PYRIDAZINES XLII[1,2]. ON THE SYNTHESIS OF N-5-SUBSTITUTED PYRIDAZINO[4,5-*b*]QUINOLIN-10(5H)-ONES

Norbert Haider, Gottfried Heinisch*, and Ivo Volf[3]

Institute of Pharmaceutical Chemistry, University of Vienna,
Währinger Straße 10, A-1090 Vienna, Austria

Abstract - Procedures for the preparation of diazaacridones **6** bearing branched or higher alkyl chains at N-5 were developed utilizing the pyridazinone **7** as a key compound. An unexpected side reaction observed in the course of the synthesis of **7** is described.

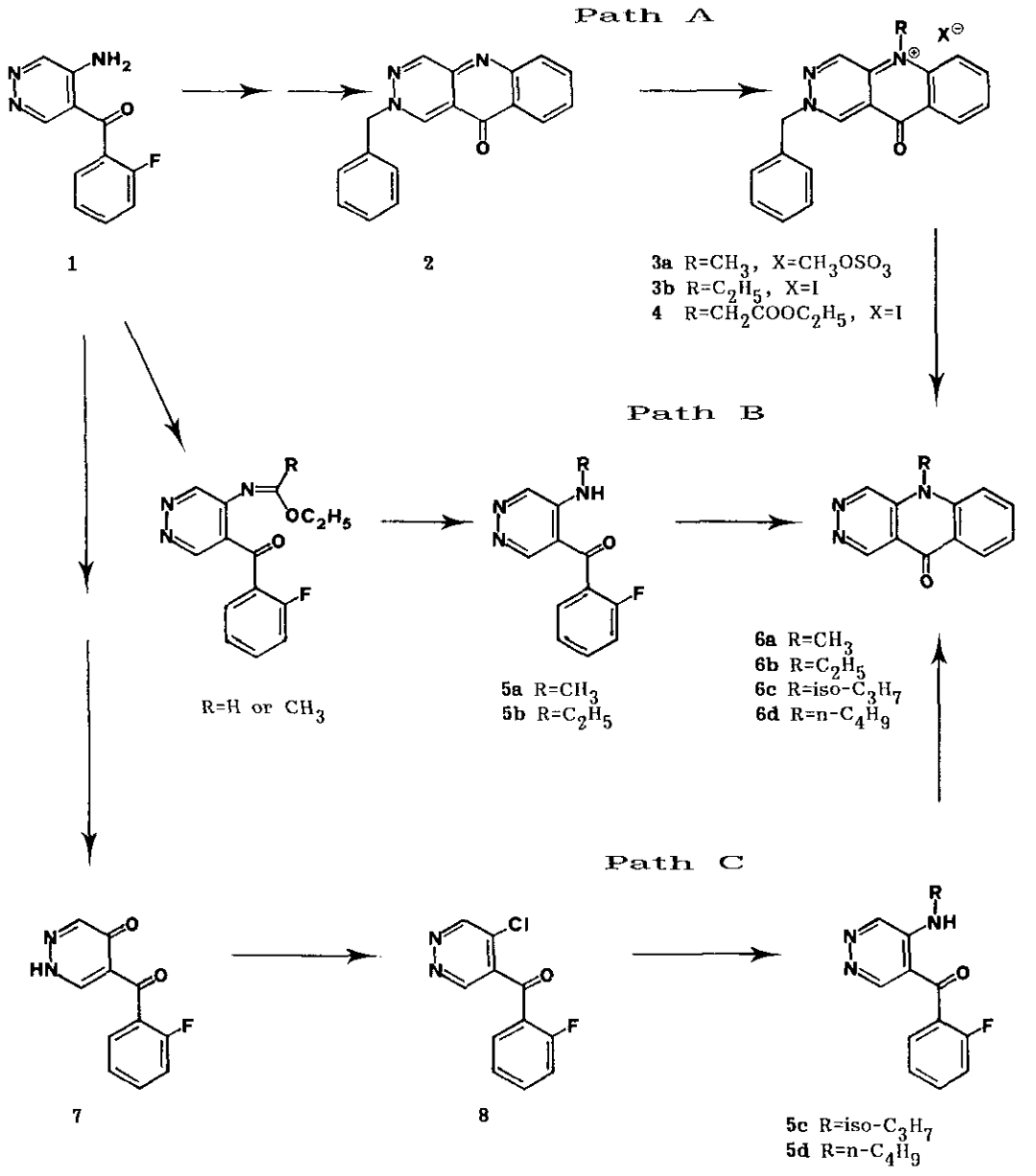
A wide variety of diaza analogues of pharmaceutically important tricyclic systems including diazaacridones like pyridazino[3,4-*b*]quinolin-10(5*H*)-ones and pyridazino[4,5-*b*]quinolin-10(5*H*)-ones has become available recently.[4,5] So far, however, only little effort has been made to find access to N-5-substituted derivatives of the latter:[6] the alkylamino ketones **5a,b** were reported to cyclize smoothly under alkaline conditions to give **6a,b**;[5] this approach, however, is limited in scope.[7] An alternative route to **6a**, consisting of quaternization of the N-2-benzyldiazaacridone **2** employing dimethyl sulfate followed by debenzylation, was described recently.[5]

Here we report on investigations of reactions of **2** with various alkylating agents as well as on the synthesis and cyclization reactions of amino ketones of type **5** substituted at the amino group by a higher or branched alkyl moiety.

Whereas treatment of **2** with diethyl sulfate in analogy to the method reported[5] gave only poor results, alkylation of **2** employing neat ethyl iodide at 150°C afforded a 89% yield of 2-benzyl-2,10-dihydro-5-ethyl-10-oxopyridazino[4,5-*b*]quinolinium iodide **3b**. Similarly, reaction of **2** with ethyl iodoacetate in 1,2-dimethoxyethane at 75°C gave, in 63% yield, 2-benzyl-2,10-dihydro-5-ethoxycarbonylmethyl-10-oxopyridazino[4,5-*b*]quinolinium iodide **4**. However, attempts to introduce higher or branched alkyl groups (n-propyl, allyl, n-butyl, or isopropyl) into **2** by employing the corresponding iodides in a similar manner remained unsuccessful owing to decomposition at elevated temperature.

Aluminium trichloride-mediated removal of the benzyl group from **3b** (according to ref.[5]) finally afforded **6b**[5] in 95% yield. The reaction sequence **1**→**2**→**3b**→**6b** gives a 75% overall yield and thus represents a route superior to the procedure formerly described (path B[5]). On the other hand, with the ethoxycarbonylmethyl compound **4**, the debenzylation attempted under various conditions[9] met with no success.

These results prompted us to elaborate an alternative approach to 5-substituted pyridazino-[4,5-*b*]quinolin-10(5*H*)-ones bearing even branched or higher alkyl chains. Since this new procedure is based on a novel synthesis of 5-alkylamino-4-pyridazinyl aryl ketones of type **5**, the limitations[7] encountered with the previously used methodology[8] could be overcome.



Scheme 1

It was found that the pyridazinone **7**, conveniently available from **1** *via* a N-benzylation - hydrolysis - debenzylation sequence,[5] could be converted into the (unstable) chloropyridazine **8**, which, in turn, could be reacted with branched or higher alkylamines, as demonstrated in the preparation of compounds **5c** and **5d**. The latter, then, could be cyclized smoothly to yield the target N-5-alkyldiazaacridones **6c** and **6d** (the sequence **8** → **5d** → **6d** was carried out as a one-pot reaction). Structural assignment for the new compounds **6c,d** is based on elemental analyses as well as on their spectral data, which are quite similar to those of compounds **6a,b**.[5]

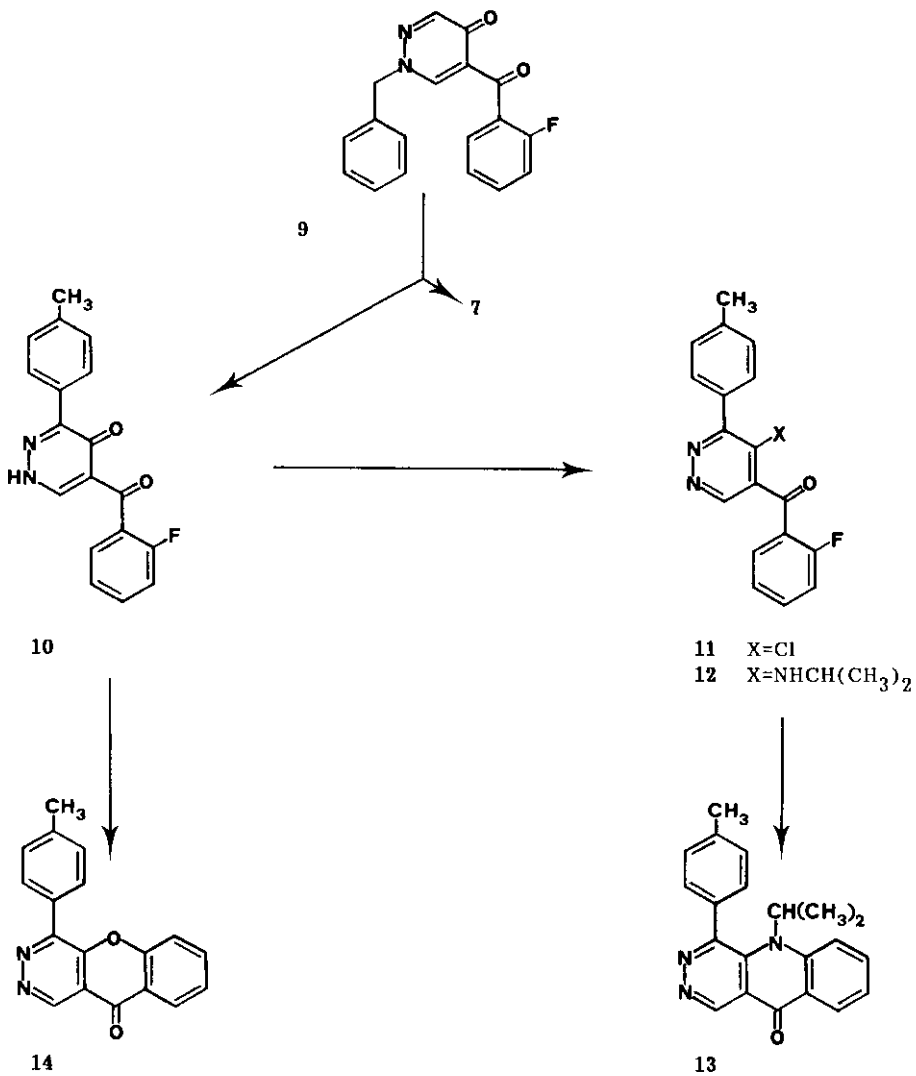
In the course of the preparation of the pyridazinone **7** by aluminium trichloride/toluene-mediated debenzylation of 1-benzyl-5-(2-fluorobenzoyl)pyridazin-4(1*H*)-one **9** according to the procedure reported[5] the formation of varying amounts (up to 20%) of a side product (**10**) was observed. Being markedly less polar than **7**, this new compound could be easily separated by column chromatography. Elemental composition ($C_{18}H_{13}FN_2O_2$) and ms data (m/z = 308, M^+) of the compound indicated an isomer of **9**. Ir- and ^{1}H-nmr-spectroscopic data (see Experimental) gave evidence for the surprising structure of a (4-tolyl)-substituted 5-(2-fluorobenzoyl)pyridazin-4(1*H*)-one. The position of the aryl substituent in compound **10** follows from observed splitting (J = 1 Hz) of the resonance signal at 8.62 ppm. This phenomenon, attributable to "through-space coupling" between the fluorine atom and the pyridazine proton,[10] suggests the latter to be located at C-6 and thus the tolyl moiety to be attached to C-3 (*ortho* to the pyridazinone oxo function).

In turn, compound **10** could be converted into the 4-aryl-5-alkyldiazaacridone **13** *via* the (unstable) chloro ketone **11** and the isopropylamino ketone **12** following the experimental procedures given for the preparation of compounds **6c,d** from **7** *via* **8** and **5c,d** (Scheme 1, path C). In addition, we found that cyclization of **10** under conditions previously proposed for the synthesis of 10*H*-[1]benzopyrano[2,3-*d*]pyridazin-10-one[5] (K_2CO_3/DMF) affords the novel diazaxanthone derivative 4-(4-tolyl)-10*H*-[1]benzopyrano[2,3-*d*]pyridazin-10-one **14** in 70% yield.

At present, no definitive conclusions can be drawn with respect to the mechanism of the surprising formation of compound **10**; further investigations on this subject are intended.

ACKNOWLEDGEMENT

The authors are grateful to Dr.W.Holzer for recording the 400 MHz ^{1}H-nmr spectrum and to Dr.A.Nikiforov for recording the mass spectra. Elemental analyses were performed by Dr.J.Zak (Institute of Physical Chemistry, University of Vienna). Support of this work by the "Hochschuljubiläumsstiftung der Stadt Wien" is gratefully acknowledged.



Scheme 2

EXPERIMENTAL

Melting points (uncorrected): Kofler hot-stage microscope; ir spectra: Jasco IRA-1 spectrophotometer; ^{1}H-nmr spectra: Varian EM 390 (90 MHz) or Bruker AC 80 (80 MHz) spectrometer; mass spectra (ms): Varian MAT 311A spectrometer (70 eV); column chromatography: silica gel (0.063-0.200 mm; Merck); medium pressure liquid chromatography (mplc): LiChroprep Si 60 (0.040-0.063 mm; Merck); thin layer chromatography (tlc): precoated aluminium sheets (Kieselgel 60 F_{254}; Merck).

2-Benzyl-2,10-dihydro-5-ethyl-10-oxopyridazino[4,5-*b*]quinolinium Iodide (**3b**)

A mixture of 287 mg (1 mmol) of **2** and 5 ml of ethyl iodide was heated in an autoclave to 150°C for 16 h. The precipitate obtained on addition of 20 ml of diethyl ether was collected and dried to give 393 mg (89%) of **3b**, which was recrystallized from ethanol to afford orange needles; mp 131.5-133°C; ir (KBr) 1655 cm^{-1}; ^{1}H-nmr (90 MHz, d_6-DMSO) δ 1.50 (t, J = 7 Hz, 3 H, CH_2CH_3), 4.85 (q, J = 7 Hz, 2 H, CH_2CH_3), 6.05 (s, 2 H, $C_6H_5CH_2$), 7.40 - 7.65 (m, 5 H, C_6H_5), 7.70 - 8.35 (m, 3 H, 6-H, 7-H, 8-H), 8.50 (m, 1 H, 9-H), 10.15, 10.50 (each s, 2 H, 1-H, 4-H) ppm; Anal. Calcd for $C_{20}H_{18}IN_3O$: C, 54.19; H, 4.09; N, 9.40. Found: C, 54.00; H, 4.43; N, 9.29.

2-Benzyl-2,10-dihydro-5-ethoxycarbonylmethyl-10-oxopyridazino[4,5-*b*]quinolinium Iodide (**4**)

A mixture of 287 mg (1 mmol) of **2**, 856 mg (4 mmol) of ethyl iodoacetate, and 15 mg of potassium carbonate in 4 ml of dry 1,2-dimethoxyethane was heated in an autoclave to 75°C for 16 h. The precipitate was purified by column chromatography (CH_2Cl_2/CH_3OH, 9:1) to give 315 mg (63%) of **4**; yellow crystals (from acetone), mp >185°C (decomp.);[11] ir (KBr) 1740, 1660 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.26 (t, J = 7 Hz, 3 H, CH_2CH_3), 4.27 (q, J = 7 Hz, 2 H, CH_2CH_3), 5.80 (s, 2 H, NCH_2CO), 6.02 (s, 2 H, $C_6H_5CH_2$), 7.35 - 8.25 (m, 8 H, C_6H_5, 6-H, 7-H, 8-H), 8.48 (m, 1 H, 9-H), 10.05, 10.48 (each s, 2 H, 1-H, 4-H) ppm.

5-Ethylpyridazino[4,5-*b*]quinolin-10(5*H*)-one (**6b**)

A mixture of 221 mg (0.5 mmol) of **3b** and 266 mg (2 mmol) of aluminium trichloride in 20 ml of dry toluene was heated to 80°C for 2 h. The solvent was removed *in vacuo* and the residue was partitioned between 1 N aqueous sodium hydroxide and CH_2Cl_2. Evaporation of the organic layer afforded 214 mg (95%) of **6b**,[5] which was recrystallized from ethanol to afford pale yellow needles; mp 212-215°C (ref.[5] mp 214-215°C); identical (ir) with an authentic sample.[5]

(5-Chloro-4-pyridazinyl) (2-Fluorophenyl) Ketone (**8**)

A solution of 218 mg (1 mmol) of **7**[5] and 1.2 ml of dry pyridine in 12 ml of phosphorus oxychloride was heated to 60°C for 45 min; the solution was slowly poured on ice and extracted with dichloromethane. After concentration of the extract *in vacuo* and purification by medium pressure liquid chromatography (CH_2Cl_2/ethyl acetate, 3:2), crude **8** was obtained as a brown oil (yield: approx. 50%), which was immediately used for the following reaction steps;[12] ^{1}H-nmr (80 MHz, $CDCl_3$) δ 7.00 - 8.00 (m, 4 H, C_6H_4F), 9.14, 9.31 (each s; 2 H, 3-H, 6-H) ppm.

[5-(iso-Propyl)amino-4-pyridazinyl] (2-Fluorophenyl) Ketone (**5c**)

To a solution of the crude chloro ketone **8**, prepared from 218 mg (1 mmol) of **7** (as described above) in 2 ml of dichloromethane were added 5 ml of isopropylamine, and the mixture was heated to 35°C for 19 h. The residue obtained on evaporation was subjected to mplc (CH_2Cl_2/CH_3OH, 9:1) to give 91 mg (35%, rel. to **7**) of **5c** as a yellow oil; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.41 (d, J = 6.5 Hz, 6 H, CH_3), 4.07 (m, 1 H, CH), 7.08 - 7.72 (m, 4 H, C_6H_4F), 8.60 (d, J_{H-F} = 2 Hz, 1 H, 3-H), 8.97 (s, 1 H, 6-H), 8.95 - 9.15 (br, 1 H, NH) ppm; Anal. Calcd for $C_{14}H_{14}FN_3O \cdot 1/8\ H_2O$: C, 64.30; H, 5.49; N, 16.07. Found: C, 64.10; H, 5.41; N,16.04.

5-(iso-Propyl)pyridazino[4,5-*b*]quinolin-10(5*H*)-one (**6c**)

To a solution of 91 mg (0.35 mmol) of **5c** in 10 ml of dimethylformamide were added 138 mg (1 mmol) of potassium carbonate, and the mixture was heated to 110°C for 4 h. The residue obtained on evaporation was partitioned between water and CH_2Cl_2. The organic layer was concentrated *in vacuo* and the residue was subjected to mplc (CH_2Cl_2/CH_3OH, 97:3) to afford 72 mg (86%; 30% rel. to **7**) of **6c**; pale yellow crystals (from ethanol); mp 212-216°C; ir (KBr) 1640 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.88 (d, J = 7 Hz, 6 H, CH_3), 5.30 (septet, J = 7 Hz, 1 H, CH), 7.30 - 7.85 (m, 3 H, 6-H, 7-H, 8-H), 8.53 (m, 1 H, 9-H), 9.72, 9.78 (each s, 2 H, 1-H, 4-H) ppm; Anal. Calcd for $C_{14}H_{13}N_3O \cdot 1/8\ H_2O$: C,69.62; H, 5.53 N, 17.40. Found: C,69.71; H, 5.47; N, 17.33.

5-(n-Butyl)pyridazino[4,5-*b*]quinolin-10(5*H*)-one (**6d**)

To a solution of the crude chloro ketone **8**, prepared from 218 mg (1 mmol) of **7** (as described above) in 2 ml of dichloromethane were added 5 ml of n-butylamine, and the mixture was heated to 60°C for 2 h. The residue obtained on evaporation[13] was dissolved in 10 ml of dimethylformamide; after addition of 138 mg (1 mmol) of potassium carbonate, the mixture was heated to 110°C for 4 h. Work-up was the same as described for **6c**, affording 89 mg (35% rel. to **7**) of **6d**; yellow crystals (from ethanol); mp 176-179°C; ir (KBr) 1640 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.10 (t, J = 7 Hz, 3 H, CH_3), 1.45 - 2.10 (m, 4 H, $C\text{-}CH_2CH_2\text{-}C$), 4.47 (t, J = 7 Hz, 2 H, $N\text{-}CH_2$), 7.30 - 7.90 (m, 3 H, 6-H, 7-H, 8-H), 8.55 (m, 1 H, 9-H), 9.58, 9.79 (each s, 2 H, 1-H, 4-H) ppm; Anal. Calcd for $C_{15}H_{15}N_3O \cdot 1/4\ H_2O$: C, 69.88; H, 6.06; N, 16.30. Found: C, 70.03; H, 6.03; N, 16.26.

5-(2-Fluorobenzoyl)-3-(4-tolyl)pyridazin-4(1*H*)-one (**10**)

A mixture of 308 mg (1 mmol) of **9** and 532 mg (4 mmol) of aluminium trichloride in 30 ml of dry toluene was heated to 80°C for 0.5 h.[5] After cooling, 2 ml of water were added; the precipitate

was subjected to mplc (CH_2Cl_2/CH_3OH, 97:3) to afford (besides 70-80% of **7**[5,14]) up to 20% of **10**; colorless crystals (from methanol); mp 215-216.5°C; ir (KBr) 1645 cm^{-1}; ^{1}H-nmr (400 MHz, d_6-DMSO) δ 2.33 (s, 3 H, CH_3), 7.20 - 7.31 (m, 4 H, 3-H and 5-H of $C_6H_4CH_3$, 3-H and 5-H of C_6H_4F), 7.55 - 7.65 (m, 2 H, 4-H and 6-H of C_6H_4F), 7.86, 7.88 (BB'-part of an AA'BB' system, 2 H, 2-H and 6-H of $C_6H_4CH_3$), 8.62 (d, J = 1 Hz, 1 H, 6-H) ppm; ms m/z = 308 (M^+, 20%); Anal. Calcd for $C_{18}H_{13}FN_2O_2$: C,70.12; H, 4.25; N, 9.09. Found: C, 70.03; H, 4.31; N, 9.20.

5-(2-Propyl)-4-(4-tolyl)pyridazino[4,5-*b*]quinolin-10(5*H*)-one (**13**)

A solution of 308 mg (1 mmol) of **10** and 1.2 ml of dry pyridine in 12 ml of phosphorus oxychloride was heated to 60°C for 45 min; the solution was slowly poured on ice and extracted with CH_2Cl_2. After concentration of the extract *in vacuo* and purification by quick column chromatography (CH_2Cl_2/ethyl acetate, 3:2), the crude chloro ketone **11** thus obtained was immediately dissolved in 5 ml of isopropylamine. The solution was heated to 40°C for 5 h. Evaporation gave a yellow oil,[15] which was dissolved in 10 ml of dimethylformamide; after addition of 138 mg (1 mmol) of potassium carbonate, the mixture was heated to 110°C for 4 h. The solvent was removed *in vacuo* and the residue was partitioned between water and CH_2Cl_2. Evaporation of the organic layer gave 99 mg (30% rel. to **10**) of **13**; yellow crystals (from ethanol); mp 202.5-206°C; ir (KBr) 1635 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.17 (d, J = 7 Hz, 6 H, CH_3), 2.46 (s, 3 H, $C_6H_4CH_3$), 4.69 (*septet*, J = 7 Hz, 1 H, CH), 7.25 - 7.81 (*m*, 7 H, 6-H, 7-H, 8-H; $C_6H_4CH_3$), 8.44 - 8.54 (m, 1 H, 9-H), 9.73 (s, 1 H, 1-H) ppm; ms m/z = 329 (M^+, 100%); Anal. Calcd for $C_{21}H_{19}N_3O \cdot 1/2\ H_2O$: C,74.53; H,5.96; N, 12.42. Found: C,74.53; H, 5.83; N, 12.01.

4-(4-Tolyl)-10*H*-[1]benzopyrano[2,3-*d*]pyridazin-10-one (**14**)

A mixture of 144 mg (0.5 mmol) of **10** and 69 mg (0.5 mmol) of potassium carbonate in 5 ml of dimethylformamide was heated to 130°C for 6 h. The solvent was removed *in vacuo* and the residue was partitioned between water and CH_2Cl_2. Evaporation of the organic layer gave 101 mg (70%) of **14**, which was recrystallized from ethanol to afford colorless crystals; mp 218-222°C; ir (KBr) 1670 cm^{-1}; ^{1}H-nmr (90 MHz, $CDCl_3$) δ 2.50 (s, 3 H, CH_3), 7.35 - 8.15 (m, 7 H, 6-H, 7-H, 8-H; $C_6H_4CH_3$), 8.35 (m, 1 H, 9-H), 9.75 (s, 1 H, 1-H) ppm; Anal. Calcd. for $C_{18}H_{12}N_3O_2$: C, 74.98; H, 4.20; N, 9.72. Found: C, 74.83; H, 4.36; N, 9.87.

REFERENCES AND NOTES

1. Pyridazines XLI: P.Y.Boamah, N.Haider, and G.Heinisch, *J.Heterocyclic Chem.*, in the press.

2. Presented as part of communications at the symposium, "Chemistry and Pharmacology of Pyridazines", Strasbourg, France, September, 1988, and at the 2nd Ibn Sina Symposium on Heterocyclic Chemistry, St.Catherine, Sinai, Egypt, November, 1988.
3. Part of planned Diploma Thesis of I.V., University of Vienna.
4. G.Heinisch and D.Laßnigg, *Arch.Pharm.*, 1987, **320**, 1222.
5. N.Haider and G.Heinisch, *J.Chem.Soc., Perkin Trans.1*, 1988, 401.
6. It has been reported that treatment of pyridazino[4,5-*b*]quinolin-10(5*H*)-one with alkyl halides gives 2-alkylated compounds exclusively.[5] The same regioselectivity is observed upon alkylation under phase-transfer conditions (methyl iodide/KOH/DMSO).[3]
7. The previously proposed synthesis of (5-alkylamino-4-pyridazinyl)aryl ketones proceeds *via* reduction of imido esters derived from the primary heterocyclic amine[8] and thus is not applicable for preparing homologues with branched side chains like **5c**.
8. N.Haider and G.Heinisch, *Heterocycles*, 1985, **23**, 2651.
9. Toluene/aluminium trichloride;[5] trifluoroacetic acid (reflux); 2 N aqueous sodium hydroxide (reflux).
10. Similar H-F couplings have been observed with compounds **1**, **5a,b**[5] and related 2-fluorobenzoyl-substituted pyridazine derivatives[5] as well as with compound **12**.
11. Owing to the extremely hygroscopic nature of compound **4** we failed in attempts to prepare a sample affording satisfactory elemental analyses.
12. Compound **8** was found to decompose rapidly upon complete evaporation of the solution.
13. ^{1}H-Nmr data (80 MHz, $CDCl_3$) of crude **5d**: δ 1.00 (t, *J* = 7 Hz, 3 H, CH_3), 1.15 - 1.90 (m, 4 H, C-CH_2CH_2-C), 3.20 - 3.65 (m, 2 H, NCH_2), 7.05 - 7.75 (m, 4 H, C_6H_4F), 8.60 (d, J_{H-F} = 2 Hz, 1 H, 3-H), 8.96 (s, 1 H, 6-H), 9.00 - 9.15 (br, 1 H, NH) ppm.
14. Mp found for compound **7**: 180.5-182.5°C (from methanol); ref.[5]: mp 175-195°C.
15. ^{1}H-Nmr (80 MHz, $CDCl_3$) of crude **12**: δ 0.93 (d, *J* = 6.5 Hz, 6 H, CH_3), 2.35 (s, 3 H, $C_6H_4CH_3$), 3.10 - 3.60 (m, 1 H, CH), 7.00 - 7.60 (m, 8 H, C_6H_4F, $C_6H_4CH_3$), 8.51 (d, J_{H-F} = 2 Hz, 1 H, 6-H) ppm.

Received, 13th March, 1989