Monatshefte für Chemie 131, 293–299 (2000)

Monatshefte für Chemie
Chemical Monthly
© Springer-Verlag 2000
Printed in Austria

The *Gould-Jacobs* Reaction of 5-Aminoquinoxaline[a]

Jozef Saloň[1], **Viktor Milata**[1,*], **Nadežda Prónayová**[2], and **Ján Leško**[2]

[1] Department of Organic Chemistry, Faculty of Chemical Technology, Slovak University of Technology, SK-81237 Bratislava, Slovak Republic
[2] Central Laboratory of Chemical Technique, Faculty of Chemical Technology, Slovak University of Technology, SK-81237 Bratislava, Slovak Republic

Summary. Reaction of 5-aminoquinoxaline with alkoxymethylene derivatives affords the corresponding quinoxalinoaminoethylenes. These undergo a thermal cyclization to yield angularly annelated 10*H*-pyrido[2,3-*f*]quinoxalines. The structures of all products were deduced from their IR, UV, mass, ^{1}H, and ^{13}C NMR spectra.

Keywords. Pyridoquinoxalines; Quinoxalinoaminoethylenes; Biological activity.

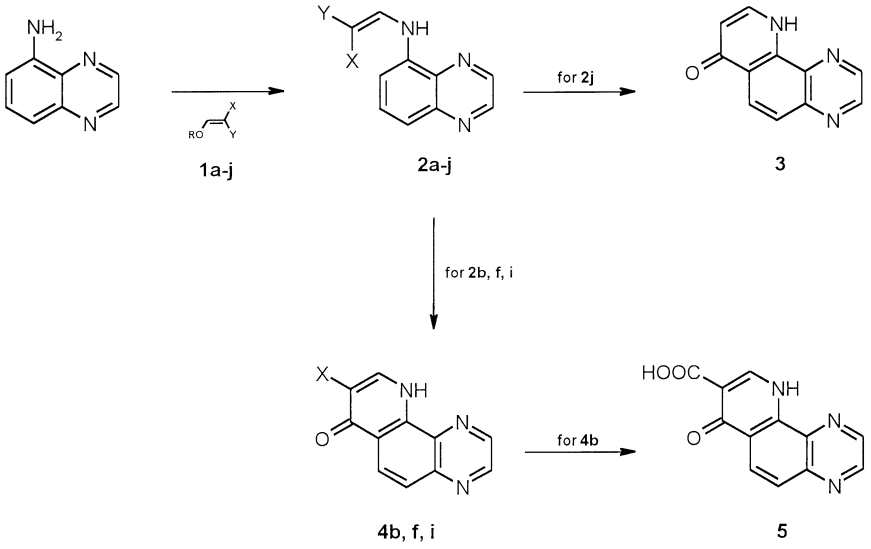
Introduction

Numerous quinoxaline derivatives have been synthesized and attracted the attention of many research groups due to their biological importance [1–7]. For example, quinoxaline-2-one has been shown to possess antiinflammatory [8], tranquilizing, and antidepressant properties [9]. Condensed quinoxalines like imidazoquinoxalines have been found to be strong cancerogens in food [10]. Within this respect and in continuation of our strategy for the synthesis of polyheterocyclic fused systems containing the quinoxaline moiety, we report the synthesis and biological activity [2, 11] of some new quinoxaline derivatives.

Results and Discussion

5-Aminoquinoxaline, prepared from the appropriate nitro derivative [4] by catalytic reduction, was subjected to nucleophilic substitution with an alkoxymethylene derivative without prior isolation. The rate of hydrogenation was depending on the content of traces of sulfur originating from the partial reduction of 2,6-dinitroaniline to 3-nitro-1,2-benzenediamine (the best amounts for this reduction was found to be between 5 and 10 g). The procedure for the preparation of 2-alkoxymethylene-3-oxobutanenitrile [12] was improved using *in situ* prepared 3-oxobutanenitrile with 3 equivalents of triethyl orthoformate and a catalytic

[a] Dedicated to Prof. *F. Sauter* on the occasion of his 70th birthday
* Corresponding author



	R	*X*	*Y*
a	Me	CO_2CH_3	CO_2CH_3
b	Et	$CO_2C_2H_5$	$CO_2C_2H_5$
c	Et	CN	CN
d	Et	$COCH_3$	$COCH_3$
e	Me	$COCH_3$	CO_2CH_3
f	Et	$COCH_3$	$CO_2C_2H_5$
g	Et	$COCH_3$	CN
h	Me	CN	CO_2CH_3
i	Et	CN	$CO_2C_2H_5$
j	Et	CO-O-C$(CH_3)_2$-O-CO	

Scheme 1

amount of acetic anhydride. The resulting aminoethylenes are moderately soluble in organic solvents; derivatives of cyanoacetic acid (**2f**, **2i**) and meldrum's acid (**2j**) are sparingly soluble and were recrystallized from xylene.

The structure of these types of compounds could be established on the basis of their spectroscopic characteristics. Higher values of the proton shifts of the olefinic protons H-9 in the ^{1}H NMR spectra as expected are caused by their interaction with the nitrogen atom of the pyrazine ring, similar to the case of 4-substituted benzazoles [12]. Because of a high vicinal coupling constant $^3J_{NH-H9}$ (13 Hz), an antiperiplanar conformation of the NH–CH moiety can be assigned. An intramolecular hydrogen bond between the carbonyl group of the acetyl or alkoxycarbonyl substituent on the double bond and the NH group was evident from the downfield shifted signals for NH, –CH=, and double bond substituent signals in the ^{1}H and ^{13}C NMR spectra as well as from their IR spectra. The geometrical isomerism of the double bond could be deduced from the NMR spectra. Although in all cases both isomers were formed, the (*E*)-isomers were preferred (**2e**, **f**). That means that the configuration with the acetyl group hydrogen bonded the amino group is preferred over a hydrogen bond with the alkoxycarbonyl group [13].

The cyanoacetic acid derivatives **2h**,**i** gave also predominantly the (*E*)-isomers, although now this preference was based on steric factors only. The possible H-bond with the alkoxycarbonyl group did not seem to play a major role [2, 12, 13]. The 3-oxobutanenitrile derivative **2g** confirmed these conclusions. All these phenomena were evident regardless of the solvents used for measuring the spectra. In all mass spectra, we observed the molecular ions; in the case of the propanedinitrile derivative **2c** it was even the base peak in the spectrum due to the strongly electron withdrawing substituent, [12]. The origin of more intense species could be explained by bond fission, mainly in the aminoethylene chain. The UV spectra reflect the introduction of the polar aminoethylene substituent into the quinoxaline skeleton (**15**: 232, 305, and 315 nm), yielding a most intense maximum at about 370 nm. The nature of the substituent of the double bond in relation to its electron withdrawing property is also displayed in the UV spectra of **2a–d**. Analogous substances possessing a similarly 4-substituted 2-methylbenzotriazole ring and the same substituents have the longest wave bonds hypsochromically shifted by about 15 nm, thus indicating greater conjugation between the substituent and the ring [12].

Thermal cyclisation under *Gould-Jacobs* reaction conditions led regioselectively to the angularly annelated 8-(non)substituted pyrido[2,3-*f*]quinoxalines **3** and **4**. Cyclization of derivatives **2b**, **2f**, and **2j** required a dilution of 1:15 (1 g of starting aminoethylene derivative: 15 cm^3 of Dowtherm) and relatively short reaction times (from 5 to 20 min); cyclization of **2i** occured successfully only after 6 h of reflux using a dilution of 1:100. Better results were obtained when no reflux condenser was used due to removal of the volatile alcohol from reaction mixture. The reaction progress was established by TLC after removing most of the Dowtherm by means of a hot air gun and subsequent development in acetone to find the remaining starting material. Angular annelation of the pyridine and pyrazine rings was confirmed by a high value of the coupling constant (9 Hz) resulting from the *ortho*-interaction of the protons. The same configurations on the 4-pyridone and the pyrazine nucleus show $^3J_{8,9} = 6$ Hz and $^3J_{2,3} = 1.8$ Hz, respectively. Hydrolysis of the resulting pyrido[2,3-*f*]quinoxaline derivative **4b** was successful only under alkaline conditions. Chemical shifts of the carbon atoms in positions 8 and 9 were found to be in agreement with those given in Ref. [14] depending on the substituent in position 8.

Experimental

Melting points were measured on a Kofler micro hot-stage, and their values were not corrected. IR (0.5 mg of substance per 300 mg KBr) and UV spectra (methanolic solutions of $1 \cdot 10^{-3}$ mol · dm^{-3}, 2 mm) were recorded with FTIR PU 9802 (Philips) and Specord (Zeiss, Jena) spectrophotometers. ^{1}H and ^{13}C NMR spectra of *DMSO*-d_6, $CDCl_3$, $CDCl_3$ + *DMSO*-d_6, $CDCl_3$ + MeOD, and CF_3COOD solutions were measured with a Varian VXR–300 apparatus (300 MHz for ^{1}H, 75 MHz for ^{13}C) with hexamethyldisiloxane as internal standard. The electron impact mass spectra were taken with an MS 902S (AEI-Kratos) instrument at 70 eV electron energy and 100 μA current trap. Elemental analyses were performed using an EA-1108 (Carlo Erba) apparatus. The results were in good agreement (±0.3%) with the calculated values.

The alkoxymethylene derivatives **1a–c** are commercially available. 3-Ethoxymethylene-2,4-pentanedione (**1d**), methyl (**1e,h**), and ethyl (**1f**,**i**) 2-alkoxymethylene-3-oxobutanoic acids, or 3-alkoxy-2-cyanopropenoic acids were synthetized by condensation of methyl or ethyl orthoformate

with the corresponding methylene compound (2,4-pentanedione, methyl or ethyl 3-oxobutanoic acid, and methyl or ethyl 2-cyanoacetate [1]).

2-Ethoxymethylene-3-oxobutanenitrile (**1g**; $C_7H_9NO_2$)

3-Oxobutanenitrile [2] which was prepared *in situ* by acid hydrolysis. 82.1 g 3-amino-2- butenenitrile (1 mol), 225 g ethyl orthoformate (1.5 mol), and 5 g of acetic acid anhydride were heated to boiling in a flask with vigorous stirring. The ethanol formed in the reaction was distilled off through a column. After 1 h the reaction ended. The mixture was cooled; light petroleum ether (100 cm^3) was added, and the vessel was left to stand at 0°C overnight. The red-brown solid was collected by suction, washed with light petroleum ether and recrystallized from ethyl orthoformate/light petroleum ether (1:1).

Transparent needles; yield (with respect to 3-oxobutanenitrile): 78%; m.p.: 72–73°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.46 (t, 3H, CH_2-CH_3), 2.41 (s, 3H, CH_3), 4.41 (q, 2H, CH_2-CH_3), 8.05 (s, 1H, 2-H) ppm.

5-Ethoxymethylene-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**1j**; $C_9H_{12}O_5$)

28.8 g 2,2-dimethyl-4,6-dioxo-1,3-dioxane [3] (0.2 mol) and 0.1 g zinc acetate in 89 g ethyl orthoformate (0.6 mol) were heated on an oil bath at 90°C for 1 h with vigorous stirring. The catalyst was filtered off, and the precipitate formed after cooling was collected by suction and washed with light petroleum ether. The product was recrystallized from diisoprophylether with addition of charcoal.

Yield: 85%; m.p.: 86–87°C; ^{1}H NMR ($CDCl_3$ δ 300 MHz): 1.53 (t, 3H, CH_2-CH_3), 1.73 (s, 6H, CH_3, CH_3), 4.52 (q, 2H, CH_2-CH_3), 8.24 (s, 1H, 2-H) ppm.

5-Substituted aminoethylene derivatives of quinoxaline (**2a**–**j**)

5-Nitroquinoxaline (6 mmol) was dissolved in 30 cm^3 of methanol, mixed with 100 mg 3% Pd/C catalyst, and hydrogenated (with magnetic stirring) under 120 kPa H_2 until the hydrogen consumption stopped (about 400 cm^3). The catalyst was filtered off, and the filtrate was treated with 10 mmol of the derivative of 3-alkoxymethylene-2-propenoic acid or with 5-ethoxymethylene-2,2-dimethyl-4,6-dioxo-1,3-dioxane (meldrum's acid). The products **2g**, **j** precipitated from the cooled solutions and were recrystallized from xylene. Compounds **2a**–**f**, **h**, **i** precipitated only after concentration of the solution and were recrystallized from ethanol.

2a: $C_{14}H_{13}N_3O_4$: yield: 62%; m.p.: 170–171°C; IR (KBr): $\nu = 1721$, 1694, 1667, 1580 cm^{-1}; UV (methanol): $\lambda_{max} = 225$ (3.04), 258 (3.33), 306 (3.17), 333 (2.89), 371 (2.90) nm (logε); ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 3.84, 3.95 (s, s, 3H, 3H, CH_3, CH_3), 760–7.88 (m, 3H, 6-H, 7-H, 8-H), 8.79 (d, 1H, 9-H), 8.91, 8.95 (d, d, $J_{2-3} = 1.8$ Hz, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 143.8, 146.0 (C_2, C_3), 133.8, 136.1 (C_{4a}, C_{8a}), 143.4 (C_5), 111.1 (C_6), 130.3 (C_7), 124.1 (C_8), 149.5 (C_9), 95.4 (C_{10}), 51.7, 51.9 (CH_3), 166.0, 168.7 (CO) ppm; MS (70 eV): *m/z* (%) = 287 (58, M^+), 225 (48), 228 (100), 196 (33), 169 (53), 156 (25), 129 (28), 102 (25).

2b: $C_{16}H_{17}N_3O_4$; yield: 64%; m.p.: 144–145°C; IR (KBr): $\nu = 1682$, 1641, 1574 cm^{-1}; UV (methanol): $\lambda_{max} = 227$ (3.09), 259 (3.40), 3.05 (3.26), 333 (2.98), 374 (2.99) nm (logε); ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.38, 1.44 (t,t, 3H, 3H, CH_2-CH_2, CH_2-CH_3), 4.31, 4.41 (q, q, 2H, 2H, CH_2-CH_3, CH_2-CH_3), 7.57–7.86 (m, 3H, 6-H, 7-H, 8-H), 8.77 (d, 1H, 9-H), 8.90, 8.94 (s, s, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 143.7, 146.0 (C_2, C_3), 133.8, 136.3 (C_{4a}, C_{8a}), 143.4 (C_5), 110.9 (C_6), 130.3 (C_7), 129.9 (C_8), 148.9 (C_9), 96.3 (C_{10}), 14.4, 14.5 (CH_3), 60.4, 60.7 (CH_2), 165.9, 168.1 (CO) ppm; MS (70 eV): *m/z* (%) = 315 (60, M^+), 269 (46), 242 (100), 196 (19), 169 (67), 129 (25), 102 (15).

2c: $C_{12}H_7N_5O$; yield: 38%; m.p.: 226–228°C; IR (KBr): $\nu = 2218$, 1634, 1607 cm^{-1}; UV (methanol): $\lambda_{max} = 255$ (3.42), 304 (3.26), 332 (3.13), 362 (3.12) nm (log). ^1H NMR ($CDCl_3$+*DMSO*–d_6, δ, 300 MHz): 7.35–7.98 (m, 3H, 6-H, 7-H, 8-H), 8.46 (s, 1H, 9-H), 8.89, 9.01 (s, s, 2H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$+*DMSO*-d_6, δ, 300 MHz): 144.1, 146.7 (C_2, C_3), 133.1, 133.9 (C_{4a}, C_{8a}), 143.2 (C_5), 112.8 (C_6), 130.6 (C_7), 125.5 (C_8), 152.7 (C_9), 77.5 (C_{10}), 112.4, 114.6 (CN) ppm; MS (70 eV): *m/z* (%) = 221 (100, M^+), 194 (43), 156 (80), 130 (52), 102 (25).

2d: $C_{14}H_{13}N_3O_2$; yield: 64%; m.p.: 214–215°C; IR (KBr): $\nu = 1634$, 1586 cm^{-1}; UV (methanol): $\lambda_{max} = 256$ (3.38), 315 (3.01), 339 (2.98), 377 (3.13) nm (logε); ^1H NMR ($CDCl_3$+MeOD, δ, 300 MHz): 2.49, 2.62 (s, s, 3H, 3H, CH_3, CH_3), 7.64–7.93 (m, 3H, 6-H, 7-H, 8-H), 8.52 (d, 1H, 9-H), 8.94, 8.96 (d, d, $J_{2-3} = 1.8$ Hz, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$+MeOD, δ, 75 MHz) 144.2, 146.2 (C_2, C_3), 134.2, 136.1 (C_{4a}, C_{8a}), 143.3 (C_5), 111.9 (C_6), 130.2 (C_7), 125.0 (C_8), 149.0 (C_9), 114.9 (C_{10}), 27.5, 32.2 (CH_3), 195.7, 201.3 (CO) ppm; MS (70 eV): *m/z* (%) = 255 (48, M^+), 212 (100), 170 (28), 156 (41), 130 (50), (22).

2e: $C_{14}H_{13}N_3O_3$; yield: 66%; m.p.: 200–201°C IR (KBr): $\nu = 1713$, 1651, 1574 cm^{-1}; UV (methanol): $\lambda_{max} = 239$ (3.22), 256 (3.30), 315 (3.05), 338 (3.02), 377 (3.17) nm (logε); ^1H NMR ($CDCl_3$, δ, 300 MHz): *E*: 2.63 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.66–7.91 (m, 3H, 6-H, 7-H, 8-H), 8.75 (d, 1H, 9-H), 8.91, 8.93 (d, d, $J_{2-3} = 1.8$ Hz, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): *E*: 144.1, 146.2 (C_2, C_3), 134.1, 136.3 (C_{4a}, C_{8a}), 143.4 (C_5), 111.9 (C_6), 130.1 (C_7), 124.9 (C_8), 149.2 (C_9), 104.2 (C_{10}), 31.4, 51.4 (CH_3), 167.3, 200.3 (CO) ppm, *Z*: 143.8, 146.1 (C_2, C_3), 134.1, 136.3 (C_{4a}, C_{8a}), 143.4 (C_5), 111.7 (C_6), 130.4 (C_7), 124.5 (C_8), 149.5 (C_9), 104.2 (C_{10}), 31.0, 51.5 (CH_3) ppm; MS (70 eV): *m/z* (%) = 271 (23, M^+), 228 (100), 196 (30), 156 (19), 130 (19), 102 (12).

2f: $C_{15}H_{15}N_3O_3$; yield: 55%; m.p.: 150–151°C; IR (KBr); $\nu = 1700$, 1636, 1580 cm^{-1}; UV (methanol): $\lambda_{max} = 240$ (3.33), 257 (3.40), 315 (3.16), 339 (3.13), 377 (3.27) nm (logε) ^1H NMR ($CDCl_3$, δ, 300 MHz): *E*: 1.40 (t, 3H, CH_2-C*H*$_3$), 2.62 (s, 3H, CH_3), 4.32 (q, 2H, C*H*$_2$-CH_3), 7.62–7.88 (m, 3H, 6-H, 7-H, 8-H), 8.72 (d, 1H, 9-H), 8.91, 8.93 (d, d, $J_{2-3} = 1.8$ Hz, 1H, 1H, 2-H, 3-H) ppm, *Z*: 1.48 (t, 3H, CH_2-C*H*$_3$), 2.56 (s, 3H, CH_3), 4.43 (q, 2H, CH_2-CH_3), 7.62–7.88 (m, 3H, 6-H, 7-H, 8-H), 8.82 (d, 1H, 9-H), 8.86, 8.87 (s, s, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): *E*: 144.0, 146.1 (C_2, C_3), 133.9, 136.2 (C_{4a}, C_{8a}), 143.3 (C_5), 111.7 (C_6), 130.1 (C_7), 124.7 (C_8), 149.0 (C_9), 104.4 (C_{10}), 14.5, 31.4 (CH_3), 60.2 (CH_2), 166.9, 200.1 (CO) ppm, *Z*: 143.6, 146.0 (C_2, C_3), 133.7, 136.0 (C_{4a}, C_{8a}), 143.3 (C_5), 111.5 (C_6), 130.3 (C_7), 124.2 (C_8), 148.9 (C_9), 105.3 (C_{10}), 14.4, 31.1 (CH_3), 60.5 (CH_2), 168.1, 196.1 (CO) ppm; MS (70 eV): *m/z* (%) = 285 (29, M^+), 242 (100), 196 (41), 156 (24), 129(24), 102 (20).

2g: $C_{13}H_{10}N_4O$; yield: 74%; m.p.: 267 (dec); IR (KBr): $\nu = 2203$, 1651, 1593 cm^{-1}; UV (methanol): $\lambda_{max} = 231$ (3.23), 261 (3.44), 314 (2.69), 339 (2.60), 377 (2.80) nm (logε); ^1H NMR ($CDCl_3$+*DMSO*-d_6, δ, 300 MHz): *E*: 2.50 (s, 3H, CH_3), 7.79–7.95 (m, 3H, 6-H, 7-H, 8-H), 8.33 (s, 1H, 9-H), 8.90, 8.98 (s, s, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$+*DMSO*-d_6, δ, 75 MHz): *E*: 144.7, 146.5 (C_2, C_3), 134.1, 135.3 (C_{4a}, C_{8a}), 143.2 (C_5), 113.0 (C_6), 130.8 (C_7), 125.8 (C_8), 150.2 (C_9), 86.5 (C_{10}), 28.8 (CH_3), 120.3 (CN), 197.5 (CO) ppm; MS (70 eV): *m/z* (%) = 238 (22, M^+), 195 (100), 156 (13), 130 (29), 102 (16).

2h: $C_{13}H_{10}N_4O_2$; yield: 51%; m.p.: 255–257°C; IR (KBr):$\nu = 2220$, 1713, 1655, 1574 cm^{-1}; UV (methanol): $\lambda_{max} = 256$ (3.48), 308 (3.29), 333 (3.10), 369 (3.12) nm (logε); ^1H NMR ($CDCl_3$+*DMSO*-d_6, δ, 300 MHz): *E*: 3.94 (s, 3H, CH_3), 7.66–7.91 (m, 3H, 6-H, 7-H, 8-H), 8.29 (d, 1H, 9-H), 8.95, 8.97 (d, d, $J_{2-3} = 1.8$ Hz, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$+*DMSO*-d_6, δ, 75 MHz): *E*: 143.9, 146.5 (C_2, C_3), 133.8, 135.2 (C_{4a}, C_{8a}), 143.2 (C_5), 111.9 (C_6), 130.8 (C_7), 124.6 (C_8), 149.6 (C_9), 77.5 (C_{10}) ppm, *Z*: 144.3, 146.3 (C_2, C_3), 133.8, 135.1 (C_{4a}, C_{8a}), 143.2 (C_5), 111.7 (C_6), 130.7 (C_7), 124.9 (C_8), 150.1 (C_9), 77.5 (C_{10}), 52.5 (CH_3), 118.0 (CN), 167.4 (CO) ppm; MS (70 eV): *m/z* (%) = 254 (55, M^+), 195 (100), 156 (20), 129 (27), 102 (16).

2i: $C_{14}H_{12}N_4O_2$; yield: 52%; m.p.: 221–222°C; IR (KBr): $\nu = 2216$, 1707, 1686, 1615 cm^{-1}; UV (methanol): $\lambda_{max} = 257$ (3.44), 308 (3.29), 333 (3.16), 370 (3.22) nm (logε); ^1H NMR ($CDCl_3$, δ, 300 MHz): *E*: 1.38 (t, 3H, CH_2-C*H*$_3$), 4.34 (q, 2H, C*H*$_2$-CH_3), 7.53–7.90 (m, 3H, 6-H, 7-H, 8-H), 8.68 (d, 1H, 9-H), 8.84, 8.99 (d, d, $J_{2-3} = 1.8$ Hz, 1H, 1H, 2-H, 3-H) ppm, *Z*: 1.41 (t, 3H, CH_2-C*H*$_3$,

4.40 (q, 2H, CH_2-CH_3), 7.53–7.90 (m, 3H, 6-H, 7-H, 8-H), 8.16 (d, 1H, 9-H), 8.91, 8.97 (d, d, $J_{2\text{-}3} = 1.8$ Hz, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): *E*: 143.5, 146.5 (C_2, C_3), 132.9, 134.6 (C_{4a}, C_{8a}), 143.3 (C_5), 111.2 (C_6), 130.4 (C_7), 124.5 (C_8), 148.9 (C_9), 78.2 (C_{10}), 14.4 (CH_3), 61.6 (CH_2), 114.8 (CN), 164.1 (CO) ppm, *Z*: 144.0, 146.3 (C_2, C_3), 133.5, 135.2 (C_{4a}, C_{8a}), 143.4 (C_5), 111.1 (C_6), 130.3 (C_7), 124.9 (C_8), 149.5 (C_9), 78.1 (C_{10}), 14.4 (CH_3), 61.6 (CH_2), 117.7 (CN), 166.8 (CO) ppm; MS (70 eV): *m/z* (%) = 268 (42, M^+), 195 (100), 156 (16), 129 (23).

2j: $C_{15}H_{13}N_3O_4$; yield : 75%; m.p.: 238–240°C; IR (KBr): $\nu = 1732$, 1682, 1624, 1599 cm^{-1}; UV (methanol): $\lambda_{max} = 234$ (3.38), 251 (3.51), 313 (3.24), 340 (3.28), 367 (3.42) nm (logε); ^{1}H NMR ($CDCl_3$+MeOD, δ, 300 MHz): 1.79 (s, 6H, CH_3, CH_3), 7.78–8.03 (m, 3H, 6-H, 7-H, 8-H), 9.00 (s, 1H, 9-H), 8.95, 8.96 (s, s, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR ($CDCl_3$+MeOD, δ, 75 MHz): 144.5, 146.5 (C_2, C_3), 133.9, 134.6 (C_{4a}, C_{8a}), 143.1 (C_5), 113.1 (C_6), 130.4 (C_7), 126.2 (C_8), 150.6 (C_9), 89.0 (C_{10}), 27.2 (CH_3), 105.5 ($C(CH_3)_2$), 164.2, 165.1 (CO) ppm; MS (70 eV): *m/z* (%) = 299 (53, M^+), 241 (76), 169 (100), 129 (22), 102 (18).

7,10-Dihydro-7-oxopyrido[2,3-f]quinoxaline (**3**; $C_{11}H_7N_3O$)

1 g **1j** (3.3 mmol) and 15 cm^3 Dowtherm were heated at 250°C for 5 min. The precipitate formed after cooling was collected by suction on a *Büchner* funnel and washed several times with heptane. The reaction was monitored by means of TLC (Silufol 254 UV, chloroform, detection: UV lamp). The crude product was recrystallized from *DMF* with addition of charcoal.

Yield: 83%; m.p.: 333–335°C; IR (KBr): $\nu = 1642$, 1620, 1584 cm^{-1} ; UV (methanol): $\lambda_{max} = 230$, 237, 267, 279, 288, 324 nm; ^{1}H NMR (CF_3COOD, δ, 300 MHz): 7.60 (d, $J_{8\text{–}9} = 5.7$ Hz, 1H, 8-H), 8.35 (d, $J_{6\text{–}5} = 9.3$ Hz, 1H, 6-H), 8.76 (d, $J_{5\text{–}6} = 9.3$ Hz, 1H, 5-H), 8.84 (d, $J_{9\text{–}8} = 5.7$ Hz, 1H, 9-H), 9.25, 9.40 (s, s, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR (CF_3COOD, δ, 75 MHz): 147.5, 149.8 (C_2, C_3), 138.6, 139.4 (C_{4a}, C_{10b}), 125.8, 130.4 (C_5, C_6), 123.2 (C_{6a}), 173.0 (C_7), 113.0 (C_8), 145.8 (C_9), 140.5 (C_{10a}) ppm; MS (70 eV): *m/z* (%) = 197 (92, M^+), 169 (100), 142 (15), 115 (38).

7,10-Dihydro-8-ethoxycarbonyl/8-acetyl/8-nitrile-7-oxopyrido[2,3-f]quinoxalines (**4b**, **4f**, **4i**)

1 g **2b**, **f**, **i** (3.2, 4.2, 4.5 mmol) and 15 cm^3 Dowtherm (100 cm^3 for **2i**) were heated at 250°C for 15 min (30 min for **2f**, 6 h for **2i**). The precipitate formed after cooling was collected by suction on a *Büchner* funnel and washed several times with heptane. the reaction was monitored by means of TLC (Silufol 254 UV, $CHCl_3$/methanol 10/1, detection UV lamp). The crude product was recrystallized from a mixture of xylene and ethanol with addition of charcoal.

4b: $C_{14}H_{11}N_3O_3$; yield: 84% m.p.: 274–276°C; IR (KBr): $\nu = 1715$, 1626, 1541 cm^{-1}; UV (methanol): $\lambda_{max} = 240$, 277, 287, 325, 347 nm; ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 1.32 (t, 3H, CH_2-CH_3), 4.28 (q, 2H, CH_2-CH_3), 7.92 (d, $J_{6\text{–}5} = 9.0$ Hz, 1H, 6-H), 8.45 (d, $J_{5\text{–}6} = 9.0$ Hz, 1H, 5-H), 8.55 (s, 1H, 9-H) 9.07, 9.15 (d, d, $J_{2\text{–}3} = 1.8$ Hz, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR (*DMSO*-d_6, δ,300 MHz): 144.1, 147.4 (C_2, C_3), 133.6, 136.1 (C_{4a}, C_{10b}), 123.9, 126.1 (C_5, C_6), 125.7 (C_{6a}), 172.4 (C_7), 113.3 (C_8), 143.9 (C_9), 143.6 (C_{10a}), 13.9 (CH_3), 59.5 (CH_2), 164.1 (CO) ppm; MS (70 eV): *m/z* (%) = 269 (53 M^+), 223 (100), 197 (88), 141 (33), 114 (20).

4f: $C_{13}N_9N_3O_2$: yield: 61%; m.p.: 360 (dec); IR (KBr): $\nu = 1671$, 1632, 1534 cm^{-1}; UV (methanol): $\lambda_{max} = 242$, 276, 323, 352 nm; ^{1}H NMR (CF_3COOD, δ, 300 MHz): 2.66 (s, 3H, CH_3), 8.29 (d, $J_{6\text{–}5} = 9.0$ Hz, 1H, 6-H), 8.62 (d, $J_{5\text{–}6} = 9.0$ Hz, 1H, 5-H), 9.13 (s, 1H, 9-H), 9.17, 9.42 (s, s, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR (CF_3COOD, δ, 75 MHz): 148.9, 149.9 (C_2, C_3), 137.0, 140.1 (C_{4a}, C_{10b}), 128.2, 129.2 (C_5, C_6), 123.6 (C_{6a}), 176.3 (C_7), 116.4 (C_8), 148.9 (C_9), 143.9 (C_{10a}), 27.2 (CH_3), 206.1 (CO)ppm: MS (70 eV): *m/z* (%) = 239 (94, M^+), 224 (100), 197 (23), 168 (19), 141 (29), 114 (16).

4i: $C_{12}H_6N_4O$; yield: 75%; m.p.: 382–383°C; IR (KBr): $\nu = 2226$, 1628, 1543 cm^{-1}; UV (methanol): $\lambda_{max} = 240$, 276, 289, 324, 346 nm; ^{1}H NMR (*DMSO*-d_6, δ, 300 MHz): 7.98 (d, $J_{6\text{–}5} = 9.0$ Hz, 1H, 6-H), 8.38 (d, $J_{5\text{–}6} = 9.0$ Hz, 1H, 5-H), 8.64 (s, 1H, 9-H) 9.12, 9.20 (d, d,

$J_{2-3} = 1.8$ Hz, 1H, 1H, 2-H, 3-H) ppm; ^{13}C NMR (*DMSO*-d_6, δ, 75 MHz): 146.3, 148.2 (C_2, C_3), 133.7, 136.7 (C_{4a}, C_{10b}), 125.3, 125.5 (C_5, C_6), 123.9 (C_{6a}), 173.7 (C_7), 97.5 (C_8), 144.9 (C_9), 144.0 (C_{10a}), 116.0 (CN) ppm; MS (70 eV): *m/z* (%) = 222 (100, M^+), 194 (49), 140 (30).

7,10-Dihydro-7-oxopyrido[2,3-f]quinoxaline-8-carboxylic acid (**5**; $C_{12}H_7N_3O_3$)

A mixture of 0.5 g ethyl ester **4b** (1.9 mmol), 150 cm^3 hot ethanol, and 5 cm^3 1 *N* NaOH was refluxed for 2 h and subsequently neutralized with HCl. The solid precipitating upon cooling was collected by suction, washed with H_2O, and dried. The samples for analyses were purified by crystallization from *DMSO*/water (100:1).

Yield: 58%; m.p.: 300 (dec); IR (KBr): $\nu = 1732$, 1632, 1547 cm^{-1}; UV (methanol): $\lambda_{max} = 240$, 273, 286, 321, 345 nm; ^{1}H NMR (CF_3COOD, δ, 300 MHz): 8.53 (d, $J_{6-5} = 9.0$ Hz, 1H, 6-H), 8.84 (d, $J_{5-6} = 9.0$ Hz, 1H, 5-H), 9.34, 9.39 (s, s, 1H, 1H, 2-H, 3-H), 9.57 (s, 1H, 9-H) ppm; ^{13}C NMR (CF_3COOD, δ, 75 MHz): 149.1, 150.3 (C_2, C_3), 137.5, 140.9 (C_{4a}, C_{10b}), 128.7, 129.4 (C_5, C_6). 123.7 (C_{6a}), 176.4 (C_7), 111.4 (C_8), 149.1 (C_9), 144.0 (C_{10a}), 171.8 (COOH) ppm; MS (70 eV): *m/z* (%) = 241 (14, M^+), 197 (100), 169 (30), 141 (25), 114 (15).

Acknowledgements

The authors thank Mrs. *O. Lakatošovà* for measurement of the UV and IR spectra and Mrs. *M. Ondrejkovičovà* for elemental analyses.

References

[1] Ohmori J, Sakamoto S, Kupota H, Shimizu-Sasamata M, Okada M, Kawasaki S, Hidaka K, Togami J, Furuya T, Murase K (1994) J Med Chem **37**: 467
[2] Milata V, Ilavský D, Chudík M (1995) Monatsh Chem **126**: 1349
[3] Terpetching E, Ott W, Kolenz G, Peters EM, Schnering HG (1988) Monatsh Chem **119**: 367
[4] Kurasewa Y, Katoh R, Takada A (1992) J Heterocycl Chem **29**: 1001
[5] Tian W, Grivas S (1992) J Heterocycl Chem **29**: 1305
[6] Geies AA, El-Dean AMK, Moustafa OS (1996) Monatsh Chem **127**: 1263
[7] Geies AA, El-Dean AMK, Moustafa OS (1997) Pharmazie **52**: 436
[8] Yamamoto H, Jap Pat 6917136, Chem Abstr **71**: 124505d
[9] Yellin TO, US Pat 3635971, Chem Abstr **76**: 99708r
[10] Wakabayashi K, Nagao M, Esumi H, Sugimura T (1992) Cancer Res (Suppl) **52**: 2092s
[11] Seman M, Belicová a, Milata V, Ilavský D (1997) Česká a slovenská farmacie **46**: 128
[12] Milata V, Ilavský D, Goljer I, Leško J, Chahinian M, Henry-Basch E (1990) Coll Czech Chem Commun **55**: 1038
[13] Couchuron B, Le Saint J, Courtot P (1983) Bull Soc Chim Fr **3/4**: 66
[14] Zalibera L', Milata V, Ilavský D (1998) Magn Reson Chem **36**: 681
[15] Grasselli JG (ed) (1973) Atlas of Spectral Data and Physical Constants for Organic Compounds. CRC Press, Ohio, p B-883

Received September 24, 1999. Accepted November 18, 1999