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Synthesis, Properties, and Reactions of 5-Substituted Derivatives of 2,3-Diphenylquinoxaline [1]

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Summary. Catalytic hydrogenation of 5-nitro-2,3-diphenylquinoxaline led to the corresponding amine which, in turn, afforded products of nucleophilic substitution on reaction with alkoxymethylene derivatives. Thermal cyclization of selected alkoxymethylene derivatives yielded substituted pyridoquinoxalines. The conditions for successful hydrolysis of ester, decarboxylation of the acid, following chlorination of pyridone and reductive removal of the chlorine atom from it to produce parental heterocycle 2,3-diphenyl-pyrido[2,3-*f*]quinoxaline were found. All of the tested products of the nucleophilic substitution showed no antibacterial activity.

Keywords. Nucleophilic substitutions; Enols; Cyclizations; Pyridoquinoxalines; Antibacterial activity.

Introduction

Numerous quinoxaline derivatives have attracted attention by their biological importance and have been synthesized by many research groups [2]. For example, quinoxaline-2-one has been shown to possess anti-inflammatory, tranquilizing, and antidepressant properties. Imidazoquinoxalines have even been found to be strong carcinogens in food [3]. Due to this and in continuation of our strategy aiming at

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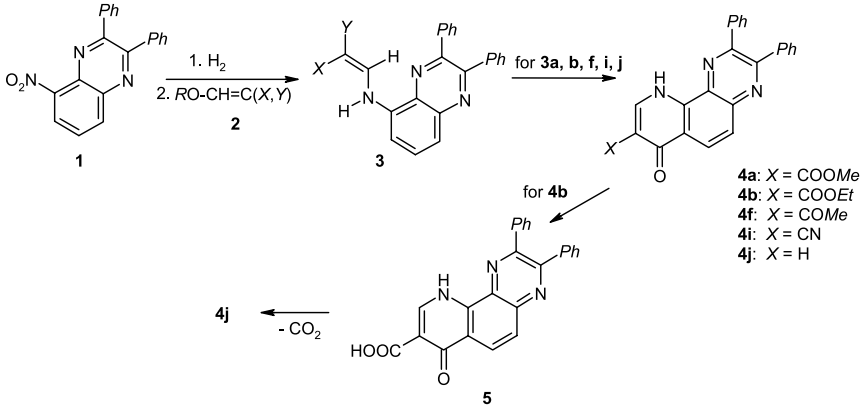
† Dedicated to Prof. Dr. *M. Uher* on the occasion of his 65th birthday

polyheterocyclic fused systems containing the quinoxaline moiety, we report the synthesis and antibacterial activity of some new quinoxaline pyridoquinoxalines.

Results and Discussion

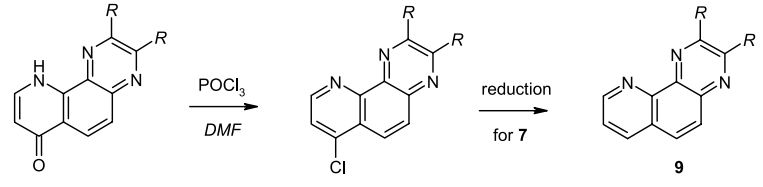
The starting material for the synthesis of 5-substituted derivatives **3** was 5-nitro-2,3-diphenylquinoxaline obtained by the reaction of benzil with 3-nitro-1,2-phenylenediamine [4]. Catalytic hydrogenation of the nitro group of 5-nitro-2,3-diphenylquinoxaline with palladium on charcoal in methanol yielded the corresponding amine **1**, which was immediately subjected to the subsequent reaction with alkoxymethylene derivatives (Scheme 1).

The relative ratio of the individual geometric isomers could be estimated from their NMR spectral data considering the integral intensities of signals. For instance, the (*E*):(*Z*) ratio for **3g** was found to be 1:10, whereas with other compounds the energetically more favored (*E*) isomers prevailed. The (*E*):(*Z*) ratio of derivatives with a cyano group (**3h**, **3i**) was 3:1, that of derivatives with bulkier acetyl group (**3e**, **3f**) was 4:1 and 6:1. This finding can most probably be explained by intramolecular hydrogen bonding between the acetyl group and an imino hydrogen. This bonding,



R, *X*, *Y* for **2**; *X*, *Y* for **3**:

a: *R* = *Me*,	*X* = COO*Me*,	*Y* = COO*Me*	**f**: *R* = *Et*,	*X* = CO*Me*,	*Y* = COO*Et*
b: *R* = *Et*,	*X* = COO*Et*,	*Y* = COO*Et*	**g**: *R* = *Et*,	*X* = CO*Me*,	*Y* = CN
c: *R* = *Et*,	*X* = CN,	*Y* = CN	**h**: *R* = *Me*,	*X* = CN,	*Y* = COO*Me*
d: *R* = *Et*,	*X* = CO*Me*,	*Y* = CO*Me*	**i**: *R* = *Et*,	*X* = CN,	*Y* = COO*Et*
e: *R* = *Me*,	*X* = CO*Me*,	*Y* = COO*Me*	**j**: *R* = *Et*,	*X*,*Y* = CO-OC(*Me*)$_2$-O-CO	



Scheme 1

however, does not exist in (*E*)-isomers of cyano derivatives, but for acetoacetate derivatives the intramolecular hydrogen bond is stronger with the carbonyl of the acetyl group than with that of the ester group. The presence of hydrogen bonding is demonstrated by the value of the coupling constant $^3J_{CH-NH}$ between 12–14 Hz. In addition, the carbonyl carbon resonates at higher field as compared with "free", non-bonded carbonyls, and the wave numbers $\bar{\nu}_{(C=O)}$ of ester and acetyl bands are found at more than 1680 cm^{-1} and 1620 cm^{-1}. The spectroscopic properties (IR, UV, ^1H and ^{13}C NMR, MS) were in accord with the structures of compounds **3**.

Thermal cyclocondensation of **3** at 250°C in an inert solvent gave exclusively the angularly fused pyrido[2,3-*f*]quinoxalines **4** (Scheme 1). The determining factors for successful ring closure are a temperature above 250°C, reaction time, high purity of the starting material, the appropriate ratio of the starting material:solvent (for diesters, 3-oxobutanoates, and *Meldrum* acid 1 g:15 cm^3 or for 2-cyano-2-propenoates 1 g:100 cm^3), and performing the reaction with direct heating using a heating jacket.

At the conditions of acid hydrolysis [5] the cyclization products **4j** (concentrated hydrochloric acid) involve the acid **5** (Scheme 1); the latter can be considered a nonalkylated (at the pyridone nitrogen atom) analogue of nalidixic acid. Alkaline hydrolysis does not lead to free acid. Probably, hydrolysis is prevented by the low solubility of the starting ester in aqueous sodium hydroxide.

Aromatization of the pyridine ring was achieved by treatment with phosphorus oxytrichloride and addition of *DMF* (necessary for the generation of the *Vilsmeier* complex) at room temperature. Chlorination was performed also with 10*H*-pyrido[2,3-*f*]quinoxalin-7-one **6** under the same conditions as above. Reductive dechlorination of **7** was effected by the catalytic method using palladium on carbon in the presence of sodium hydroxide. This produces the parent heterocycle **9**, unsubstituted on the pyridine ring.

The activity of **3a**–**3j** against two *Gram*-positive (*E. coli*, *S. enterica*) and two *Gram*-negative (*S. aureus*, *B. subtilis*) bacteria was tested. Unfortunately, the data indicated that these compounds have much weaker antibacterial activities as compared to nalidixic acid.

Experimental Section

Melting points were measured on a *Kofler* micro hot-stage, and their values were not corrected. IR (0.5 mg, 300 mg KBr) and UV spectra (methanol, $c = 1 \cdot 10^{-3}$ mol·dm^{-3}, cell width 2 mm) were recorded with FTIR PU 9802 (Philips) and Specord (Zeiss, Jena) spectrophotometers. ^1H and ^{13}C NMR spectra were measured with a Varian VXR-300 apparatus (300 MHz for ^1H, 75 MHz for ^{13}C) with hexamethyldisiloxane as internal standard. EI mass spectra were taken with an MS 902S (AEI-Kratos) instrument at 70 eV and 100 μA current trap. The reactions were monitored using TLC (Silufol 254 UV, $CHCl_3$/MeOH = 10/1, UV detection at 254 nm). Elemental analyses agreed satisfactory with the calculated values.

5-Nitro-2,3-diphenylquinoxaline (**1**) was prepared according to Ref. [6]. The alkoxymethylene derivatives dimethyl methoxymethylene malonate (**2a**), diethyl ethoxymethylene malonate (**2b**) and ethoxymethylenepropane dinitrile (**2c**) are commercially available. Others were synthesized by condensation of alkyl orthoformate with an activated methylene component (derivatives of malonic and 3-oxobutanoic acid, 2,4-pentadione) [7, 8]. Details of the preparation of **6**, ethoxymethylene *Meldrum*'s acid **2j**, and a new procedure for preparing **2g** are described in Ref. [9].

*Preparation of **3a–3j***

5-Nitro-2,3-diphenylquinoxaline (10 mmol) was dissolved in 100 cm^3 of methanol, mixed with 350 mg of 3% Pd/C catalyst, and hydrogenated (with magnetic stirring) under 120 kPa H_2 until the H_2 consumption stopped (about 670 cm^3). The mixture was filtered into the methanolic solution of corresponding alkoxymethylene derivative (10 mmol) and shortly boiled with magnetic stirring. After cooling the reaction mixture is evaporated *in vacuo* to dryness and the residue is recrystallized from indicated solvent.

2-[(2,3-Diphenylquinoxalin-5-ylamino)methylene]malonic acid dimethyl ester (**3a**, $C_{26}H_{21}N_3O_4$)

Yield: 68%; mp 221–223°C (methanol/benzene); IR: $\bar{\nu} = 1720$, 1624 (C=O) cm^{-1}; UV: $\lambda_{max} = 262$, 302, 368, 383 nm; MS(EI): m/z (%) = 440 ($M^+ + 1$, 17), 439 (M^+, 60), 408 (7), 407 (16), 379 (6), 345 (12), 321 (25), 320 (100), 308 (7), 282 (11); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.86$ (s, OCH_3), 3.93 (s, OCH_3), 7.33–7.64 (m, 2 × Ph), 7.67–7.82 (m, 6-H + 7-H), 7.95 (d, $J = 8.1$ Hz, 8-H), 8.85 (d, $J = 14.1$ Hz, 9-H), 11.33 (d, $J = 14.1$ Hz, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 51.2$ (OCH_3), 51.3 (OCH_3), 95.0 (C_{10}), 113.3 (C_6), 121.8 (C_8), 128.6, 128.8, 129.6, 129.8, 137.8, 138.7 (CH_{Ph}), 129.0, 129.1 (C_{Ph}), 130.1 (C_7), 131.2 (C_{4a}), 134.9 (C_5), 140.9 (C_{8a}), 153.6 (C_9), 151.7, 154.0 (C_2, C_3), 165.0, 167.0 (CO) ppm.

2-[(2,3-Diphenylquinoxalin-5-ylamino)methylene]malonic acid diethyl ester (**3b**, $C_{28}H_{25}N_3O_4$)

Yield: 72%; mp 170–172°C (ethanol/benzene); IR: $\bar{\nu} = 1725$, 1652 (C=O) cm^{-1}; UV: $\lambda_{max} = 265$, 312, 323, 389 nm; MS(EI): m/z (%) = 468 ($M^+ + 1$, 29), 467 (M^+, 89), 423 (33), 422 (100), 376 (13), 349 (27), 348 (30), 321 (12), 320 (19), 115 (13); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (t, OCH_2CH_3), 1.42 (t, OCH_2CH_3), 4.29 (q, OCH_2CH_3), 4.37 (q, OCH_2CH_3), 7.30–7.54 (m, 2 × Ph), 7.54–7.62 (m, 6-H + 7-H), 8.05 (d, $J = 8.2$ Hz, 8-H), 8.71 (d, $J = 13.2$ Hz, 9-H), 11.28 (d, $J = 13.2$ Hz, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.3$ (OCH_2CH_3), 14.5 (OCH_2CH_3), 60.3 (OCH_2CH_3), 60.7 (OCH_2CH_3), 95.9 (C_{10}), 112.8 (C_6), 121.8 (C_8), 129.3, 129.5, 129.8, 131.3, 137.9, 138.9 (CH_{Ph}), 128.8, 129.0 (C_{Ph}), 130.1 (C_7), 132.1 (C_{4a}), 134.9 (C_5), 140.4 (C_{8a}), 150.6, 152.2 (C_2, C_3), 154.5 (C_9), 165.1, 168.9 (CO) ppm.

2-[(2,3-Diphenylquinoxalin-5-ylamino)methylene]malononitrile (**3c**, $C_{24}H_{15}N_5$)

Yield: 65%; mp 253–256°C (xylene); IR: $\bar{\nu} = 2216$ (CN) cm^{-1}; UV: $\lambda_{max} = 259$, 298, 360 nm; MS(EI): m/z (%) = 374 ($M^+ + 1$, 27), 373 (M^+, 100), 372 (10), 309 (12), 308 (50), 269 (14), 167 (7), 140 (16), 115 (12), 77 (12); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 7.32$–7.62 (m, 2 × Ph), 7.86 (d, $J = 8.2$ Hz, 6-H), 7.89 (d, $J = 8.2$ Hz, 8-H), 8.04 (dd, $J = 8.2$, 8.2 Hz, 7-H), 9.02 (s, 9-H), 10.79 (s, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 54.1$ (C_{10}), 113.9 (CN), 116.0 (CN), 114.4 (C_6), 122.3 (C_8), 128.0, 128.4, 129.6, 129.9, 137.7, 138.6 (CH_{Ph}), 128.7, 128.9 (C_{Ph}), 130.0 (C_7), 131.0 (C_{4a}), 134.1 (C_5), 140.4 (C_{8a}), 152.1, 153.7 (C_2, C_3), 155.9 (C_9) ppm.

3-[(2,3-Diphenylquinoxalin-5-ylamino)methylene]pentane-2,4-dione (**3d**, $C_{26}H_{21}N_3O_2$)

Yield: 51%; mp 201-203°C (ethanol/benzene); IR: $\bar{\nu} = 1632$ (C=O) cm^{-1}; UV: $\lambda_{max} = 258$, 301, 333, 370, 386 nm; MS(EI): m/z (%) = 408 ($M^+ + 1$, 31), 407 (M^+, 96), 392 (21), 364 (26), 322 (34), 296 (13), 283 (23), 282 (100), 77 (12), 43 (24); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.86$ (s, OCH_3), 3.93 (s, OCH_3), 7.22–7.44 (m, 2 × Ph), 7.48–7.52 (m, 6-H + 7-H), 7.96 (d, $J = 8.1$ Hz, 8-H), 8.58 (d, $J = 12.6$ Hz, 9-H), 13.80 (d, $J = 12.6$ Hz, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.6$ (OCH_3),

31.6 (OCH_3), 113.7 (C_{10}), 114.2 (C_6), 123.3 (C_8), 128.0, 128.3, 129.7, 129.9, 137.9, 138.7 (CH_{Ph}), 128.7, 128.9 (C_{Ph}), 130.1 (C_7), 131.2 (C_{4a}), 134.2 (C_5), 137.9 (C_{8a}), 151.9, 152.1 (C_2, C_3), 153.7 (C_9), 195.8, 199.9 (CO) ppm.

2-[(2,3-Diphenylquinoxalin-5-ylamino)methylene]-3-oxobutanoic acid methylester (**3e**, $C_{26}H_{21}N_3O_3$)

Yield: 73%; mp 206–208°C (ethanol/benzene); IR: $\bar{\nu} = 1696$, 1672 (C=O) cm^{-1}; UV: $\lambda_{max} = 238$, 258, 355 nm; MS(EI): m/z (%) = 424 ($M^+ + 1$, 28), 423 (M^+, 100), 391 (37), 380 (15), 363 (27), 362 (35), 348 (15), 322 (18), 320 (34), 282 (58); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = (E)$ 2.61 (s, CH_3), 3.83 (s, OCH_3), 7.37–7.92 (m, 2 × Ph + 6-8 H), 8.77 (d, $J = 13.8$ Hz, 9-H), 13.85 (d, $J = 13.8$ Hz, NH), (*Z*) 2.55 (s, CH_3), 3.89 (s, OCH_3), 7.37–7.92 (m, 2 × Ph + 6-8 H), 8.88 (d, $J = 14.7$ Hz, 9-H), 12.14 (d, $J = 14.7$ Hz, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = (E)$ 31.5 (CH_3), 51.4 (OCH_3), 104.1 (C_{10}), 112.0 (C_6), 124.4 (C_8), 128.4, 128.5, 129.8, 130.3, 138.1, 138.9 (CH_{Ph}), 129.2, 129.4 (C_{Ph}), 129.9 (C_7), 132.1 (C_{4a}), 136.0 (C_5), 141.2 (C_{8a}), 149.4 (C_9), 152.1, 154.5 (C_2, C_3), 167.4, 199.9 (CO), (*Z*) 30.9 (CH_3), 51.3 (OCH_3), 105.0 (C_{10}), 111.3 (C_6), 123.9 (C_8), 128.4, 128.5, 129.8, 130.3, 138.1, 138.9 (CH_{Ph}), 129.2, 129.4 (C_{Ph}), 130.2 (C_7), 131.8 (C_{4a}), 135.7 (C_5), 141.3 (C_{8a}), 148.5 (C_9), 151.8, 154.5 (C_2, C_3), 168.0, 196.3 (CO) ppm.

2-[(2,3-Diphenylquinoxalin-5-ylamino)methylene]-3-oxobutanoic acid ethylester (**3f**, $C_{27}H_{23}N_3O_3$)

Yield: 70%; mp 183–184°C (ethanol/benzene); IR: $\bar{\nu} = 1696$, 1648 (C=O) cm^{-1}; UV: $\lambda_{max} = 242$, 259, 353 nm; MS(EI): m/z (%) = 438 ($M^+ + 1$, 29), 437 (M^+, 100), 393 (25), 392 (56), 364 (45), 363 (47), 349 (28), 322 (32), 320 (43), 282 (70); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = (E)$ 1.39 (t, OCH_2CH_3), 2.61 (s, CH_3), 4.31 (q, OCH_2CH_3), 7.37–7.92 (m, 2 × Ph + 6-8 H), 8.77 (d, $J = 13.5$ Hz, 9-H), 13.83 (d, $J = 13.5$ Hz, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = (E)$ 14.5 (OCH_2CH_3), 31.5 (CH_3), 60.1 (OCH_2CH_3), 104.3 (C_{10}), 111.8 (C_6), 124.4 (C_8), 128.3, 128.4, 129.8, 130.3, 138.1, 139.0 (CH_{Ph}), 129.2, 129.4 (C_{Ph}), 129.9 (C_7), 132.0 (C_{4a}), 136.1 (C_5), 141.3 (C_{8a}), 149.2 (C_9), 152.0, 154.5 (C_2, C_3), 167.1, 199.9 (CO) ppm.

2-[(2,3-Diphenylquinoxalin-5-ylamino)methylene]-3-oxobutanenitrile (**3g**, $C_{25}H_{18}N_4O$)

Yield: 79%; mp 242°C (decomp) (xylene); IR: $\bar{\nu} = 2207$ (CN), 1655 (C=O) cm^{-1}; UV: $\lambda_{max} = 237$, 257, 350 nm; MS(EI): m/z (%) = 391 ($M^+ + 1$, 28), 390 (M^+, 100), 375 (15), 348 (12), 347 (48), 308 (22), 283 (15), 282 (73), 77 (12), 43 (18); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = (Z)$ 2.49 (s, CH_3), 7.38–7.78 (m, 2 × Ph + 6, 7-H), 7.96 (d, $J = 8.4$ Hz, 8-H), 8.11 (d, $J = 13.5$ Hz, 9-H), 13.54 (d, $J = 13.5$ Hz, NH); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = (Z)$ 2.34 (s, CH_3), 7.35–7.85 (m, 2 × Ph + 6, 7-H), 8.10 (d, $J = 8.2$ Hz, 8-H), 8.82 (d, $J = 13.8$ Hz, 9-H), 13.40 (d, $J = 13.8$ Hz, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = (Z)$ 28.8 (CH_3); 86.5 (C_{10}), 111.7 (C_6), 119.9 (CN), 125.3 (C_8), 128.4, 128.5, 129.8, 130.2, 137.9, 138.7 (CH_{Ph}), 129.3, 129.6 (C_{Ph}), 129.8 (C_7), 131.6 (C_{4a}), 134.8 (C_5), 141.2 (C_{8a}), 148.9 (C_9), 152.4, 154.8 (C_2, C_3), 196.6 (CO) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = (Z)$ 28.4 (CH_3); 85.6 (C_{10}), 113.2 (C_6), 119.9 (CN), 124.2 (C_8), 128.2, 128.2, 129.7, 129.9, 137.9, 138.5 (CH_{Ph}), 129.1, 129.3 (C_{Ph}), 130.5 (C_{4a}), 130.6 (C_7), 134.4 (C_5), 140.4 (C_{8a}), 150.9 (C_9), 151.6, 154.1 (C_2, C_3), 196.2 (CO) ppm.

2-Cyano-3-(2,3-diphenylquinoxalin-5-ylamino)propenoic acid methyl ester (**3h**, $C_{25}H_{18}N_4O_2$)

Yield: 69%; mp 243–245°C (xylene); IR: $\bar{\nu} = 2216$ (CN), 1696 (C=O) cm^{-1}; UV: $\lambda_{max} = 261$, 302, 369 nm; MS(EI): m/z (%) = 407 ($M^+ + 1$, 28), 406 (M^+, 100), 347 (22), 346 (24), 345 (31), 309 (14),

308 (62), 282 (13), 114 (11), 77 (12); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = (E)$ 3.81 (s, OCH_3), 7.38–8.07 (m, 2 × Ph + 6, 7, 8-H), 8.91 (d, $J = 13.8$ Hz, 9-H), 14.25 (d, $J = 13.8$ Hz, NH), (*Z*) 3.78 (s, OCH_3), 7.38–8.07 (m, 2 × Ph + 6, 7, 8-H), 9.08 (d, $J = 14.7$ Hz, 9-H), 12.20 (d, $J = 14.7$ Hz, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = (E)$ 51.8 (OCH_3), 76.9 (C_{10}); 114.3 (C_6); 115.3 (CN); 122.5 (C_8), 128.0, 128.2, 129.6, 129.9, 138.0, 138.5 (CH_{Ph}), 128.7, 128.9 (C_{Ph}), 130.5 (C_{4a}), 130.7 (C_7), 134.4 (C_5), 140.5 (C_{8a}), 152.0, 154.2 (C_2, C_3), 153.7 (C_9), 164.6 (CO) ppm, (*Z*) 52.0 (OCH_3), 75.8 (C_{10}), 112.6 (C_6), 117.8 (CN), 123.6 (C_8), 128.0, 128.2, 129.6, 129.9, 138.1, 138.3 (CH_{Ph}), 128.7, 128.9 (C_{Ph}), 130.5 (C_{4a}), 130.7 (C_7), 134.4 (C_5), 140.6 (C_{8a}), 151.7 (C_9), 151.5, 154.4 (C_2, C_3), 166.6 (CO) ppm.

2-Cyano-3-(2,3-diphenylquinoxalin-5-ylamino)propenoic acid ethyl ester
(**3i**, $C_{26}H_{20}N_4O_2$)

Yield: 68%; mp 238–239°C (xylene); IR: $\bar{\nu} = 2216$ (CN), 1688 (C=O) cm^{-1}; UV: $\lambda_{max} = 240$, 259, 352 nm; MS(EI): m/z (%) = 421 ($M^+ + 1$, 28), 420 (M^+, 100), 375 (8), 347 (20), 346 (19), 345 (26), 309 (12), 308 (47), 282 (12), 77 (15); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = (E)$ 1.38 (t, OCH_2CH_3), 4.37 (q, OCH_2CH_3), 7.33–8.05 (m, 2 × Ph + 6, 7, 8-H), 8.43 (d, $J = 13.8$ Hz, 9-H), 14.12 (d, $J = 13.8$ Hz, NH), (*Z*) 1.32 (t, OCH_2CH_3), 4.27 (q, OCH_2CH_3), 7.33–8.05 (m, 2 × Ph + 6, 7, 8-H), 8.89 (d, $J = 14.5$ Hz, 9-H), 12.19 (d, $J = 14.5$ Hz, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = (E)$ 14.2 (OCH_2CH_3), 60.8 (OCH_2CH_3), 76.8 (C_{10}), 114.3 (C_6), 115.4 (CN), 122.7 (C_8), 128.1, 128.1, 129.6, 130.0, 138.0, 138.3 (CH_{Ph}), 129.1, 129.3 (C_{Ph}), 130.5 (C_7), 130.6 (C_{4a}), 134.4 (C_5), 140.5 (C_{8a}), 151.8, 154.1 (C_2, C_3), 153.5 (C_9), 164.4 (CO), (*Z*) 14.2 (OCH_2CH_3), 60.8 (OCH_2CH_3), 76.0 (C_{10}), 112.5 (C_6), 117.8 (CN), 123.5 (C_8), 128.1, 128.1, 129.6, 130.0, 138.1, 138.5 (CH_{Ph}), 129.1, 129.3 (C_{Ph}), 130.5 (C_{4a}), 130.6 (C_7), 134.4 (C_5), 140.5 (C_{8a}), 151.6 (C_9), 151.4, 153.9 (C_2, C_3), 166.2 (CO) ppm.

5-[(2,3-Diphenylquinoxalin-5-ylamino)methylene]-2,2-dimethyl-[1,3]-dioxane-4,6-dione
(**3j**, $C_{27}H_{21}N_3O_4$)

Yield: 62%; mp 258–260°C (xylene); IR: $\bar{\nu} = 1722$, 1688 (C=O) cm^{-1}; UV: $\lambda_{max} = 257$, 298, 377 nm; MS(EI): m/z (%) = 451 (M^+, 18), 393 (30), 350 (22), 349 (82), 348 (52), 321 (50), 320 (100), 143 (14), 115 (18); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.78$ (s, $C(CH_3)_2$), 7.35–7.81 (m, 2 × Ph + 6, 7-H), 8.00 (d, $J = 8.1$ Hz, 8-H), 8.95 (d, $J = 14.7$ Hz, 9-H), 14.11 (d, $J = 14.7$ Hz, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.2$ ($C(CH_3)_2$), 88.9 (C_{10}), 105.2 ($C(CH_3)_2$), 112.2 (C_6), 125.8 (C_8), 128.4, 128.5, 129.8, 130.2, 137.7, 138.7 (CH_{Ph}), 129.4, 129.6 (C_{Ph}), 129.8 (C_7), 131.7 (C_{4a}), 134.3 (C_5), 141.1 (C_{8a}), 150.1 (C_9), 152.4, 154.9 (C_2, C_3), 163.7, 164.9 (CO) ppm.

Thermal Cyclization of Selected Aminoethylene Derivatives

A mixture of **3a**, **3b**, **3f**, **3i**, or **3j** (1 g; 2.3, 2.1, 2.3, 2.4, or 2.2 mmol) and 15 cm^3 of Dowtherm (100 cm^3 for **3i**) was refluxed at 250°C for 20, 20, 20, 360, or 10 min. The precipitate formed after cooling was collected by suction on a *Büchner* funnel and washed several times with *n*-heptane. The reaction was monitored by TLC (Silufol 254 UV, $CHCl_3$) until the starting material disappeared. The crude product was recrystallized from *DMF*.

7-Oxo-2,3-diphenyl-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid methyl ester
(**4a**, $C_{25}H_{17}N_3O_3$)

Yield: 82%; mp 320–325°C; IR: $\bar{\nu} = 1721$, 1628 (C=O) cm^{-1}; UV: $\lambda_{max} = 245$, 318, 366, 382 nm; MS(EI): m/z (%) = 408 ($M^+ + 1$, 12), 407 (M^+, 41), 376 (17), 375 (12), 374 (17), 364 (5), 363 (18), 350 (26), 349 (100), 348 (22), 347 (9), 320 (9), 319 (15), 318 (5), 304 (13), 273 (6), 272 (32), 216 (5), 188 (7), 187.5 (15), 174.5 (5), 173.5 (6), 169 (7), 143 (17), 141 (11), 115 (9), 114 (8), 113 (9), 77 (13), 73

(42), 53 (10), 51 (5); ^{1}H NMR (300 MHz, CF_3COOD): $\delta = 3.91$ (s, OCH_3), 7.13–7.43 (m, 2 × Ph), 8.35 (d, $J = 9.0$ Hz, 5-H), 8.71 (d, $J = 9.0$ Hz, 6-H), 9.30 (s, 9-H) ppm; ^{13}C NMR (75 MHz, CF_3COOD): $\delta = 56.6$ (OCH_3), 111.9 (C_8), 123.7 (C_{6a}), 124.1 (C_5), 130.9 (C_6), 131.4 (C_{4a}), 131.4, 132.1, 132.3, 132.5, 135.9, 136.9 (CH_{Ph}), 134.7, 137.1 (C_{Ph}), 136.1 (C_{10b}), 139.7 (C_{10a}), 149.2 (C_9), 156.7, 162.4 (C_2, C_3), 169.7 (CO), 175.6 (C_7) ppm.

7-Oxo-2,3-diphenyl-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid ethyl ester (**4b**, $C_{26}H_{19}N_3O_3$)

Yield: 91%; mp 306–308°C; IR: $\bar{\nu} = 1712$, 1628 (C=O) cm^{-1}; UV: $\lambda_{max} = 243$, 312, 365, 380 nm; MS(EI): m/z (%) = 422 ($M^+ + 1$, 13), 421 (M^+, 42), 420 (6), 377 (6), 376 (12), 375 (14), 374 (17), 350 (26), 349 (100), 348 (20), 347 (10), 320 (9), 319 (18), 318 (21), 273 (6), 272 (34), 216 (6), 190 (5), 188 (5), 187.5 (14), 173.5 (5), 169 (8), 143 (14), 141 (13), 115 (9), 114 (8), 113 (8), 77 (12), 73 (6), 53 (8); ^{1}H NMR (300 MHz, CF_3COOD): $\delta = 1.21$ (t, OCH_2CH_3), 4.41 (q, OCH_2CH_3), 7.10–7.42 (m, 2 × Ph), 8.34 (d, $J = 9.0$ Hz, 5-H), 8.70 (d, $J = 9.0$ Hz, 6-H), 9.31 (s, 9-H) ppm; ^{13}C NMR (75 MHz, CF_3COOD): $\delta = 14.6$ (OCH_2CH_3), 68.0 (OCH_2CH_3), 112.1 (C_8), 123.7 (C_{6a}), 124.0 (C_5), 130.9 (C_6), 131.4 (C_{4a}), 131.4, 132.1, 132.2, 132.5, 135.8, 136.9 (CH_{Ph}), 134.7, 137.1 (C_{Ph}), 136.1 (C_{10b}), 139.7 (C_{10a}), 149.0 (C_9), 156.6, 162.4 (C_2, C_3), 169.3 (CO), 175.8 (C_7) ppm.

8-Acetyl-2,3-diphenyl-10H-pyrido[2,3-f]quinoxalin-7-one (**4f**, $C_{25}H_{17}N_3O_2$)

Yield: 94%; mp 287–289°C; IR: $\bar{\nu} = 1676$, 1624 (C=O) cm^{-1}; UV: $\lambda_{max} = 247$, 283, 311, 368, 382 nm; MS(EI): m/z (%) = 392 ($M^+ + 1$, 14), 391 (M^+, 80), 390 (9), 377 (27), 376 (100), 363 (15), 349 (12), 348 (10), 288 (10), 270 (8), 190 (5), 187.5 (7), 170 (8), 143 (7), 115 (5), 114 (7), 87 (6), 77 (9), 53 (6); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.89$ (s, CH_3), 7.37–7.62 (m, 2 × Ph), 7.90 (d, $J = 9.0$ Hz, 5-H), 8.44 (d, $J = 9.0$ Hz, 6-H), 8.65 (s, 9-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 30.4$ (CH_3), 118.2 (C_5), 120.7 (C_8), 123.0, 123.7 (C_{Ph}), 126.4 (C_{6a}), 127.7, 128.7, 129.3, 129.6, 137.7, 138.0 (CH_{Ph}), 129.5 (C_6), 131.3 (C_{4a}), 135.7 (C_{10b}), 141.6 (C_{10a}), 143.1 (C_9), 151.9, 154.7 (C_2, C_3), 174.2 (C_7), 196.0 (CO) ppm.

7-Oxo-2,3-diphenyl-7,10-dihydropyrido[2,3-f]quinoxaline-8-carbonitrile (**4i**, $C_{24}H_{14}N_4O$)

Yield: 79%; mp >350°C; MS(EI): m/z (%) = 375 ($M^+ + 1$, 25), 374 (M^+, 100), 373 (85), 169 (5), 168 (42), 140 (24), 117 (6), 113 (9), 77 (9), 51 (5); ^{1}H NMR (300 MHz, CF_3COOD): $\delta = 7.29$–7.60 (m, 2 × Ph), 8.23 (d, $J = 9.3$ Hz, 5-H), 8.71 (s, 9-H), 8.82 (d, $J = 9.3$ Hz, 6-H) ppm; ^{13}C NMR (75 MHz, CF_3COOD): $\delta = 101.9$ (C_8), 119.8 (C_5), 127.9 (C_{6a}), 131.2 (C_{4a}), 131.5, 132.3, 132.5, 136.3 (CH_{Ph}), 134.1 (CN), 134.3 (C_6), 134.6, 137.2 (C_{Ph}), 138.0 (C_{10b}), 139.0 (C_{10a}), 149.9 (C_9), 154.5, 161.0 (C_2, C_3), 178.7 (C_7) ppm.

2,3-Diphenyl-10H-pyrido[2,3-f]quinoxalin-7-one (**4j**, $C_{24}H_{15}N_3O_3$)

Yield: 80%; mp 350–352°C; IR: $\bar{\nu} = 1622$ (C=O) cm^{-1}; UV: $\lambda_{max} = 242$, 266, 313, 365 nm; MS(EI): m/z (%) = 350 ($M^+ + 1$, 25), 349 (M^+, 100), 348 (65), 321 (8), 320 (17), 174.5 (5), 143 (37), 115 (31), 114 (7), 88 (8), 77 (6), 51 (5); ^{1}H NMR (300 MHz, $CDCl_3$ + *Me*OD): $\delta = 6.69$ (d, $J = 6.5$ Hz, 8-H), 7.36–7.58 (m, 2 × Ph), 7.99 (d, $J = 9.0$ Hz, 5-H), 8.06 (d, $J = 6.5$ Hz, 9-H), 8.55 (d, $J = 9.0$ Hz, 6-H) ppm; ^{13}C NMR (75 MHz, CF_3COOD): $\delta = 113.5$ (C_8), 122.2 (C_5), 123.7 (C_{6a}), 131.3 (C_{4a}), 132.2 (C_6), 131.6, 131.7, 132.5, 135.0, 137.4 (CH_{Ph}), 134.6, 136.2 (C_{Ph}), 137.7 (C_{10b}), 139.1 (C_{10a}), 148.5 (C_9), 155.4, 162.1 (C_2, C_3), 173.4 (C_7) ppm.

7-Oxo-2,3-diphenyl-7,10-dihydropyrido[2,3-f]quinoxaline-8-carboxylic acid (**5**, $C_{24}H_{15}N_3O_3$)

A mixture of 1.0 g of **4b** (2.4 mmol) and 20 cm^3 of 36% HCl was refluxed with stirring for 30 min. The solid which precipitated on cooling was collected by suction, washed with 3×50 cm^3 of H_2O, and dried. For analyses the sample was recrystallized from a mixture of *DMSO* and water (10:1) to give a colourless solid **5** (750 mg, 79%). Mp 279–281°C; IR: $\bar{\nu} = 1700$, 1622 (C=O) cm^{-1}; UV: $\lambda_{max} = 243$, 311, 365 nm; ^{1}H NMR (300 MHz, CF_3COOD): $\delta = 7.30$–7.59 (m, $2 \times$ Ph), 8.50 (d, $J = 9.0$ Hz, 5-H), 8.85 (d, $J = 9.0$ Hz, 6-H), 9.51 (s, 9-H) ppm; ^{13}C NMR (75 MHz, CF_3COOD): $\delta = 112.0$ (C_8), 124.0 (C_5), 124.2 (C_{6a}), 131.2 (C_6), 131.6 (C_{4a}), 131.6, 132.3, 132.4, 132.7, 134.9, 137.3 (CH_{Ph}), 136.0, 136.2 (C_{Ph}), 137.1 (C_{10b}), 140.0 (C_{10a}), 149.9 (C_9), 156.8, 162.5 (C_2, C_3), 171.5 (CO), 176.7 (C_7) ppm.

Decarboxylation of Acid ***5***

A mixture of 75 mg of **5** (0.19 mmol) and 5 cm^3 of quinoline was refluxed for 3 h under Ar. After cooling, 50 cm^3 of *n*-heptane were added with stirring. The precipitate was collected by suction, washed several times with diethylether, dried, and purified as described for **4**, yielding 38 mg of **4j** (58%).

7-Chloro-2,3-diphenyl-pyrido[2,3-f]quinoxaline (**7**, $C_{23}H_{14}ClN_3$)

To a stirred mixture of 500 mg of pyridone **4j** (1.4 mmol) in 5 cm^3 of freshly distilled $POCl_3$ 10 cm^3 of dry *DMF* were added drop by drop. After stirring for 1 day at rt, the viscous liquid was added dropwise into 100 cm^3 of cold H_2O. The precipitated solid was collected by suction, washed with H_2O, and dried. Crystallisation from *DMF* gave 980 mg of **7** as colourless solid (93%). Mp 273–274°C; IR: $\bar{\nu} = 1372$, 702 cm^{-1}; UV: $\lambda_{max} = 248$, 262, 304, 356, 369 nm; MS(EI): m/z (%) = 370 ($M^+ + 3$, 25), 369 ($M^+ + 2$, 33), 368 ($M^+ + 1$, 45), 367 (M^+, 100), 366 (67), 266 (28), 265 (26), 264 (82), 263 (33), 184.5 (6), 184 (7), 183.5 (20), 183 (7), 182.5 (7), 161 (13), 127 (8), 126 (69), 100 (7), 99 (22), 77 (16), 76 (8), 75 (6), 51 (11), 50 (5); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.70 (m, $2 \times$ Ph), 7.79 (d, $J = 4.2$ Hz, 8-H), 8.28 (d, $J = 9.3$ Hz, 5-H), 8.51 (d, $J = 9.3$ Hz, 6-H), 9.15 (d, $J = 4.2$ Hz, 9-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 123.7$ (C_5), 125.6 (C_8), 126.8 (C_{6a}), 128.3, 128.4, 130.0, 130.3, 128.9, 129.2 (CH_{Ph}), 129.1 (C_6), 138.7 (C_{4a}), 138.6, 138.8 (C_{Ph}), 142.4 (C_{10b}), 143.1 (C_7), 146.8 (C_{10a}), 150.5 (C_9), 153.8, 154.7 (C_2, C_3) ppm.

7-Chloropyrido[2,3-f]quinoxaline (**8**, $C_{11}H_6ClN_3$)

To a stirred mixture of 500 mg of **6** (1.4 mmol) in 4 cm^3 of freshly distilled $POCl_3$ 5 cm^3 of dry *DMF* were added drop by drop. After stirring for 1 day at rt, the viscous liquid was added dropwise to 50 cm^3 of cold H_2O, stirred with charcoal, and filtered. Then the reaction mixture was neutralized with 17% aqueous NH_4OH. The precipitated solid was collected by suction, washed with H_2O, and dried. Crystallisation from *DMF* gave 300 mg of **8** as colourless solid (55%). Mp 292–293°C; IR: $\bar{\nu} = 2800$, 1130, 831 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.79$ (d, $J = 4.7$ Hz, 8-H), 8.20 (d, $J = 9.0$ Hz, 5-H), 8.51 (d, $J = 9.0$ Hz, 6-H), 9.10 (d, $J = 4.7$ Hz, 9-H), 9.34 (d, $J = 1.9$ Hz, 2-H), 9.39 (d, $J = 1.9$ Hz, 3-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 145.1$, 146.4 (C_2, C_3), 141.1, 144.4 (C_{4a}, C_{10b}), 125.9, 129.1 (C_5, C_6), 126.7 (C_{6a}), 143.0 (C_7), 124.0 (C_8), 150.5 (C_9), 146.9 (C_{10a}) ppm.

2,3-Diphenylpyrido[2,3-f]quinoxaline (**9**, $C_{23}H_{15}N_3$)

A mixture of 500 mg of **8** (1.4 mmol), 54 mg of solid NaOH, 30 cm^3 of ethanol, and 150 mg of 10% Pd/C catalyst was hydrogenated with magnetic stirring under 120 kPa H_2 overnight. The product **9** was insoluble in the reaction mixture. It was crystallized together with catalyst from ethanol to give 290 mg of yellow flakes (62%). It was not proved to be identical with the compound prepared disorderly from

its tetrahydroderivative in Ref. [10] as judged from their data (mp 250°C and UV: $\lambda_{max} = 297$, 356, 367, 414). Mp 237–238°C; IR: $\bar{\nu} = 1362$, 702 cm^{-1}; UV: $\lambda_{max} = 242$, 259, 299, 304, 354, 367 nm; MS(EI): m/z (%) = 334 ($M^+ + 1$, 27), 333 (M^+, 100), 332 (75), 231 (14), 230 (86), 229 (55), 166.5 (17), 166 (9), 155.5 (7), 128 (5), 127 (44), 101 (6), 100 (21), 77 (10), 76 (10), 51 (9), 50 (6), 39 (5); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.31$–7.68 (m, 2 × Ph), 7.69 (d, $J = 4.2$ Hz, 8-H), 8.02 (d, $J = 9.0$ Hz, 6-H), 8.16 (d, $J = 9.0$ Hz, 5-H), 8.31 (dd, $J = 8.1$, 1.7 Hz, 7-H), 9.25 (dd, $J = 4.2$, 1.7 Hz, 9-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 123.4$ (C_5), 128.2 (C_8), 128.2, 128.3, 130.0, 130.4, 128.8, 129.0 (CH_{Ph}), 128.8 (C_{6a}), 130.0 (C_6), 136.4 (C_7), 138.9 (C_{4a}), 139.0, 139.1 (C_{Ph}), 142.5 (C_{10b}), 145.5 (C_{10a}), 150.8 (C_9), 153.3, 154.1 (C_2, C_3) ppm.

We were also interested in the potential antimicrobial activity of the synthetised compounds. The basic antimicrobial screening was realised on the standard set of the *Gram*-negative (*Escherichia coli* CNCTC 326/71, *Salmonella enterica* CCM 4420) and *Gram*-positive bacterial strains (*Bacillus subtilis* CCM 2216, *Staphylococcus aureus* CNCTC 78/71). The bacterial strains were from the collections of the microorganisms CNCTC (Czechoslovak National Collection of Type Cultures, Prague) and CCM (Czechoslovak Collection of Microorganisms, Brno).

Antimicrobial activity was characterised by value of MIC (minimal inhibitory concentration). The MIC was defined as the lowest concentration of compound that completely inhibited growth of bacteria after 24 h incubation at 37°C. The MIC was determined by serial tenfold dilutions in tubes containing *Mueller-Hinton* broth as the assay medium. The final inoculum ranged from 5×10^5 to 1×10^6 CFU/cm^3. For the experiments the compounds were dissolved in *DMSO*. Concentrations of tested substances ranged from 1 to 100 $\mu g/cm^3$. Nalidixic acid was used for control (*E. coli* MIC/$\mu g/cm^3 = 4$, *S. enterica* MIC/$\mu g/cm^3 = 16$, *S. aureus* MIC/$\mu g/cm^3 = 128$, *B. subtilis* MIC/$\mu g/cm^3 = 64$). For the tested compounds MIC was found to be $>100\ \mu g/cm^3$.

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