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# Synthesis of Pyridazine Derivatives. XXIII. Synthesis of Isomeric Azolopyrido (3,2-*d*) — and Azolopyrido (2,3-*d*) pyridazines

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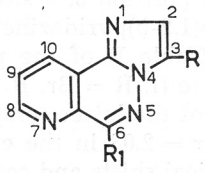
The synthesis of six new parent azolopyridopyridazines (I—VI) is described. Electrophilic substitutions were studied on two isomeric imidazopyridopyridazines and it was found that position 3 is attacked.

Recently we have described the synthesis of several polyazaheterocycles derived from pyrido(2,3-*d*)pyridazine[1]. In this paper we describe the synthesis of several new parent tricyclic systems derived from pyrido(2,3-*d*)pyridazine and some electrophilic substitutions on imidazo(1,2-*b*)pyrido(3,2-*d*)pyridazines (I) and imidazo(1,2-*b*)pyrido(2,3-*d*)pyridazines (II) as representatives of the above types of compounds.



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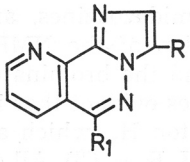

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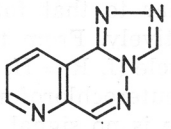

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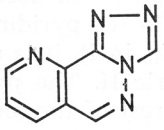

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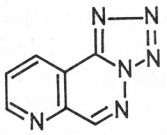
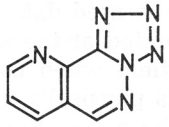
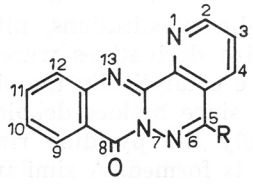


V



VI



VII

The parent isomeric systems with fused imidazole ring, *i. e.* I and II (R = $R_1$ = H) were prepared conveniently through hydrogenolysis of their 6-chloro analogues, I (R = H, $R_1$ = Cl)[1] and II (R = H, $R_1$ = Cl) which were prepared[1,2] earlier. For the synthesis of the *s*-triazolo and tetrazolo analogues (III—VI) the isomeric 5- and 8-hydrazinopyrido(2,3-*d*)pyridazines, themselves obtained by hydrazinolysis of the corresponding methylthio analogues were used as starting materials. The fused *s*-triazolo ring was formed subsequently in the reaction with diethoxymethyl acetate to give III or IV. Similarly, the tetrazolo derivatives V and VI were formed by nitrosation of the corresponding hydrazinopyrido(2,3-*d*)-pyridazines. All these parent tricyclic polyazaheterocycles represent stable 14-$\pi$ electron systems with aromatic character. This is shown by the NMR spectra (Table I) since proton chemical shifts are in the range typical for aromatic protons.

Besides, a new tetracyclic system was prepared in a reaction between 5,8-dichloropyrido(2,3-*d*)pyridazine and anthranilic acid. The NMR spectrum of the obtained 5-chloropyrido(3',2':4,5)pyridazino-(6,1-*b*)quinazolin-8-one (VII, R = Cl) is consistent with the proposed structure.

Some bicyclic poliazaheterocycles with bridgehead nitrogen were investigated only recently for their reactivity against electrophilic attack. Such systems are imidazo(1,2-*a*)pyridines,[3,4] imidazo(1,2-*a*)pyrimidines,[5,6] pyrrolo(1,2-*a*)pyrazine[7] and pyrazolo(1,5-*a*)-pyridine.[7] To our knowledge there are no known data about such reactions in the field of related tricyclic compounds.

Both isomeric polyazaheterocyclic systems I and II underwent bromination or nitration easily and only monosubstituted products could be isolated under the conditions employed. By means of NMR spectra we could conclusively prove that the attack was in all cases on the imidazole ring at position 3, a situation similar to that found with imidazoazines, and imidazo(1,2-*b*)pyridazine[8,9] respectively. From the correlation of the NMR spectra (Table I) of the parent tricycle (I, R = H, $R_1$ = Cl) and the brominated derivative (I, R = Br, $R_1$ = Cl) in deuterochloroform it becomes evident that in the case of the latter compound there is no signal for the proton $H_3$, which appears at $\tau$ = 2.08 in the case of the parent compound (I, R = H, $R_1$ = Cl). All other chemical shifts and coupling constants are in both cases almost identical.

Furthermore, NMR spectra permit also differentiation between both isomeric systems, *i. e.* the orientation of the pyridine ring. As may be seen from the presented data, if the proton *para* to the ring nitrogen in the pyridine ring is oriented at the same site as the fused imidazole ring ($H_{10}$ in I), it is shifted downfield when compared to the proton $H_7$ of the isomeric II. The pyridine ring is physically and chemically quite different from the rest of the molecule and the orientation of the imidazole ring as in I or II exerts a distinct steric substituent effect. This, as a function of the ring orientation has been recently observed with related pyrido(2,3-*d*)-5- or 8-pyridazones[10] and with some polycyclic polyazaheterocycles which we investigated recently.[11,12]

Among other electrophilic substitutions, nitration was easily performed and the corresponding 3-nitro derivatives were obtained (I or II, R = $NO_2$, $R_1$ = Cl). Attempts to remove catalytically the chlorine atom in both isomeric systems were not successful since besides dehalogenation partial reduction of a hetero ring, most probably the pyridine ring, takes place easily and a mixture of several products is formed. A similar experience was encountered

TABLE I

*Chemical Shifts and Coupling Constants of Some Imidazo(1,2-b)pyrido(3,2-d)- and -(2,3-d)pyridazines*

Chemical shift — τ

| Compound | $H_2$ | $H_3$ | $H_7$ | $H_8$ | $H_9$ | $H_{10}$ |
|---|---|---|---|---|---|---|
| I, R = H, $R_1$ = Cl | 2.36 (d) | 2.08 (d) | | 0.91 (q) | 2.18 (q) | 1.22 (q) |
| I, R = Br, $R_1$ = Cl | 2.35 (s) | | | 0.90 (q) | 2.18 (q) | 1.10 (q) |
| II, R = H, $R_1$ = Cl | 2.25 (d) | 2.10 (d) | 1.52 (q) | 2.35 (q) | 0.82 (q) | |

Coupling constants, cps

| Compound | $J_{H_2,H_3}$ | $J_{H_9,H_{10}}$ | $J_{H_8,H_9}$ | $J_{H_8,H_{10}}$ | $J_{H_7,H_8}$ | $J_{H_7,H_9}$ |
|---|---|---|---|---|---|---|
| I, R = H, $R_1$ = Cl | 1.5 | 8.5 | 4.5 | 1.5 | | |
| I, R = Br, $R_1$ = Cl | | 8.5 | 4.5 | 1.5 | | |
| II, R = H, $R_1$ = Cl | 1.5 | | 4.5 | | 8.5 | 1.5 |

s = singlet, d = doublet, q = quartet

recently with 5-chloropyrido(2,3-*d*)pyridazin-8(7H)one where a tetrahydro derivative is supposed to be formed.[2]

## EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage and are corrected. NMR spectra were recorded with a Varian A-60 spectrometer using deuterochloroform solutions and tetramethylsilane as internal standard.

Pyrido(2,3-*d*)pyridazin-5(6H)-thione and pyrido(2,3-*d*)pyridazin-8(7H)-thione were prepared as described by Kakimoto and Tanooka[10].

*Imidazo(1,2-b)pyrido(3,2-d)pyridazine* (I, R = $R_1$ = H)

Concentrated ammonia (3 ml.) and palladized charcoal (0.5 g. of 5%) were added to a solution of 6-chloroimidazo(1,2-*b*)pyrido(3,2-*d*)pyridazine[1] (I, R = H, $R_1$ = Cl) (1.2 g.) in methanol (100 ml.). The mixture was hydrogenated under atmospheric pressure at room temperature until the necessary quantity of hydrogen was absorbed (about 1 hr). The catalyst was removed by filtration and the filtrate evaporated to dryness. Water (2. ml.) was added to the residue, the mixture filtered and the residue crystallized from ethyl acetate and *n*-hexane (1 : 4) to give the pure compound, mp. 113—115° in 82% yield.

*Anal.* $C_9H_6N_4$ (170.17) calc'd:. C 63.52; H 3.55; N 32.93%
found: C 63.87; H 4.12; N 33.08%

The compound forms a sulfate, m.p. 318—321°, or hydrochloride, m.p. over 310°.

*Imidazo(1,2-*b*)pyrido(2,3-*d*)pyridazine* (II, R = $R_1$ = H)

This compounds was prepared in essentially the same way as the above isomeric tricycle, starting from 6-chloroimidazo(1,2-*b*)pyrido(2,3-*d*)pyridazine[1,2] (II, R = H, $R_1$ = Cl; 1.02 g.). The product was crystallized from *n*-hexane, m. p. 166—167° (yield 24%).

*Anal.* $C_9H_6N_4$ (170.17) calc'd.: C 63.52; H 3.55; N 32.93%
found: C 63.32; H 3.68; N 32.92%

*5-Methylthiopyrido(2,3-*d*)pyridazine*

Pyrido(2,3-*d*)pyridazin-5(6H)-thione[10] (1.6 g.), a solution of 0.56 g. potassium hydroxide in methanol (10 ml.) and MeI (1.5 g.) were heated under reflux for 3 hrs. The reaction mixture was evaporated *in vacuo* and the residue extracted four times with 25 ml. of hot benzene. The combined extracts were evaporated to about 20 ml. and some *n*-hexane was added. The separated yellow needles (1.2 g.) were crystallized from a mixture of *n*-hexane and benzene to give the pure compound, m. p. 93—95°.

*Anal.* $C_8H_7N_3S$ (177.23) calc'd.: C 54.23; H 3.98; N 23.72%
found: C 54.56; H 4.12; N 23.91%

*8-Methylthiopyrido(2,3-*d*)pyridazine*

The compound was prepared from pyrido(2,3-*d*)pyridazin-8(7H)-thione[10] in essentially the same way as described for the 5-methylthio analog. It was crystallized from benzene and *n*-hexane, mp. 110° (yield 87%).

*Anal.* $C_8H_7N_3S$ (177.23) calc'd.: C 54.23; H 3.98; N 23.72%
found: C 54.53; H 4.16; N 23.89%

*5-Hydrazinopyrido(2,3-*d*)pyridazine*

5-Methylthiopyrido(2,3-*d*)pyridazine (0.5 g.), hydrazine hydrate (1.5 ml. of 80%) and methanol (5.5 ml.) were heated under reflux for 2.5 hrs. The product was obtained from the cooled reaction mixture by filtration, it was washed with *n*-hexane and for analytical purposes crystallized from methanol, m. p. 240° (dec.) (yield 56%).

*Anal.* $C_7H_7N_5$ (161.17) calc'd.: C 52.16; H 4.38; N 43.46%
found: C 52.06; H 4.47; N 43.02%

Its benzylidene derivative was prepared in the usual way, m. p. 220° (from ethanol).

*Anal* $C_{14}H_{11}N_5$ (249.27) calc'd.: C 67.45; H 4.45; N 28.10%
found: C 67.10; H 4.68; N 27.85%

*8-Hydrazinopyrido(2,3-*d*)pyridazine*

A mixture of 8-methylthiopyrido(2,3-*d*)pyridazine (5.8 g.), methanol (50 ml.) and hydrazine hydrate (4 ml. of 80%) was heated under reflux until no more methyl mercaptan was evolved (about 12 hrs). The reaction mixture was evaporated *in vacuo* and the residue crystallized from ethanol, m. p. 190—195°. For analytical purposes the hydrobromide was prepared as follows. 200 mg. of the base was dissolved in 5 ml. of ethanol and few drops of concentrated hydrobromic acid were added. Upon standing for several hours the salt separated, m. p. 270° (yield 37%).

*Anal.* $C_7H_8BrN_5$ (242.09) calc'd.: C 34.73; H 3.33; N 28.94%
found: C 34.58; H 3.53; N 28.78%

The benzylidene derivative was prepared from the base in the usual way, m. p. 201—202° (from ethanol).

*Anal.* $C_{14}H_{11}N_5$ (249.27) calc'd.: C 67.45; H 4.45; N 28.10%
found: C 67.58; H 4.68; N 27.85%

*Pyrido(3,2-*d*)-s-triazolo(4,3-*b*)pyridazine* (III)

5-Hydrazinopyrido(2,3-*d*)pyridazine (100 mg.) and diethoxymethyl acetate (200 mg.) were mixed together. Some heat was evolved and ethanol and ethyl acetate (5 ml., 1 : 1)

were added to the cooled mixture and the reaction mixture heated on a water bath for 10 min. Upon cooling the product separated in the form of needles (80 mg.). For analytical purposes it was crystallized from methanol, m. p. 220—222°.

*Anal.* $C_8H_5N_5$ (171.16) calc'd.: C 56.13; H 2.94; N 40.92%
found: C 55.99; H 3.45; N 40.55%

*Pyrido(2,3-*d*)-*s*-triazolo(4,3-*b*)pyridazine* (IV)

8-Hydrazinopyrido(2,3-*d*)pyridazine (100 mg.) was treated with diethoxymethyl acetate (150 mg.). After the exothermic reaction had subsided, a precipitate began to separate. The product was filtered off, washed with some ethanol, crystallized from a mixutre of ethanol and ethyl acetate (1 : 1) and for analytical purposes sublimed at 230°/1.5 mm. M. p. 265°, yield 89%.

*Anal.* $C_8H_5N_5$ (171.16) calc'd.: C 56.13; H 2.94; N 40.92%
found: C 56.16; H 3.22; N 41.42%

*Pyrido(3,2-*d*)tetrazolo(5,1-*b*)pyridazine* (V)

5-Hydrazinopyrido(2,3-*d*)pyridazine (161 mg.) was dissolved in acetic acid (4 ml. of 30%) and to the ice cold solution a solution of sodium nitrite (70 mg.) in water (1 ml.) was aded portionwise. The reaction mixture was left on ice for 30 min., the precipitate filtered off and washed with 2 ml. of iced water. Upon crystallization from ethanol the pure compound, m. p. 204°, was obtained in 69% yield.

*Anal.* $C_7H_4N_6$ (172.15) calc'd.: C 48.84; H 2.34; N 48.82%
found: C 49.02; H 2.63; N 48.65%

*Pyrido(2,3-*d*)tetrazolo(5,1-*b*)pyridazine* (VI)

It was prepared in essentially the same way as the above isomeric tetrazolo compound. Upon crystallization from a mixture of ethanol and *N,N*-dimethylformamide (3 : 1) the pure compound, m. p. 228—229°, was obtained in 53% yield.

*Anal.* $C_7H_4N_6$ (172.15) calc'd.: C 48.84; H 2.34; N 48.82%
found: C 48.98; H 2.79; N 48.92%

*3-Bromoimidazo(1,2-*b*)pyrido(3,2-*d*)pyridazine* (I, R = Br, $R_1$ = H)

Compound I (R = $R_1$ = H; 0.85 g.) was dissolved in glacial acetic acid (5 ml.) and treated dropwise with excess of bromine until the solution remained colored. The separated hydrobromide salt was collected (46%) and crystallized from glacial acetic acid, m. p. 268—269°.

*Anal.* $C_9H_6Br_2N_4$ (330.00) calc'd.: C 32.75; H 1.83; N 16.97%
found: C 32.64; H 2.06; N 16.82%

The free base was obtained after neutralizing an aqueous solution of the above salt with sodium bicarbonate and was crystallized from ethanol, m. p. 181—183°.

*Anal.* $C_9H_5BrN_4$ (249.08) calc'd.: C 43.40; H 2.02; N 22.50%
found: C 43.22; H 2.53; N 22.32%

*3-Bromo-6-chloroimidazo(1,2-*b*)pyrido(3,2-*d*)pyridazine* (I, R = Br, $R_1$ = Cl)

*a)* To a solution of I (R = H, $R_1$ = Cl; 1.0 g.)[1] glacial acetic acid (10 ml.) a solution of bromine in glacial acetic acid was added dropwise in excess at room temperature. After addition was complete, the colored solution was stirred for 15 min. and the product was filtered off and crystallized from ethanol, m. p. 248—250°. Yield 1.3 g. (93%).

*Anal.* $C_9H_4BrClN_4$ (283.53) calc'd: C 38.12; H 1.42; N 19.76%
found: C 37.98; H 1.70; N 19.88%

*b)* To a solution of I (R = H, $R_1$ = Cl; 0.5 g.) in chloroform (15 ml.) *N*-bromosuccinimide (0.45 g.) was added. The mixture was then heated under reflux for

5 min. and left aside to cool down for 30 min. The mixture was shaken with a saturated solution of sodium bicarbonate, the chloroform layer separated and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the product was crystallized from ethanol, m.p. 250° (yield 0.6 g., 87%). The compound is identical to the product as prepared under *a)*.

*3-Bromo-6-chloroimidazo(1,2-*b*)pyrido(2,3-*d*)pyridazine* (II, R = Br, $R_1$ = Cl)

*a)* Bromination with a solution of bromine in glacial acetic acid was carried out as described above for the isomeric I, employing II (R = H, $R_1$ = Cl)[1,2] as the starting material. The crude product was purified by crystallization from ethanol and had m.p. 260—262°. Yield 1.3 g. (94%).

*Anal.* $C_9H_4BrClN_4$ (283.53) calc'd: C 38.12; H 1.42; N 19.76%
found: C 38.37; H 1.68; N 19.72%

*b)* Bromination with *N*-bromosuccinimide as described above, yielded the same compound as obtained under *a)* in 87% yield.

*6-Chloro-3-nitroimidazo(1,2-*b*)pyrido(3,2-*d*)pyridazine* (I, R = $NO_2$, $R_1$ = Cl)

To a stirred solution of I (R = H, $R_1$ = Cl; 1.0 g.) in concentrated sulfuric acid (4 ml.), cooled to — 10°, concentrated nitric acid (1.2 ml., d = 1.42) was added dropwise during 5—10 min. The mixture was then stirred at room temperature for 20 min. and poured onto 40 g. ice. The separated product was filtered and crystallized from ethanol, m.p. 231°. Yield 0.8 g. (67%).

*Anal.* $C_9H_4ClN_5O_2$ (249.62) calc'd.: C 43.20; H 1.61; N 28.06%
found: C 43.12; H 1.98; N 27.89%

*6-Chloro-3-nitroimidazo(1,2-*b*)pyrido(2,3-*d*)pyridazine* (II, R = $NO_2$, $R_1$ = Cl)

The same procedure as described for the synthesis of the isomeric nitro compound was followed. The crude product was crystallized from ethanol, m.p. 223—224°, yield 0.78 g. (65%).

*Anal.* $C_9H_4ClN_5O_2$ (249.62) calc'd.: C 43.20; H 1.61; N 28.06%
found: C 42.97; H 2.02; N 28.32%

*5-Chloropyrido(3',2':4,5)pyridazino(6,1-*b*)quinazolin-8-one* (VII, R = Cl)

5,8-Dichloropyrido(2,3-*d*)pyridazine (2.0 g.) was suspended in ethanol (30 ml.), anthranilic acid (1.37 g.) and concentrated hydrochloric acid (2 ml.) were added. The mixture was heated under reflux for 1 hr. and after about 30 min. the reaction mixture thickened. The filtered product was purified by sublimation at 280—290°/1 mm, m.p. over 320°. Yield 83%. NMR ($CF_3COOH$ and $(CF_3CO)_2O$, 1 : 1); $\tau : H_2 = 0.45$; $H_3 \cong 1.50$ (Partly covered by aromatic multiplet); $H_4 = 1.05$; $H_{9,10,11,12} \cong 1.85$. $J_{2,3} = 4.5$; $J_{2,4} = 2.0$; $J_{3,4} = 8.5$ cps.

*Anal.* $C_{14}H_7ClN_4O$ (282.69) calc'd.: C 59.47; H 2.50; N 19.82%
found: C 59.04; H 2.69; N 20.29%

*5-Hydrazinopyrido(3' 2':4,5)pyridazino(6,1-*b*)quinazolin-8-one* (VII, R = $NHNH_2$)

The above chloro compound (1.42 g.) and hydrazine hydrate (5 ml. of 80%) were heated under reflux for 5 hr. The cooled reaction mixture was diluted with water (10 ml.) and the separated product filtered off (yield 0.8 g., 54%). For analytical purposes crystallization was effected from *N,N*-dimethylformamide, m.p. 298—301°.

*Anal.* $C_{14}H_{10}N_6O$ (278.27) calc'd.: C 60.42; H 3.62; N 30.20%
found: C 60.25; H 3.47; N 30.02%

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## IZVLEČEK

**Sinteza piridazinovih derivatov. XXIII. Sinteza izomernih azolopirido(3,2-*d*)- in azolopirido(2,3-*d*)piridazinov**

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Opisana je sinteza šest novih osnovnih azolopiridopiridazinov (I—VI). Raziskave elektrofilnih substitucij so pokazale, da potekajo te pri obeh izomernih imidazopiridopiridazinih na položaju 3.

ODDELEK ZA KEMIJO
FAKULTETA ZA NARAVOSLOVJE IN TEHNOLOGIJO
LJUBLJANA

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