PYRIDAZINES, 69.[1] 2-FLUOROPHENYL 3-PYRIDAZINYL KETONE AS A VERSATILE PRECURSOR FOR BENZO-ANNELATED HETEROCYCLIC SYSTEMS

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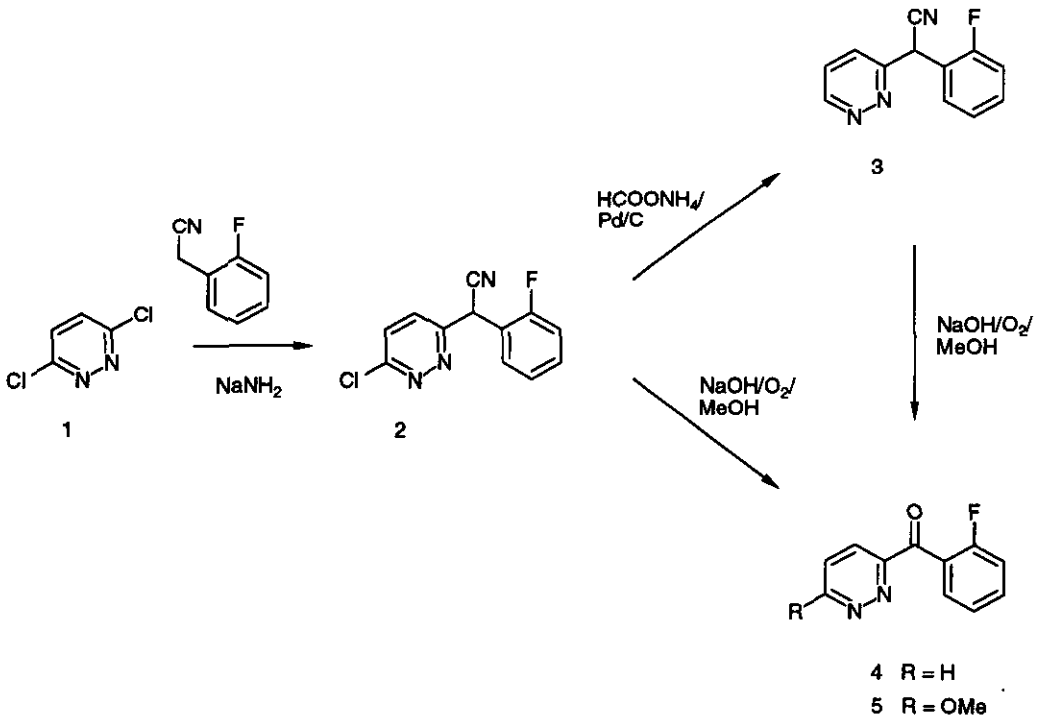
Abstract - The fluorophenyl pyridazinyl ketone (**4**), conveniently prepared from 3,6-dichloropyridazine, was shown to be a valuable precursor for so far not accessible pyridazinyl-substituted benzo-annelated five-, six-, or seven-membered heterocycles (**9**, **11**, **6a, b**) and for the two novel diazaacridones (**12**) and (**13**).

In continuation of an ongoing program aimed at the synthesis of bi- and tricyclic systems starting from functionalized aryl pyridazinyl ketones,[2] we here report on an efficient pathway to 2-fluorophenyl 3-pyridazinyl ketone (**4**) and on the exploitation of this novel bifunctional building block for the construction of a variety of pyridazinyl-substituted as well as pyridazine-fused heterocyclic ring systems.

Based on a previously published procedure[3] permitting convenient access to phenyl 3-pyridazinyl ketone, the 2-fluorophenyl-3-pyridazinylmethane derivatives (**2-5**) were prepared starting from commercially available 3,6-dichloropyridazine (**1**). Thus, **1** was reacted with the sodium salt of 2-fluorophenylacetonitrile to give the nitrile (**2**). Catalytic transfer hydrogenation employing ammonium formate as the hydrogen source[4] was found to permit reductive dechlorination without concomitant affection of the nitrile function.[5] Compound (**3**), obtained in 55% overall yield, then smoothly underwent oxidative decyanation[6] in methanolic sodium

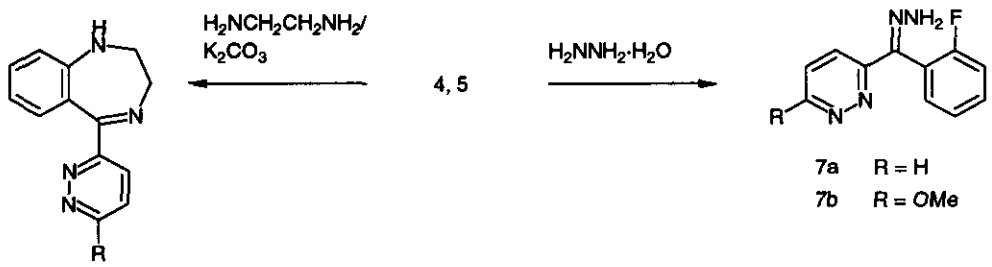
hydroxide to give the title ketone (**4**). Applying this oxidation procedure to the chloro-substituted nitrile (**2**) was found not only to generate the carbonyl function, but also to result in nucleophilic displacement of the chloro substituent by a methoxy group to afford compound (**5**).

Scheme 1



Preparation of compounds (**6a, b**), being of pharmaceutical interest as novel representatives of heteroaryl-substituted 1,4-benzodiazepines, could be achieved by reacting the fluoro ketones (**4, 5**) with ethylenediamine. Treatment of these ketones with hydrazine hydrate resulted in the formation of the hydrazones[7] (**7a, b**) which, however, were found to withstand ring-closure to the corresponding indazoles (by intramolecular fluorine substitution) even under drastic conditions.[8]

Scheme 2



6a R = H
6b R = OMe

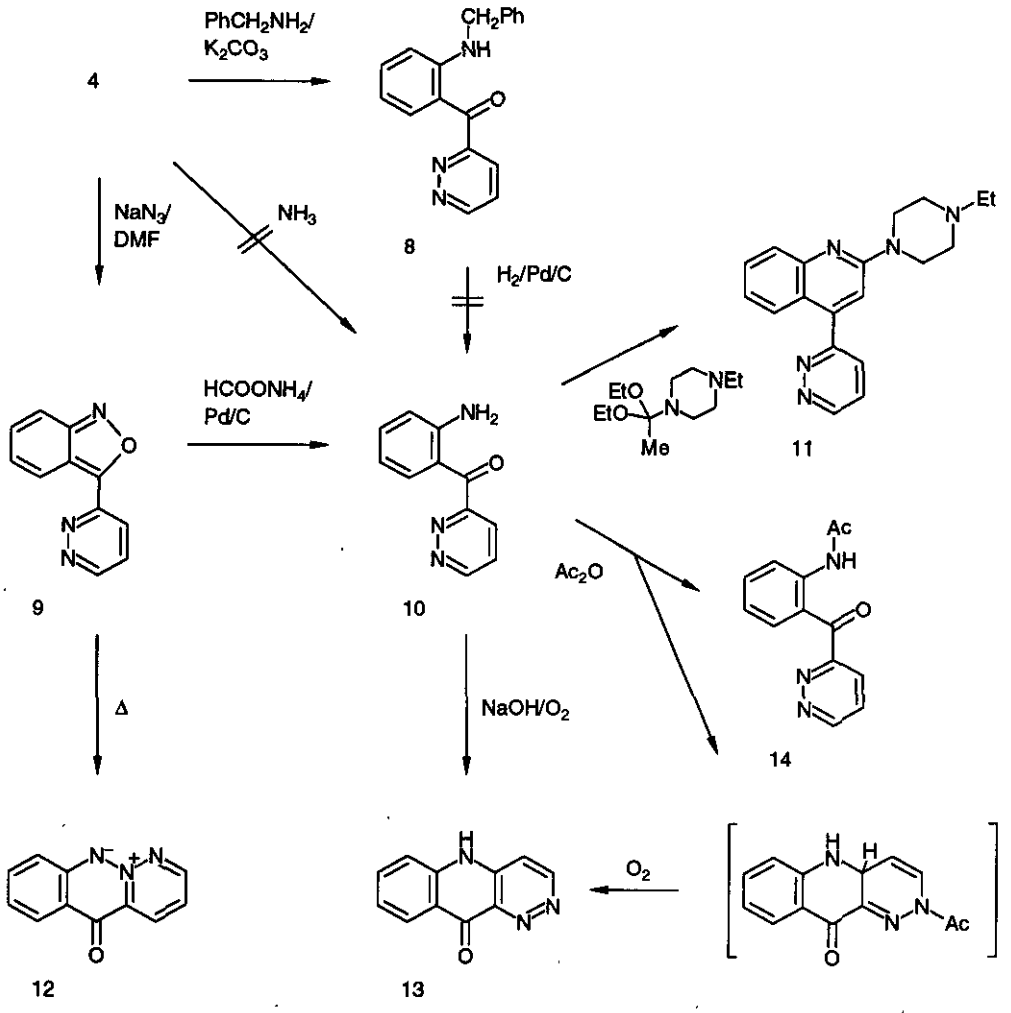
7a R = H
7b R = OMe

Similar to previous observations with 2-fluorophenyl 4-pyridazinyl ketone,[9] treatment of the *o*-fluoro ketone (**4**) with sodium azide in refluxing dimethylformamide permits preparation of the pyridazinyl-substituted 2,1-benzisoxazole (**9**) *via* an intermediate azido compound, probably by an intramolecular 1,3-dipolar cycloaddition mechanism.[10] The anthranil (**9**) thus obtained in high yield proved to be a valuable precursor for 2-aminophenyl 3-pyridazinyl ketone (compound **10**) which represents a pyridazine analogue of 2-aminobenzophenone. It should be noted that this bifunctional building block[11] is neither accessible directly from the fluoro ketone (**4**) (by reaction with ammonia) nor by hydrogenolytic debenzylation (Pd/C) of the easily available benzylamino ketone (**8**). The synthesis of compound (**10**) now was accomplished by reductive opening (catalytic transfer hydrogenation;[4] ammonium formate, Pd/C) of the isoxazole ring in **9**.

The synthetic utility of the amino ketone (**10**) could be demonstrated by its convenient conversion into the quinoline derivative (**11**) which was considered an interesting target compound in view of the recently reported anti-ulcer activity of 4-aryl-substituted 2-piperazinylquinolines.[12] Moreover, intramolecular S_N^H reaction of **10** was found to represent an efficient route to the novel diazaacridone (**13**):[13] refluxing of **10** in aqueous sodium hydroxide (air oxygen as the oxidant) gives **13** in almost quantitative yield.

A first hint for the susceptibility of pyridazine C-4 in compound (**10**) towards attack of the amino function was given on attempted preparation of the amide (**14**). Along with a 58% yield of **14**, the tricyclic compound (**13**) was isolated as a side product (25% yield). Formation of the latter under these conditions has to be interpreted in terms of nucleophilic attack of the amino function to an initially formed *N*-1-acetylated pyridazinium species, oxidation by air oxygen and subsequent loss of the acetyl moiety. It is of interest to note that in the case of the isomeric 2-aminophenyl 4-pyridazinyl ketone, an intermediate *N*-acetyldihydrodiazaacridone had been isolated.[9,14]

Scheme 3



Prompted by previous observations of intramolecular N-N bond formation on pyrolysis of 2-pyridyl-substituted 2,1-benzisoxazoles,[15] we finally could elaborate an effective synthesis of the mesoionic tricyclic compound (**12**) (an isomer of the diazaacridone **13**), which represents a hitherto unknown ring system: refluxing of the anthranil (**9**) in 1,2,4-trichlorobenzene gave a 75% yield of the inner salt (**12**) which was fully characterized by elemental analysis, ms, ir, ^{1}H-nmr and ^{13}C-nmr data (see Experimental).

In summary, the fluorophenyl pyridazinyl ketone (**4**) proved to be a precursor for so far not accessible pyridazinyl-substituted derivatives of 2,1-benzisoxazole, quinoline, and 1,4-benzodiazepine. Moreover, compound (**4**) provides convenient access to the two diazaacridones (**12**) and (**13**).

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage microscope and are uncorrected. Ir spectra were recorded for KBr pellets on a Jasco IRA-1 and on a Perkin Elmer 1605 FT-IR spectrophotometer; ^{1}H-nmr spectra were recorded on a Varian EM 390 (90 MHz), a Bruker AC 80 (80 MHz), or a Bruker AM 400 (400 MHz) spectrometer with TMS as internal reference (chemical shifts in δ ppm), the ^{13}C-nmr spectrum was recorded on the Bruker AM 400 instrument. Mass spectra were obtained on a Hewlett-Packard 5890A/5970B GC/MSD or on a Shimadzu GC/MS-QP 1000 instrument. Column chromatography was carried out on Merck Kieselgel 60, 0.063-0.200 mm. Microanalyses were performed by Mag. J. Theiner, Institute of Physical Chemistry, University of Vienna.

2-(2-Fluorophenyl)-2-(6-chloro-3-pyridazinyl)acetonitrile (**2**)

To a solution of 2-fluorophenylacetonitrile (20.27 g, 150 mmol) in 500 ml of toluene (dried over molecular sieve, 4Å), sodium amide (11.7 g, 300 mmol) was added at 0°C. After stirring for 10 min, 3,6-dichloro-pyridazine (22.35 g, 150 mmol) was added in small portions, the ice bath was removed, and stirring was continued for 3 h. After cooling, the mixture was neutralized with 2 *N* H_2SO_4 and extracted exhaustively with toluene. The organic layer was dried (Na_2SO_4), concentrated *in vacuo* and the residue was subjected to flash chromatography (dichloromethane) to give 26.0 g (70%) of a yellow oil, which was used without purification for further reactions. A sample of the product was recrystallized from ethanol to afford colorless needles, mp 67-69°C. *Anal.* Calcd for $C_{12}H_7N_3ClF$: C, 58.20; H, 2.85; N, 16.97. Found: C, 58.05; H, 2.82; N, 16.85. Ms: *m/z* (rel. int.) 247/249 (54/17%, M^+), 228/230 (100/35), 211 (10), 158 (12), 134 (10), 107 (13). Ir (cm^{-1}): 2240 (CN). ^{1}H-Nmr ($CDCl_3$) δ: 5.80 (s, 1 H, PhCH), 6.9-7.8 (m, 6 H, H-4, H-5, C_6H_4).

2-(2-Fluorophenyl)-2-(3-pyridazinyl)acetonitrile (**3**)

A mixture of **2** (9.90 g, 40 mmol), ammonium formate (7.56 g, 120 mmol) and Pd/C (10%; 1.25 g) in methanol (250 ml) was stirred under an atmosphere of argon at 40°C. Additional portions of ammonium formate were added until the starting material was completely consumed (tlc monitoring; ethyl acetate). After removal of the catalyst and evaporation of the solvent, the residue thus obtained was partitioned between dichloromethane and water. The organic layer was dried (Na_2SO_4) and evaporated. Recrystallisation from ethanol gave 6.84 g (77%) of **3** as colorless crystals, mp 91-92°C. *Anal.* Calcd for $C_{12}H_8N_3F$: C, 67.60; H, 3.78; N, 19.71. Found: C, 67.53; H, 3.65; N, 19.78. Ms: *m/z* (rel. int.) 213 (45%, M^+), 212 (36), 194 (100), 158 (10), 107 (11). Ir (cm^{-1}): 2240 (CN). ^{1}H-Nmr ($CDCl_3$) δ: 5.85 (s, 1 H, PhCH), 7.0-7.9 (m, 6 H, H-4, H-5, C_6H_4), 9.20 (dd, J_{4-6} = 2 Hz, J_{5-6} = 5 Hz, 1 H, H-6).

General Procedure for the Preparation of the Ketones (**4**) and (**5**)

To a solution of **3** (5.3 g, 25 mmol) or **2** (6.2 g, 25 mmol), respectively, and benzyltriethylammonium chloride (450 mg, 2 mmol) in 150 ml of methanol, 5 ml of 30% aqueous NaOH were added dropwise. The solution was stirred vigorously at room temperature, while a stream of air was bubbled through, until the starting material was completely consumed (tlc monitoring; light petroleum/ethyl acetate, 1:1). Water (150 ml) was added, and the mixture was extracted exhaustively with dichloromethane. The extract was dried (Na_2SO_4) and evaporated to give a dark residue.

2-Fluorophenyl 3-Pyridazinyl Ketone (**4**)

The oily residue obtained as described above was purified by flash chromatography (light petroleum/ethyl acetate, 1:1) to give 3.8 g (75%) of **4** as colorless crystals, mp 79-80°C (ethanol/water). *Anal.* Calcd for $C_{11}H_7N_2OF$: C, 65.35; H, 3.49; N, 13.86. Found: C, 65.37; H, 3.52; N, 13.94. Ms: *m/z* (rel. int.) 202 (46%, M^+), 174 (66), 123 (100), 95 (51), 75 (30). Ir (cm^{-1}): 1660 (CO). ^{1}H-Nmr ($CDCl_3$) δ: 7.1-8.0 (m, 5 H, H-5, C_6H_4), 8.20 (dd, J_{4-5} = 8 Hz, J_{4-6} = 2 Hz, 1 H, H-4), 9.40 (dd, J_{4-6} = 2 Hz, J_{5-6} = 5 Hz, 1 H, H-6).

2-Fluorophenyl 6-Methoxy-3-pyridazinyl Ketone (**5**)

Water (100 ml) was added to the solid residue obtained as described above, the precipitate was collected and washed with water. Yield: 4.4 g (76%) of colorless needles, mp 106-107°C (ethanol/water). *Anal.* Calcd for $C_{12}H_9N_2O_2F$: C, 62.07; H, 3.91; N, 12.06. Found: C, 62.27; H, 4.00; N, 11.99. Ms: *m/z* (rel. int.) 232 (52%, M^+), 204 (31), 189 (61), 123 (100), 95 (54), 75 (25). Ir (cm^{-1}): 1660 (CO). ^{1}H-Nmr ($CDCl_3$) δ: 4.25 (s, 3 H, CH_3), 7.0-7.9 (m, 5 H, H-5, C_6H_4), 8.15 (d, J = 9 Hz, 1 H, H-4).

General Procedure for the Preparation of the 1,4-Benzodiazepines (**6a**) and (**6b**)

A mixture of the appropriate 2-fluorophenyl 3-pyridazinyl ketone (**4** or **5**, respectively, 1 mmol), ethylenediamine (600 mg, 10 mmol), and K_2CO_3 (138 mg, 1 mmol) in toluene (15 ml) was refluxed for 24 h. After cooling, the mixture was extracted with 2 *N* HCl; the aqueous layer was made alkaline (pH = 8) with 2 *N* NaOH and was extracted exhaustively with dichloromethane. The extract was washed with water, dried (Na_2SO_4) and evaporated.

2,3-Dihydro-5-(3-pyridazinyl)-1*H*-1,4-benzodiazepine (**6a**)

Purification by column chromatography (ethyl acetate/methanol, 4:1) afforded 170 mg (75%) of **6a** as yellow crystals, mp 125-126°C (ethyl acetate/charcoal). *Anal.* Calcd for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.98. Found: C, 69.79; H, 5.33; N, 24.94. Ms: *m/z* (rel. int.) 224 (100%, M^+), 223 (82), 196 (49), 169 (21), 168 (23), 140 (10), 117 (13), 115 (11), 77 (10). Ir (cm^{-1}): 3600-3000 (br, NH). ^{1}H-Nmr ($CDCl_3$) δ: 3.7-3.9 (m, 2

H, CH_2), 4.1-4.2 (m, 2 H, CH_2), 4.2-4.5 (br m, 1 H, NH), 6.5-7.4 (m, 4 H, C_6H_4), 7.55 (dd, J_{4-5} = 9 Hz, J_{5-6} = 5 Hz, 1 H, H-5), 7.95 (dd, J_{4-5} = 9 Hz, J_{4-6} = 2 Hz, 1 H, H-4), 9.20 (dd, J_{4-6} = 2 Hz, J_{5-6} = 5 Hz, 1 H, H-6).

2,3-Dihydro-5-(6-methoxy-3-pyridazinyl)-1*H*-1,4-benzodiazepine (**6b**)

Recrystallisation from ethanol/charcoal afforded 178 mg (70%) of **6b** as yellow crystals, mp 175-176°C. *Anal.* Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 55.92; H, 5.80; N, 21.74. Ms: *m/z* (rel. int.) 254 (100%, M^+), 226 (34), 154 (9), 77 (10). Ir (cm^{-1}): 3300 (NH). ^{1}H-Nmr ($CDCl_3$) δ: 3.5-3.9 (m, overlapped by br m, together 3 H, CH_2, NH), 4.0-4.2 (m, 2 H, CH_2), 4.20 (s, 3 H, OCH_3), 6.6-7.4 (m, overlapped by d, J = 9 Hz, together 5 H, H-5, C_6H_4), 8.00 (d, J = 9 Hz, 1 H, H-4).

General Procedure for the Preparation of the Hydrazones (**7a**) and (**7b**)

A mixture of the appropriate 2-fluorophenyl 3-pyridazinyl ketone (**4** or **5**, respectively, 1 mmol) and hydrazine hydrate (3 ml; 80% aqueous solution) was heated to 120°C for 30 min. After addition of 20 ml of water, the suspension was extracted exhaustively with dichloromethane. The extract was washed with water, dried (Na_2SO_4) and evaporated.

2-Fluorophenyl 3-Pyridazinyl Ketone Hydrazone (**7a**)

Recrystallisation from ethyl acetate gave 195 mg (90%) of **7a** as colorless needles, mp 152-153°C. *Anal.* Calcd for $C_{11}H_9N_4F$: C, 61.11; H, 4.20; N, 25.91. Found: C, 61.34; H, 4.23; N, 26.04. Ms: *m/z* (rel. int.) 216 (25%, M^+), 215 (100), 197 (14), 187 (10), 168 (10), 133 (27). Ir (cm^{-1}): 3440, 3320, 3230 (NH_2). ^{1}H-Nmr ($CDCl_3$) δ: 5.99 (br s, 2 H, NH_2), 7.2-7.5 (m, 5 H, H-5, C_6H_4), 8.17 (dd, J_{4-5} = 9 Hz, J_{4-6} = 2 Hz, 1 H, H-4), 9.01 (dd, J_{4-6} = 2 Hz, J_{5-6} = 5 Hz, 1 H, H-6).

2-Fluorophenyl 6-Methoxy-3-pyridazinyl Ketone Hydrazone (**7b**)

Column chromatography (ethyl acetate) gave 104 mg (42%) of **7b** as colorless crystals, mp 139-140°C (ethyl acetate). *Anal.* Calcd for $C_{12}H_{11}N_4OF$: C, 58.53; H, 4.50; N, 22.75. Found: C, 58.62; H, 4.62; N, 22.98. Ms: *m/z* (rel. int.) 245 (100%, M^+), 227 (11). Ir (cm^{-1}): 3430, 3320, 3250 (NH). ^{1}H-Nmr ($CDCl_3$) δ: 4.10 (s, 3 H, OCH_3), 5.85 (br s, 2 H, NH_2), 6.95 (d, J = 9 Hz, 1 H, H-5), 7.1-7.6 (m, 4 H, C_6H_4), 8.15 (d, J = 9 Hz, 1 H, H-4).

2-Benzylaminophenyl 3-Pyridazinyl Ketone (**8**)

A mixture containing **4** (202 mg, 1 mmol), benzylamine (1070 mg, 10 mmol), and K_2CO_3 (138 mg, 1 mmol) in 20 ml of toluene was refluxed for 36 h. After filtration, the solution was evaporated and the residue was partitioned between dichloromethane and 0.1 *N* HCl. The organic layer was dried (Na_2SO_4) and evaporated. Recrystallisation from diisopropyl ether/ethanol afforded 238 mg (82%) of **8** as yellow crystals, mp 97°C.

Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.80; H, 5.05; N, 14.63. Ms: *m/z* (rel. int.) 289 (39%, M^+), 270 (100), 260 (90), 184 (21), 182 (17), 180 (24), 91 (55), 77 (16), 65 (17). Ir (cm^{-1}): 3380 (NH), 1630 (CO). ^{1}H-Nmr ($CDCl_3$) δ: 4.55 (d, J = 6 Hz, s after addition of D_2O, 2 H, $PhCH_2$), 6.5-8.0 (m, 11 H, H-4, H-5, C_6H_4, C_6H_5), 9.25-9.5 (br t, overlapped by dd, J_{4-6} = 2 Hz, J_{5-6} = 5 Hz, together 2 H, NH, H-6).

3-(3-Pyridazinyl)-2,1-benzisoxazole (**9**)

A suspension of **4** (202 mg, 1 mmol) and NaN_3 (78 mg, 1.2 mmol) in 10 ml of DMF was stirred at 120°C for 15 h. After evaporation of the solvent, water (10 ml) was added, the precipitate was filtered off and washed thoroughly with water. The filtrate was extracted exhaustively with dichloromethane; the organic layer was dried (Na_2SO_4) and evaporated. Recrystallisation of the combined materials from ethanol afforded 150 mg (76%) of **9** as colorless needles, mp 165-166°C. *Anal.* Calcd for $C_{11}H_7N_3O$ C, 67.00; H, 3.58; N, 21.31. Found: C, 66.95; H, 3.60; N, 21.33. Ms: *m/z* (rel. int.) 198 (79%), 197 (100, M^+), 196 (76), 168 (30), 142 (34), 140 (36), 114 (63), 90 (48), 63 (85). ^{1}H-Nmr ($CDCl_3$) δ: 7.20 (dd, J_{4-5} = 9 Hz, J_{5-6} = 6 Hz, 1 H, H-5), 7.41 (ddd, J_{4-6} = 1 Hz, J_{5-6} = 6 Hz, J_{6-7} = 9 Hz, 1 H, H-6), 7.66 (d, J_{6-7} = 9 Hz, 1 H, H-7) overlapped by 7.68 (dd, J_{4-5} = 8 Hz, J_{5-6} = 5 Hz, 1 H, pyridazine H-5), 8.27 (dd, J_{4-5} = 8 Hz, J_{4-6} = 1.5 Hz, 1 H, pyridazine H-4), 8.50 (d, J_{4-5} = 9 Hz, 1 H, H-4), 9.23 (dd, J_{4-6} = 1.5 Hz, J_{5-6} = 5 Hz, 1 H, pyridazine H-6).

2-Aminophenyl 3-Pyridazinyl Ketone (**10**)

A mixture of **9** (197 mg, 1 mmol), ammonium formate (68 mg, 1.1 mmol) and Pd/C (10%; 60 mg) in 25 ml of methanol was stirred under an atmosphere of N_2 at 60°C. Additional portions of ammonium formate were added until the starting material was completely consumed (tlc monitoring; dichloromethane/methanol, 9:1). After removal of the catalyst and evaporation of the solvent, the residue was partitioned between dichloromethane and water. The organic layer was dried (Na_2SO_4), evaporated and recrystallized from ethyl acetate to give 131 mg (66%) of **10** as yellow crystals, mp 195°C. *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.31; H, 4.55; N, 21.09. Found: C, 66.04; H, 4.41; N, 20.86. Ms: *m/z* (rel. int.) 199 (35%, M^+), 170 (100), 117 (11), 92 (19), 65 (22). Ir (cm^{-1}): 3430, 3300, 3170 (NH_2), 1625 (CO). ^{1}H-Nmr ($CDCl_3$) δ: 6.48 (ddd, J_{3-5} = 1 Hz, J_{4-5} = 7 Hz, J_{5-6} = 8 Hz, 1 H, aniline H-5), 6.88 (dd, J_{3-4} = 9 Hz, J_{3-5} = 1 Hz, 1 H, aniline H-3), 7.3-7.4 (m, 2 H, aniline H-4, aniline H-6), 7.46 (br s, 2 H, NH_2), 7.89 (dd, J_{4-5} = 8 Hz, J_{5-6} = 5 Hz, 1 H, H-5), 7.97 (dd, J_{4-5} = 8 Hz, J_{4-6} = 2 Hz, 1 H, H-4), 9.37 (dd, J_{4-6} = 2 Hz, J_{5-6} = 5 Hz, 1 H, H-6).

2-(4-Ethyl-1-piperazinyl)-4-(3-pyridazinyl)quinoline (**11**)

A mixture of dimethylacetamide dimethyl acetal (1.33 g, 10 mmol) and dry 1-ethylpiperazine (2.28 g, 20 mmol) was heated to 190°C for a period of 5 h during which a slow stream of dry N_2 was bubbled through the solution. After cooling, compound (**10**) (199 mg, 1 mmol) was added and the mixture was heated to 130°C for

2 h. The excess reagent was removed *in vacuo* and the residue was subjected to column chromatography (dichloromethane/methanol, 9:1) and subsequent recrystallisation from ethyl acetate to yield 170 mg (53%) of **11** as colorless crystals, mp 120-124°C. *Anal.* Calcd for $C_{19}H_{21}N_5 \cdot \frac{1}{2}H_2O$: C, 69.49; H, 6.75; N, 21.32. Found: C, 69.77; H, 6.45; N, 21.05. Ms: *m/z* (rel. int.) 319 (12%, M^+), 235 (100), 97 (27), 84 (25), 57 (14). ^{1}H-Nmr ($CDCl_3$) δ: 1.20 (t, J = 7 Hz, 3 H, $CH_2\underline{CH_3}$), 2.3-2.6 (m, 6 H, NCH_2), 3.8-4.0 (m, 4 H, $ArNCH_2$), 6.90 (s, 1 H, quinoline H-3), 7.1-7.9 (m, 6 H, quinoline-H, pyridazine H-4, pyridazine H-5), 9.35 (dd, J_{4-6} = 2 Hz, J_{5-6} = 5 Hz, 1 H, pyridazine H-6).

5,10-Dihydro-5-oxopyridazino[2,3-*b*]cinnolin-11-ium Hydroxide Inner Salt (**12**)

A solution of the 2,1-benzisoxazole (**9**) (197 mg, 1 mmol) in 20 ml of 1,2,4-trichlorobenzene was heated to 220°C for 20 h. After removal of the solvent *in vacuo*, the solid residue was purified by column chromatography (ethyl acetate/methanol, 3:2) to yield 147 mg (75%) of **12** as yellow crystals, mp 249-250°C (ethanol). *Anal.* Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 66.83; H, 3.66; N, 21.24. Ms: *m/z* (rel. int.) 197 (100%, M^+). Ir (cm^{-1}): 1630 (CO), 1585. ^{1}H-Nmr (DMSO-d_6) δ: 7.52 (ddd, J = 8 Hz, 5 Hz, 3 Hz, 1 H, cinnoline-H), 7.57 (dd, J_{2-3} = 5 Hz, J_{3-4} = 9 Hz, 1 H, H-3), 7.85-7.9 (m, 2 H, cinnoline-H), 8.21 (d, J = 9 Hz, 1 H, cinnoline-H), 8.84 (dd, J_{2-4} = 2 Hz, J_{3-4} = 9 Hz, 1 H, H-4), 9.15 (dd, J_{2-3} = 5 Hz, J_{2-4} = 2 Hz, 1 H, H-2). ^{13}C-Nmr (DMSO-d_6) δ: 169.5, 152.9, 147.4, 134.2, 133.6, 132.7, 125.8, 125.5, 123.9, 120.9, 118.1.

Pyridazino[4,3-*b*]quinolin-10(5*H*)-one (**13**)

A suspension of **10** (199 mg, 1 mmol) in 20 ml of 2 *N* aqueous NaOH was refluxed for 36 h. After cooling, the solution was made weakly acidic (ph = 4-5) with 2 *N* aqueous HCl. The precipitate was collected and washed with water and methanol to give 180 mg (91%) of **13** as pale yellow crystals, mp >300°C. *Anal.* Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 66.75; H, 3.82; N, 21.03. Ms: *m/z* (rel. int.) 197 (100%, M^+), 168 (20), 141 (30), 140 (31), 114 (34), 51 (32). Ir (cm^{-1}): 3300-2600 (br, NH), 1650 (CO). ^{1}H-Nmr ($CDCl_3$) δ: 7.37 (dd, J_{7-8} = 8 Hz, J_{8-9} = 9 Hz, H-8), 7.55 (d, J_{6-7} = 9 Hz, 1 H, H-6), 7.67 (d, J_{3-4} = 6 Hz, 1 H, H-4), 7.83 (ddd, J_{6-7} = 9 Hz, J_{7-8} = 8 Hz, J_{7-9} = 1.5 Hz, 1 H, H-7), 8.30 (dd, J_{8-9} = 9 Hz, J_{7-9} = 1.5 Hz, 1 H, H-9), 9.91 (d, J_{3-4} = 6 Hz, 1 H, H-3).

N-[2-(3-Pyridazinylcarbonyl)phenyl]acetamide (**14**)

A solution of **10** (199 mg, 1 mmol) in 20 ml (212 mmol) of acetic anhydride was heated to 100°C for 20 min. After removal of the reagent *in vacuo*, the residue was taken up in dichloromethane. Insoluble material (compound **13**) was filtered off, and the filtrate was evaporated. The crude product was purified by column chromatography (dichloromethane/methanol, 94:6) to give 140 mg (58%) of **14** as colorless crystals, mp 112-113°C. *Anal.* Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.70; H, 4.52; N, 17.39. Ms:

m/z (rel. int.) 241 (19%, M^+), 213 (14), 212 (16), 199 (31), 198 (36), 171 (48), 170 (100), 122 (27), 120 (15), 92 (21), 65 (16). Ir (cm^{-1}): 3300 (NH), 1700 (CO), 1650 (CO). ^{1}H-Nmr ($CDCl_3$) δ: 2.25 (s, 3 H, CH_3), 7.0-8.2 (m, overlapped by dd, J_{4-5} = 8 Hz, J_{5-6} = 5 Hz and dd, J_{4-5} = 8 Hz, J_{4-6} = 2 Hz, together 5 H, aniline H-4, H-5, H-6, pyridazine H-5, H-4), 8.80 (d, *J* = 9 Hz, 1 H, aniline H-3), 9.40 (dd, J_{4-6} = 2 Hz, J_{5-6} = 5 Hz, 1 H, pyridazine H-6), 11.0-11.3 (br s, 1 H, NH).

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REFERENCES AND NOTES

1. Part 68: G. Heinisch and T. Langer, *J. Heterocycl. Chem.*, submitted for publication.
2. For a recent review see: N. Haider and G. Heinisch, *Heterocycles*, 1993, **35**, 519.
3. G. Heinisch and T. Langer, *Synth. Commun.*, submitted for publication.
4. S. Ram and R. E. Ehrenkaufer, *Synthesis*, 1988, 91.
5. Careful tlc monitoring of this reaction step is required to avoid the formation of undesired reduction products.
6. A. Donetti, O. Boniardi, and A. Ezhaya, *Synthesis*, 1980, 1009.
7. So far, no assignment can be made regarding E/Z isomerism; attempts employing NOE difference spectroscopy remained unsuccessful.
8. Prolonged refluxing of **7a** with potassium carbonate in DMF solution as well as heating of a sample of neat **7a** to about 160°C did not effect any conversion, as indicated by tlc.
9. N. Haider, G. Heinisch, and J. Moshuber, *Arch. Pharm.* (Weinheim, Ger.), 1992, **325**, 119.
10. J. H. Hall, F. E. Behr, and R. L. Reed, *J. Am. Chem. Soc.*, 1972, **94**, 4952.
11. In the series of 2-aminophenyl 3-pyridazinyl ketones, so far only representatives bearing substituents at the amino group and/or at the benzene ring have been known: N. Haider, G. Heinisch, and G. Kemetmüller, *J. Heterocycl. Chem.*, 1990, **27**, 1645.
12. K. Hino, K. Kawashima, M. Oka, Y. Nagai, H. Uno, and J. Matsumoto, *Chem. Pharm. Bull.*, 1989, **37**, 110.
13. A first representative of the pyridazino[4,3-*b*]quinoline ring system (i.e. 6,7,8,9-tetrahydro-3-methylpyridazino[4,3-*b*]quinoline) has been described previously: A. Turck, J. F. Brument, and G. Quéguiner, *J. Heterocycl. Chem.*, 1983, **20**, 101.
14. M. Grabenwöger, N. Haider, and G. Heinisch, *Liebigs Ann. Chem.*, 1989, 481.
15. R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Heterocycl. Chem., 1974,* **11**, 125.

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