Pyridazines. XXXVII [1,2]. Novel Triazanaphthalene Derivatives *via* Intramolecular Cyclization Reactions of *vic*-Disubstituted Pyridazines

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8-Phenylpyrido[3,4-*d*]pyridazines bearing various amino substituents at C-5 (**7a-d, 8**) were prepared from ethyl 5-benzyl-4-pyridazinecarboxylate **1** *via* the fused pyridone **5**. The isomeric 4-phenylpyrido[2,3-*d*]pyridazines having the amino functions attached to C-2 (**10a-f**) were obtained by a one-pot cyclization of the amino ketone **1** with appropriate acetamide acetals. These novel triazanaphthalene derivatives are of interest as analogues of diuretic and antithrombotic agents.

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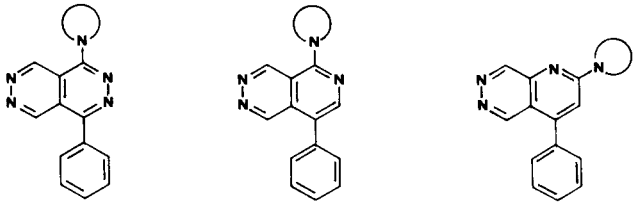
For more than one decade there has been considerable interest in the chemistry and structure-activity relationship of polyazanaphthalene-derived diuretics [5,6]. In particular, pyrido[3,4-*d*]pyridazines bearing aryl- as well as cycloamino-substituents were found to be effective inhibitors of vasopressin activity in the distal nephron [7]. Previous results from our laboratory in the field of pyridazino[4,5-*d*]pyridazines [8] had shown that also compounds of type **A**, having the aryl- and the cycloamino-substituent attached to the same nucleus of the condensed system, exhibit significant potassium-saving diuretic activity.

In extension of these investigations we now report on the preparation of the isosteric pyrido[3,4-*d*]pyridazines **B** as well as isomers thereof, namely the pyrido[2,3-*d*]pyridazines **C**. The proposed synthetic pathways (Schemes 1 and 2), characterized by intramolecular cyclization of appropriately 4,5-disubstituted pyridazines, assure variability of the cycloamino substituent in both types of target compounds within a wide range.



A B C

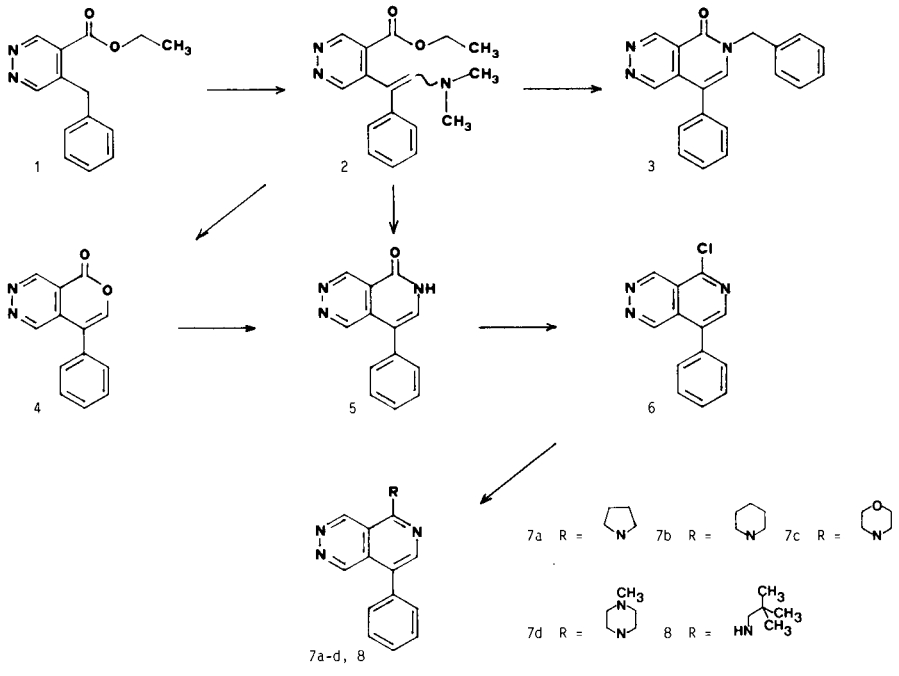
The carbon skeleton of the pyridine moiety in compounds **7** simply could be constructed by condensation of the activated methylene group in ethyl 5-benzyl-4-pyridazinecarboxylate **1** [9] with dimethylformamide dimethyl acetal (*DMFDMA*). Pyridine ring closure then was achieved by treatment of crude **2** thus obtained [14] with ammonium acetate in refluxing ethanol. Structure proof of the resulting 8-phenylpyrido[3,4-*d*]pyridazin-5(6*H*)-one **5** rests on ir and ^{1}H-nmr spectra together with elemental analysis.

On attempted purification of the enamino ester **2** by means of recrystallization the formation of the lactone **4** was observed. This novel pyrano[3,4-*d*]pyridazine could be obtained in up to 51% yield simply by stirring a solution of **2** in ethyl acetate/aqueous acetic acid. Treatment of **4** with ammonium acetate in boiling ethanol again afforded the pyridone **5** (>95% yield).

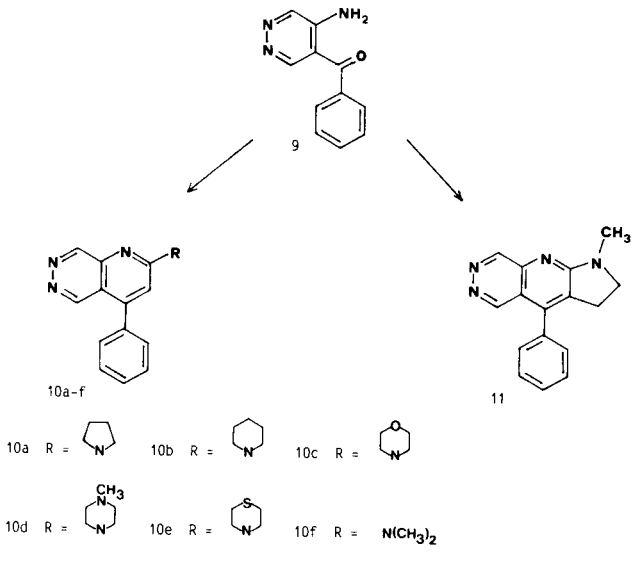
In accordance with observations in the pyridazino-[4,5-*d*]pyridazine series [8], initial attempts to replace the oxo function in compound **5** by chlorine using phosphorus oxychloride gave only poor results. However, addition of pyridine to the reaction mixture also in this case improves the conversion markedly: under these conditions the chloro compound **6** is obtained in 66% yield [15]. Finally, the novel 8-phenyl-5-cycloaminopyrido[3,4-*d*]pyridazines **7a-d** were prepared in reasonable yields (*cf.* Table 1) simply by heating **6** with an excess of the appropriate cyclic amine. Expectedly, displacement of chlorine in compound **6** by a *N*-monoalkylamino moiety could be achieved in a similar manner. The newly synthesized secondary amine **8** appears to be of interest as a diaza analogue of the blood-platelet-aggregation inhibitor 1-neopentylamino-4-phenylphthalazine [16]. The enamino ester **2** represents a suitable starting compound also for the preparation of *N*-6-alkylated 8-arylpyrido[3,4-*d*]pyridazin-5(6*H*)-ones, as demonstrated in the synthesis of compound **3** by reaction of **2** with benzylamine.

In order to prepare pyrido[2,3-*d*]pyridazines of type **C** a recently applied procedure for the annelation of a pyridine moiety to a preformed 1,2-diazine system [17] was employed. It is characterized by cyclocondensation of an appropriate amino ketone like compound **9** with a *N,N*-dialkylacetamide acetal and thus represents an application of the method used by Eiden *et al.* for the preparation of various types of fused dialkylaminopyridines [18,19,20]. Thus, reaction of the 5-amino-4-pyridazinyl phenyl ketone

Scheme 1



Scheme 2



9 [21] with a variety of acetamide acetal derivatives [22] gave the novel 6-cycloamino- or dialkylamino-substituted triazanaphthalenes **10a-f** in satisfactory yields (*cf.* Table 2). In a similar manner, also the novel tricyclic compound **11** could be prepared.

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. For analytical tlc, DC-Alufolien, Kieselgel 60 F_{254} (Merck) were used. Column chromatography was performed on Kieselgel 60 (70-230 mesh; Merck).

Reaction of Ethyl 5-Benzyl-4-pyridazinecarboxylate with Dimethylformamide Dimethyl Acetal.

A mixture of 2.2 g (9.1 mmoles) of ethyl 5-benzyl-4-pyridazinecarboxylate (**1**) [9] and 4 ml (30.4 mmoles) of dimethylformamide dimethyl acetal (*DMFDMA*) was heated to 100° for 3 hours. After concentration *in vacuo*, the residue was subjected to column chromatography (ethyl acetate) to give ethyl 5-(2-dimethylamino-1-phenylethenyl)-4-pyridazinecarboxylate (**2**) as a brown oil (2.1 g, 77%), which was immediately used for the following transformations without further purification.

6-Benzyl-8-phenylpyrido[3,4-*d*]pyridazin-5(6*H*)-one (**3**).

To a solution of 149 mg (0.5 mmole) of compound **2** in 20 ml of absolute ethanol were added 0.4 ml of acetic acid and 0.3 ml (2.5 mmoles) of benzylamine, and the mixture was heated to 60° for 2 hours. After cooling, the precipitate was collected, washed with cold ethanol and dried to afford 83 mg (53%) of compound **3** as colorless crystals, mp 224-225° (ethyl acetate); ^{1}H-nmr (deuteriochloroform): δ 10.05, 9.50 (each d, J = 1.5 Hz, H-1, H-4, 2H), 7.7-7.3 (m, phenyl-H, H-7, 11H), 5.35 (s, CH_2, 2H); ir: cm^{-1} 1665 (C=O).

Anal. Calcd. for $C_{20}H_{15}N_3O \cdot 1/8H_2O$: C, 76.11; H, 4.87; N, 13.31. Found: C, 76.14; H, 4.79; N, 13.14.

8-Phenyl-5*H*-pyrano[3,4-*d*]pyridazin-5-one (**4**).

A solution of 297 mg (1 mmole) of **2** in 20 ml of ethyl acetate, containing 1 ml of acetic acid and 0.5 ml of water, was stirred at room

Table 1

5-Alkylamino- and 5-Cycloamino-8-phenylpyrido[3,4-*d*]pyridazines **7a-d, 8**

Compound No.	% Yield	Mp (°C) (solvent)	Molecular Formula	Elemental Analyses % Calcd./Found C	H	N	^{1}H-NMR δ (ppm)
7a	54	189-190 ethyl acetate	$C_{17}H_{16}N_4 \cdot \frac{1}{2}H_2O$ (285.31)	71.57 71.27	6.01 5.77	19.63 19.54	9.85, 9.50 (each d, J = 1.5 Hz, H-1, H-4, 2H), 8.45 (s, H-7, 1H), 7.6-7.4 (m, phenyl-H, 5H), 4.1-3.9 (m, CH_2, 4H), 2.2-2.0 (m, CH_2, 4H)
7b	59	165 2-propanol	$C_{18}H_{18}N_4$ (290.37)	74.46 74.47	6.25 6.24	19.26 19.17	9.65, 9.60 (each d, unresolved, H-1, H-4, 2H), 8.50 (s, H-7, 1H), 7.6-7.4 (m, phenyl-H, 5H), 3.7-3.5 (m, CH_2, 4H), 1.9-1.7 (m, CH_2, 4H)
7c	55	209-210 ethanol	$C_{17}H_{16}N_4O$ (292.34)	69.85 69.75	5.52 5.62	19.16 19.16	9.75, 9.65 (each d, J = 1.5 Hz, H-1, H-4, 2H), 8.60 (s, H-7, 1H), 7.6-7.4 (m, phenyl-H, 5H), 4.1-3.9 (m, CH_2, 4H), 3.8-3.6 (m, CH_2, 4H)
7d	62	138 2-propanol	$C_{18}H_{19}N_5$ (305.38)	70.80 70.51	6.27 6.40	22.93 22.94	9.70, 9.60 (each d, unresolved, H-1, H-4, 2H), 8.55 (s, H-7, 1H), 7.6-7.4 (m, phenyl-H, 5H), 3.8-3.6 (m, CH_2, 4H), 2.8-2.6 (m, CH_2, 4H), 2.45 (s, CH_3, 3H)
8	62	83-92 acetone	$C_{16}H_{20}N_4 \cdot \frac{1}{2}$acetone (321.43)	72.86 72.72	7.21 7.33	17.43 17.55	9.60 (s, H-1, H-4, 2H), 8.45 (s, H-7, 1H), 7.6-7.4 (m, phenyl-H, 5H), 5.90 (t, J = 6 Hz, NH, 1H), 4.40 (d, J = 6 Hz, CH_2, 2H), 2.15 (s, acetone-CH_3, 3H), 1.10 (s, CH_3, 9H)

Table 2

2-Dialkylamino- and 2-Cycloamino-4-phenylpyrido[2,3-*d*]pyridazines **10a-f**

Compound No.	% Yield	Mp (°C) (solvent)	Molecular Formula	Elemental Analyses % Calcd./Found C	H	N	^{1}H-NMR δ (ppm)
10a	79	203 methanol	$C_{17}H_{16}N_4$ (276.34)	73.89 73.77	5.84 5.96	20.27 20.07	9.45, 9.20 (each d, J = 1.5 Hz, H-5, H-8, 2H), 7.6-7.4 (m, phenyl-H, 5H), 6.85 (s, H-3, 1H), 3.8-3.5 (m, CH_2, 4H), 2.2-2.0 (m, CH_2, 4H)
10b	64	165-166 ethyl acetate	$C_{18}H_{18}N_4$ (290.37)	74.46 74.59	6.25 6.38	19.29 19.35	9.40, 9.20 (each d, J = 1.5 Hz, H-5, H-8, 2H), 7.6-7.4 (m, phenyl-H, 5H), 7.10 (s, H-3, 1H), 4.0-3.8 (m, CH_2, 4H), 1.8-1.6 (m, CH_2, 6H)
10c	84	209 methanol	$C_{17}H_{16}N_4O$ (292.34)	69.85 69.71	5.52 5.58	19.16 19.27	9.50, 9.30 (each d, J = 1.5 Hz, H-5, H-8, 2H), 7.7-7.5 (m, phenyl-H, 5H), 7.15 (s, H-3, 1H), 3.95 (s, CH_2, 8H)
10d	56	156 butanone	$C_{18}H_{19}N_5 \cdot \frac{1}{4}H_2O$ (309.89)	69.77 69.99	6.34 6.27	22.60 22.57	9.40, 9.20 (each d, J = 1.5 Hz, H-5, H-8, 2H), 7.7-7.4 (m, phenyl-H, 5H), 7.15 (s, H-3, 1H), 4.1-3.9 (m, CH_2, 4H), 2.7-2.5 (m, CH_2, 4H), 2.35 (s, CH_3, 3H)
10e	54	212 ethyl acetate	$C_{17}H_{16}N_4S$ (308.40)	66.21 65.98	5.23 5.12	18.17 18.29	9.45, 9.25 (each d, J = 1.5 Hz, H-5, H-8, 2H), 7.6-7.4 (m, phenyl-H, 5H), 7.10 (s, H-3,1H), 4.3-4.1 (m, CH_2, 4H), 2.8-2.6 (m, CH_2, 4H)
10f	95	216 ethanol	$C_{15}H_{14}N_4$ (250.30)	71.98 71.83	5.64 5.72	22.38 22.49	9.45, 9.20 (each d, J = 1.5 Hz, H-5, H-8, 2H), 7.6-7.5 (m, phenyl-H, 5H), 7.00 (s, H-3, 1H), 3.30 (s, CH_3, 3H)

temperature for 20 hours. The resulting mixture was concentrated *in vacuo*, taken up in water and extracted with dichloromethane. The organic layer was washed with aqueous sodium bicarbonate and water, then dried and evaporated. Recrystallization from ethyl acetate yielded 114 mg (51%) of colorless crystals, mp 180-181°; ^{1}H-nmr (deuteriochloroform): δ 9.90, 9.45 (each d, J = 1.5 Hz, H-1, H-4, 2H), 7.7-7.35 (m, phenyl-H, H-7, 6H); ir: cm^{-1} 1745 (C=O).

Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.60; N, 12.49. Found: C, 69.41; H, 3.68; N, 12.30.

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

Method A.

A solution of 291 mg (1.3 mmoles) of **4** and 1.0 g (13 mmoles) of ammonium acetate in 25 ml of absolute ethanol was refluxed for 2 hours.

After cooling, the precipitate was collected, washed with water, and dried to afford 278 mg (96%) of pale yellow crystals, mp >300° (from ethanol); ^{1}H-nmr (deuteriodimethylsulfoxide): δ 12.5 (br, NH, 1H), 9.80, 9.45 (each d, J = 1.5 Hz, H-1, H-4, 2H), 7.75 (s, H-7, 1H), 7.7-7.5 (m, phenyl-H, 5H); ir: cm^{-1} 1690 (C=O).

Anal. Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 70.05; H, 4.29; N, 18.95.

Method B.

A solution of 297 mg (1 mmole) of **2** and 770 mg (10 mmoles) of ammonium acetate in 20 ml of absolute ethanol was refluxed for 2 hours. After concentration *in vacuo*, the residue was triturated with water. The precipitate was collected, washed with water, and dried to give 192 mg (86%) of a product being identical (mp, ir) with compound **5** prepared as described above.

5-Chloro-8-phenylpyrido[3,4-*d*]pyridazine (**6**).

A mixture of 314 mg (1.4 mmoles) of **5**, 0.5 ml of pyridine and 5 ml of freshly distilled phosphorus oxychloride was heated to 100° for 1 hour. After cooling, the solution was slowly poured into ice-water and extracted with dichloromethane. The organic layer was washed with aqueous sodium carbonate and water, then dried and evaporated to give 223 mg (66%) of **6** as a solid, mp 201-204°, which was immediately used for the following transformations without further purification; ^{1}H-nmr (deuteriochloroform): δ 10.05, 9.75 (each d, J = 1.5 Hz, H-1, H-4, 2H), 8.80 (s, H-7, 1H), 7.75-7.45 (m, phenyl-H, 5H).

General Procedure for the Preparation of the 5-Cycloamino-8-phenylpyrido[3,4-*d*]pyridazines **7a-d**.

A mixture of 121 mg (0.5 mmole) of **6** and 8 ml of dry cycloamine (pyrrolidine, piperidine, morpholine, or 1-methylpiperazine, respectively) was refluxed for 3 hours. After removal of the excess of the amine *in vacuo*, the residue was taken up in dichloromethane [23]. The organic layer was extracted two times with 0.1 *N* hydrochloric acid, dried and evaporated; recrystallization afforded pale yellow crystals. For recrystallization solvents, yields, melting points, analytical and ^{1}H-nmr data see Table 1.

N-(2,2-Dimethylpropyl)-8-phenylpyrido[3,4-*d*]pyridazine-5-amine (**8**).

A mixture of 121 mg (0.5 mmole) of **6** and 8 ml of neopentylamine was heated to reflux for 3 hours. The excess of neopentylamine was removed *in vacuo* and the residue taken up in dichloromethane. The organic layer was extracted two times with 0.1 *N* hydrochloric acid, dried, and evaporated. Purification by column chromatography (dichloromethane:methanol, 95:5), followed by recrystallization from acetone afforded pale yellow crystals. For yield, melting point, analytical and ^{1}H-nmr data see Table 1.

4-Phenyl-2-pyrrolidinopyrido[2,3-*d*]pyridazine (**10a**).

A mixture of 1.33 g (10 mmoles) of dimethylacetamide dimethyl acetal (*DMADMA*) and 1.42 g (20 mmoles) of dry pyrrolidine was heated to 150° for 5 hours during which a slow stream of dry argon was bubbled through the solution. After cooling, 199 mg (1 mmole) of **9** [21] were added and the mixture was kept at 35° for 0.5 hours. The residue left on evaporation *in vacuo* was recrystallized from methanol to afford pale yellow needles. For yield, melting point, analytical and ^{1}H-nmr data see Table 2.

General Procedure for the Preparation of the 2-Cycloamino-4-phenylpyrido[2,3-*d*]pyridazines **10b-e**.

A mixture of 1.33 g (10 mmoles) of *DMADMA* and 20 mmoles of dry amine (piperidine, morpholine, 1-methylpiperazine, or thiomorpholine, respectively) was heated to 190° for 5 hours during which a slow stream of dry argon was bubbled through the solution. After cooling, 199 mg (1 mmole) of **9** [21] were added and the mixture was heated to 130° for 15 hours. Evaporation *in vacuo*, followed by recrystallization gave the pure products. Recrystallization solvents, yields, melting points, analytical and ^{1}H-nmr data are summarized in Table 2.

2-Dimethylamino-4-phenylpyrido[2,3-*d*]pyridazine (**10f**).

A mixture of 199 mg (1 mmole) of **9** [21] and 2 ml of *DMADMA* was refluxed for 2 hours. The excess reagent was removed *in vacuo* and the residue recrystallized from ethanol to give colorless needles. For yield, melting point, analytical and ^{1}H-nmr data see Table 2.

2,3-Dihydro-1-methyl-4-phenyl-1*H*-pyrrolo[3,2:5,6]pyrido[2,3-*d*]pyridazine (**11**).

To a filtered solution of crude 2,2-diethoxy-1-methylpyrrolidine, prepared from 1.584 g (16 mmoles) of 1-methyl-2-pyrrolidinone according to reference [24], in 8 ml of absolute ethanol (still containing some sodium ethoxide [18]) were added 199 mg (1 mmole) of **9** [21], and the mixture was warmed to 35° for 0.5 hours. After cooling, the precipitate was collected and recrystallized from ethanol to afford 220 mg (84%) of compound **11** as colorless needles, mp 216° (sublimation above 170°); ^{1}H-nmr (deuteriochloroform): δ 9.35, 8.95 (each d, J = 1 Hz, H-5, H-8, 2H), 7.6-7.3 (m, phenyl-H, 5H), 3.70 (t, J = 8 Hz, N-CH_2, 2H), 3.15 (s, CH_3, 3H), 3.05 (t, J = 8 Hz, C-CH_2, 2H).

Anal. Calcd. for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.03; H, 5.50; N, 21.22.

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[15] Due to limited stability, compound **6** was employed in further reactions without purification.

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