

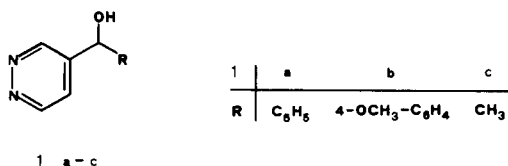
Gottfried Heinisch\* and Richard Waglechner

Institute of Pharmaceutical Chemistry, University of Vienna, Währingerstraße 10,  
A-1090 Wien, Austria  
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Treatment of phenyl(4-pyridazinyl)methanols **1a** and **1b** with *p*-toluenesulfonic acid at elevated temperatures causes transformation into the C-4 substituted pyrazole derivatives **8a** and **8b**. Limitations of this novel rearrangement reaction as well as mechanistic considerations are discussed. Furthermore, the preparation of hitherto unknown 4-pyridazinylmethanols **1b**, **3**, and **7** is described.

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We recently reported the unsuccessful attempts to convert 4-(1-hydroxyalkyl)pyridazines into the corresponding alkyl ethers under various reaction conditions previously applied with success in the etherification of (1-hydroxyalkyl)pyridines [1]. Moreover, we have shown, that 4-(1-chloroalkyl)pyridazines are attacked by alkoxide ions predominantly at the heteroaromatic ring, thus yielding 5-alkoxy-4-alkylpyridazines rather than the desired 4-(1-alkoxyalkyl)pyridazines [1]. These findings prompted us to carry out reactions of alcohols **1a** [3], **1c** [4] and **1b** with 2-dimethylaminoethanol in the presence of *p*-toluenesulfonic acid, according to a method reported for the preparation of biologically active alkyl ethers of phenyl(2-pyridyl)methanols [5].

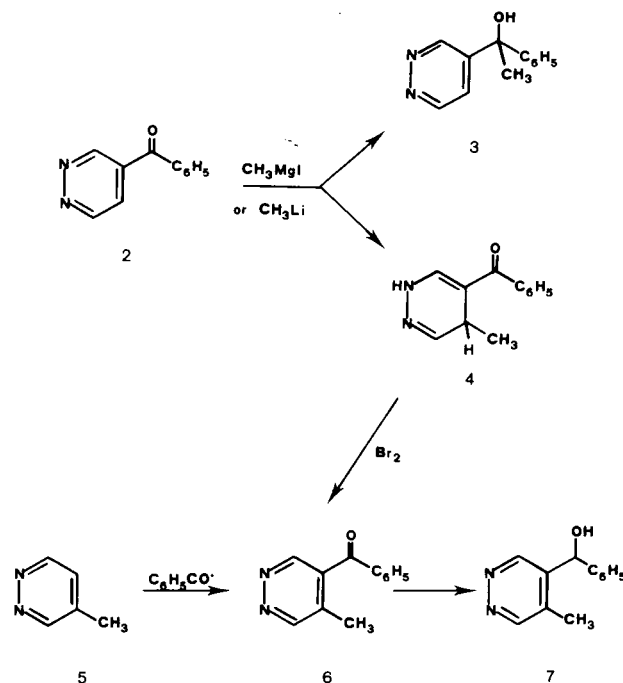


Scheme 1

We now report a novel type of pyridazine → pyrazole ring contraction observed in the course of these investigations. Furthermore, the syntheses of hitherto unknown alcohols **1b**, **3** and **7** being of interest for studying the limitations of this rearrangement reaction, are described.

Compound **1b** was easily obtained by reduction of (4-methoxyphenyl)-4-pyridazinylmethanone [6] with sodium borohydride. In order to prepare 1-phenyl-1-(4-pyridazinyl)ethanol (**3**), reactions of **2** with organometallic reagents were examined. Treatment of **2** with methylmagnesium iodide, led to two isomeric compounds. The main product (59% yield) was shown to be the expected tertiary alcohol **3**, whereas the <sup>1</sup>H-nmr and <sup>13</sup>C-nmr data indicated, that the second product (20% yield) resulted from an attack of the methyl carbanion at the 1,2-diazine system [7]. Therefore we assumed the new compound to be a dihydropyridazine derivative [8]. As a consequence, oxidation of this compound with bromine in acetic acid leads to a diarylketone **6**, the structure of which was conclusively established by <sup>1</sup>H-nmr spectroscopy: Two singlets at 9.08 and 9.28

ppm, clearly proved the methyl group being attached to carbon atom 5. Furthermore, an identical product was obtained on homolytic benzoylation [9] of **5**. Assignment of structure **4** to the dihydropyridazine derivative mentioned above follows from spectroscopic evidence: whereas the ir spectrum (potassium bromide disc or chloroform solution) does not display any absorption between 1700 and 1600 cm<sup>-1</sup>, J-modulated <sup>13</sup>C-nmr spectroscopy clearly indicates a keto group (singlet at 192 ppm). Considering the multiplicity of the methyl group in the <sup>1</sup>H-nmr spectrum (doublet, J = 7 Hz), six of the nine theoretically possible isomers have to be dismissed. Signal intensities, splitting patterns and chemical shift considerations, respectively, allow us to eliminate two further structures. In agreement with the thus proposed structure of a 2,5-dihydropyridazine the <sup>1</sup>H-nmr spectrum exhibits two doublets at 6.93 ppm (J = 4 Hz) and 7.02 ppm (J = 4 Hz), the latter doublet collapsing to a singlet on NH → ND exchange. In addition, the signal



Scheme 2

of the C-5 proton (split by coupling with the methyl protons as well as H-6) occurred as a doublet ( $J = 4$  Hz) on irradiating the methylene protons.

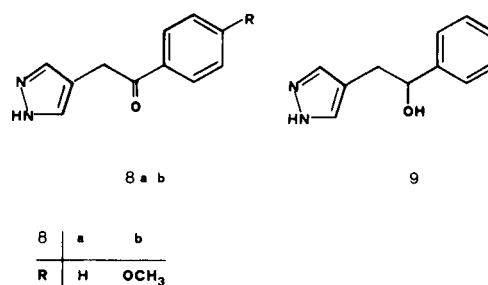
By use of methyllithium instead of methylmagnesium iodide the attack of the organometallic reagent at the heteroaromatic ring could be minimized, thus furnishing **3** in 75% yield; only minor amounts of **4** (ca. 4%), accompanied by its oxidation product **6** (ca. 3%), were formed.

When phenyl(4-pyridazinyl)methanol (**1a**, 1 mmole) was reacted with 2-dimethylaminoethanol (1.1 mmoles)/*p*-toluenesulfonic acid (1.2 mmoles) at 150°, three products, separable by column chromatography on silica gel (ethyl acetate) followed by crystallisation, were obtained. Two of them were identified by comparison with authentic materials [3] as 4-benzylpyridazine and the ketone **2**, both resulting from thermally induced dismutation of **1a** [11].

Surprisingly, the third compound isolated in 29% yield, was found to be not the expected dimethylaminoethyl ether of **1a** but an isomer of the starting alcohol, as shown by elemental analyses and mass spectrum. Further experiments revealed that the same products are obtained by reacting **1a** with *p*-toluenesulfonic acid in other solvents (e.g. triethyleneglycol) or in absence of a solvent. Under these conditions, however, the yields decreased drastically [12].

An ir absorption at 1685  $\text{cm}^{-1}$  together with a singlet at 197 ppm in the off resonance decoupled  $^{13}\text{C}$ -nmr spectrum (deuteriodimethylsulfoxide solution) proved a keto function in the new compound. The base peak in mass spectrum was observed at  $m/e$  105 ( $\text{C}_6\text{H}_5\text{CO}$ ), which indicates the keto group to be in conjugation with the benzene ring. Moreover, the uv spectrum resembles closely that of acetophenone [13]. Furthermore, a methylene group indicated by  $^1\text{H}$ -nmr and  $^{13}\text{C}$ -nmr spectra has to be attached directly to the C=O group. This has been shown by the  $^1\text{H}$ -nmr spectrum of the alcohol obtained quantitatively by sodium borohydride reduction.

Considering these findings together with signals of seven protons at 7.5-8.1 ppm in the  $^1\text{H}$ -nmr spectrum, the rearrangement product of **1a** obviously is a diazole derivative. The nature of the heteroaromatic ring as well as the position of the side chain was established unambiguously by oxidation with potassium permanganate affording pyrazole-4-carboxylic acid (54% yield, shown by melting point and ir spectrum to be identical with a compound prepared from 4-methylpyrazole according to lit [14]), along with benzoic acid (59% yield). In addition to already discussed uv and ms data, assignment of structure **8a** i.e. 1-phenyl-2-(4-pyrazolyl)ethanone is based on the  $^1\text{H}$ -nmr spectrum of protonated **8a** [15], which clearly indicates the keto group not being attached to the pyrazole ring. According to these results the previously mentioned reduction product of **8a** has to have structure **9** [16].



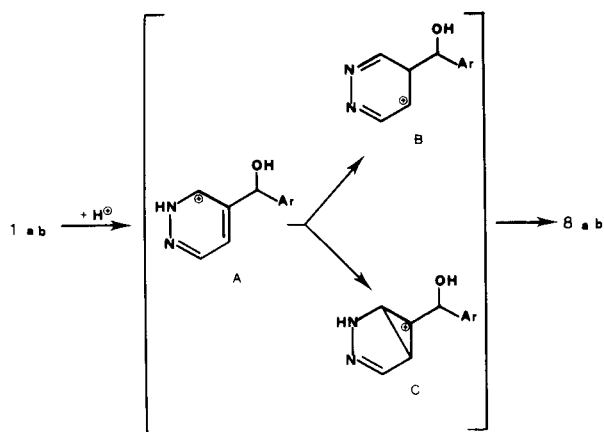
Scheme 3

Similar results were obtained on reaction of alcohol **1b** with *p*-toluenesulfonic acid/2-dimethylaminoethanol under identical conditions. Again, a pyrazole derivative **8b** was formed instead of an ether of **1b**, together with (4-methoxyphenyl)-4-pyridazinylmethanone [6] and 4-(4-methoxybenzyl)pyridazine. The structure of the latter by-product was confirmed by unequivocal synthesis *via* homolytic substitution of pyridazine in analogy to a reported method [3].

Although there are several examples of pyridazine  $\rightarrow$  pyrazole ring contraction known in literature [17] the rearrangement of **1a**, **1b**, to **8a**, **8b** to our knowledge seems unprecedented, as it involves a transformation of a pyridazine having attached a carbon atom to C-4 into a C-4 alkylated pyrazole. Obviously, the driving force of the reaction is given by the fact that enol forms of **8a** and **8b** (shown by  $^1\text{H}$ -nmr spectroscopy to be existent in strongly acidic media; see below) represent fully conjugated systems. This assumption is supported by the finding that reaction of 1-(4-pyridazinyl)ethanol (**1c**) with *p*-toluenesulfonic acid under equal conditions does not lead to a pyrazole derivative but affords only products of dismutation i.e. 4-ethylpyridazine and 1-(4-pyridazinyl)ethanone [11].

No definitive conclusions with respect to the mechanism of the rearrangement could be drawn from experiments starting with 1-phenyl-1-(4-pyridazinyl)ethanol (**3**), (4-chlorophenyl)-5-amino-4-pyridazinylmethanol [18] or (5-methyl-4-pyridazinyl)phenylmethanol (**7**) prepared by reduction of **6** with sodium borohydride [19]. On the other hand further informations cannot be expected from experiments using **1a**, deuterated at C-5 or at the benzylic carbon atom, respectively: as shown by  $^1\text{H}$ -nmr spectrum in deuteriotrifluoroacetic acid solution, the hydrogen atoms of the methylene group in **8a** are exchanged by deuterium quantitatively, even at room temperature.

However, from the structure of the reaction products **8a**, **8b** it becomes evident that the ring contraction requires carbon( $\alpha$ )-carbon( $\beta$ ) bond fission. As a tentative explanation we may assume initial protonation of N-2 in **1a**, **1b** rather than protonation of oxygen, resulting in intermediate formation of carbeniumions B or C as indicated in the scheme below [20]. In both cases rearrangement would then involve C-3/C-4 bond fission.



Scheme 4

Assuming intermediate formation of an aryl-4-pyridazinyl methyl cation one might expect the reaction course being influenced by electron donating substituents attached to the phenyl ring *e.g.* methoxy group in **1b**. However, there is no significant difference in yields of **8a** and **8b**. These mechanistic considerations are not contradicted by the failure of attempts to convert phenyl-4-pyridazinylmethanols, substituted at C-5 by a methyl group or an amino group, respectively, because under these circumstances formation of a fully conjugated system is impossible.

The novel ring contraction reaction obviously requires a diaza heteroaromatic system as shown by the fact that no analogous pyridine  $\rightarrow$  pyrrole rearrangement is observed under the applied reaction conditions: phenyl(3-pyridyl)methanol as well as phenyl(4-pyridyl)methanol were found to remain completely unaffected. Extension of these investigations to phenyl(3-pyridazinyl)methanols as well as to other diaziny phenyl methanols seems to be of interest.

## EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. The IR spectra (potassium bromide) were recorded on a Jasco IRA-1 spectrometer. The  $^1H$ -NMR spectra were obtained on a Varian EM 390 (90 MHz) and on a Varian WM 250 (250 MHz). The  $^{13}C$ -NMR spectra were recorded on a Varian WM 250 (62.9 MHz). Chemical shifts are reported in ppm from TMS as an internal standard and are given in  $\delta$  units. The UV spectra (solvent: methanol) were measured on a Beckman 25 spectrometer. Electron impact mass spectra were obtained at 70 eV using a Varian MAT CH-7, for chemical ionization mass spectra a Finnigan 4500 was used. Medium pressure column chromatography was performed on Lobar columns (size B, LiChroprep Si 60, 0.040-0.063 mm; Merck), 4-6 ml/minute; detection at 280 nm; before medium pressure column chromatography the mixtures were chromatographed on short columns of silica gel 60 (0.063-0.200 mm; Merck). Thin layer chromatograms were performed on DC-Plastikfolien, Kieselgel 60 F 254 (Merck). For preparative separations PSC-Fertigplatten, Kieselgel 60 F 254 s (Merck) were used. Light petroleum refers to the fraction with a bp 50-70°. Elemental analyses were carried out by Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna.

(4-Methoxyphenyl)-4-pyridazinylmethanol (**1b**).

(4-Methoxyphenyl)-4-pyridazinylmethanone (856 mg, 4 mmol) [6] was

dissolved in 20 ml methanol and sodium borohydride (38 mg, 1 mmol) was added within 15 minutes. The mixture was stirred at room temperature for 30 minutes until there was no starting material detectable by TLC (ethyl acetate). The solution was acidified with 2 N sulfuric acid and the methanol was distilled off *in vacuo*. Upon cooling the residual solution was made alkaline with 50% sodium hydroxide solution and was repeatedly extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* yielding **1b** (840 mg, 97%) as white crystals from 2-butanone, mp 100-103°;  $^1H$ -NMR (deuteriochloroform, 90 MHz):  $\delta$  3.80 (s,  $CH_3$ , 3H), 4.75 (s, OH, exchangeable with deuterium oxide, 1H), 5.80 (s, benzylic H, 1H), 6.9 (m, phenyl H-3,5, 2H), 7.2 (m, phenyl H-2,6, 2H), 7.6 (m, H-4, 1H), 9.1 (m, H-3,6, 2H).

*Anal.* Calcd. for  $C_{12}H_{12}N_2O_2$ : C, 66.65; H, 5.59; N, 12.95. Found: C, 66.59; H, 5.63; N, 12.77.

### Reaction of **2** with Methylmagnesium Iodide.

To the Grignard reagent prepared from magnesium (150 mg, 6.25 mmol) and methyl iodide (888 mg, 6.25 mmol) in 12 ml of dry diethyl ether **2** (920 mg, 5 mmol) [3] dissolved in 60 ml dry diethylether:benzene (1:1) was added. The mixture was refluxed under nitrogen for 2 hours and then quenched cautiously by adding ice water and enough 30% ammonium chloride solution to dissolve the solid. The organic layer was separated and the aqueous phase repeatedly extracted with dichloromethane. The combined organic phases were washed successively with saturated sodium hydrogen carbonate solution and twice with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on a silica gel column using dichloromethane:ethyl acetate (1:1) as the eluent giving from fraction I a mixture of compound **4** and unconverted **2**, from fraction II compound **3** (591 mg, 59%). Fraction I was submitted to medium pressure column chromatography using dichloromethane:ethyl acetate (1:1) as the eluent yielding compound **4** (202 mg, 20%) from the first fraction, the second fraction gave compound **2** (89 mg), mp 106-108° (lit mp 106-108° [3]).

### 1-Phenyl-1-(4-pyridazinyl)ethanol (**3**).

Compound **3** was obtained as white crystals from toluene, mp 121-123°;  $^1H$ -NMR (deuteriochloroform, 90 MHz):  $\delta$  1.94 (s,  $CH_3$ , 3H), 5.17 (s, broad, OH, 1H), 7.4 (m, phenyl H, 5H), 7.6 (m, H-5, 1H), 8.9 (m, H-6, 1H), 9.1 (m, H-3, 1H); ms:  $m/e$  200 ( $M^+$ , 35), 121 (46), 80 (36), 51 (40), 43 (100).

*Anal.* Calcd. for  $C_{12}H_{12}N_2O$ : C, 71.98; H, 6.04; N, 13.99. Found: C, 71.98; H, 6.11; N, 13.94.

### (2,5-Dihydro-5-methyl-4-pyridazinyl)phenylmethanone (**4**).

Compound **4** was obtained as pale yellow needles from diisopropylether, mp 150-151°;  $^1H$ -NMR (deuteriodimethylsulfoxide, 250 MHz):  $\delta$  1.00 (d,  $J = 7$  Hz,  $CH_3$ , 3H), 3.5 (m, on irradiating at 1.00: d,  $J = 4$  Hz, H-5, 1H), 6.93 (d,  $J = 4$  Hz, H-6, 1H), 7.02 (d,  $J = 4$  Hz, after deuterium oxide addition: s, H-3, 1H), 7.5 (m, phenyl H, 5H), 10.20 (d,  $J = 4$  Hz, NH, exchangeable with deuterium oxide, 1H);  $^{13}C$ -NMR (deuteriodimethylsulfoxide):  $\delta$  19 ( $CH_3$ ), 25 (C-5), 107 (C-4), 128-130 (phenyl C-2,3,4,5,6), 139 (phenyl C-1), 140 (C-6), 145 (C-3), 192 (C=O); ms:  $m/e$  200 ( $M^+$ , 37), 185 (100), 105 (86), 77 (87), 51 (28).

*Anal.* Calcd. for  $C_{12}H_{12}N_2O$ : C, 71.98; H, 6.04; N, 13.99. Found: C, 71.99; H, 6.26; N, 13.92.

### Reaction of **2** with Methylolithium.

Methylolithium in diethyl ether (2.8 ml, 4.4 mmol) was added under argon to a stirred solution of **2** (736 mg, 4 mmol) [3] in 40 ml dry tetrahydrofuran at -78° within 10 minutes. Stirring was continued for 20 minutes and then the mixture was allowed to warm to room temperature. After quenching with a mixture of 20 g of ice water and 20 ml of dichloromethane the organic phase was separated and the aqueous layer was repeatedly extracted with dichloromethane. The combined organic layers were washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was submitted to medium pressure column chromatography using ethyl acetate as the eluent yielding from

fraction I compound **4** (33 mg, 4%, all spectral data are in agreement with that of compound **4** described above), from fraction II unconverted **2** (15 mg), mp 106-108° (lit mp 106-108° [3]), from fraction III compound **6** (26 mg, 3%, all spectral data are in agreement with that of **6** prepared by homolytic benzoylation of 4-methylpyridazine; see below), from fraction IV compound **3** (599 mg, 75%, all spectral data are in agreement with that of compound **3** described above).

#### Reaction of **2** with Phenylmagnesium Bromide.

Compound **2** (552 mg, 3 mmoles) [3] in 50 ml dry diethyl ether:toluene (1:1) was reacted with the Grignard reagent prepared from magnesium (90 mg, 3.75 mg-atoms) and bromobenzene (589 mg, 3.75 mmoles) in 1 ml of dry diethylether in a manner similar to the reaction of **2** with methylmagnesium iodide. The residue obtained after analogous work up was submitted to medium pressure column chromatography using dichloromethane:ethyl acetate (5:1) as the eluent yielding from fraction I a mixture of several unidentified by-products (190 mg), from fraction II (2,5-dihydro-5-phenyl-4-pyridazinyl)phenylmethanone (258 mg, 33%) and from fraction III compound **2** (42 mg), mp 106-108° (lit mp 106-108° [3]).

#### (2,5-Dihydro-5-phenyl-4-pyridazinyl)phenylmethanone.

This compound was obtained as white needles from water/ethanol, mp 199-200°; <sup>1</sup>H-nmr (deuteriodimethylsulfoxide, 250 MHz): δ 4.73 (d, J = 4 Hz, H-5, 1H), 7.06 (d, J = 4 Hz, H-6, 1H), 7.3 (m, phenyl H, H-3, 6H), 7.5 (m, phenyl H, 5H), 10.36 (d, J = 4 Hz, NH, exchangeable with deuterium oxide, 1H); <sup>13</sup>C-nmr (deuteriodimethylsulfoxide): δ 37 (C-5), 105 (C-4), 127 - 130 (phenyl C-2,2',3,3',4,4',5,5',6,6'), 139 (phenyl C-1), 140 (C-6), 142 (C-3), 143 (phenyl C-1'), 192 (C=O); ms: m/e 262 (M<sup>+</sup>, 100), 261 (41), 185 (90), 157 (21), 105 (51), 77 (74), 51 (26).

Anal. Calcd. for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O: C, 77.84; H, 5.38; N, 10.68. Found: C, 78.07; H, 5.52; N, 10.64.

#### (5-Methyl-4-pyridazinyl)phenylmethanone (**6**). Method A.

To a solution of **4** (60 mg, 0.3 mmole) in 1 ml acetic acid a solution of bromine (240 mg, 1.5 mmoles) in 5 ml acetic acid was added and the mixture was stirred for 30 minutes. The reaction mixture was diluted with water and the excess of bromine was destroyed by addition of a 50% sodium hydroxide solution. After repeated extraction with diethylether the combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on a short silica gel column using ethylacetate as the eluent giving white crystals (58 mg, 98%), mp 99-101°; <sup>1</sup>H-nmr (deuteriochloroform, 90 MHz): δ 2.39 (s, CH<sub>3</sub>, 3H), 7.7 (m, phenyl H, 5H), 9.08 (s, H-3 or H-6, 1H), 9.28 (s, H-3 or H-6, 1H); ir: 1650 cm<sup>-1</sup> (C=O); ms: m/e 198 (M<sup>+</sup>, 40), 105 (100), 77 (59), 51 (20).

Anal. Calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.75; H, 5.20; N, 14.14.

#### Method B.

A saturated aqueous solution of ferrosulfate heptahydrate (8.34 g, 30 mmoles) and a solution (80%) of tert-butyl hydroperoxide in di-*t*-butylperoxide (2.7 g, 30 mmoles) were added dropwise and simultaneously at 0° to a stirred mixture of freshly distilled benzaldehyde (3.18 g, 30 mmoles), freshly distilled 4-methylpyridazine (940 mg, 10 mmoles) [21], 2*N* sulfuric acid (20 ml) and acetic acid (in order to bring the benzaldehyde into solution). After stirring for an additional hour the reaction mixture was repeatedly extracted with dichloromethane. The combined extracts were successively washed with water, aqueous sodium hydrogen carbonate solution and water and then dried over anhydrous sodium sulfate and evaporated *in vacuo*. After medium pressure column chromatography using ethylacetate as the eluent the residue was purified by sublimation at 70° (10<sup>-2</sup> mbar) yielding compound **6** (543 mg, 27%, all spectral data are in agreement with that of **6**, obtained by method A).

#### (5-Methyl-4-pyridazinyl)phenylmethanone (**7**).

Compound **6** (99 mg, 0.5 mmole) was reduced with sodium borohydride in a manner similar to the preparation of **1b**. After treatment with diethyl ether white crystals (89 mg, 89%), mp 124°, were obtained; <sup>1</sup>H-nmr

(deuteriochloroform, 90 MHz): δ 2.10 (s, CH<sub>3</sub>, 3H), 5.98 (s, benzylic H, 1H), 6.3 (s, broad, OH, 1H), 7.30 (s, phenyl H, 5H), 8.62 (s, H-3 or H-6, 1H), 9.28 (s, H-3 or H-6, 1H); ms: m/e 200 (M<sup>+</sup>, 33), 75 (100), 58 (27), 57 (85), 45 (76).

Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.90; H, 6.12; N, 14.07.

#### Reaction of **1a** with *p*-Toluenesulfonic Acid/2-Dimethylaminoethanol.

Compound **1a** (1116 mg, 6 mmoles) [3], 2-dimethylaminoethanol (587 mg, 6.6 mmoles) and *p*-toluenesulfonic acid monohydrate (1368 mg, 7.2 mmoles) were heated in a Kugelrohr apparatus at 150° *in vacuo* (10<sup>-2</sup> mbar) for 2.5 hours. After cooling the residue together with the distillate was dissolved in dichloromethane and filtered through a short silica gel column using ethylacetate as the eluent to eliminate polymers and the *p*-toluenesulfonic acid. Fractional crystallisation from chloroform:ethylacetate (3:1) gave compound **8a** (251 mg, 22%). The products of the mother liquor were separated by medium pressure column chromatography using chloroform:ethylacetate (1:1) as the eluent giving from fraction I compound **2** (120 mg, 11%), mp 106-108° (lit mp 106-108° [3]) and from fraction II a mixture of compound **8a** and 4-benzylpyridazine. Recrystallisation of fraction II from benzene gave additional **8a** (77 mg, 7%), from the mother liquor 4-benzylpyridazine (82 mg, 8%, shown by <sup>1</sup>H-nmr spectrum to be identical with authentic material [3]) was obtained.

#### 1-Phenyl-2-(4-pyrazolyl)ethanone (**8a**).

Compound **8a** was obtained as white needles, from benzene, mp 153-155°; <sup>1</sup>H-nmr (deuteriodimethylsulfoxide, 250 MHz): δ 4.22 (s, CH<sub>2</sub>, 2H), 7.6 (m, phenyl H-3,4,5, pyrazole H-3,5, 5H), 8.0 (m, phenyl H-2,6, 2H), 12.7 (s, broad, NH, exchangeable with deuterium oxide, 1H); <sup>1</sup>H-nmr (deuteriotrifluoroacetic acid, 250 MHz): δ 4.68 (s, CH<sub>2</sub>, 2H), 7.6 (m, phenyl H-3,5, 2H), 7.8 (m, phenyl H-4, 1H), 8.1 (m, phenyl H-2,6, 2H), 8.32 (s, pyrazole H-3,5, 2H); <sup>13</sup>C-nmr (deuteriodimethylsulfoxide): δ 34 (CH<sub>2</sub>), 112 (pyrazole C-4), 128 (phenyl C-2,3,4,5,6), 133 (pyrazole C-3,5), 136 (phenyl C-1), 197 (C=O); ir: 1685 cm<sup>-1</sup> (C=O); uv: 243 nm (ε = 11400), 279 nm (ε = 1100); ms: m/e 186 (M<sup>+</sup>, 34), 105 (100), 77 (26).

Anal. Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.62; H, 5.61; N, 15.02.

#### Reaction of **1a** with *p*-Toluenesulfonic Acid.

Compound **1a** (93 mg, 0.5 mmole) [3] and *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmole) were heated in a Kugelrohr apparatus at 150° *in vacuo* (10<sup>-2</sup> mbar) for 2.5 hours. The products obtained were separated by preparative tlc (eluent: chloroform:ethyl acetate, 3:1, four development steps). Compound **8a** (10 mg, 11%) was isolated and shown to be identical (mp, ir spectrum) with the product prepared in the manner described above.

#### Reaction of **1b** with *p*-Toluenesulfonic Acid/2-Dimethylaminoethanol.

Compound **1b** (324 mg, 1.5 mmoles) was reacted with *p*-toluenesulfonic acid monohydrate (342 mg, 1.8 mmoles) and 2-dimethylaminoethanol (147 mg, 1.65 mmoles) in a manner similar to the reaction of **1a**. Medium pressure column chromatography (ethyl acetate) affords from fraction I (4-methoxyphenyl)-4-pyridazinylmethanone (68 mg, 21%), mp 106-107° (lit mp 106-107° [6]), from fraction II compound **8b** (88 mg, 27%) and from fraction III 4-(4-methoxybenzyl)pyridazine (48 mg, 16%, all spectral data are in agreement with that of an authentic sample obtained by reaction of pyridazine with 4-methoxybenzyl radicals; see below.).

#### 1-(4-Methoxyphenyl)-2-(4-pyrazolyl)ethanone (**8b**).

Compound **8b** was obtained as white needles from water/methanol, mp 152-155°; <sup>1</sup>H-nmr (deuteriodimethylsulfoxide, 90 MHz): δ 3.85 (s, CH<sub>3</sub>, 3H), 4.12 (s, CH<sub>2</sub>, 2H), 7.1 (m, phenyl H-3,5, 2H), 7.50 (s, pyrazole H-3,5, 2H), 8.0 (m, phenyl H-2,6, 2H), 12.6 (s, broad, NH, 1H); ir: 1675 cm<sup>-1</sup> (C=O); ms: m/e 216 (M<sup>+</sup>, 4), 135 (100), 107 (11), 77 (17).

Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>·1/8 H<sub>2</sub>O: C, 65.97; H, 5.65; N, 12.82. Found: C, 66.02; H, 5.64; N, 12.76.

#### 1-Phenyl-2-(4-pyrazolyl)ethanol (**9**).

Compound **8a** (30 mg, 0.16 mmole) was reduced with sodium boro-

hydride in a manner similar to the preparation of **1b** and white needles (23 mg, 76%) from diisopropyl ether, mp 121-123° were obtained; <sup>1</sup>H-nmr (deuteriochloroform, 250 MHz): δ 2.74 (d, J = 7 Hz, CH<sub>2</sub>, 2H), 4.62 (dt, J = 5 Hz, J = 7 Hz, benzylic H, after deuterium oxide addition: t, J = 7 Hz, 1H), 5.25 (d, J = 5 Hz, OH, exchangeable with deuterium oxide, 1H), 7.3 (m, phenyl H, pyrazole H-3,5, 7H), 11.9 (s, broad, NH, exchangeable with deuterium oxide, 1H); electron impact ms: m/e 82 (100), 79 (24), 77 (20), 55 (51); chemical ionization ms (methane): m/e 189 (M<sup>+</sup> + H, 100), 171 (16).

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.29; H, 6.64; N, 14.81.

#### Oxidation of **8a** with Potassium Permanganate.

To a suspension of **8a** (80 mg, 0.43 mmole) in 1 ml of water a solution of potassium permanganate (158 mg, 1 mmole) in 4 ml water was added. The mixture was refluxed for 30 minutes until there was no more **8a** detectable by tlc (ethyl acetate). The hot reaction mixture was filtered and the filtrate was acidified with 2 N hydrochloric acid. After evaporation to dryness extraction with diethylether gave benzoic acid (31 mg, 59%), mp 122°. From the residue by extraction with 2-propanol under reflux followed by crystallisation from water pyrazole-4-carboxylic acid (26 mg, 54%), mp 175° dec, (lit mp 175° dec [14]) was obtained. The ir spectrum completely agreed with the ir spectrum of pyrazole-4-carboxylic acid prepared by oxidation of 4-methylpyrazole according to lit [14].

#### Reaction of **7** with *p*-Toluenesulfonic Acid/2-Dimethylaminoethanol.

Compound **7** (80 mg, 0.4 mmole) was reacted in a Kugelrohr apparatus with 2-dimethylaminoethanol (39 mg, 0.44 mmole) and *p*-toluenesulfonic acid monohydrate (91 mg, 0.48 mmole) for 2.5 hours at 180° *in vacuo* (10<sup>-2</sup> mbar). The residue consists of unconverted starting materials. The distillate obtained, was shown by <sup>1</sup>H-nmr spectrum (deuteriochloroform, 90 MHz) to contain **6** (8% yield, signals a) and 4-benzyl-5-methylpyridazine (8% yield, signals b): δ 2.25 (s, CH<sub>3</sub>, b), 2.39 (s, CH<sub>3</sub>, a), 4.00 (s, CH<sub>2</sub>, b), 7.2 (m, phenyl H, b), 7.7 (m, phenyl H, a), 8.91 (s, H-3 or H-6, b), 8.97 (s, H-3 or H-6, b), 9.08 (s, H-3 or H-6, a), 9.28 (s, H-3 or H-6, a).

#### Homolytic *p*-Methoxybenzylation of Pyridazine.

Pyridazine (800 mg, 10 mmoles) was treated with silver nitrate (510 mg, 3 mmoles) and 4-methoxyphenylacetic acid (8.3 g, 50 mmoles) in 10 ml 2 N sulfuric acid in a manner similar to a procedure described in lit [3]. After work up, unreacted pyridazine was distilled off (50°, 10<sup>-2</sup> mbar). The distillate obtained at 150° (10<sup>-2</sup> mbar) on medium pressure column chromatography using ethyl acetate as the eluent yielded from fraction I (4-methoxyphenyl)-4-pyridazinylmethanone (40 mg, 2%), mp 106-107° (lit mp 106-107° [6]) and from fraction II 4-(4-methoxybenzyl)pyridazine (420 mg, 21%).

#### 4-(4-Methoxybenzyl)pyridazine.

Obtained as white needles from ethyl acetate/light petroleum. mp 48°; <sup>1</sup>H-nmr (deuteriochloroform, 90 MHz): δ 3.75 (s, CH<sub>3</sub>, 3H), 3.90 (s, benzylic H, 2H), 6.9 (m, phenyl H-3,5, 2H), 7.1 (m, phenyl H-2,6, 2H), 7.3 (m, H-5, 1H), 9.1 (m, H-3,6, 2H); ms: m/e 200 (M<sup>+</sup>, 76), 141 (23), 121 (100), 77 (24), 57 (36).

*Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.07; H, 6.10; N, 13.95.

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