8.898(2)
Volume ($Å^3$)	1282.1
Z	4
F(000)	536
D_x (gcm^{-3})	1.317
μ(MoKα) (cm^{-1})	0.817
Size of crystal (mm)	0.4 x 0.4 x 0.6
Scan method	ω - 2θ
θ_{max} (deg)	25
2θ scan width (deg)	0.8 + 0.4tgθ
Scan rate ($degmin^{-1}$)	min 2.0, max 20.1
Maximum scan time (s)	40
Aperture (mm)	2.4 + 0.9tgθ
Background	1/4 of the scan time at each of the scan limit
Reference reflections	1 2 9, 0 3 $\bar{9}$, $\bar{4}$ 0 2
Intensity decrease (%)	1.4
Measured reflections	4832
Averaged reflections	1235
Mean discrepancy on I (%)	4.2
Observed reflections	802
Unobserved reflections	433

Table 4. Refinement parameters

Scale factor	0.949
Number of contributing reflections (m)	904
Number of variables (n)	146
m/n ratio	6.2
Weighting function	empirical
	$w = W_f \cdot W_s$
	$W_f(\lvert F_o\rvert<4.0) = (\lvert F_o\rvert/4.0)^{3.0}$
	$W_f(4.0<\lvert F_o\rvert<12.0) = 1.0$
	$W_f(12.0<\lvert F_o\rvert) = (12.0/\lvert F_o\rvert)^{1.5}$
	$W_s(\sin\theta<0.27) = (\sin\theta/o.27)^{2.0}$
	$W_s(0.27<\sin\theta<0.35) = 1.0$
	$W_s(0.35<\sin\theta) = (0.35/\sin\theta)^{2.0}$
$[\Sigma(\Delta F)^2/(m-n)]^{1/2}$	0.354
R	0.045
R_w	0.045
Average shift/error	0.03
Maximum shift/error	0.30 (U H(74))
Final difference map	
$\Delta\rho_{max}$ (eÅ^{-3})	0.18
$\Delta\rho_{min}$ (eÅ^{-3})	-0.24

Table 5. Final Fractional Coordinates ($\times10^4$) and Equivalent Isotropic Temperature Factors, U_{eq} (Å$^2\times10^3$) of Nonhydrogen Atoms

	x	y	z	U_{eq}
N(1)	89(1)	2500	1166(3)	67(2)
N(2)	376(1)	2500	-79(3)	75(2)
C(3)	1087(2)	2500	96(3)	62(2)
C(31)	1352(2)	4304(4)	-658(3)	80(2)
C(4)	1718(1)	2500	2678(3)	63(2)
O	2281(1)	2500	2240(3)	102(2)
N(5)	1569(1)	2500	4192(3)	56(1)
C(51)	2090(2)	2500	5297(5)	81(3)
N(6)	973(1)	2500	4807(2)	49(1)
C(7)	464(1)	2500	3945(3)	44(1)
C(71)	-171(1)	2500	4726(3)	44(1)

C(72)	-194(1)	2500	6280(3)	53(2)
C(73)	-773(2)	2500	7028(4)	62(2)
C(74)	-1349(2)	2500	6255(4)	66(2)
C(75)	-1332(2)	2500	4722(4)	69(2)
C(76)	-748(1)	2500	3954(4)	58(2)
C(8)	562(1)	2500	2359(3)	48(2)
C(9)	1158(1)	2500	1755(3)	50(2)

Table 6. Bond Lengths and Angles for Nonhydrogen Atoms

Bond lengths (Å)

N(1) - N(2)	1.257(4)	N(5) - C(51)	1.459(5)
N(1) - C(8)	1.445(4)	N(6) - C(7)	1.304(3)
N(2) - C(3)	1.480(4)	C(7) - C(8)	1.425(4)
C(3) - C(9)	1.483(4)	C(7) - C(71)	1.487(4)
C(3) - C(31)	1.525(4)	C(71) - C(72)	1.384(4)
C(9) - C(4)	1.420(4)	C(72) - C(73)	1.371(5)
C(9) - C(8)	1.345(4)	C(73) - C(74)	1.376(5)
C(4) - N(5)	1.381(4)	C(74) - C(75)	1.365(5)
C(4) - O	1.229(4)	C(75) - C(76)	1.388(5)
N(5) - N(6)	1.349(3)	C(76) - C(71)	1.378(4)

Bond angles (°)

C(8)-N(1)-N(2)	109.1(2)	N(5)-N(6)-C(7)	120.0(2)
N(1)-N(2)-C(3)	112.2(3)	N(6)-C(7)-C(8)	117.8(2)
N(2)-C(3)-C(9)	101.7(2)	N(6)-C(7)-C(71)	116.1(2)
N(2)-C(3)-C(31)	108.1(2)	C(8)-C(7)-C(71)	126.1(2)
C(31)-C(3)-C(9)	113.7(2)	C(7)-C(8)-N(1)	129.1(2)
C(31)-C(3)-C(31)'	110.8(3)	C(7)-C(8)-C(9)	121.8(2)
C(3)-C(9)-C(4)	131.0(3)	N(1)-C(8)-C(9)	109.1(2)
C(3)-C(9)-C(8)	107.9(2)	C(7)-C(71)-C(72)	119.9(2)
C(4)-C(9)-C(8)	121.1(3)	C(7)-C(71)-C(76)	122.2(2)
C(9)-C(4)-N(5)	112.5(2)	C(76)-C(71)-C(72)	117.9(3)
C(9)-C(4)-O	126.1(3)	C(71)-C(72)-C(73)	121.0(3)
N(5)-C(4)-O	121.4(3)	C(72)-C(73)-C(74)	121.0(3)
C(4)-N(5)-N(6)	126.8(2)	C(73)-C(74)-C(75)	118.5(3)
C(4)-N(5)-C(51)	119.5(2)	C(74)-C(75)-C(76)	120.9(3)
N(6)-N(5)-C(51)	113.7(2)	C(75)-C(76)-C(71)	120.6(3)

Acknowledgement

The authors wish to express their gratitude to the Research Council of Slovenia for partial financial support of this investigation.

REFERENCES

1. Franck-Neumann, M.; Leclerc, G.; Tetrahedron Lett., 1969, 1063.
2. Farina, F.; Martin, M. V.; Sanchez, F.; Tito, A.; Heterocycles, 1982, *18*, 175.
3. King, R.R.; J. Org. Chem., 1982, *47*, 5397.
4. Stanovnik, B.; Kupper, M.; Tišler, M.; Leban,I.; Golič L.; J. Chem. Soc., Chem. Commun., 1984, 268, and references cited therein.
5. Stanovnik, B.; Furlan B.; Sarka, A.; Tišler, M.; Žličar, M.; Heterocycles, 1984, *22*, 2479.
6. Stanovnik, B.; Božnar, B.; Koren, B.; Petriček, S.; Tišler, M.; Heterocycles, 1985, *23*, 1.
7. Furlan, B.; Stanovnik, B.; Tišler, M.; Synthesis, 1986, 78.
8. Stanovnik, B.; Furlan, B.; Kupper, M.; Malež, L.; Štimac, A.; Tišler, M.; Žličar, M.; J. Heterocyclic Chem., 1988, *25*, 393.
9. Leban, I.; Golič, L.; Stanovnik, B.; Tišler, M.; Acta Crystal., 1987 *C 43*, 1814.
10. Leban, I.; Golič, L.; Stanovnik, B.; Tišler, M.; Acta Crystal., 1988, *C 44*, 193.
11. Hüttel, R.; Riedel, J.; Martin, H.; Franke, K.; Chem. Ber., 1960, *93*, 1433, and references cited therein.
12. Duffin, G.F.; Kendall, J.D.; J. Chem. Soc., 1959, 3789.
13. Andrews, S.D.; Day, A.C.; Raymond, P.; Whiting, M.C.; Org. Synth., 1970, *50*, 27.
14. Koenig, J.J.; Wermuth, C.G.; Tetrahedron, 1974, *30*, 501.
15. Dietrich-Buchecker, C.; Franck-Neumann, M.; Tetrahedron, 1977, *33*, 745.
16. Main, P.; Fiske, S.J.; Hull, S.E.; Lessinger, L.; Germain, G.; Declercq, J.P.; Woolfson, M.M.; MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. University of York, England and Louvain, Belgium (1980).
17. Cromer, D.T.; Mann, J.B.; Acta Cryst., 1968, *A24*, 321.
18. Stewart, R.F.; Davidson, E.R.; Simpson, W.R.; J. Chem. Phys., 1965, *42*, 3175.
19. Cromer, D.T.; Liberman, D.J.; J. Chem. Phys., 1979, *53*, 1891.
20. Stewart, J.M.; Machin, P.A.; Dickinson, C.W.; Ammon, H.L.; Heck H.; H. Flack, H.; The XRAY76 System. Tech. Rep. TR-446. Computer Science Center, University of Maryland, College Park, Maryland (1976).
21. The atomic coordinates and F_o-F_c table for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
22. Dunitz, J.D.; X-ray Analysis and the Structure of Organic Molecules, Ithaca: Cornell Univ. Press (1979), p. 338.