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Application of Organolithium and Related Reagents in Synthesis, Part XII [1]. Synthesis of Phenyl- and Pyridylpyrido-pyridazinones and their Derivatives

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Summary. The preparation of the pyridazinones **10a**, **10b**, **11a**, **11b**, and **12a**, **12b** from the ketoamides **7**, **8**, and **9** and hydrazine hydrate is described. It was found that from ketoamides **8b** and **9b** in addition to the expected pyridopyridazinones **11b** and **12b** also aminopyridopyridazines **14** and **15** were formed and that ketoamide **7b** gave exclusively aminopyridopyridazine **13**. The pyridopyridazinones **10b**, **11b**, and **12b** were alkylated with alkyl iodides.

Keywords. Pyridinecarboxamides; Lithiation; Benzoylpyridinecarboxamides; Pyridinecarbonyl-pyridinecarboxamides; Pyridopyridazinones; Aminopyridopyridazines.

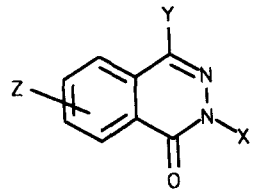
Anwendungen von Organolithium und verwandten Reagenzien in organischen Synthesen, Teil XII [1]. Synthese von Phenyl- und Pyridylpyridopyridazinonen und ihren Derivaten

Zusammenfassung. Die Darstellung der Pyridazinone **10a**, **10b**, **11a**, **11b** und **12a**, **12b** aus Ketoamiden **7**, **8** und **9** und Hydrazinhydrat wird beschrieben. Es wurde festgestellt, daß aus Ketoamiden **8b** und **9b** außer den erwarteten Pyridopyridazinonen **11b** und **12b** auch Aminopyridopyridazine **14** und **15** enstanden und daß das Ketoamid **7b** ausschließlich ins Aminopyridopyridazin **13** überführt wurde. Die Pyridopyridazinone **10b**, **11b** und **12b** wurden mit Alkyljodiden alkyliert.

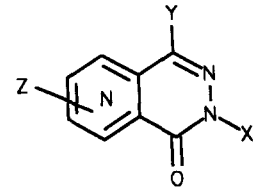
Introduction

"The observed inhibition of platelet aggregation, antihypertensive, antispasmodic, diuretic, and aldose reductase activity [2] of compounds **A** and **B** have promoted a widespread interest in their synthesis."

We were particularly interested in developing a new strategy for the preparation of compounds of the type **B**. The key step in their synthesis was formation of the *ortho*-benzoyl and *ortho*-pyridinecarbonyl derivatives of N,N-dialkylpyridine-carboxamides **7**, **8**, and **9** via a lithiation-electrophilic substitution sequence of the corresponding pyridinecarboxamides **1**, **2**, and **3** [3].



A



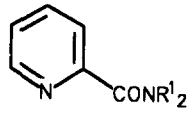
B

Results and Discussion

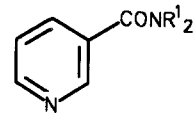
To this end, at first the tertiary pyridinecarboxamides **1**, **2**, and **3** were allowed to react with lithium diisopropylamide (*LDA*) in diethyl ether at −78 °C, generating the regioselectively lithiated species **4**, **5**, and **6**. The N,N-diethylamides **1a**, **2a**, and **3a** reacted with *LDA* to form the lithioamides **4a**, **5a**, and **6a** which instantly added across the carybonyl group of the parent compounds to give the ketoamides **7a**, **8a** and **9a**. In contrast with the N,N-diethylamides, the N,N-diisopropylamides **1b**, **2b**, and **3b** reacted with *LDA* to generate the lithioamides **4b**, **5b**, and **6b** which were sufficiently stable to react with electrophiles other than the internal carbonyl group. The treatment of the solution of the lithiated species with the N,N-dimethylbenzamide furnished the desired ketoamides **7b**, **8b**, and **9b**. In the next step, the ketoamides **7**, **8**, and **9** were subjected to react with hydrazine hydrate in boiling diethylene glycol.

In the case of N,N-diethylketoamides **7a**, **8a**, and **9a** the corresponding pyridopyridazinones **10a** (89%), **11a** (95%), and **12a** (96%) were formed.

On the other hand, N,N-diisopropylketoamides, **8b** and **9b** furnished mixtures of products. Thus, ketoamides **8b** and **9b** gave pyridopyridazinones **11b** (66%) and **12b**



1



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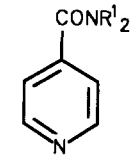
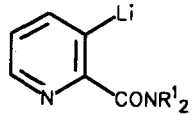


3

a, R^1 = Et; b, R^1 = Pr^i



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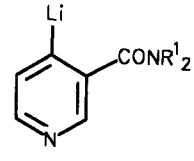

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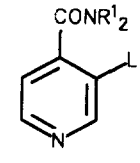
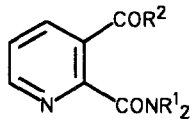


6

a, R^1 = Et; b, R^1 = Pr^i



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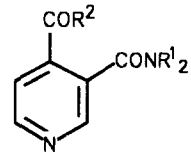

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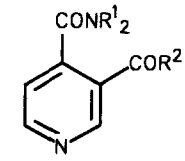
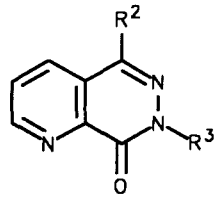


9

	R^1	R^2
a	Et	2-Py for 7
	Et	3-Py for 8
	Et	4-Py for 9
b	Pr^i	Ph

(53%) together with N,N-diisopropylaminopyridopyridazines **14** (10%) and **15** (8%), respectively. In contrast with the ketoamides **8b** and **9b**, the ketoamide **7b** gave only N,N-diisopropylaminopyridopyridazine **13** (42%). The pyridopyridazinone **10b** was obtained directly from 3-benzoylpicolinic acid and hydrazine hydrate in 87% yield.



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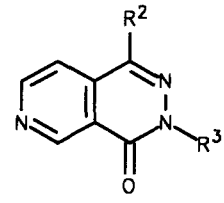

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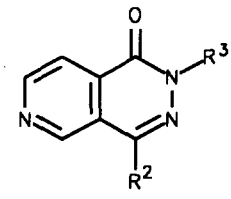
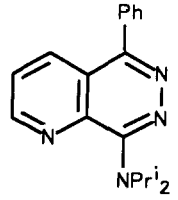


12

	R^2	^{3}
a	2-Py for 10	H
	3-Py for 11	H
	4-Py for 12	H
b	Ph	H

	R^2	R^3
c	Ph	Me
d	Ph	Et
e	Ph	Pr^i
f	Ph	Ph



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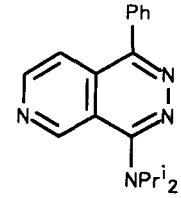

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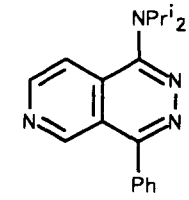

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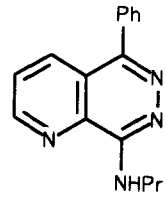
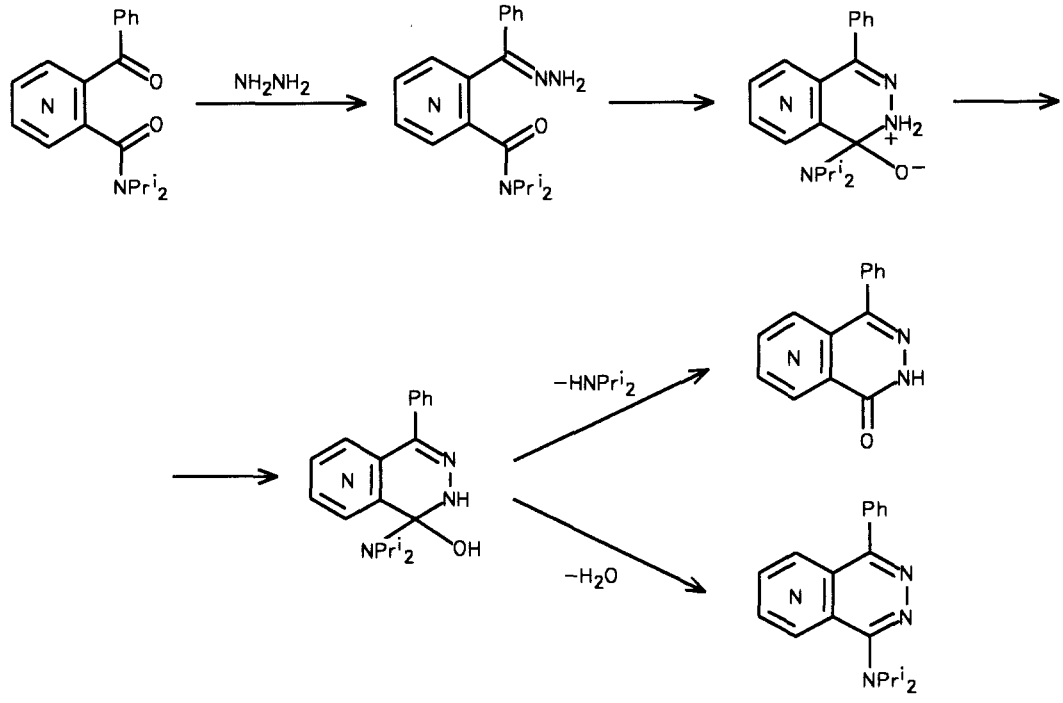


16

Although the observed formation of a mixture of pyridopyridazinones and N,N-diisopropylaminopyridopyridazines cannot be unequivocally explained, it may be assumed that they are formed according to the reaction sequence presented in Scheme 1. It has been postulated [4] that the formation of pthalazinones from unhindered *ortho*-ketoacids or their derivatives undoubtedly involves the initial formation of the hydrazones which further reacts intramolecularly with the carboxyl carbonyl. Therefore, formation of the pyridopyridazinones or the diisopropylaminopyridopyridazines depends upon elimination of diisopropylamine or water, respectively.



Scheme 1

The pyridopyridazinones **10b**, **11b**, and **12b**, on the reaction with alkyl halides (*Me*I, *Et*I and *Pr*^{i}I) in the presence of potassium hydroxide, were converted into the corresponding N-alkylpyridopyridazinones **10c** (84%), **10d** (81%), **11c** (91%), **11d** (80%), **11e** (77%), **12c** (91%), **12d** (84%) and **12e** (76%). The pyridopyridazinone **10f** was obtained from 3-benzoylpicolinic acid and phenylhydrazine in 90% yield.

This represents an effective synthetic route for the preparation of pyridopyridazinones, starting from easily available pyridinecarboxamides.

It was also found that during heating under reflux in 18% hydrochloric acid of the N,N-diisopropylaminopyridopyridazine (**13**), the elimination of one of the isopropyl groups took place with the formation of N-isopropylaminopyridopyridazine (**16**) in 96% yield.

Experimental Part

Melting points were determined using a Boetius hot stage apparatus and are uncorrected. A Zeiss–Jena Specord 71-IR spectrometer was used for the IR spectra. ^{1}H-NMR spectra were recorded on 60 MHz Tesla BS-467 spectrometer; Me_4Si ($\delta = 0$ ppm) was used as internal reference. A LKB-2091 GCMS spectrometer was used for mass spectra. TLC tests were done on Merck silica gel plates (Kiselgel GF-254 type 60, layer thickness 0.25 mm). Column chromatography separations were done on Macherey Nagel & Co. silica gel (Silicagel type 60 35–70 mesh) using 30 g of silica gel per 1 g of the separated mixture.

N,N-Dialkylpyridinecarboxamides **1–3**

N,N-Dialkylpyridinecarboxamides **1**, **2**, and **3**, with the exception of N,N-diethyl-3-pyridinecarboxamide **2a** which is commercially available, were obtained according to the procedure given previously [3]. All amides were purified by distillation, column chromatography on silica gel (benzene–acetone 1:9) and redistillation or recrystallization before use. Analytical and spectral data of N,N-dialkylpyridinecarboxamides **1–3** were given previously [3].

N,N-Diethyl-2-pyridinecarboxamide (**1a**). B.p. 103–105 °C/1.3 mm Hg, m.p. 29–30 °C (Ref. [5], b.p. 122.5–123 °C/3 mm Hg, m.p. 26–28 °C).

N,N-Diethyl-3-pyridinecarboxamide (**2a**). B.p. 115–117 °C/1.1 mm Hg, (Ref. [5], b.p. 128.5–129 °C/3 mm Hg, m.p. 21–23 °C).

N,N-Diethyl-4-pyridinecarboxamide (**3a**). B.p. 119–121 °C/1.3 mm Hg (Ref. [5], b.p. 123–123.5 °C/3 mm Hg, m.p. 22–24 °C).

N,N-Diisopropyl-2-pyridinecarboxamide (**1b**). B.p. 128–132 °C/2.5 mm Hg, m.p. 77–79 °C (benzene–hexane 1:1) (Ref. [3], b.p. 125–127 °C/2.3 mm Hg, m.p. 78–80 °C).

N,N-Diisopropyl-3-pyridinecarboxamide (**2b**). B.p. 165–170 °C/8 mm Hg, m.p. 99–101 °C (benzene–hexane 1:1) (Ref. [3], b.p. 133–134 °C/2 mm Hg, m.p. 100–101 °C).

N,N-Diisopropyl-4-pyridinecarboxamide (**3b**). B.p. 167–170 °C/4.5 mm Hg, m.p. 102–104 °C (benzene–hexane 1:1) (Ref. [3], b.p. 145–146 °C/2.4 mm Hg, m.p. 102–104 °C).

General Procedure for the Preparation of N,N-Diethylpyridinecarbonylpyridinecarboxamides **7a–9a**

A solution of *LDA* (0.025 mol, prepared prior to use from 0.026 mol of diisopropylamine and 0.025 mol of *n*-butyllithium [3]) in dry diethyl ether (50 cm^3) was added dropwise to a stirred solution of N,N-diethylpyridinecarboxamide **1a**, **2a** or **3a** (4.46 g, 0.025 mol) in dry diethyl ether (50 cm^3) and dry benzene (20 cm^3) at −78 °C. Stirring at −78 °C was continued for 1 h. In the case of the amide **1a** after that time methanol (2.5 cm^3) was added and the mixture was allowed to reach room temperature. For the amides **2a** and **3a** the reaction mixture was allowed to reach room temperature at first; it was stirred for 1 h and then methanol (2.5 cm^3) was added. After stirring at room temperature for 15 min, water (1 cm^3) was added to the resulting mixture. Separated lithium hydroxide was filtered off, washed with benzene and the combined organic solutions were dried over magnesium sulfate. The solvents were removed and the residue was analyzed by TLC (benzene–acetone 1:9). See below for individual differences in isolation and purification of the products. Analytical and spectral data of N,N-diethylpyridinecarbonylpyridinecarboxamides **7a**, **8a** and **9a** were given previously [3].

N,N-Diethyl-3-(2-pyridinecarbonyl)-2-pyridinecarboxamide (**7a**). TLC test of the residue indicated only one component. The residue was recrystallized from benzene–hexane 1:4 giving N,N-diethyl-3-(2-pyridinecarbonyl)-2-pyridinecarboxamide (**7a**), m.p. 97–99 °C (Ref. [3], m.p. 98–99 °C). Yield 3.29 g, 93% based on stoichiometry requiring 2 mol of the starting amide **1a** to give 1 mol of the product **7a**.

N,N-Diethyl-4-(3-pyridinecarbonyl)-3-pyridinecarboxamide (**8a**). TLC test of the residue indicated two components. They were separated by column chromatography (benzene–acetone 1:9). The first compound eluted was identified as the starting amide **2a** (1.92 g, 43%). The second compound was identified as N,N-diethyl-4-(3-pyridinecarbonyl)-3-pyridinecarboxamide (**8a**), m.p. 59–60 °C (diethyl ether) (Ref. [3], m.p. 59–60 °C). Yield 2.48 g, 70% based on stoichiometry requiring 2 mol of the starting amide **2a** to give 1 mol of the product **8a**.

N,N-Diethyl-3-(4-pyridinecarbonyl)-4-pyridinecarboxamide (**9a**). TLC test of the residue indicated two components. They were separated by column chromatography (benzene–acetone 1:9). The first compound eluted was identified as the starting amide **3a** (2.10 g, 47%). The second compound was identified as N,N-diethyl-3-(4-pyridinecarbonyl)-4-pyridinecarboxamide (**9a**), m.p. 98–99.5 °C (acetone–hexane 1:1) (Ref. [3], m.p. 98–99 °C). Yield 2.44 g, 69% based on stoichiometry requiring 2 mol of the starting amide **3a** to give 1 mol of the product **9a**.

General Procedure for the Preparation of N,N-Diisopropylbenzoylpyridinecarboxamides **7b–9b**

A solution of *LDA* (0.050 mol, prepared prior to use from 0.052 mol of diisopropylamine and 0.050 mol of *n*-butyllithium [3]) in dry diethyl ether (100 cm^3) was added dropwise to a stirred solution of N,N-diisopropylpyridinecarboxamide **1b**, **2b** or **3b** (10.31 g, 0.050 mol) in dry diethyl ether (100 cm^3) and dry benzene (40 cm^3) at −78 °C. After 1 h at −78 °C, N,N-dimethylbenzamide (7.46 g, 0.050 mol) in dry diethyl ether (50 cm^3) was added and stirring at −78 °C was continued for further 2 h. Then the cooling bath was removed, the reaction mixture was allowed to reach room temperature and water (5 cm^3) was added. After stirring for 15 min separated lithium hydroxide was filtered off, washed with benzene and the combined organic solutions were dried over magnesium sulfate. The solvents were removed and the residue was recrystallized first from methanol–water 1:1 and then from acetone–hexane 3:7 giving pure products. Analytical and spectral data of N,N-diisopropylbenzoylpyridinecarboxamides **7b**, **8b**, and **9b** were given previously [3].

N,N-Diisopropyl-3-benzoyl-2-pyridinecarboxamide (**7b**). M.p. 120–122 °C (Ref. [3], m.p. 121–123 °C). Yield 9.16 g (59%).

N,N-Diisopropyl-4-benzoyl-3-pyridinecarboxamide (**8b**). M.p. 134–135 °C (Ref. [3], m.p. 137–138 °C). Yield 11.33 g (73%).

N,N-Diisopropyl-3-benzoyl-4-pyridinecarboxamide (**9b**). M.p. 133–134 °C (Ref. [3], m.p. 131–133 °C). Yield 9.78 g (63%).

General Procedure for the Reaction of Ketoamides **7**, **8**, *and* **9** *with Hydrazine Hydrate*

The appropriate ketoamide (0.020 mol), 98% solution of hydrazine monohydrate (3.06 g, 0.060 mol) and diethylene glycol (40 cm^3) were placed in the flask equipped with a thermometer and a reflux condenser and were heated for 1 h at 145–155 °C. The reflux condenser was then replaced with a distillation condenser, the reaction mixture was heated up to 195–200 °C, the distillation condenser was again replaced with a reflux condenser and the mixture was kept at this temperature for the required time. After the reaction the hot solution was poured into water (100 cm^3), the obtained suspension was adjusted to $pH = 8$ with 18% hydrochloric acid, the separated precipitate was filtered after 4 h of cooling in a refrigerator and washed with water (10 cm^3). See below for individual differences in isolation and purification of the products. Times of heating in 195–200 °C (time of reaction), melting points, recrystallization solvents, yields, IR, ^{1}H-NMR and mass spectra and the analytical data of the products are given in Tables 1 and 2.

Table 1. Preparation of the compounds **10–16**

Compound (Formula)	Time of reaction [h]	Melting point [°C] (Recrystal. solvent)	Yield [%]	Analysis Found [%] (Required [%])		
				C	H	N
10a	0.1	272.5–274	89	64.2	3.9	25.3
($C_{12}H_8N_4O$)		(propanol)		(64.3)	(3.6)	(25.0)
10b	1.0	249–251	87	69.6	4.1	18.5
($C_{13}H_9N_3O$)		(propanol)		(69.9)	(4.1)	(18.8)
		Ref. [7] m.p. 236				
10c	1.0	205–206.5	84	71.2	4.7	17.4
($C_{14}H_{11}N_3O$)		(methanol)		(70.9)	(4.7)	(17.7)
		Ref. [8] m.p. 173–175				
10d	1.0	151–152.5	81	71.4	5.3	16.6
($C_{15}H_{13}N_3O$)		(methanol)		(71.7)	(5.2)	(16.7)
		Ref. [8] m.p. 164				
10f	1.0	239–241	90	76.1	4.6	13.7
($C_{19}H_{13}N_3O$)		(ethanol)		(76.2)	(4.4)	(14.0)
11a	1.0	301.5–302.5	96	64.6	3.9	24.7
($C_{12}H_8N_4O$)		(propanol)		(64.3)	(3.6)	(25.0)
11b	1.5	263.5–264	65	69.8	4.3	19.1
($C_{13}H_9N_3O$)		(propanol)		(69.9)	(4.1)	(18.8)
11c	1.0	163–164	91	71.0	4.9	17.6
($C_{14}H_{11}N_3O$)		(methanol)		(70.9)	(4.7)	(17.7)
11d	1.0	142–144	80	71.6	5.4	16.5
($C_{15}H_{13}N_3O$)		(methanol)		(71.7)	(5.2)	(16.7)
11e	10.0	87–89	77	72.5	5.6	15.5
($C_{16}H_{15}N_3O$)		(methanol–water 1:1)		(72.4)	(5.7)	(15.8)
12a	1.0	306–307.5	96	64.3	3.9	25.3
($C_{12}H_8N_4O$)		(propanol)		(64.3)	(3.6)	(25.0)
12b	1.5	301–303	53	69.7	4.0	19.1
($C_{13}H_9N_3O$)		(propanol)		(69.9)	(4.1)	(18.8)
12c	1.0	149–150	91	71.0	4.9	17.7
($C_{14}H_{11}N_3O$)		(methanol)		(70.9)	(4.7)	(17.7)
12d	1.0	136–138	84	71.7	5.3	16.6
($C_{15}H_{13}N_3O$)		(methanol)		(71.7)	(5.2)	(16.7)
12e	3.0	143–145	76	72.4	5.7	15.6
($C_{16}H_{15}N_3O$)		(methanol–water 1:1)		(72.4)	(5.7)	(15.8)
13	1.5	147–155	42	74.7	7.0	18.2
($C_{19}H_{22}N_4$)		(heptane)		(74.5)	(7.2)	(18.3)
14	1.5	64–66	10	74.4	7.0	18.4
($C_{19}H_{22}N_4$)		(hexane)		(74.5)	(7.2)	(18.3)
15	1.5	102–104	8	74.7	7.3	18.1
($C_{19}H_{22}N_4$)		(hexane)		(74.5)	(7.2)	(18.3)
16	0.25	186–187.5	96	72.5	6.0	21.0
($C_{16}H_{16}N_4$)		(heptane)		(72.7)	(6.1)	(21.2)

Table 2. Spectral data of the compounds **10–16**

Compound	IR [cm^{-1}]	MS [M^+, m/e]	^{1}H-NMR [ppm on δ scale]
10a	1680 (CO) 2600–3400 (NH)[a]		9.9–8.1 (m, *Ar*-H)[d]
10b	1690 (CO) 2700–3400 (NH)[a]		9.5 (1H, d, $J = 5$ Hz, 2-H), 9.2 (1H, d, $J = 8$ Hz, 4-H), 8.6 (1H, dd, $J = 5$ and 8 Hz, 3-H), 7.6 (5H, s, *Ph*-H)[d]
10c	1670 (CO)[b]		9.1 (1H, dd, $J = 1.5$ and 4 Hz, 2-H), 8.1 (1H, dd, $J = 1.5$ and 8.5 Hz, 4-H), 7.2–7.8 (6H, m, 3- and *Ph*-H), 3.9 (3H, s, CH_3–H)[e]
10d	1670 (CO)[a]		9.1 (1H, dd, $J = 1.5$ and 4.5 Hz, 2-H), 8.1 (1H, dd, $J = 1.5$ and 8.5 Hz, 4-H), 7.3–7.9 (6H, m, 3- and *Ph*-H), 4.4 (2H, q, $J = 7$ Hz, CH_2–H), 1.4 (3H, t, $J = 7$ Hz, CH_3–H)[e]
10f	1685 (CO)[a]		9.5 (1H, d, $J = 6$ Hz, 2-H), 9.3 (1H, d, $J = 9$ Hz, 4-H), 8.7 (1H, dd, $J = 6$ and 9 Hz, 3-H), 7.7 (10H, s, *Ph*-H)[d]
11a	1675 (CO) 2200–3200 (NH)[a]		10.1 (1H, s, 5-H), 8.9–9.5 (4H, m, *Ar*-H), 8.2–8.7 (2H, m, *Ar*-H)[d]
11b	1680 (CO) 2500–3300 (NH)[a]		10.1 (1H, s, 5-H), 9.2 (1H, d, $J = 6.5$ Hz, 7-H), 8.4 (1H, d, $J = 6.5$ Hz, 8-H), 7.6 (5H, s, *Ph*-H)[d]
11c	1670 (CO)[b]		9.4 (1H, s, 5-H), 8.6 (1H, d, $J = 5$ Hz, 7-H), 7.1–7.5 (6H, m, 8- and *Ph*-H), 3.7 (3H, s, CH_3–H)[e]
11d	1670 (CO)[b]		9.8 (1H, s, 5-H), 8.9 (1H, d, $J = 5$ Hz, 7-H), 7.4–7.8 (6H, m, 8- and *Ph*-H), 4.4 (2H, q, $J = 7$ Hz, CH_2–H), 1.5 (3H, t, $J = 7$ Hz, CH_3–H)[e]
11e	1660 (CO)[a]		9.8 (1H, s, 5-H), 9.0 (1H, d, $J = 4.5$ Hz, 7-H), 7.2–8.0 (6H, m, 8- and *Ph*-H), 5.5 (1H, sept, $J = 7$ Hz, CH–H), 1.5 (6H, d, $J = 7$ Hz, CH_3–H)[e]
12a	1685 (CO) 2200–3300 (NH)[a]		9.8 (1H, s, 5-H), 8.9–9.5 (4H, m, 7-, 8-, α- and α'-H), 8.5 (2H, d, $J = 5.5$ Hz, β- and β'-H)[d]
12b	1690 (CO) 2200–3300 (NH)[a]		9.3 (1H, s, 5-H), 8.7–9.2 (2H, m, 7- and 8-H), 7.4 (5H, s, *Ph*-H)[d]
12c	1600 (CO)[b]		9.1 (1H, s, 5-H), 8.9 (1H, d, $J = 5$ Hz, 7-H), 8.2 (1H, d, $J = 5$ Hz, 8-H), 7.5 (5H, s, *Ph*-H), 3.8 (3H, s, CH_3–H)[e]
12d	1665 (CO)[b]		9.2 (1H, s, 5-H), 9.0 (1H, d, $J = 5$ Hz, 7-H), 8.3 (1H, d, $J = 5$ Hz, 8-H), 7.4–7.8 (5H, s, *Ph*-H), 4.4 (2H, q, $J = 7$ Hz, CH_2–H), 1.5 (3H, t, $J = 7$ Hz, CH_3–H)[e]
12e	1670 (CO)[a]		9.2 (1H, s, 5-H), 8.9 (1H, d, $J = 5$ Hz, 7-H), 8.3 (1H, d, $J = 5$ Hz, 8-H), 7.2–7.9 (5H, m, *Ph*-H), 5.5 (1H, sept, $J = 7$ Hz, CH–H), 1.4 (6H, d, $J = 7$ Hz, CH_3–H)[e]
13	2980 (CH aliphatic)[b]	306	9.0 (1H, dd, $J = 1.5$ and 4 Hz, 2-H), 8.2 (1H, dd, $J = 1.5$ and 8.5 Hz, 4-H), 7.3–7.9 (6H, m, 3- and *Ph*-H), 4.6 (2H, sept, $J = 7$ Hz, CH–H), 1.5 (12H, d, $J = 7$ Hz, CH_3–H)[e]

Table 2. *(Continued)*

Compound	IR [cm^{-1}]	MS [M^+, m/e]	^{1}H-NMR [ppm on δ scale]
14	2990 (CH aliphatic)[b]	306	9.6 (1H, s, 5-H), 8.8 (1H, d, J = 6 Hz, 7-H), 7.3–7.9 (6H, m, 8- and *Ph*-H), 4.1 (2H, sept, J = 7 Hz, CH–H), 1.4 (12H, d, J = 7 Hz, CH_3–H)[e]
15	2995 (CH aliphatic)[b]	306	9.4 (1H, s, 5-H), 8.9 (1H, d, J = 5.5 Hz, 7-H), 7.3–8.1 (6H, m, 8- and *Ph*-H), 4.0 (2H, sept, J = 7 Hz, CH–H), 1.4 (12H, d, J = 7 Hz, CH_3–H)[e]
16	3420 (NH)[c]	264	9.0 (1H, dd, J = 1.5 and 4.5 Hz, 2-H), 8.2 (1H, dd, J = 1.5 and 8 Hz, 4-H), 7.2–7.8 (6H, m, 3- and *Ph*-H), 6.5 (1H, br d, J = 8 Hz, N–H; after shaking with D_2O this signal disappears), 4.6 (1H, sept, J = 6.5 Hz, CH–H), 1.4 (6H, d, J = 6.5 Hz, CH_3–H)[e]

Spectra were recorded in: [a] KBr, [b] $CHCl_3$, [c] $CHBr_3$, [d] CF_3COOH, [e] $CDCl_3$

5-(2-Pyridyl)pyrido[2,3-d]pyridazin-8(7H)-one (**10a**), *1-(3-pyridyl)pyrido[3,4-d]pyridazin-4-(3H)-one* (**11a**) *and 4-(4-pyridyl)pyrido[3,4-d]pyridazin-1(2H)-one* (**12a**). Pyridopyridazinones **10a**, **11a**, and **12a** were obtained from the corresponding ketoamides **7a**, **8a**, and **9a** (5.67 g, 0.020 mol). They were purified by recrystallization of the crude precipitates.

8-(N,N-Diisopropylamino)-5-phenylpyrido[2,3-d]pyridazine (**13**). Aminopyridopyridazine **13** was obtained from N,N-diisopropyl-3-benzoyl-2-pyridinecarboxamide (**7b**) (6.21 g, 0.020 mol). Analysis of the obtained precipitate (TLC, benzene–ethyl acetate 3:7) indicated the presence of at least three components (R_f 0.75, 0.40, and a spot remaining at the start) which were separated by column chromatography (benzene–ethyl acetate 3:7). The first compound eluted was identified as (**13**). The second compound was identified as the starting ketoamide **7b** (1.55 g, 25%), m.p. 119–122 °C. The third fraction was not eluted and identified.

1-Phenylpyrido[3,4-d]pyridazin-4(3H)-one (**11b**) *and 4-(N,N-diisopropylamino)-1-phenylpyrido-[3,4-d]pyridazine* (**14**). **11b** and **14** were obtained from N,N-diisopropyl-4-benzoyl-3-pyridine-carboxamide (**8b**) (6.21 g, 0.020 mol). The obtained precipitate was recrystallized giving **11b**. Analysis of the propanol filtrate (TLC, benzene–ethyl acetate 3:7) indicated the presence of at least two components (R_f 0.58 and 0.31) which were separated by column chromatography (benzene–ethyl acetate 3:7). The first compound eluted was identified as **14** and the second compound was identified as the starting ketoamide **8b** (1.43 g, 23%), m.p. 133–135 °C.

4-Phenylpyrido[3,4-d]pyridazin-1(2H)-one (**12b**) *and 1-(N,N-diisopropylamino)-4-phenylpyrido-[3,4-d]pyridazine* (**15**). **12b** and **15** were obtained from **9b** (6.21 g, 0.020 mol). The obtained precipitate was recrystallized giving **12b**. Analysis of the propanol filtrate (TLC, benzene–ethyl acetate 3:7) indicated the presence of at least two components (R_f 0.55 and 0.27) which were separated by column chromatography (benzene–ethyl acetate 3:7). The first compound eluted was identified as **15** and the second one was identified as the starting ketoamide **9b** (1.55 g, 25%), m.p. 131–134 °C.

5-Phenylpyrido[2,3-d]pyridazin-8(7H)-one (**10b**) *and 5,7-diphenylpyrido[2,3-d]-pyridazin-8(7H)-one* (**10f**)

The 3-benzoylpicolinic acid [6] (2.27 g, 0.010 mol) and hydrazine hydrate (0.55 g, 0.011 mol) for **10b** or phenylhydrazine (1.19 g, 0.011 mol) for **10f** and ethanol (20 cm^3) were heated under reflux for 1 h.

Then the solvent was removed completely for **10b** and about 2/3 of the previous volume for **10f**. The residue was purified by recrystallization. Melting points, recrystallization solvents, yields, IR and ^{1}H-NMR spectra and the analytical data of the products are given in Tables 1 and 2.

General Procedure for the Preparation of the N-Alkylpyridopyridazinones **10c, d, 11c–e** *and* **12c–e**

The pyridopyridazinones **10, 11** or **12** (2.23 g, 0.010 mol), potassium hydroxide (1.12 g, 0.020 mol) and methanol (40 cm^3) were heated under reflux for 15–20 min. Then the appropriate alkyl iodide (0.020 mol) was added dropwise and heating under reflux was continued for the required time. After reaction, methanol was removed, water (10 cm^3) was added to the obtained solid residue, unsoluble precipitate was filtered and washed with cold water (3 cm^3 portions) until neutral. The product was purified by recrystallization. Times of reactions, melting points, recrystallization solvents, yields, IR and ^{1}H-NMR spectra and analytical data of the products are given in Tables 1 and 2.

8-(N-Isopropylamino)-5-phenylpyrido[2,3-d]pyridazine (**16**)

13 (0.49 g, 0.016 mol) was heated under reflux in 18% hydrochloric acid (8 cm^3). After 3–4 min of reflux very vigorous evolution of a gas was observed. Then the reaction mixture was cooled, diluted with water (4 cm^3) and alkalized in a cooling bath with 20% sodium hydroxide to $pH = 9$–10. The separated precipitate was filtered and washed with cold water (2 cm^3 portions) until neutral. The obtained product **16** was recrystallized. Time of reaction, melting point, recrystallization solvent, yield, IR, ^{1}H-NMR and mass spectra and analytical data of the product **16** are given in Tables 1 and 2.

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