Preparation of Some Novel Pyrimido[4,5-*c*]pyridazine Derivatives from 3-Alkylamino- and 3-Arylamino-4-pyridazinecarboxamides

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Facile syntheses of pyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones **4**, pyrimido[4,5-*c*]pyridazin-5(8*H*)-ones **7-10**, and dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones **5,6** starting from 3-chloro-4-pyridazinecarbonitrile **1** *via* aminocarbonitriles **2** and aminocarboxamides **3** are described. In addition, a convenient access to the new aminopyridazinecarbonitrile **11** from the chloronitrile **1**, employing the tetrazolo[1,5-*b*]pyridazine **12** as the key intermediate, is reported.

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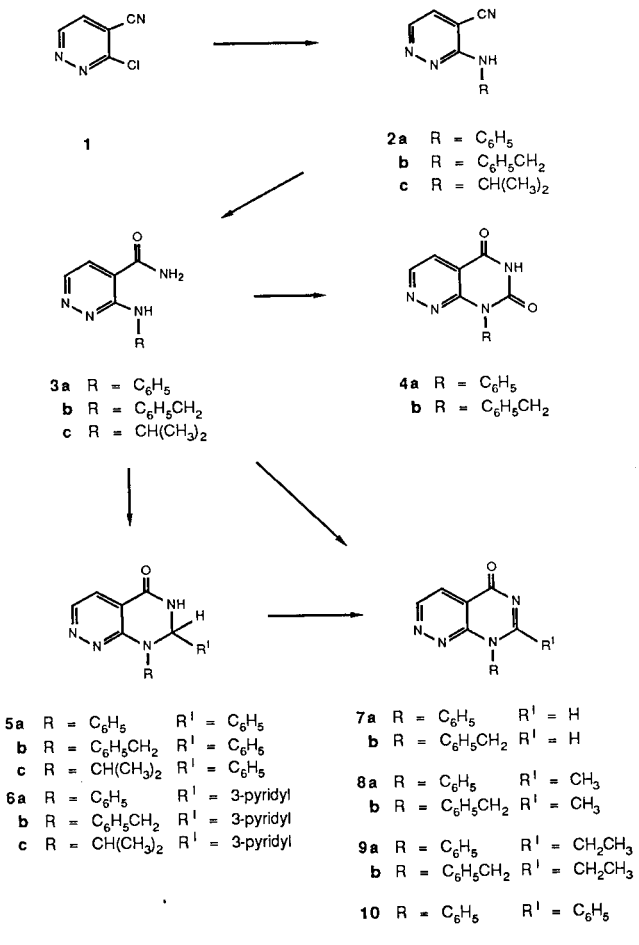
There is continuing interest in the chemistry of azaquinazolines [3-8] which mainly arises from the large variety of biological activities observed with quinazoline derivatives [9]. Within a program aimed at the synthesis of heterocycle-annelated pyridazines starting from an appropriately disubstituted 1,2-diazine system [10-14], we now succeeded in the preparation of several types of so far not accessible diazaquinazoline derivatives.

Scheme 1



In the syntheses presented in this paper the conveniently available 3-chloro-4-pyridazinecarbonitrile **1** [15,16] is employed as starting material. The new bicyclic compounds prepared include *N*-8-substituted pyrimido[4,5-*c*]-pyridazine-5,7(6*H*,8*H*)-diones, pyrimido[4,5-*c*]pyridazin-5(8*H*)-ones as well as several dihydro derivatives thereof bearing various substituents at C-7 and N-8 [17]. In all these cases, 3-arylamino- or 3-alkylamino-4-pyridazinecarb oxamides **3a-c** represent the key intermediates. They were found to be readily accessible by refluxing the nitriles **2a-c** in aqueous ammonia solution [18]. Synthesis of the phenylamino nitrile **2a** was described recently [1], the alkylaminonitriles **2b,c** were obtained in a similar way by reacting the chloronitrile **1** with two equivalents of the corresponding amine in refluxing ethanol. For yields, analytical and spectroscopic data of compounds **2b,c** and **3a-c** see Tables 1,2.

In order to find access to *N*-8-substituted compounds of type **4** [19], we initially tried to react **3a** with 1,1'-carbonyldiimidazole. Whereas this reaction gave only polymeric products, cyclisation of **3a** as well as of **3b** with urea at 200° (in analogy to refs [20,21]) afforded the target compounds **4a,b** in moderate yields. From the ir data (see Experimental) it becomes evident these compounds to exist in the dioxo form proposed in Scheme 1.

The known diuretic activity of 1,2-dihydro-2-arylpyrido-[2,3-*d*]pyrimidin-4(3*H*)-ones [5] prompted us to investigate cyclisation reactions of the amides **3a-c** also with aromatic aldehydes. It turned out that pyrimidine ring closure smoothly can be accomplished by heating compounds **3a-c** with benzaldehyde or 3-pyridinecarbaldehyde, respectively, at 180° in the absence of a solvent. The ir spectra (potassium bromide) of compounds **5a-c** and **6a-c** thus obtained (*cf.* Tables 3,4) clearly show an oxo function being present. Existence of the latter compounds in the lactam form also in solution (deuteriodimethylsulfoxide) is

Table 1

3-Alkylamino-4-pyridazinecarbonitriles **2b,c** and 3-Arylamino- and 3-Alkylamino-4-pyridazinecarboxamides **3a-c**

Compound No.	R	% Yield	Mp (°C)	Recrystallization Solvent	Molecular Formula	Elemental Analyses % Calcd./Found C	H	N
2b	$C_6H_5CH_2$	80	132-133	ethanol	$C_{12}H_{10}N_4$ (210.24)	68.56 68.51	4.79 4.94	26.65 26.62
2c	$CH(CH_3)_2$	30	76-77	light petroleum	$C_8H_{10}N_4$ (162.19)	59.24 59.28	6.21 6.28	34.54 34.48
3a	C_6H_5	70	182-183	ethanol	$C_{11}H_{10}N_4O$ (214.23)	61.67 61.64	4.71 4.79	26.15 26.54
3b	$C_6H_5CH_2$	70	182-183	ethanol	$C_{12}H_{12}N_4O$ (228.25)	63.15 63.09	5.30 5.37	24.55 24.53
3c	$CH(CH_3)_2$	50	208-209	water	$C_8H_{12}N_4O$ (180.21)	53.32 53.26	6.71 6.64	31.09 30.87

Table 2

Spectroscopic Data of Compounds **2b,c** and **3a-c**

Compound No.	IR cm^{-1}	MS m/e (% base peak)	^{1}H-NMR δ (ppm) [a]
2b	2240 [b]	210 (M^+, 3), 91 (100)	8.70 (d, J = 5 Hz, H-6, 1H), 8.0 (br, NH, 1H), 7.80 (d, J = 5 Hz, H-5, 1H), 7.3 (m, phenyl-H, 5H), 4.70 (d, J = 6 Hz, CH_2, 2H)
2c	2240 [b]	162 (M^+, 60), 120 (100)	8.65 (d, J = 5 Hz, H-6, 1H), 7.30 (d, J = 5 Hz, H-5, 1H), 5.1-4.4 (m, NH, CH, 2H), 1.4 (d, J = 7 Hz, CH_3, 6H)
3a	1670 [c], 1620 [d]	214 (M^+, 43), 213 (100)	10.7 (s, NH, 1H), 8.90 (d, J = 5 Hz, H-6, 1H), 8.7 (br, NH, 1H), 8.2 (br, NH, 1H), 8.0-6.9 (m, H-5, phenyl-H, 6H)
3b	1670 [c], 1620 [d]	228 (M^+, 31), 91 (100)	8.65 (d, J = 5 Hz, H-6, 1H), 8.6-8.3 (br, NH, 2H), 7.9 (br, NH, 1H), 7.65 (d, J = 5 Hz, H-5, 1H), 7.4 (m, phenyl-H, 5H), 4.80 (d, J = 6 Hz, CH_2, 2H)
3c	1670 [c], 1620 [d]	180 (M^+, 49), 39 (100)	8.60 (d, J = 5 Hz, H-6, 1H), 8.3 (br, NH, 1H), 8.1-7.7 (br, NH, 2H), 7.60 (d, J = 5 Hz, H-5, 1H), 4.6-4.1 (m, CH, 1H), 1.20 (d, J = 7 Hz, CH_3, 6H)

[a] Deuteriodimethylsulfoxide solution, except for compound **2c**: deuteriochloroform solution. [b] ν C≡N. [c] ν C=O. [d] δ N-H.

evidenced by the observation of coupling between H-6 and H-7 in the ^{1}H-nmr spectra. Interestingly, the signals of the benzylic protons in compounds **5b** and **6b** appear as AB systems; this magnetic inequivalence may be attributed to restricted rotation of the benzyl substituent together with chirality of C-7. Likewise, a rotation barrier may be the reason for the observation of two well-separated doublets of the methyl groups in the isopropyl-substituted compounds **5c** and **6c** (*cf.* Table 4).

In addition, also diazaquinazolinones of type **7-10** (*cf.* Scheme 1) appeared to be of interest from a pharmaceutical point of view, considering the antiinflammatory activity of 1,2-disubstituted 4(1*H*)-quinazolinones [22]. Initial attempts to achieve pyrimidine ring formation by treatment of **3a** with acid chlorides (acetyl chloride, benzoyl chloride, ethyl chloroformylformate) did not result in any conversion. On the other hand, refluxing of **3a** in acetic anhydride gave a mixture of several products [23], containing only minor amounts (*ca.* 20%) of the desired compound **8a**. However, oxidation of 7,8-diaryl-7,8-dihydropyrimido-[4,5-*c*]pyridazin-5(6*H*)-ones employing potassium permanganate in acetone provides a convenient access to the corresponding diazaquinazolinones bearing aryl moieties at C-7 and N-8. This was exemplified by the conversion of **5a** into **10** in 80% yield. Moreover, it was found that 7-alkyl-diazaquinazolinones like **8a,b** and **9a,b** can be prepared in a single step from the amides **3a,b** by condensation with ortho esters (triethyl orthoacetate, -propionate). In a similar manner, also the C-7-unsubstituted compounds **7a,b** could be made available by refluxing **3a,b** in triethyl orthoformate according to a method reported in ref [20]. Also with these new compounds the analytical and spectroscopic data are in full agreement with the assigned structure (*cf.* Scheme 1, Tables 3,4).

The convenient availability of 3-chloro-4-pyirdazinecarbonitrile **1** [15,16] and its utility as starting material in the syntheses of compounds **2-10** prompted us to further in-

Table 3

7,8-Dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones **5a-c**, **6a-c** and Pyrimido[4,5-*c*]pyridazin-5(8*H*)-ones **7a,b**, **8a,b**, **9a,b**, and **10**

Compound No.	R	R'	% Yield	Mp (°C) [a]	Molecular Formula	Elemental Analyses % Calcd./Found C	H	N
5a	C_6H_5	C_6H_5	60	214-215	$C_{18}H_{14}N_4O \cdot 1/2\ H_2O$ (311.34)	70.14 69.97	5.27 5.13	17.22 17.71
5b	$C_6H_5CH_2$	C_6H_5	50	195-196	$C_{19}H_{16}N_4O$ (316.36)	72.14 71.98	5.10 5.12	17.71 17.73
5c	$CH(CH_3)_2$	C_6H_5	70	229-230	$C_{15}H_{16}N_4O$ (268.32)	67.15 67.05	6.01 6.10	20.88 20.88
6a	C_6H_5	3-pyridyl	70	229-230	$C_{17}H_{13}N_5O$ (303.32)	67.32 67.00	4.32 4.43	23.09 22.81
6b	$C_6H_5CH_2$	3-pyridyl	50	205-207	$C_{18}H_{15}N_5O$ (317.35)	68.13 67.73	4.76 4.85	22.07 22.12
6c	$CH(CH_3)_2$	3-pyridyl	60	233-234	$C_{14}H_{15}N_5O$ (269.30)	62.44 62.36	5.61 5.65	26.01 25.63
7a	C_6H_5	H	40 (60) [b]	>190 dec	$C_{12}H_8N_4O$ (224.22)	64.28 64.04	3.60 3.79	24.99 24.99
7b	$C_6H_5CH_2$	H	64 (80) [b]	195-198	$C_{13}H_{10}N_4O$ (238.25)	65.54 65.14	4.23 4.38	23.52 23.14
8a	C_6H_5	CH_3	30 (50) [b]	250-252	$C_{13}H_{10}N_4O$ (238.25)	65.54 65.04	4.23 4.40	23.52 23.48
8b	$C_6H_5CH_2$	CH_3	18 (30) [b]	160-165 dec	$C_{14}H_{12}N_4O \cdot 1/2\ H_2O$ (261.28)	65.49 65.70	4.91 4.91	21.82 21.34
9a	C_6H_5	CH_2CH_3	30 (55) [b]	>180 dec	$C_{14}H_{12}N_4O$ (252.28)	66.65 66.43	4.79 4.94	22.21 21.80
9b	$C_6H_5CH_2$	CH_2CH_3	62 (80) [b]	158-160	$C_{15}H_{14}N_4O$ (266.30)	67.65 67.54	5.30 5.32	21.04 20.96
10	C_6H_5	C_6H_5	40 (80) [b]	268-271	$C_{18}H_{12}N_4O$ (300.32)	71.99 71.63	4.03 4.18	18.66 18.55

[a] Recrystallisation solvent: ethanol, except for compound **7a**: ethyl acetate. [b] Yield of crude product.

vestigate its suitability as an educt for the preparation of the hitherto unknown 3-amino-4-pyridazinecarbonitrile **11**. In contrast to the successful conversion of **1** into compounds **2** employing aliphatic or aromatic amines, reaction of **1** with ethanolic ammonia (even when performed in a sealed tube) afforded **11** in only <10% yield. On the other hand, attempts to remove the benzyl moiety from the readily accessible benzylamino nitrile **2b** by means of aluminium trichloride in toluene [24] met with no success; moreover, we failed in attempted debenzylation of **2b** under hydrogenolytic conditions (Pd/C). In neutral medium, no reaction occurred, whereas in acidic solution a very unstable product (still bearing the benzyl moiety) was formed, obviously due to reduction of the nitrile function. This assumption is supported by a similar behavior of the phenylamino nitrile **2a**, affording compound **13a** under identical conditions.

Scheme 2

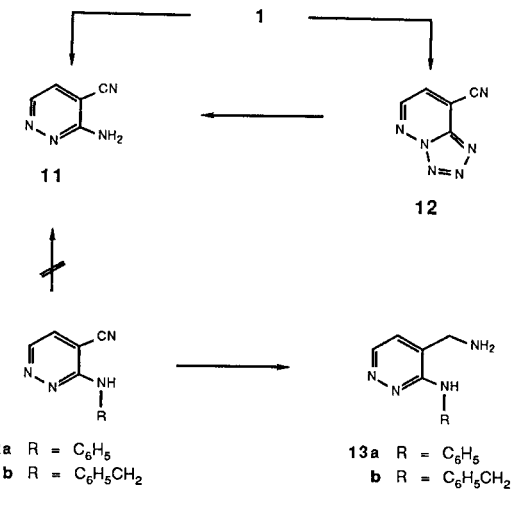


Table 4

Spectroscopic Data of Compounds **5a-c**, **6a-c**, **7a,b**, **8a,b**, **9a,b**, and **10**

Compound No.	IR (cm^{-1}) ν C=O	MS m/e (% base peak)	^{1}H-NMR, δ (ppm) [a]
5a	1680	302 (M^+, 24), 77 (100)	9.60 (d, J = 3 Hz, exchangeable with deuterium oxide, NH, 1H), 8.95 (d, J = 5 Hz, H-3, 1H), 7.80 (d, J = 5 Hz, H-4, 1H), 7.4 (m, phenyl-H, 10H), 6.35 (d, J = 3 Hz, H-7, 1H)
5b	1670	316 (M^+, 68), 182 (100)	9.4 (br, exchangeable with deuterium oxide, NH, 1H), 8.85 (d, J = 5 Hz, H-3, 1H), 7.70 (d, J = 5 Hz, H-4, 1H), 7.4 (m, phenyl-H, 10H), 5.90 (d, J = 3 Hz, H-7, 1H), 5.6 (d, J_{AB} = 15 Hz, benzyl-H, 1H), 4.3 (d, J_{AB} = 15 Hz, benzyl-H, 1H)
5c	1675	268 (M^+, 14), 149 (100)	9.4 (br, exchangeable with deuterium oxide, NH, 1H), 8.80 (d, J = 5 Hz, H-3, 1H), 7.70 (d, J = 5 Hz, H-4, 1H), 7.3 (m, phenyl-H, 5H), 6.05 (unresolved, d, H-7, 1H), 4.95 (sp, J = 6 Hz, CH, 1H), 1.35 (d, J = 6 Hz, CH_3, 3H), 1.10 (d, J = 6 Hz, CH_3, 3H)
6a	1690	303 (M^+, 63), 77 (100)	9.6 (br, exchangeable with deuterium oxide, NH, 1H), 8.95 (d, J = 5 Hz, H-3, 1H), 8.5 (m, pyridine H-2, H-6, 2H), 7.9-7.7 (m, H-4, pyridine H-4, 2H), 7.5-7.2 (m, phenyl-H, pyridine H-5, 6H), 6.55 (unresolved, d, H-7, 1H)
6b	1685	317 (M^+, 20), 91 (100)	9.4 (br, exchangeable with deuterium oxide, NH, 1H), 8.85 (d, J = 5 Hz, H-3, 1H), 8.5 (m, pyridine H-2, H-6, 2H), 7.8-7.6 (m, H-4, pyridine H-4, 2H), 7.5-7.2 (m, phenyl-H, pyridine H-5, 6H), 6.10 (d, J = 4 Hz, H-7, 1H), 5.5 (d, J_{AB} = 15 Hz, benzyl-H, 1H), 4.4 (d, J_{AB} = 15 Hz, benzyl-H, 1H)
6c	1675	269 (M^+, 29), 149 (100)	9.4 (br, exchangeable with deuterium oxide, NH, 1H), 8.80 (d, J = 5 Hz, H-3, 1H), 8.55 (m, pyridine H-2, H-6, 2H), 7.7-7.6 (m, H-4, pyridine H-4, 2H), 7.5-7.3 (m, pyridine H-5, 1H), 6.20 (unresolved, d, H-7, 1H), 5.00 (sp, J = 6 Hz, CH, 1H), 1.35 (d, J = 6 Hz, CH_3, 3H), 1.15 (d, J = 6 Hz, CH_3, 3H)
7a	1665	224 (M^+, 21), 77 (100)	9.60 (d, J = 5 Hz, H-3, 1H), 8.85 (s, H-7, 1H), 8.30 (d, J = 5 Hz, H-4, 1H), 7.7 (m, phenyl-H, 5H)
7b	1670	238 (M^+, 100), 92 (100)	9.55 (d, J = 5 Hz, H-3, 1H), 9.05 (s, H-7, 1H), 8.20 (d, J = 5 Hz, H-4, 1H), 7.5-7.2 (m, phenyl-H, 5H), 5.70 (s, benzyl-H, 2H)
8a	1660	238 (M^+, 6), 51 (100)	9.50 (d, J = 5 Hz, H-3, 1H), 8.25 (d, J = 5 Hz, H-4, 1H), 7.65 (s, phenyl-H, 5H), 2.20 (s, CH_3, 3H)
8b	1660	252 (M^+, 66), 182 (100)	9.55 (d, J = 5 Hz, H-3, 1H), 8.25 (d, J = 5 Hz, H-4, 1H), 7.3 (m, phenyl-H, 5H), 5.95 (s, benzyl-H, 2H), 2.55 (s, CH_3, 3H)
9a	1665	252 (M^+, 60), 143 (100)	9.60 (d, J = 5 Hz, H-3, 1H), 8.30 (d, J = 5 Hz, H-4, 1H), 7.70 (s, phenyl-H, 5H), 2.45 (q, J = 7 Hz, CH_2, 2H), 1.15 (t, J = 7 Hz, CH_3, 3H)
9b	1660	266 (M^+, 56), 182 (100)	9.55 (d, J = 5 Hz, H-3, 1H), 8.25 (d, J = 5 Hz, H-4, 1H), 7.4-7.2 (s, phenyl-H, 5H), 5.95 (s, benzyl-H, 2H), 2.85 (q, J = 7 Hz, CH_2, 2H), 1.15 (t, J = 7 Hz, CH_3, 3H)
10	1660	300 (M^+, 18), 77 (100)	9.60 (d, J = 5 Hz, H-3, 1H), 8.35 (d, J = 5 Hz, H-4, 1H), 7.7-7.3 (m, phenyl-H, 10H)

[a] Deuteriodimethylsulfoxide solution.

However, it turned out that tetrazolo[1,5-*b*]pyridazine-8-carbonitrile **12** can be conveniently prepared by treatment of the chloronitrile **1** with sodium azide in dimethyl formamide and that **12** represents a valuable precursor for the amino nitrile **11**. In accordance with reports in the literature [25], also for this new tetrazolopyridazine **12** there is no indication for an isomeric azidopyridazine being present as shown from the ir spectrum. By refluxing **12** in chlorobenzene with triphenylphosphine, following a procedure recently developed by Kappe and Pfaffenschlager [26,27] degradation to the target amino nitrile **11** (*via* a triphenylphosphoranylideneamino intermediate) can be achieved in 51% overall yield (based on **1**) [28]. In view of the high synthetic utility of *N*-heteroaromatic *o*-aminonitriles [30-33], compound **11** should represent a versatile building block for various kinds of fused pyridazines. Investigations on this matter are in progress.

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 a Varian EM 390 (90 MHz) instrument; chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Electron

impact mass spectra were obtained at 70 eV using a Varian MAT CH-7. For analytical tlc, DC-Alufolien, Kieselgel 60 F_{254} (Merck) were used. Column chromatography was performed on Kieselgel 60 (70-230 mesh; Merck).

3-Benzylamino-4-pyridazinecarbonitrile (**2b**).

A solution of 1.39 g (10 mmoles) of **1** [16] and 2.14 g (20 mmoles) of benzylamine in 15 ml of absolute ethanol was refluxed for 5 hours. After evaporation, the residue was washed with water and recrystallized to afford colorless needles. For yield, melting point and analytical data *cf.* Table 1, for spectroscopic data *cf.* Table 2.

3-Isopropylamino-4-pyridazinecarbonitrile (**2c**).

A solution of 834 mg (6 mmoles) of **1** [16] and 708 mg (12 mmoles) of isopropylamine in 5 ml of absolute ethanol was refluxed for 5 hours. The solvent was removed *in vacuo* and the residue was extracted with diethyl ether. The crude product obtained on evaporation of the extract was purified by column chromatography (ethyl acetate:light petroleum, 2:1), followed by recrystallisation to yield pale yellow needles. For yield, melting point and analytical data *cf.* Table 1, for spectroscopic data *cf.* Table 2.

General Procedure for the Preparation of the Amides **3a-c** from the Nitriles **2a-c**.

A mixture of 5 mmoles of **2a** [1], **2b**, or **2c** and 10 ml of 1% aqueous ammonia was refluxed for 15 hours. The precipitate (**3a** or **3b**, respectively) was collected and recrystallized to give pale yellow crystals. In the case of **3c**, the mixture was extracted with ethyl acetate. Evaporation of the extract, followed by recrystallisation afforded pale yellow crystals. Yields, melting points and analytical data are summarized in Table 1, for spectroscopic data see Table 2.

Methyl 3-Phenylamino-4-pyridazinecarboximidoate.

To a solution of 490 mg (2.5 mmoles) of **2a** [1] in 5 ml of methanol was added 0.5 ml of 1% aqueous sodium hydroxide and the mixture was left in the refrigerator for 24 hours. The precipitate was collected, washed with water and dried. Recrystallisation from toluene yielded 490 mg (86%) of yellow needles, mp 130°; ^{1}H-nmr (deuteriochloroform): δ 11.6 (br, exchangeable with deuterium oxide, NH, 1H), 8.80 (d, J = 5 Hz, H-6, 1H), 8.1-7.0 (m, H-5, phenyl-H, 6H), 3.85 (s, CH_3, 3H); ir: cm^{-1} 1620 (C=N); ms: m/e 228 (M^+, 72), 77 (100).

Anal. Calcd. for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.16; H, 5.32; N, 24.57.

Methyl 3-Phenylamino-4-pyridazinecarboxylate.

To a suspension of 342 mg (1.5 mmoles) of methyl 3-phenylamino-4-pyridazinecarboximidoate in 10 ml of water were added 1.5 ml of 2*N* hydrochloric acid. After stirring for 10 minutes, the mixture was neutralized by addition of 2*N* aqueous sodium hydroxide. The precipitate was collected, washed with water and dried to give 280 mg (67%) of the product. A sample was recrystallized from light petroleum to afford yellow needles, mp 91-92°; ^{1}H-nmr (deuteriochloroform): δ 9.8 (br, exchangeable with deuterium oxide, NH, 1H), 8.85 (d, J = 5 Hz, H-6, 1H), 8.0-7.0 (m, H-5, phenyl-H, 6H), 4.00 (s, CH_3, 3H); ir: cm^{-1} 1700 (C=O); ms: m/e 229 (M^+, 35), 228 (100).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.72; H, 4.86; N, 18.27.

Preparation of 3-Phenylamino-4-pyridazinecarboxamide (**3a**) from Methyl 3-Phenylamino-4-pyridazinecarboxylate.

Dry ammonia was bubbled through a solution of 458 mg (2 mmoles) of methyl 3-phenylamino-4-pyridazinecarboxylate in 10 ml of methanol for 2.5 hours. The precipitate was collected, washed with cold methanol and dried to yield 342 mg (80%) of a product being identical (mp, ir) with the amide **3a** prepared as described above.

8-Phenylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**4a**).

To 400 mg (6.7 mmoles) of urea were added 214 mg (1 mmole) of **3a** at 150° and the mixture was heated to 200° for 30 minutes. After cooling, water was added and the mixture was made weakly acidic by addition of 2*N* hydrochloric acid. The precipitate was dissolved in 2*N* aqueous sodium hydroxide and re-precipitated using 2*N* acetic acid. Recrystallisation from ethanol gave 53 mg (22%) of colorless crystals, mp >260°; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 12.2 (br, exchangeable with deuterium oxide, NH, 1H), 9.30 (d, J = 5 Hz, H-3, 1H), 8.15 (d, J = 5 Hz, H-4, 1H), 7.7-7.4 (m, phenyl-H, 5H); ir: cm^{-1} 1730 (C=O), 1700 (C=O); ms: m/e 240 (M^+, 38), 239 (100).

Anal. Calcd. for $C_{12}H_8N_4O_2 \cdot 1/3\ H_2O$: C, 58.55; H, 3.55; N, 22.76. Found: C, 58.19; H, 3.63; N, 23.08.

8-Benzylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**4b**).

Preparation as described for **4a**, starting from 228 mg (1 mmole) of **3b**. Recrystallization from ethanol afforded 135 mg (53%) of pale yellow crystals, mp 240-245° dec; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 12.2 (br, exchangeable with deuterium oxide, NH, 1H), 9.35 (d, J = 5 Hz, H-3, 1H), 8.15 (d, J = 5 Hz, H-4, 1H), 7.5-7.2 (m, phenyl-H, 5H), 5.55 (s, benzyl-H, 2H); ir: cm^{-1} 1720 (C=O), 1690 (C=O); ms: m/e 254 (M^+, 26), 91 (100).

Anal. Calcd. for $C_{13}H_{10}N_4O_2 \cdot 1/8\ H_2O$: C, 60.87; H, 4.03; N, 21.84. Found: C, 60.96; H, 4.02; N, 22.07.

General Procedure for the Preparation of the 7,8-Dihydropyrimido-[4,5-*c*]pyridazin-5(6*H*)-ones **5a-c** and **6a-c**.

A mixture of 0.5 mmole of the amide **3a**, **3b** or **3c** and 1 ml of benzaldehyde or 3-pyridinecarbaldehyde, respectively, was heated to 180° for 1.5 hours (for **5a-c**) or 0.5 hours (for **6a-c**). After cooling, the solidified reaction product was washed with cyclohexane and recrystallized to give pale yellow crystals. Yields, melting points and analytical data are listed in Table 3, for spectroscopic data see Table 4.

General Procedure for the Preparation of the Pyrimido[4,5-*c*]pyridazin-5(8*H*)-ones **7a,b**, **8a,b** and **9a,b**.

A mixture of 0.7 mmole of the amide **3a**, **3b** or **3c**, respectively, and 10 ml of the appropriate ortho ester (triethyl orthoformate, -acetate or -propionate) was refluxed until tlc indicated completion of the reaction (6-20 hours). After removal of the reagent *in vacuo*, the residue was washed with light petroleum and recrystallized (compound **8a** was pre-purified by column chromatography; ethyl acetate:methanol, 10:1) to afford brownish crystals (compounds **7a**, **8a** and **9a**) or pale yellow crystals (compounds **7b**, **8b** and **9b**). Yields, melting points and analytical data are summarized in Table 3, for spectroscopic data *cf.* Table 4.

7,8-Diphenylpyrimido[4,5-*c*]pyridazin-5(8*H*)-one (**10**).

A solution of 100 mg (0.3 mmole) of **5a** and 95 mg (0.6 mmole) of potassium permanganate in 10 ml of acetone was refluxed for 2 hours. Manganese dioxide was filtered off and washed with ethanol. The combined filtrate and washings were evaporated to give the crude product. Recrystallisation afforded brownish crystals. For yield, melting point and analytical data *cf.* Table 3, for spectroscopic data *cf.* Table 4.

Catalytic Hydrogenation of Compounds **2a,b**.

A mixture of 250 mg (1.3 mmoles) of **2a** [1], 25 ml of ethanol, 2 ml of 2*N* hydrochloric acid and 10% palladium on charcoal was hydrogenated for 2 hours. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was partitioned between dilute sodium hydroxide solution and ethyl acetate. Evaporation of the extract gave the crude product which was purified by column chromatography. Elution with ethyl acetate-methanol (2:1) afforded 140 mg (55%) of 3-phenylamino-4-pyridazinemethanamine as a colorless oil; ^{1}H-nmr (deuteriochloroform): δ 8.50 (d, J = 5 Hz, H-6, 1H), 7.8-6.8 (m, NH_2, H-5, phenyl-H, 8H), 3.80 (s, CH_2, 2H); ms: m/e 200.1057 (Calcd. for $C_{11}H_{12}N_4$: 200.1062).

Catalytic hydrogenation of compound **2b** under identical conditions afforded an oily product which rapidly became dark; ^{1}H-nmr (deuteriochloroform): δ 8.40 (d, J = 5 Hz, H-6, 1H), 7.6-7.1 (m, NH_2, phenyl-H, 7H), 6.90 (d, J = 5 Hz, H-5, 1H), 4.75 (s, benzyl-H, 2H), 3.80 (s, CH_2, 2H) [34].

Tetrazolo[1,5-*b*]pyridazine-8-carbonitrile (**12**).

To a solution of 556 mg (4 mmoles) of **1** [16] in 10 ml of dimethyl formamide were added 312 mg (4.8 mmoles) of sodium azide and the mixture was stirred at room temperature for 4 hours. After removal of the solvent *in vacuo*, the residue was treated with water and extracted with dichloromethane. Evaporation of the extract and recrystallisation from ethanol yielded 467 mg (80%) of colorless crystals, mp 155-157°; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 9.30 (d, J = 5 Hz, H-6, 1H), 8.60 (d, J = 5 Hz, H-7, 1H); ir: cm^{-1} 2240 (C≡N); ms: m/e 90 (25), 64 (100).

Anal. Calcd. for $C_5H_2N_6$: C, 41.10; H, 1.38; N, 57.52. Found: C, 41.03; H, 1.56; N, 57.24.

Reaction of Compound **12** with Triphenylphosphine.

A solution of 200 mg (1.37 mmoles) of **12** and 367 mg (1.4 mmoles) of triphenylphosphine in 5 ml of chlorobenzene was refluxed for 2 hours. The solvent was removed *in vacuo* and the residue was triturated with cyclohexane. Recrystallization from benzene-cyclohexane afforded 460 mg (88%) of 3-triphenylphosphoranylideneamino-4-pyridazinecarbonitrile as colorless crystals, mp 188-224° dec; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 8.45 (d, J = 5 Hz, H-6, 1H), 8.0-7.5 (m, H-5, phenyl-H, 16H); ir: cm^{-1} 2240 (C≡N).

Anal. Calcd. for $C_{23}H_{17}N_4P$: C, 72.62; H, 4.51; N, 14.73. Found: C, 72.51; H, 4.62; N, 14.57.

Preparation of 3-Amino-4-pyridazinecarbonitrile (**11**).

A mixture of 300 mg (0.86 mmole) of 3-triphenylphosphoranylideneamino-4-pyridazinecarbonitrile and 10 ml of 80% acetic acid was refluxed for 20 minutes. After cooling, 20 ml of water and 10 ml of ethyl acetate were added and the aqueous layer was evaporated *in vacuo*. Trituration of the residue with ethyl acetate afforded 65 mg of **11**, work-up of the organic layer gave additional 10 mg of the product (total yield, 73%), colorless crystals, mp 193-194° (from ethanol); ^{1}H-nmr (deuteriodimethylsulfoxide): δ 8.55 (d, J = 5 Hz, H-6, 1H), 7.65 (d, J = 5 Hz, H-5, 1H), 7.2 (br, NH_2, 2H); ir: cm^{-1} 3120 (NH), 2240 (C≡N), 1660 (NH).

Anal. Calcd. for $C_5H_4N_4$: C, 50.00; H, 3.36; N, 46.65. Found: C, 49.84; H, 3.41; N, 46.49.

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