Formation of 2-Benzoyl-2,5-dihydro-3-pyridazinecarbonitrile Derivatives in the Reissert Reaction of Pyridazines

Dedicated to Prof. Dr. F. Vieböck on the occasion of his 85th anniversary

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Pyridazines **1a,b** on treatment with potassium cyanide/benzoyl chloride in a mixed solvent system gave 2-benzoyl-2,5-dihydro-3-pyridazinecarbonitriles **3a,b** together with products resulting from attack of one mole of cyanide ion and three moles of benzoyl chloride (**5a,b**). The structures of these novel compounds are proved. A plausible reaction mechanism is proposed, involving rearrangement of initially formed **2a,b** into **3a,b**. Furthermore, the synthesis of the pyridazine Reissert compound **2a** is reported.

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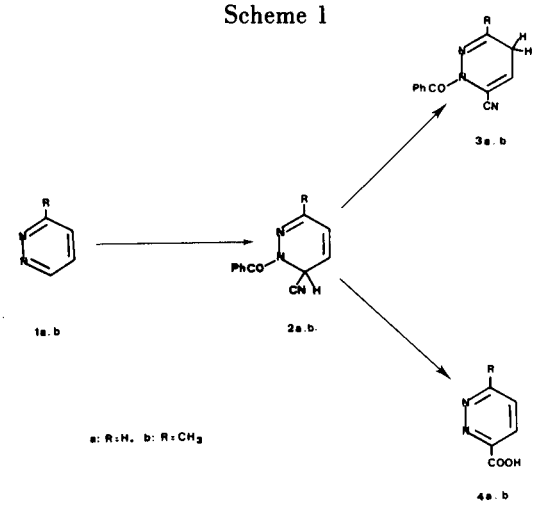
Reissert compounds of benzoannelated heteroaromatics have received much attention due to their synthetic value [2]. However, there are only few papers dealing with Reissert-type reactions of monocyclic heteroaromatics [2a, 2c,3,4,5,6]. The first examples of monocyclic Reissert compounds (derived from pyrimidine and 3-methylpyridazine) recently were reported by Popp *et al.* [5].

We now describe another so far unknown monocyclic Reissert compound, namely 2-benzoyl-2,3-dihydro-3-pyridazinecarbonitrile (**2a**). Furthermore, we wish to report on novel 2-benzoyl-2,5-dihydro-3-pyridazinecarbonitrile derivatives obtained from 3-methylpyridazine (**1b**) and pyridazine (**1a**), respectively.

Whereas **1b** on reaction with trimethylsilyl cyanide/freshly distilled benzoyl chloride gives the normal Reissert compound **2b** [5], a compound mp 109-111° was isolated chromatographically when **1b** was treated with potassium cyanide and benzoyl chloride in a water/methylene chloride mixture according to a procedure reported in the literature [7]. Elemental analysis and ms molecular weight determination did show this compound to be a *N*-benzoylmethyldihydropyridazinecarbonitrile, but the ir spectrum significantly differs from that of **2b** [8]. As tlc on silica gel (ethyl acetate/light petroleum) indicates also the presence of **2b** in the reaction mixture, isomerisation of initially formed **2b** seemed to be a reasonable assumption. Actually, **2b** was found partly to be transformed into the novel compound simply on standing in methylene chloride solution for prolonged time. This rearrangement could also be observed in the course of tlc examinations of **2b** on silica gel; at attempted column chromatography, **2b** was found to be rearranged quantitatively. Together with the finding that **2b** on treatment with hydrobromic acid/glacial acetic acid is degradated to 6-methyl-3-pyridazinecarboxylic acid **4b** [9], which supports the structure proposed in literature [5], the ^{1}H-nmr spectrum of **3b**, exhibiting a two poton doublet at 3.0 ppm and a one proton triplet at 6.2 ppm (J = 4.5 Hz), permits unequivocal differentiation between the nineteen theoretically possible isomers and assignment of the structure **3b** (2-benzoyl-2,5-dihydro-6-methyl-3-pyridazinecarbonitrile). This proposal further is supported by investigation of other products discussed below, which were obtained in Reissert reactions of **1a** and **1b** employing the mixed solvent system method.

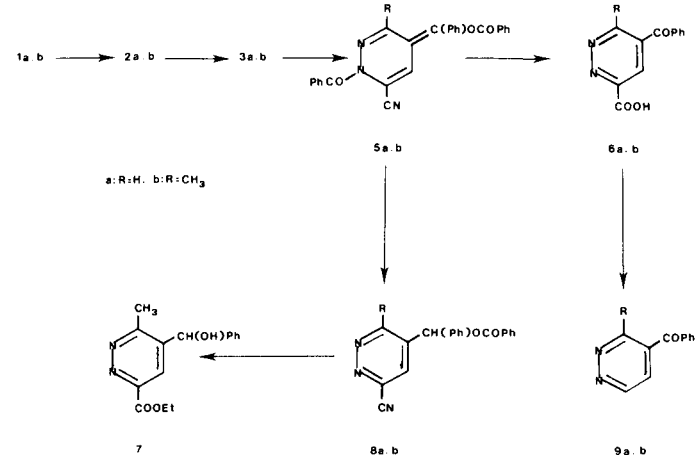
The Reissert salt of pyridazine was obtained recently by Popp *et al.* [5] by application of the trimethylsilyl cyanide method using undistilled benzoyl chloride. We now could prepare the pyridazine Reissert compound **2a** in 24% yield by employing freshly distilled benzoyl chloride in this procedure. The structure proof rests on spectral data as well as on degradation to the known 3-pyridazinecarboxylic acid **4a** [10]. Like observed on **2b**, also **2a** shows a high tendency to isomerize, yielding **3a**. It is of interest to note, that the ir spectra of **3a** and **3b** exhibit significant absorption bands at 2235 cm^{-1} attributable to ν C≡N vibrations, whereas in the spectra of **2a** and **2b** [8] no signals appear in this region. In accordance with the results of the Reissert-type reaction of **1b** carried out in water/methylene chloride, **1a** under these conditions afforded **3a** in about 12% yield.

Scheme 1



In addition to the rearranged Reissert compounds **3a,b**, both reaction mixtures gave products which, considering elemental compositions and molecular weights, obviously resulted by attack of one mole of cyanide ion and three moles of benzoyl chloride. According to the spectral data and the results of degradation experiments described below, the structures of these novel compounds are to be formulated as *E,Z*-2-benzoyl-5-(benzoyloxy)phenylmethylene-2,5-dihydro-3-pyridazinecarbonitriles **5a,b**.

Scheme 2



The ir spectrum of each compound is characterized by a ν C≡N signal (**5a**: 2235 cm^{-1}, **5b**: 2230 cm − 1) and two absorption bands in the ν C≡N region giving indication for the presence of an ester group as well as of a carboxamide function. Since no definitive conclusion with respect to the positions of the substituents could be drawn from the ^{1}H-nmr spectra, hydrolysis reactions of **5a** and **5b** were investigated. Stirring **5a** or **5b** in 5*N* aqueous potassium hydroxide/methylene chloride in presence of benzyltriethylammonium chloride at room temperature for several hours resulted in hydrolytic cleavage of the C_6H_5CO-N-bonds as shown by the ir specta of compounds **8a,b** obtained. Subsequently, another benzoyl group was removed by treating **8b** with ethanolic potassium hydroxide solution at room temperature. Under these mild conditions, also the nitrile group was converted into an ester function as indicated by spectral data of the resulting compound **7**. The ^{1}H-nmr spectrum unambiguously shows a phenyl pyridazinylmethanol moiety being present. A one proton singlet at 8.5 ppm in the spectrum of **7** as well as a one proton singlet at 8.0 ppm in the spectrum of **8b** indicate that both α-positions are occupied by substituents in these compounds. However, these data do not permit discrimination between the isomeric structures to be taken into consideration.

From reports in the literature it is well known, that pyridazine carboxylic acids easily can be decarboxylated [11]. This prompted us to react **5a** and **5b** with concentrated hydrobromic acid/glacial acetic acid [12], anticipating that under these conditions ester hydrolysis should take place; the resulting compounds then were expected to undergo transformation into pyridazine carboxylic acids in analogy to a mechanism proposed for hydrolysis of Reissert compounds [3]. Actually, **5a** yielded a *C*-benzoylpyridazine carboxylic acid (**6a**), which, when heated *in vacuo* above 150°, was converted quantitatively into the known 4-benzoylpyridazine **9a** [13]. Similarly, **5b** could be converted to 4-benzoyl-3-methylpyridazine (**9b**) *via* the ketocarboxylic acid **6b**. The structure of the final product of this reaction sequence was easily established on the basis of the ^{1}H-nmr spectrum, exhibiting doublets at 9.3 ppm and 7.4 ppm, respectively, (J = 5 Hz), along with analytical data. Compound **6b** was also obtained after refluxing **8b** in aqueous/ethanolic potassium hydroxide solution, obviously by oxidation of the intermediate alcohol during work-up. These experiments together with spectroscopic data (see experimental) can be seen to be an unequivocal proof for the structures of compounds **5a,b**, **6a,b**, **7**, **8a** and **8b**.

On basis of these findings it becomes obvious the first reaction step in the formation of **5a** and **5b** is migration of the C-4/C-5 double bonds in the initially formed Reissert compounds **2a,b** [14], leading to 2,5-dihydropyridazine derivatives. Attack of benzoyl chloride at the activated methylene group of compounds **3a** and **3b**, respectively, then would afford phenyl dihydropyridazinylketones, which are anticipated to be in equilibrium with fully conjugated enoles. Esterification of the latter by excess acid chloride would finally give **5a** and **5b**, respectively. In fact, this assumption could be proved by converting **3a** into **5a** with benzoyl chloride in aqueous potassium cyanide/methylene chloride.

Further reactions of pyridazine Reissert compounds with respect to the synthesis of potentially bioactive substances are under investigation.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. The ir spectra were recorded on a Jasco IRA-1 spectrometer. The ^{1}H-nmr spectra were obtained on a Varian EM 390 (90 MHz). Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV using a Varian MAT CH-7. 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. 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.

Reaction of **1a** and **1b** with Potassium Cyanide/Benzoyl Chloride.

To a stirred mixture of 0.05 moles (4.00 g) pyridazine **1a** or 0.05 moles (4.70 g) 3-methylpyridazine **1b**, respectively, in 30 ml methylene chloride and 0.25 moles (16.30 g) of potassium cyanide in 20 ml water was added under nitrogen a solution of 0.25 moles (35.14 g) benzoyl chloride in 10 ml anhydrous methylene chloride within three hours. The reaction mixture was stirred at room temperature for another 48 hours and then extracted with methylene chloride. The combined extracts were dried over

anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue yielded 1.10 g (5.3%) of **5a** or 3.50 g (16%) of **5b**, respectively, as yellow crystals, when treated with ethanol. Column chromatography of the mother liquors on silica gel (ethyl acetate/light petroleum 1:1) additionally yielded 1.16 g (5.5%) of **5a** or 0.92 g (4.3%) of **5b**, respectively.

Furthermore, 1.24 g (12%) of **3a** or 3.05 g (27%) of **3b**, respectively, were obtained as amorphous solids.

Compound **5a** (analytical sample obtained by recrystallisation from ethanol/water): mp 199-201°; ir (potassium bromide): 2235 cm^{-1} (C≡N), 1745 (C=O, ester), 1685 (C=O, amide); nmr (deuteriochloroform): δ 8.4-7.3 (m, phenyl-H, 15 H), 7.8 (d, pyridazine-H-6, 1H, $J_{4,6}$ = 3.0 Hz), 7.0 (d, pyridazine-H-4, 1H); ms: 419 (M^+, 2), 105 (100).

Anal. Calcd. for $C_{26}H_{17}N_3O_3$: C, 74.5; H, 4.1; N, 10.0. Found: C, 74.2; H, 4.2; N, 10.3.

Compound **5b** (analytical sample was obtained by recrystallisation from ethanol/water), mp 187-189°; ir (potassium bromide): 2230 cm^{-1} (C≡N), 1735 (C=O, ester); 1665 (C=O, amide); nmr (deuteriochloroform): δ 8.3-7.3 (m, phenyl-H, 15H), 6.9 (s, pyridazine-H-4, 1H), 2.2 (s, CH_3, 3H); ms: 433 (M^+, 1), 105 (100).

Anal. Calcd. for $C_{27}H_{19}N_3O_3$: C, 74.8; H, 4.4; N, 9.7. Found: C, 74.6; H, 4.5; N, 9.7.

Compound **3a** (tan crystals were obtained by recrystallisation from ethyl acetate/light petroleum), mp 82-84°; ir (potassium bromide): 2235 cm^{-1} (C≡N), 1660 (C=O); nmr (deuteriochloroform): δ 8.0-7.3 (m, phenyl-H, 5H), 7.0-6.9 (m, pyridazine-H-6, 1H), 6.2-5.8 (m, pyridazine-H-4, 1H), 3.2-3.0 (m, pyridazine-H-5, 2H); ms: 211 (M^+, 4), 105 (100).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.2; H, 4.3; N, 19.9. Found: C, 68.0; H, 4.6; N, 19.6.

Compound **3b** (tan crystals were obtained by recrystallisation from light petroleum), mp 109-111°; ir (potassium bromide): 2235 cm^{-1} (C≡N), 1655 (C=O); nmr (deuteriochloroform): δ 8.0-7.3 (m, phenyl-H, 5H), 6.2 (t, pyridazine-H-4, 1H, $J_{4,5}$ = 4.5 Hz), 3.0 (d, pyridazine-H-5, 2H), 2.0 (s, CH_3, 3H); ms: 225 (M^+, 5), 105 (100).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.3; H, 4.9; N, 18.7. Found: C, 69.1; H, 5.0; N, 18.4.

2-Benzoyl-2,3-dihydro-3-pyridazinecarbonitrile (**2a**).

A solution of 1.70 g (21 mmoles) of **1a** in 20 ml of anhydrous methylene chloride was treated with 5.25 g (53 mmoles) trimethylsilyl cyanide and 7.42 g (53 mmoles) benzoyl chloride following the procedure reported in lit [5]. After work-up, 1.06 g (24%) of a brown solid was obtained, yellow crystals (from ethanol), mp 94-100°; ir (potassium bromide): 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.9-7.4 (m, phenyl-H, 5H), 7.3-7.2 (m, pyridazine-H-6, 1H), 6.4-6.0 (m, pyridazine-H-5, H-4, H-3, 3H); ms: 211 (M^+, 1), 105 (100).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.2; H, 4.3; N, 19.9. Found: C, 68.2; H, 4.3; N, 19.7.

2-Benzoyl-2,5-dihydro-3-pyridazinecarbonitriles **3a,b** by Rearrangement of **2a,b**.

Compounds **2a,2b** (1 mmole) were subjected to medium pressure column chromatography [silica gel, ethyl acetate/light petroleum (3:7)]. The residues obtained by evaporation of the eluates were crystallized, yielding 129 mg (60%) **3a** or 203 mg (90%) **3b**, respectively. By mp and ir data, the products were shown to be identical with compounds **3a** or **3b**, respectively, obtained from **1a** or **1b**, respectively.

Conversion of **3a** into **5a**.

To a stirred mixture of 211 mg (1 mmole) of **3a** in 10 ml of methylene chloride and 260 mg (4 mmoles) of potassium cyanide in 4 ml of water containing 5 mg (0.02 mmole) of benzyltriethylammonium chloride a solution of 560 mg (4 mmoles) of benzoyl chloride in 10 ml of dry methylene chloride was added within 4 hours. After stirring for another 48 hours, the mixture was extracted with methylene chloride. The organic layer was extracted with saturated aqueous sodium hydrogencarbonate solution in order to remove benzoic acid and then evaporated to dryness. Medium pressure column chromatography [silica gel, ethyl acetate/light petroleum (2:8)] yielded 32 mg (15%) of a product shown to be identical with **5a** obtained from **1a** as described above.

Degradation of **2a,b** to **4a,b**.

A mixture of 211 mg (1 mmole) of **2a** or 225 mg (1 mmole) of **2b**, respectively, 1 ml of glacial acetic acid and 1 ml of concentrated hydrobromic acid was refluxed for 15 minutes. After concentrating the mixture *in vacuo* and addition of 20 ml of water, by-products were extracted wtih methylene chloride. The aqueous layers, after treatment with Norite, were adjusted to *p*H 3 with concentrated ammonia.

Compound **4a** was obtained as colourless crystals by concentrating the solution and recrystallizing the precipitate from water, yield 30 mg (24%), mp 202-203° (lit [10], mp 200-201°). Identity with an authentic sample of pyridazine-3-carboxylic acid was proved by the ir and the ^1H-nmr spectroscopic data.

Compound **4b** was obtained as an impure amorphous solid by concentrating the aqueous solution. It was characterized by transformation into its methyl ester.

Esterification of **4b**.

The aqueous solution of **4b** obtained as described above was treated with ethereal diazomethane solution in the usual manner. After removal of the diethyl ether *in vacuo*, the aqueous layer was repeatedly extracted with ethyl acetate/methanol (9:1). The combined organic layers were filtered over a short column of silica gel and the solvent was removed *in vacuo*. Kugelrohr distillation (90°, 4 × 10^{-2} mbar) yielded 40 mg (26%) of a colourless oil; ir (methylene chloride): 1725 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.1 (d, pyridazine-H-4, 1H, $J_{4,5}$ = 9.0 Hz), 7.5 (d, pyridazine-H-5, 1H), 4.1 (s, OCH_3, 3H), 2.8 (s, CH_3, 3H); high resolution ms calcd. for $C_7H_8N_2O_2$: 152.059; found M^+ = 152.059.

5-(Benzoyloxy)phenylmethyl-3-pyridazinecarbonitriles **8a,8b**.

A solution of 419 mg (1 mmole) of **5a** or 433 mg (1 mmole) of **5b**, respectively, in a mixture of 10 ml of methylene chloride and 10 ml of 5*N* aqueous potassium hydroxide containing 50 mg (0.2 mmoles) of benzyltriethylammonium chloride was stirred for 20 hours. The organic layers were filtered over a short column of silica gel. After evaporation of the solvent *in vacuo*, 80 mg (25%) of **8a** or 320 mg (97%) of **8b**, respectively, were obtained.

Compound **8a** (analytical sample was obtained by recrystallisation from ethyl acetate/light petroleum): colourless crystals, mp 119-121°; ir (potassium bromide): 1720 cm^{-1} (C=O); nmr (deuteriochloroform): δ 9.5 (d, pyridazine-H-6, 1H, $J_{4,6}$ = 2.3 Hz), 8.3-8.1 (m, phenyl-H, 2H), 7.8 (d, pyridazine-H-4, 1H), 7.7-7.3 (m, phenyl-H, 8H), 7.1 (s, OCH, 1H); ms: 315 (M^+, 3), 105 (84), 73 (100).

Anal. Calcd. for $C_{19}H_{13}N_3O_2$: C, 72.4; H, 4.2; N, 13.3. Found: C, 72.3; H, 4.3; N, 13.1.

Compound **8b** (analytical sample was obtained by recrystallisation from ethyl acetate/light petroleum), colourless crystals, mp 127-129°; ir (potassium bromide): 2255 cm^{-1} (C≡N), 1735 (C=O); nmr (deuteriochloroform): δ 8.3-8.1 (m, phenyl-H, 2H), 8.0 (s, pyridazine-H-4, 1H), 7.7-7.3 (m, phenyl-H, 8H), 7.2 (s, OCH, 1H), 2.9 (s, CH_3, 3H); ms: 329 (M^+, 8), 105 (100).

Anal. Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.9; H, 4.6; N, 12.8. Found: C, 73.0; H, 4.7; N, 12.8.

Ethyl 6-Methyl-5-(phenyl)hydroxymethyl-3-pyridazinecarboxylate (**7**).

A solution of 329 mg (1 mmole) of **8b** in 15 ml 5% ethanolic potassium hydroxide was stirred at room temperature for 90 minutes. After adjusting the solution to *p*H 7 with 2*N* hydrochloric acid and removing the ethanol *in vacuo*, the mixture was extracted repeatedly with methylene chloride. The organic layers were dried over anhydrous sodium sulfate and evaporated to dryness. The resulting solid was recrystallized from diethyl ether/light petroleum, yielding 115 mg (42%) of colourless crystals, mp 97-99°; ir (potassium bromide): 3240 cm^{-1} (OH), 1735 (C=O), 1270 (C-O); nmr (deuteriochloroform): δ 8.5 (s, pyridazine-H-4, 1H), 7.5-7.2 (m, phenyl-H, 5H), 6.0 (d, OCH, 1H, $J_{OCH,OH}$ = 3.6 Hz), 4.5 (q, CH_2, 2H, J_{CH_2,CH_3} = 7.5 Hz), 4.0 (d, OH, 1H), 2.6 (s, CCH_3, 3H), 1.5 (t, CH_2CH_3, 3H); ms: 272 (M^+, 8), 228 (16), 200 (100).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.2; H, 5.9; N, 10.3. Found: C, 66.3;

H, 6.0; N, 10.2.

5-Benzoyl-3-pyridazinecarboxylic Acid (**6a**·H_2O).

A solution of 420 mg (1 mmole) of **5a** in 4 ml of glacial acetic acid and 4 ml of concentrated hydrobromic acid was refluxed for 20 minutes and then concentrated to a volume of one ml *in vacuo*. In order to remove coloured by-products and benzoic acid, the solution was extracted with methylene chloride (at *p*H 8) and diethyl ether (at *p*H 3). Subsequent extraction at *p*H 1 with methylene chloride, followed by drying of the organic layer with sodium sulfate and removal of the solvent yielded, after crystallisation from ethanol/diethyl ether, 145 mg (59%) of colourless crystals, mp 89-90°; ir (potassium bromide): 1690 cm^{-1} (C=O, acid), 1665 (C=O, ketone); nmr (dimethylsulfoxide-d_6): δ 9.7 (d, pyridazine-H-6, 1H, $J_{4,6}$ = 2.3 Hz), 8.3 (d, pyridazine-H-4, 1H), 8.0-7.5 (m, phenyl-H, 5H), 5.0-2.8 (OH); ms: 228 (9), 105 (100).

Anal. Calcd. for $C_{12}H_8N_2O_3 \cdot H_2O$: C, 58.5; H, 4.1; N, 11.4. Found: C, 58.4; H, 4.3; N, 11.2.

5-Benzoyl-6-methyl-3-pyridazinecarboxylic Acid (**6b**).

a) Compound **5b** (433 mg, 1 mmole) was treated with glacial acetic acid/concentrated hydrobromic acid as described above, yielding 150 mg (62%) of colourless crystals, mp 136-141° (diethyl ether/light petroleum); ir (potassium bromide): 1745 cm^{-1} (C=O, acid), 1670 (C=O, ketone); nmr (deuteriochloroform): δ 9.5 (s, OH, 1H), 8.2 (s, broad, pyridazine-H-4, 1H), 7.9-7.3 (m, phenyl-H, 5H), 2.8 (s, CH_3, 3H); ms: 242 (M^+, 25), 105 (100).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.4; H, 4.2; N, 11.6. Found: C, 64.3; H, 4.4; N, 11.5.

b) A mixture of 329 mg (1 mmole) of **8b** in 20 ml of ethanol and 10 ml of 5% aqueous sodium hydroxide was refluxed for two hours. Ethanol was removed *in vacuo* and the remaining solution was adjusted to *p*H 1 with 2*N* hydrochloric acid. After repeated extraction with methylene chloride, the combined organic layers were dried over anhydrous sodium sulfate and evaporated. Benzoic acid was removed by heating the residue in a Kugelrohr apparatus (75°, 8 × 10^{-3} mbar) for 5 hours. The residue was crystallized from diethyl ether/light petroleum, yielding 82 mg (34%) of a compound shown to be identical with **6b** (prepared as described above) by mp, ir and nmr spectroscopic data.

Decarboxylation of **6a**.

Compound **6a**·H_2O (25 mg, 0.1 mmole) was distilled in a Kugelrohr apparatus (150°, 3 × 10^{-2} mbar) for three hours, yielding 17 mg (90%) of **9a**, mp 107-108° (lit [13], mp 106-108°). The product was shown to be identical with an authentic sample by ir and nmr spectroscopic data.

4-Benzoyl-3-methylpyridazine (**9b**).

Compound **6b** (121 mg, 0.5 mmole) was distilled in a Kugelrohr apparatus (170°, 2 × 10^{-1} mbar) for one hour, yielding 74 mg (77%) of **9b** as a yellow oil; ir (methylene chloride): 1665 cm^{-1} (C=O); nmr (deuteriochloroform): δ 9.3 (d, pyridazine-H-6, 1H, $J_{5,6}$ = 5.0 Hz), 8.0-7.5 (m, phenyl-H, 5H), 7.4 (d, pyridazine-H-5, 1H), 2.7 (s, CH_2, 3H); ms: 198 (M^+, 29), 105 (100).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.7; H, 5.2; N, 14.0.

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