Pyridazines. XLI [1,2]
Synthesis of Novel Pyrido[3,4-*d*]pyridazine Derivatives from 4,5-Disubstituted Pyridazines

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Dedicated to Prof. Dr. H. Junek on the occasion of his 60th anniversary.

Pyrido[3,4-*d*]pyridazines **2-5, 21** bearing one, two, or three aryl substituents in the pyridine moiety are shown to be conveniently accessible from 4-aroyl-5-methylpyridazines or 4,5-diaroylpyridazines, respectively, by condensation reactions with appropriate C-N fragments. In addition, the novel pyridazine-annelated pyridones **24, 25** were found to be easily available from ethyl 5-methyl-4-pyridazinecarboxylate.

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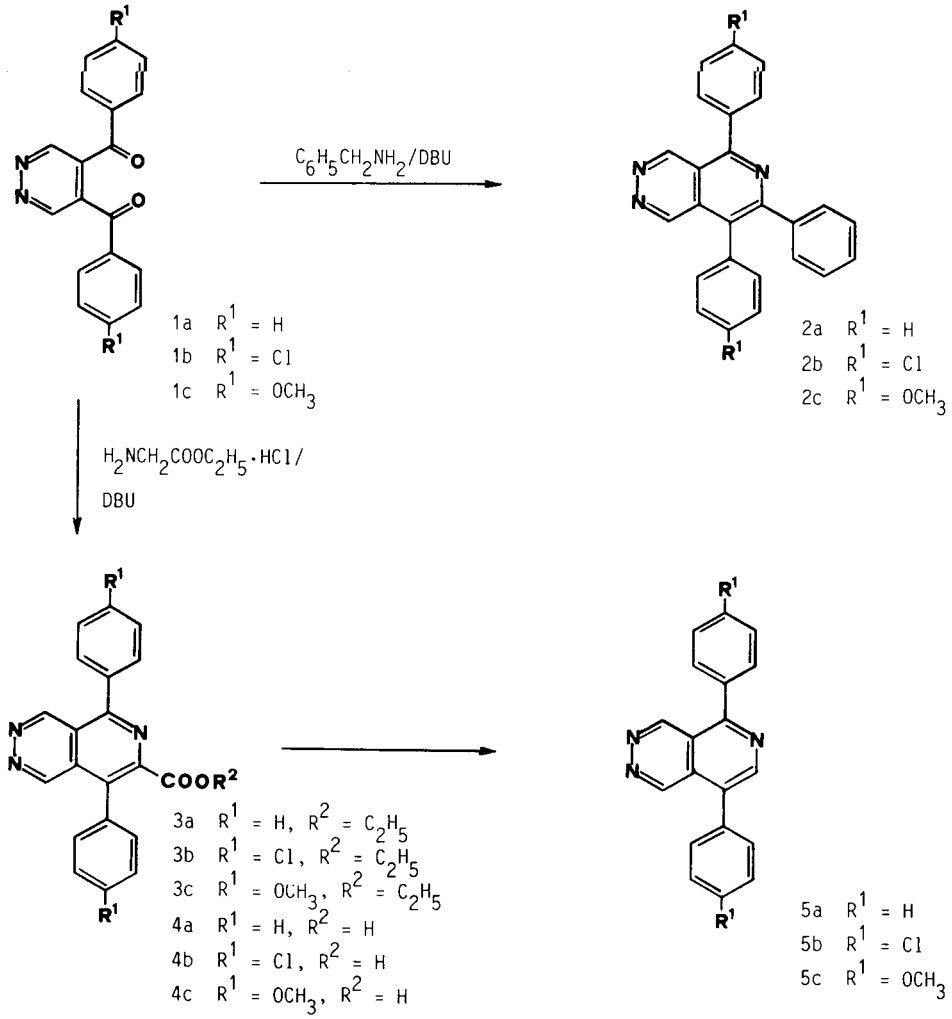
Recently, we reported on the synthesis of a variety of cycloaminosubstituted pyridopyridazines starting from a preformed 1,2-diazine system [4]. In extension of these investigations we now became interested in transformations of 4,5-diaroyl- and 4-aroyl-5-methylpyridazines into pyrido[3,4-*d*]pyridazines having one, two or three aryl substituents attached to the pyridine part of the condensed system.

The synthetic utility of *o*-diaroyl heterocycles with regard to the construction of pyrido-fused systems was

Scheme 1



demonstrated by Tashiro and co-workers [5] in the azole series. We now found 4,5-diaroylpyridazines **1a-c**, conveniently available by radical substitution of the parent system [6], to represent versatile building blocks for triazanaphthalene derivatives of type **2-5**. Condensation of the diketones **1a-c** with excess benzylamine was mediated by the strong base 1,8-diazabicyclo[5.4.0]undec-7-ene (*DBU*) to afford the triaryldiazaisoquinolines **2a-c**. Whereas employment of aminoacetonitrile as a CH_2NH_2 synthon gave only intractable tars, the use of ethyl glycinate/*DBU* in toluene solution enabled us to perform the desired pyridine ring annelation. In turn, the esters **3a-c** thus obtained, could be hydrolyzed in refluxing aqueous sodium hydroxide. Thermally induced decarboxylation of the resulting carboxylic acids **4a-c** finally provided access to the target diaryldiazaisoquinolines **5a-c**.

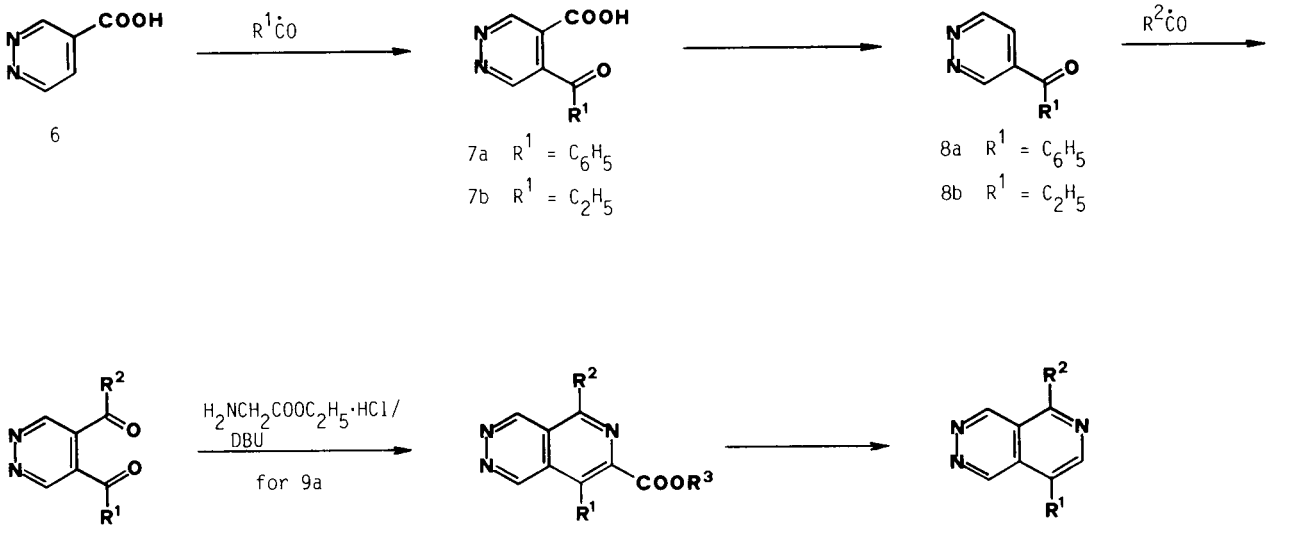
Also unsymmetrical diketones of type **9** were employed in this investigation. For their preparation 4-pyridazinecarboxylic acid [7] (**6**) was chosen as the substrate. Homolytic benzoylation of **6**, followed by decarboxylation to give **8a** was described previously [8]; a similar reaction sequence now was found to give 4-propionylpyridazine in 36% overall yield, being superior to procedures thus far described [6,9]. Subsequent radical aroylation of the ketones **8a,b** then afforded the novel 4,5-diacylpyridazines **9a,b**. Whereas treatment of the alkanoylaroylpyridazine **9b** with ethyl glycinate/*DBU* resulted in an inseparable multi-component mixture, we succeeded in the corresponding reaction of the diaroylpyridazine **9a**. Expectedly, in this case a mixture of two isomeric compounds **10** + **11** was formed. Attempted separation by means of chromatography or crystallisation met with failure; neither did we succeed in the separation of the isomeric carboxylic acids **12** and **13** as well as the diaryltriazanaphthalenes **14** and **15**, prepared in the same manner as described for compounds **5a-c** (hydrolysis followed by decarboxylation).

In contrast to the successful conversion of 4,5-diaroylpyridazines into diazaisoquinolines, reaction of benzylamine with the keto ester **16** did not result in pyridine ring annelation. The only product we could isolate after several hours of refluxing **16** with a large excess of benzylamine in ethanol turned out to be the *N*-benzylamide **17**. In accordance with previous findings with 5-benzoyl-4-pyridazinecarboxamide [10] also for this novel compound a ring-chain tautomerism appears to be obvious, as indicated by the ^{1}H-nmr spectrum of a deuteriodimethyl sulfoxide solution.

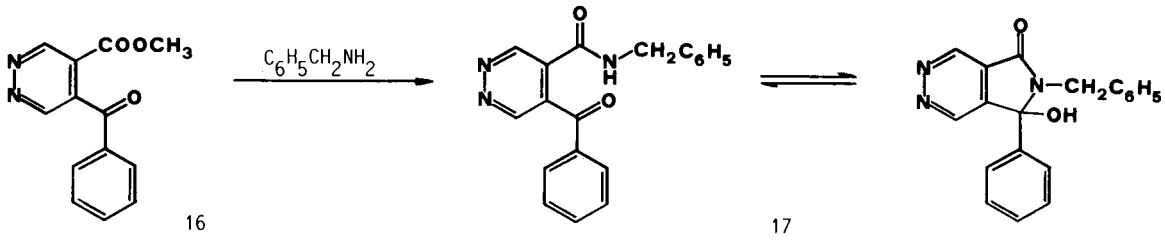
Pyrido[3,4-*d*]pyridazines bearing a single aryl moiety (at C-5) were found to be conveniently obtained as outlined in Scheme 4. Thus, the 4-aroyl-5-methylpyridazines **19a,b** [11] could be reacted with dimethylformamide dimethyl acetal (*DMFDMA*) to give the enaminoketones **20a,b**, for which, according to a coupling constant J_{AB} = 14 Hz, *E*-configuration has to be assigned. Treatment of the latter with ammonium acetate in ethanol affords the target compounds **21a,b** in satisfactory overall yields.

It turned out that activation of a methyl group attached to the pyridazine nucleus (C-4 or C-5) sufficient to permit

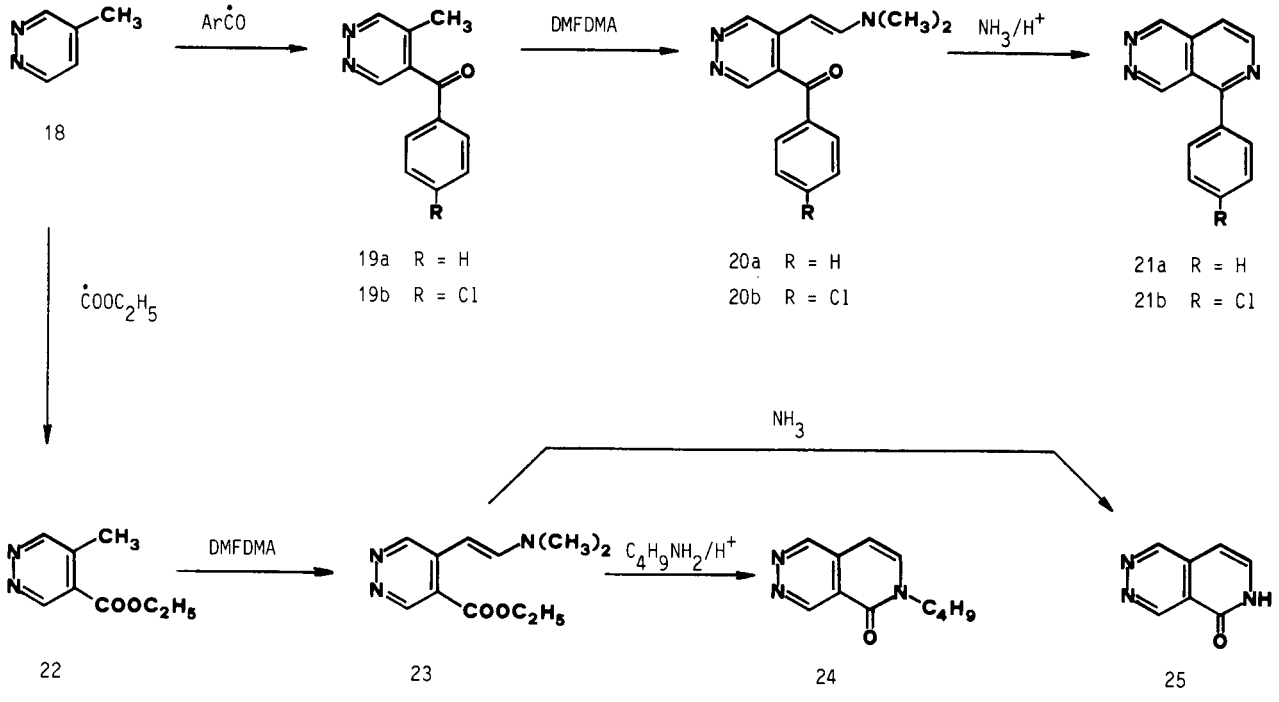
Scheme 2



Scheme 3



Scheme 4



condensation with *DMFDMA* [13] not only can be accomplished by an aroyl substituent (like in compounds **19**), but also by an ester group, as is the case in compound **22** [15]. Thus, the ester **22** could be transformed into the *E*-enamino ester **23**, which finally provided an easy access to the pyridazine-annelated *N*-alkylpyridone **24** as well as the parent lactam **25** upon action of *n*-butylamine/trifluoroacetic acid or ammonia in ethanol, respectively.

Structure proof for all the newly synthesized pyrido-[3,4-*d*]pyridazine derivatives rests on correct elemental analyses as well as on spectroscopic data.

In conclusion, the described results clearly demonstrate the utility of appropriately 4,5-disubstituted pyridazines for the annelation of a pyridine moiety to the 1,2-diazine system. These starting materials, which are conveniently available by radical substitution reactions, provide considerable variety in the substitution pattern of the pyridine part of the bicyclic system.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ir spectra (potassium bromide) were recorded on a JASCO IRA-1 spectrometer. The ^{1}H-nmr spectra were obtained on either a Varian EM 390 (90 MHz) or a Bruker AC 80 (80 MHz) instrument; chemical shifts are reported in ppm from tetramethylsilane as an internal standard and are given in δ units. For analytical tlc, DC-Alufolien, Kieselgel 60 F_{254} (Merck) were used; column chromatography was performed on Kieselgel 60 (70-230 mesh, Merck).

4,5-Bis(4-chlorobenzoyl)pyridazine (**1b**).

To a vigorously stirred solution of 3.2 g (40 mmoles) of pyridazine, 16.9 g (120 mmoles) of 4-chlorobenzaldehyde and 33.36 g (120 mmoles) of ferrous sulfate (heptahydrate) in 70 ml of 6*N* sulfuric acid and 200 ml of acetic acid were added 15 ml (120 mmoles) of a 80% solution of *t*-butyl hydroperoxide in di-*t*-butyl peroxide at 0-5°. After stirring for 1 hour at room temperature, the mixture was filtered and the filtrate was extracted with dichloromethane. The organic layer was washed with 2*N* aqueous

sodium hydroxide and water, dried, and evaporated. Column chromatography (ethyl acetate-light petroleum, 3:5), followed by recrystallisation from 2-propanol gave 4.3 g (30%) of off-white crystals, mp 165-169°; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 10.10 (s, H-3, H-6, 2 H), 8.1-7.6 (AA'BB' system, $J_{AB} \approx 8$ Hz, C_6H_4Cl, 8 H); ir: cm^{-1} 1670 (C=O).

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2O_2$: C, 60.53; H, 2.82; N, 7.84. Found: C, 60.31; H, 2.92; N, 7.94.

5,7,8-Triphenylpyrido[3,4-*d*]pyridazine (**2a**).

A solution of 288 mg (1 mmole) of 4,5-dibenzoylpyridazine [6] (**1a**) and 1 ml (6.5 mmoles) of *DBU* in 22 ml of benzylamine was heated to 120° for 18 hours. After cooling, the solution was diluted with 100 ml of dichloromethane and extracted several times with 2*N* hydrochloric acid. Evaporation of the organic layer, followed by recrystallisation from ethanol afforded 228 mg (63%) of colorless needles, mp 235-236°; ^{1}H-nmr (deuteriochloroform): δ 9.85, 9.55 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 8.0-7.2 (m, C_6H_5, 15 H).

Anal. Calcd. for $C_{25}H_{17}N_3$: C, 83.54; H, 4.77; N, 11.69. Found: C, 83.12; H, 4.84; N, 11.57.

5,8-Bis(4-chlorophenyl)-7-phenylpyrido[3,4-*d*]pyridazine (**2b**).

Preparation as described for **2a**, starting from 357 mg (1 mmole) of **1b**. Purification by column chromatography (dichloromethane-ethyl acetate, 4:1), followed by recrystallisation from methanol yielded 177 mg (42%) of yellow needles, mp 237-238°; ^{1}H-nmr (deuteriochloroform): δ 9.85, 9.55 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 8.0-7.1 (m, C_6H_4Cl, C_6H_5, 13 H).

Anal. Calcd. for $C_{25}H_{15}Cl_2N_3 \cdot \frac{1}{2}H_2O$: C, 68.66; H, 3.69; N, 9.61. Found: C, 68.74; H, 3.66; N, 9.63.

5,8-Bis(4-methoxyphenyl)-7-phenylpyrido[3,4-*d*]pyridazine (**2c**).

Preparation as described for **2a**, starting from 348 mg (1 mmole) of 4,5-bis(4-methoxybenzoyl)pyridazine [6] (**1c**). Recrystallisation from methanol afforded 185 mg (44%) of yellow crystals, mp 200-204°; ^{1}H-nmr (deuteriochloroform): δ 9.90, 9.60 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 7.90 (BB'-part of an AA'BB' system, $J_{AB} \approx 8$ Hz, $C_6H_4OCH_3$, 2 H), 7.7-6.9 (m, $C_6H_4OCH_3$, C_6H_5, 11 H), 3.95 (s, OCH_3, 3 H), 3.90 (s, OCH_3, 3 H).

Anal. Calcd. for $C_{27}H_{21}N_3O_2$: C, 77.31; H, 5.05; N, 10.02. Found: C, 76.97; H, 5.11; N, 10.05.

Ethyl 5,8-Diphenylpyrido[3,4-*d*]pyridazine-7-carboxylate (**3a**).

To a solution of 576 mg (2 mmoles) of **1a** [6] and 3.4 ml (22 mmoles) of *DBU* in 40 ml of toluene were added 2.8 g (20 mmoles) of ethyl glycinate hydrochloride, and the mixture was refluxed for 18 hours. After cooling, the solution was separated from resinous material by decantation; it was then washed with water, dried, and evaporated. Recrystallisation of the residue from ethanol gave 575 mg (81%) of yellow crystals, mp 141-142°; ^{1}H-nmr (deuteriochloroform): δ 9.90, 9.55 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 8.0-7.4 (m, C_6H_5, 10 H), 4.15 (q, J = 7 Hz, CH_2CH_3, 2 H), 1.00 (t, J = 7 Hz, CH_2CH_3, 3 H); ir: cm^{-1} 1730 (C=O).

Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.23; H, 5.02; N, 11.67.

Ethyl 5,8-Bis(4-chlorophenyl)pyrido[3,4-*d*]pyridazine-7-carboxylate (**3b**).

Preparation as described for **3a**, starting from 714 mg (2 mmoles) of **1b**. Recrystallisation from ethanol gave 1.052 g (65%) of yellow needles, mp 205-206°; ^{1}H-nmr (deuteriochloroform): δ 9.85, 9.55 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 8.0-7.3 (m, C_6H_4Cl, 8 H), 4.25 (q, J = 7 Hz, CH_2CH_3, 2 H), 1.10 (t, J = 7 Hz, CH_2CH_3, 3 H); ir: cm^{-1} 1720 (C=O).

Anal. Calcd. for $C_{22}H_{15}Cl_2N_3O_2$: C, 62.28; H, 3.56; N, 9.90. Found: C, 62.06; H, 3.65; N, 9.94.

Ethyl 5,8-Bis(4-methoxyphenyl)pyrido[3,4-*d*]pyridazine-7-carboxylate (**3c**).

Preparation as described for **3a**, starting from 696 mg (2 mmoles) of **1c** [6]. Recrystallisation from methanol gave 415 mg (50%) of yellow crystals, mp 185-186°; ^{1}H-nmr (deuteriochloroform): δ 9.95, 9.60 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 7.85 (BB'-part of an AA'BB' system, $J_{AB} \approx 8$ Hz, $C_6H_4OCH_3$, 2 H), 7.5-7.0 (m, $C_6H_4OCH_3$, 6 H), 4.25 (q, J = 7 Hz, CH_2CH_3, 2H), 3.95 (s, OCH_3, 6 H), 1.10 (t, J = 7 Hz, CH_2CH_3, 3 H); ir: cm^{-1} 1725 (C=O).

Anal. Calcd. for $C_{24}H_{21}N_3O_4$: C, 69.39; H, 5.10; N, 10.11. Found: C, 69.11; H, 5.17; N, 10.37.

5,8-Diphenylpyrido[3,4-*d*]pyridazine-7-carboxylic Acid (**4a**).

A suspension of 355 mg (1 mmole) of the ester **3a** in 15 ml of 2*N* aqueous sodium hydroxide was refluxed for 18 hours. The resulting solution was acidified (*p*H 1) by addition of 2*N* hydrochloric acid and the precipitate was collected and dried to afford 265 mg (81%) of colorless crystals, mp 225-226° (from ethanol); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 9.80, 9.45 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 8.1-7.5 (m, C_6H_5, 10 H); ir: cm^{-1} 1725 (C=O).

Anal. Calcd. for $C_{20}H_{13}N_3O_2 \cdot \frac{1}{4}H_2O$: C, 72.39; H, 4.10; N, 12.66. Found: C, 72.54; H, 4.18; N, 12.43.

5,8-Bis(4-chlorophenyl)pyrido[3,4-*d*]pyridazine-7-carboxylic Acid (**4b**).

A mixture of 424 mg (1 mmole) of the ester **3b** and 120 mg (3 mmoles) of sodium hydroxide in 20 ml of 50% aqueous ethanol was refluxed for 18 hours. The resulting solution was concentrated under reduced pressure to about half the volume and acidified (*p*H 1) by addition of 2*N* hydrochloric acid. The precipitate was collected and dried to afford 230 mg (58%) of colorless crystals, mp 244-245° (from 1-butanol); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 14.5-12.5 (br, COOH, 1 H), 9.75, 9.35 (each d, unresolved, H-1, H-4, 2 H), 8.1-7.3 (m, C_6H_4Cl, 8 H); ir: cm^{-1} 1720 (C=O).

Anal. Calcd. for $C_{20}H_{11}Cl_2N_3O_2 \cdot \frac{1}{2}H_2O$: C, 59.28; H, 2.98; N, 10.37. Found: C, 59.10; H, 3.10; N, 9.99.

5,8-Bis(4-methoxyphenyl)pyrido[3,4-*d*]pyridazine-7-carboxylic Acid (**4c**).

Preparation as described for **4b**, using 415 mg (1 mmole) of **3c** and 480 mg (12 mmoles) of sodium hydroxide. Precipitation of the acid afforded 332 mg (86%) of colorless crystals, mp 244-246° (from 1-butanol); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 14.5-12.5 (br, COOH, 1 H), 9.70, 9.35 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 7.85 (BB'-part of an AA'BB' system, $J_{AB} \approx 8$ Hz, $C_6H_4OCH_3$, 2 H), 7.5-7.1 (m, $C_6H_4OCH_3$, 6 H), 3.90 (s, OCH_3, 3 H), 3.85 (s, OCH_3, 3 H); ir: cm^{-1} 1715 (C=O).

Anal. Calcd. for $C_{22}H_{17}N_3O_4$: C, 68.21; H, 4.42; N, 10.85. Found: C, 67.91; H, 4.72; N, 10.63.

5,8-Diphenylpyrido[3,4-*d*]pyridazine (**5a**).

In a vacuum sublimation apparatus, 327 mg (1 mmole) of the acid **4a** were heated to 240° for 1 hour. The condensate was dissolved in 20 ml of dichloromethane and the solution was ex-

tracted with 2*N* aqueous sodium hydroxide. Evaporation of the organic layer, followed by recrystallisation from ethanol yielded 150 mg (53%) of pale yellow crystals, mp 183-184°; ^{1}H-nmr (deuteriochloroform): δ 9.95, 9.85 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 9.20 (s, H-7, 1 H), 8.0-7.5 (m, C_6H_5, 10 H).

Anal. Calcd. for $C_{19}H_{13}N_3 \cdot 1/8\ H_2O$: C, 79.91; H, 4.68; N, 14.71. Found: C, 79.88; H, 4.80; N, 14.48.

5,8-Bis(4-chlorophenyl)pyrido[3,4-*d*]pyridazine (**5b**).

A mixture of 396 mg (1 mmole) of the acid **4b** and 396 mg of copper powder was heated in a Kugelrohr distillation apparatus at 10^{-2} mbar to 245° for 1 hour. The distillate was dissolved in 20 ml of dichloromethane and the solution was extracted with 2*N* aqueous sodium hydroxide. Evaporation of the organic layer, followed by recrystallisation from ethanol yielded 282 mg (80%) of colorless crystals, mp 247-248°; ^{1}H-nmr (deuteriochloroform): δ 9.80, 9.70 (each d, unresolved, H-1, H-4, 2H), 9.05 (s, H-7, 1 H), 7.9-7.5 (m, C_6H_4Cl, 8 H).

Anal. Calcd. for $C_{19}H_{11}Cl_2N_3$: C, 64.79; H, 3.15; N, 11.93. Found: C, 64.55; H, 3.24; N, 11.77.

5,8-Bis(4-methoxyphenyl)pyrido[3,4-*d*]pyridazine (**5c**).

Preparation as described for **5b**, starting from 387 mg (1 mmole) of the acid **4c**. Recrystallisation from methanol yielded 258 mg (75%) of pale yellow needles, mp 178-180°; further purification was achieved by sublimation (200°, 10^{-2} mbar); ^{1}H-nmr (deuteriochloroform): δ 9.80, 9.75 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 9.00 (s, H-7, 1 H), 7.75 (BB'-part of an AA'BB' system, $J_{AB} \approx 8$ Hz, $C_6H_4OCH_3$, 2H), 7.50 (BB'-part of an AA'BB' system, $J_{AB} \approx 8$ Hz, $C_6H_4OCH_3$, 2 H), 7.25-7.05 (overlapping AA' parts of 2 AA'BB' systems, $C_6H_4OCH_3$, 4 H), 3.95 (s, OCH_3, 6 H).

Anal. Calcd. for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.35; H, 5.02; N, 12.25.

5-Propionyl-4-pyridazinecarboxylic Acid [9] (**7b**) from **6**.

To a vigorously stirred solution of 3.72 g (30 mmoles) of 4-pyridazinecarboxylic acid [7] (**6**) and 5.22 g (90 mmoles) of propionaldehyde in 50 ml of 6*N* sulfuric acid and 20 ml of acetic acid were added dropwise and simultaneously a saturated aqueous solution of 25.02 g (90 mmoles) of ferrous sulfate (heptahydrate) and 11.25 ml (90 mmoles) of a 80% solution of *t*-butyl hydroperoxide in di-*t*-butyl peroxide at 0-5°. After additional stirring at 0° for 0.5 hours and at room temperature for 1 hour, the precipitate was collected, washed with water, and dried to afford 2.33 g (43%) of colorless crystals, mp 164-166°, being identical (mp, ir) with an authentic sample [9]; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 9.65, 9.55 (each d, J = 1.5 Hz, H-3, H-6, 2 H), 2.90 (q, J = 7 Hz, CH_2CH_3, 2 H), 1.10 (t, J = 7 Hz, CH_2CH_3, 3 H).

5-Benzoyl-4-(4-methoxybenzoyl)pyridazine (**9a**).

To a vigorously stirred solution of 5.52 g (30 mmoles) of 4-benzoylpyridazine [8] (**8a**) and 12.24 g (90 mmoles) of 4-methoxybenzaldehyde in 60 ml of 2*N* sulfuric acid and 60 ml of acetic acid were added dropwise and simultaneously a saturated aqueous solution of 25.02 g (90 mmoles) of ferrous sulfate (heptahydrate) and 11.25 ml (90 mmoles) of a 80% solution of *t*-butyl hydroperoxide in di-*t*-butyl peroxide at 0-5°. Stirring was continued at room temperature for 1 hour, then the precipitate was collected, dried, and dissolved in dichloromethane. The solution was washed with 2*N* aqueous sodium hydroxide and water, then dried and evaporated. Purification by column chromatography (dichloromethane-ethyl acetate, 4:1) afforded 4.96 g (52%) of a yellow oil, which was used for the following transformations without further purification; ^{1}H-nmr (deuteriochloroform): δ 9.50 (s, H-3, H-6, 2 H), 7.9-6.8 (m, C_6H_5, $C_6H_4OCH_3$, 9 H), 3.90 (s, OCH_3, 3 H); ir: cm^{-1} 1660 (C=O).

5-Propionyl-4-benzoylpyridazine (**9b**).

To a vigorously stirred solution of 4.1 g (30 mmoles) of 4-propionylpyridazine [6,9] (**8b**) and 9.2 g (90 mmoles) of benzaldehyde in 20 ml of 6*N* sulfuric acid and 60 ml of acetic acid were added dropwise and simultaneously a saturated aqueous solution of 25.02 g (90 mmoles) of ferrous sulfate (heptahydrate) and 11.25 ml (90 mmoles) of a 80% solution of *t*-butyl hydroperoxide in di-*t*-butyl peroxide at 0-5°. Stirring was continued at room temperature for 1 hour, then the mixture was extracted with dichloromethane. The extract was washed successively with a saturated aqueous sodium bicarbonate solution and water, dried, and evaporated. Column chromatography (dichloromethane-ethyl acetate, 9:1), followed by recrystallisation from ethyl acetate-light petroleum afforded 3.1 g (43%) of yellow needles, mp 92-94°; ^{1}H-nmr (deuteriochloroform): δ 9.65, 9.35 (each d, unresolved, H-3, H-6, 2 H), 7.9-7.3 (m, C_6H_5, 5 H), 3.00 (q, J = 7 Hz, CH_2CH_3, 2 H), 1.10 (t, J = 7 Hz, CH_2CH_3, 3 H); ir: cm^{-1} 1720 (C=O), 1680 (C=O).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.89; H, 5.13; N, 11.43.

Reaction of 5-Benzoyl-4-(4-methoxybenzoyl)pyridazine (**9a**) with Ethyl Glycinate/*DBU*.

To a solution of 636 mg (2 mmoles) of **9a** and 3.4 ml (22 mmoles) of *DBU* in 40 ml of toluene were added 2.8 g (20 mmoles) of ethyl glycinate hydrochloride, and the mixture was refluxed for 18 hours. After cooling, the solution was separated from resinous material by decantation; it was then washed with water, dried, and evaporated. Recrystallisation of the residue from ethyl acetate afforded 493 mg (64%) of an unseparable mixture of ethyl 8-(4-methoxyphenyl)-5-phenylpyrido[3,4-*d*]pyridazine-7-carboxylate (**10**) and its isomer, ethyl 5-(4-methoxyphenyl)-8-phenylpyrido[3,4-*d*]pyridazine-7-carboxylate (**11**); ^{1}H-nmr (deuteriochloroform): δ 9.90, 9.85, 9.60, 9.50 (each d, J = 1.5 Hz, H-1, H-4 of both isomers), 8.0-7.0 (m, C_6H_5, $C_6H_4OCH_3$ of both isomers), 4.30-4.05 (2 overlapping q, J = 7 Hz, CH_2CH_3 of both isomers), 3.95 (s, OCH_3 of both isomers), 1.25-0.95 (2 overlapping t, J = 7 Hz, CH_2CH_3 of both isomers); ir: cm^{-1} 1745 (C=O).

Anal. Calcd. for $C_{23}H_{19}N_3O_3$: C, 71.68; H, 4.97; N, 10.90. Found: C, 71.58; H, 5.07; N, 10.69.

Hydrolysis of the Esters **10/11**.

A mixture of 774 mg (2 mmoles) of the isomeric esters **10/11** and 240 mg (6 mmoles) of sodium hydroxide in 20 ml of 50% aqueous ethanol was refluxed for 18 hours. The resulting solution was concentrated under reduced pressure to about half the volume and acidified (*p*H 1) by addition of 2*N* hydrochloric acid. The precipitate was collected and dried to afford 571 mg (80%) of an unseparable mixture of 8-(4-methoxyphenyl)-5-phenylpyrido[3,4-*d*]pyridazine-7-carboxylic acid (**12**) and its isomer, 5-(4-methoxyphenyl)-8-phenylpyrido[3,4-*d*]pyridazine-7-carboxylic acid (**13**); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 9.80, 9.75, 9.45, 9.35 (each d, J = 1.5 Hz, H-1, H-4 of both isomers), 8.0-7.1 (m, C_6H_5, $C_6H_4OCH_3$ of both isomers), 3.90, 3.85 (each s, OCH_3 of both isomers); ir: cm^{-1} 1720 (C=O).

Anal. Calcd. for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.63; H, 4.33; N, 11.82.

Decarboxylation of the Acids **12/13**.

A mixture of 500 mg (1.4 mmoles) of the isomeric acids **12/13** and 500 mg of copper powder was heated in a Kugelrohr distillation apparatus at 10^{-2} mbar to 240° for 1 hour. The distillate was dissolved in 20 ml of dichloromethane and the solution was extracted with 2*N* aqueous sodium hydroxide. Evaporation of the organic layer, followed by recrystallisation from methanol gave 245 mg (56%) of an unseparable mixture of 8-(4-methoxyphenyl)-5-phenylpyrido[3,4-*d*]pyridazine (**14**) and its isomer, 5-(4-methoxyphenyl)-8-phenylpyrido[3,4-*d*]pyridazine (**15**); ^{1}H-nmr (deuteriochloroform): δ 9.85, 9.80, 9.75 (each d, unresolved, H-1, H-4 of both isomers), 9.05 (s, H-7 of both isomers), 7.9-7.0 (m, C_6H_5, $C_6H_4OCH_3$ of both isomers), 3.90 (s, OCH_3 of both isomers).

Anal. Calcd. for $C_{20}H_{15}N_3O \cdot 1/8\ H_2O$: C, 76.11; H, 4.87; N, 13.31. Found: C, 75.96; H, 4.96; N, 13.21.

Reaction of Methyl 5-Benzoyl-4-pyridazinecarboxylate with Benzylamine.

A solution of 968 mg (4 mmoles) of methyl 5-benzoyl-4-pyridazine-carboxylate [10,16] (**16**) in a mixture of 32 ml of benzylamine and 20 ml of ethanol was refluxed for 3 hours, cooled, and evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane-ethyl acetate, 5:1), followed by recrystallisation from ethyl acetate-light petroleum to give 206 mg (16%) of 6-benzyl-6,7-dihydro-7-hydroxy-7-phenyl-5*H*-pyrrolo[3,4-*d*]pyridazin-5-one (**17**) as colorless crystals, mp 162-164°; ^{1}H-nmr (deuteriodimethyl sulfoxide/deuterium chloride/deuterium oxide [17]): δ 9.75, 9.70 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 7.40-7.30 (m, C_6H_5, 5 H), 7.20-7.10 (m, C_6H_5, 5 H), 4.65-4.15 (AB system, J_{AB} = 15.5 Hz, CH_2, 2 H); ir: cm^{-1} 1710 (C=O).

Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.94; H, 4.81; N, 13.17.

(5-Methyl-4-pyridazinyl)(4-chlorophenyl)ketone (**19b**).

To a vigorously stirred solution of 3.8 g (40 mmoles) of 4-methylpyridazine [18] (**18**) and 17 g (120 mmoles) of 4-chlorobenzaldehyde in 60 ml of 6*N* sulfuric acid and acetic acid (as much as necessary to obtain a clear solution) were added dropwise and simultaneously a saturated aqueous solution of 33.36 g (120 mmoles) of ferrous sulfate (heptahydrate) and 15 ml (120 mmoles) of a 80% solution of *t*-butyl hydroperoxide in di-*t*-butyl peroxide at 0-10°. After additional stirring at room temperature for 1 hour, the mixture was filtered and the filtrate was extracted with dichloromethane. The extract was washed subsequently with 2*N* aqueous sodium hydroxide and water, then dried and evaporated. The residue was subjected to column chromatography (dichloromethane-ethyl acetate, 5:4): collection of peak 1 afforded 2.72 g (29%) of compound **19b** as brownish crystals, mp 107-109° (from ethanol); ^{1}H-nmr (deuteriochloroform): δ 9.30, 9.05 (each s, H-3, H-6, 2 H), 7.85-7.45 (AA'BB' system, $J_{AB} \approx 8$ Hz, C_6H_4Cl, 4 H), 2.35 (s, CH_3, 3 H); ir: cm^{-1} 1650 (C=O).

Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 62.04; H, 4.01; N, 11.97.

Collection of peak 2 gave 1.05 g (11%) of (3,5-dimethyl-4-pyridazinyl)(4-chlorophenyl)ketone as colorless crystals, mp 138-141° (from ethyl acetate); ^{1}H-nmr (deuteriochloroform): δ 8.90 (s, H-6, 1 H), 7.8-7.4 (AA'BB' system, $J_{AB} \approx 8$ Hz, C_6H_4Cl, 4 H), 2.70 (s, CH_3, 3 H), 2.25 (s, CH_3, 3 H); ir: cm^{-1} 1665 (C=O).

Anal. Calcd. for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.21; H, 4.58; N, 11.37.

E-[5-(2-Dimethylaminoethenyl)-4-pyridazinyl]phenylketone (**20a**).

A solution of 396 mg (2 mmoles) of (5-methyl-4-pyridazinyl)-phenylketone [12] (**19a**) in 6 ml of dimethylformamide dimethyl acetal was heated to 100° for 18 hours. The mixture was evaporated and purified by column chromatography (ethyl acetate-ethanol, 18:1) to afford 321 mg (63%) of yellow crystals, mp 106-107° (from ethyl acetate-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.30, 8.75 (each d, unresolved, H-3, H-6, 2 H), 8.0-7.5 (m, C_6H_5, 5 H), 7.35 (d, J_{AB} = 14 Hz, *trans*-CH=C*H*-N, 1 H), 5.25 (d, J_{AB} = 14 Hz, *trans*-C*H*=CH-N, 1 H), 2.90 (s, CH_3, 6 H); ir: cm^{-1} 1640 (C=O), 1615.

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.12; H, 5.89; N, 16.75.

E-[5-(2-Dimethylaminoethenyl)-4-pyridazinyl](4-chlorophenyl)-ketone (**20b**).

Preparation as described for **20a**, starting from 464 mg (2 mmoles) of **19b**. Purification by column chromatography (ethyl acetate-ethanol, 9:1) afforded 437 mg (76%) of yellow crystals, mp 82-85° (from methanol); ^{1}H-nmr (deuteriochloroform): δ 9.25, 8.65 (each d, unresolved, H-3, H-6, 2 H), 7.85-7.40 (AA'BB' system, $J_{AB} \approx 8$ Hz, C_6H_4Cl, 4 H), 7.35 (d, J_{AB} = 14 Hz, *trans*-CH=C*H*-N, 1 H), 5.20 (d, J_{AB} = 14 Hz, *trans*-C*H*=CH-N, 1 H), 2.90 (s, CH_3, 6 H); ir: cm^{-1} 1640 (C=O), 1620.

Anal. Calcd. for $C_{15}H_{14}ClN_3O \cdot H_2O$: C, 58.92; H, 5.27; N, 13.74. Found: C, 58.76; H, 5.23; N, 13.41.

5-Phenylpyrido[3,4-*d*]pyridazine (**21a**).

A solution of 299 mg (1.2 mmoles) of **20a** and 924 mg (12 mmoles) of ammonium acetate in 20 ml of ethanol was refluxed for 2 hours. The mixture was evaporated and the residue was partitioned between water and dichloromethane. Evaporation of the organic layer, followed by column chromatography (ethyl acetate) yielded 123 mg (50%) of brownish needles, mp 124-127° (from toluene-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.85, 9.75 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 9.20 (d, J = 5.5 Hz, H-7, 1 H), 8.0-7.5 (m, H-8, C_6H_5, 6 H).

Anal. Calcd. for $C_{13}H_9N_3 \cdot 1/8\ H_2O$: C, 74.54; H, 4.23; N, 19.97. Found: C, 74.59; H, 4.23; N, 19.97.

5-(4-Chlorophenyl)pyrido[3,4-*d*]pyridazine (**21b**).

A solution of 288 mg (1 mmole) of **20b** and 231 mg (3 mmoles) of ammonium acetate in 20 ml of ethanol was refluxed for 2 hours. After evaporation, the residue was triturated with water, filtered and dried to afford 218 mg (76%) of brownish needles, mp 188-189° (from ethanol); ^{1}H-nmr (deuteriochloroform): δ 9.75, 9.70 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 9.15 (d, J = 5.5 Hz, H-7, 1 H), 7.75 (d, J = 5.5 Hz, H-8, 1 H), 7.8-7.5 (AA'BB' system, $J_{AB} \approx 8$ Hz, C_6H_4Cl, 4 H).

Anal. Calcd. for $C_{13}H_8ClN_3 \cdot 1/8\ H_2O$: C, 64.02; H, 3.41; N, 17.22. Found: C, 63.96; H, 3.55; N, 16.87.

E-Ethyl 5-(2-Dimethylaminoethenyl)-4-pyridazinecarboxylate (**23**).

A solution of 166 mg (1 mmole) of ethyl 5-methyl-4-pyridazine-carboxylate [15] (**22**) in 2 ml of dimethylformamide dimethyl acetal was heated to 100° for 4 hours. The mixture was evaporated and the residue was subjected to column chromatography (dichloromethane-methanol, 19:1) to afford 200 mg (90%) of an oily residue, which was crystallized from cyclohexane to give yellow crystals, mp 122-123°; ^{1}H-nmr (deuteriochloroform): δ 9.20, 9.10 (each s, H-3, H-6, 2 H), 7.50 (d, J_{AB} = 14 Hz, *trans*-CH=C*H*-N, 1 H), 6.25 (d, J_{AB} = 14 Hz, *trans*-C*H*=CH-N, 1 H),

4.35 (q, J = 7 Hz, CH_2CH_3, 2 H), 3.05 (s, NCH_3, 6 H), 1.40 (t, J = 7 Hz, CH_2CH_3, 3 H); ir: cm^{-1} 1710 (C=O), 1620.

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.29; H, 6.75; N, 18.69.

6-(*n*-Butyl)pyrido[3,4-*d*]pyridazin-5(6*H*)-one (**24**).

A solution of 110 mg (0.5 mmoles) of **23** and 3 drops of trifluoroacetic acid in 4 ml of *n*-butylamine was refluxed for 1 hour. The mixture was evaporated and the residue was partitioned between water and dichloromethane. The organic layer was evaporated to give a brownish residue which was extracted several times with boiling light petroleum. Concentration of the combined extracts afforded 85 mg (83%) of colorless crystals, mp 85-86° (from ethyl acetate-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.95, 9.45 (each d, J = 1.5 Hz, H-1, H-4, 2 H), 7.60 (d, J = 7 Hz, H-7, 1 H), 6.55 (d, J = 7 Hz, H-8, 1 H), 3.10 (t, J = 7 Hz, NCH_2, 2 H), 2.0-1.2 (m, C-CH_2CH_2-C, 4 H), 1.0 (t, J = 7 Hz, CH_3, 3 H); ir: cm^{-1} 1670 (C=O).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.79; H, 6.45; N, 20.59.

Pyrido[3,4-*d*]pyridazin-5(6*H*)-one (**25**).

A solution of 221 mg (1 mmole) of **23** in 30 ml of absolute ethanol was saturated with dry ammonia and heated in an autoclave to 200° for 5 hours. After cooling, the solution was treated with charcoal, filtered, and evaporated to give 120 mg (81%) of nearly colorless crystals, mp >310° (from 2-propanol); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 12.3 (br, NH, 1 H), 9.65 (s, H-1, H-4, 2 H), 7.75 (d, J = 7 Hz, H-7, 1 H), 6.70 (d, J = 7 Hz, H-8, 1 H); ir: cm^{-1} 1700 (C=O).

Anal. Calcd. for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.10; H, 3.59; N, 28.55.

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REFERENCES AND NOTES

[1] As Pyridazines **XL** counts: J. Easmon, G. Heinisch, W. Holzer and B. Rosenwirth, *Arzneim.-Forsch.*, in press.

[2] Presented as part of a communication at the 7th Scientific Meeting of the Austrian Pharmaceutical Society, Vienna, Austria, April 1988.

[3] Part of planned Ph.D. Thesis of P. Y. B..

[4] P. Y. Boamah, N. Haider, G. Heinisch and J. Moshuber, *J. Heterocyclic Chem.*, **25**, 879 (1988).

[5a] S. Mataka, K. Takahashi and M. Tashiro, *Synthesis*, 687 (1979); [b] S. Mataka, K. Takahashi and M. Tashiro, *ibid.*, 842 (1980); [c] S. Mataka, K. Takahashi, Y. Tsuda and M. Tashiro, *Heterocycles*, **14**, 789 (1980); [d] S. Mataka, K. Takahashi and M. Tashiro, *J. Heterocyclic Chem.*, **18**, 1073 (1981); [e] S. Mataka, K. Takahashi and M. Tashiro, *Heterocycles*, **20**, 1285 (1983).

[6] M. Braun, G. Hanel and G. Heinisch, *Monatsh. Chem.*, **109**, 63 (1978).

[7] G. Heinisch, *ibid.*, **104**, 953 (1973).

[8] G. Heinisch, I. Kirchner, I. Kurzmann, G. Lötsch and R. Waglechner, *Arch. Pharm. (Weinheim)*, **316**, 508 (1983).

[9] G. Heinisch and I. Kirchner, *Monatsh. Chem.*, **110**, 365 (1979).

[10] N. Haider, G. Heinisch, I. Kurzmann-Rauscher and M. Wolf, *Ann. Chem.*, 167 (1985).

[11] Compound **19a** was prepared as described in ref [12]; by applying this method (radicalic aroylation of **18** using 4-chlorobenzaldehyde/*t*-butyl hydroperoxide/ferrous sulfate) besides the required ketone **19b** a side product was obtained in 11% yield. Due to elemental analysis and spectroscopic data its structure could be determined as (3,5-dimethyl-4-pyridazinyl)(4-chlorophenyl)ketone, obviously formed by additional attack of a methyl radical (originating from *t*-BuO$^\cdot$) at C-3 of compound **19b**.

[12] G. Heinisch and R. Waglechner, *J. Heterocyclic Chem.*, **21**, 1727 (1984).

[13] In accordance to ref [14], 4-methylpyridazine (**18**) was found not to react with *DMFDMA* even at reflux temperature.

[14] B. Stanovnik, personal communication.

[15] G. Heinisch and G. Lötsch, *Tetrahedron*, **41**, 1199 (1985).

[16] S. Chimichi and R. Nesi, *J. Chem. Soc., Perkin Trans. 1*, 2215 (1979).

[17] Addition of one drop of deuterium chloride/deuterium oxide to the sample solution leads to suppression of additional signals (*ca.* 10% of the main signals) observed in neutral solution, which obviously result from the ring-opened amide (ring-chain tautomerism of compound **17**).

[18] R. Mizzoni and P. Spoerri, *J. Am. Chem. Soc.*, **76**, 2201 (1954).