Synthesis of Some *N,N'*-Diphenylalkanediamides and their Photosynthesis-Inhibiting Activity

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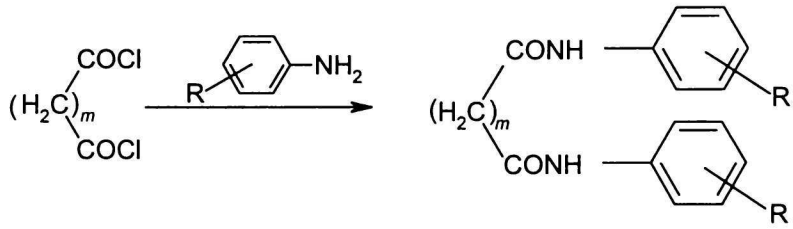
A set of twelve new *N,N'*-diphenylalkanediamides was prepared by the reactions of acyl chlorides with appropriate anilines. The inhibition of oxygen evolution rate (OER) in spinach chloroplasts by the synthesized compounds was investigated. With the exception of *N,N'*-bis(3,4-dichlorophenyl)butanediamide (IC_{50} = 22 μmol dm^{-3}), the other studied derivatives of *N,N'*-diphenylbutanediamide did not affect photosynthetic activity of spinach chloroplasts. The OER-inhibiting activity of *N,N'*-bis(3,4-dichlorophenyl)alkanediamides (alkane = butane, pentane, hexane, octane, nonane) showed a linear decrease with increasing lipophilicity of the studied compounds.

Various dicarboxylic diamides are useful as technical substances or as intermediates for herbicides, agrochemicals, and polymers [1—3]. Some of such compounds show biological activity which can be modified by structural changes. For example, the antimalarial activity of bisquinolines depends on the length of the connecting chain between the quinoline parts; the derivative of butanediamide was the most efficient one [4]. 2,3-Diarylpentanediamides are antibacterial [5], derivatives of substituted propanediamide were prepared as insecticides [6]. *N,N'*-Substituted 2-halobutanediamides [7] as well as *N'*-substituted *N*-furfuryloxamides [8] show herbicidal activity.

Compounds which possess the free amino hydrogen atom needed for binding to the receptor site, possibly by forming hydrogen bonds, *e.g.* acyl and thioacyl anilides, phenyl carbamates, *etc.*, inhibit efficiently photosynthetic electron transport [9—11]. The interactions of such herbicides with the photosynthetic apparatus and a model for orientation of herbicides within the three-dimensional structure of their target, the D_1 protein of photosystem 2 were reported by *Draber et al.* [12]. The herbicidal activity of benzanilides was found to increase by inserting of chloro substituents in several positions on both aromatic rings of the molecule [13]. Also other polychlorosubstituted compounds, *e.g.* derivatives of 2,4,5-trichlorophenoxyacetic acid [14] or anilides of 2-pyrazinecarboxylic acid [15], were found to be significant inhibitors of photosynthetic electron transport in plant chloroplasts. Using EPR spectroscopy it has been found that the substituted benzanilides interact with the intermediate D^+, *i.e.* tyrosine radical (Tyr_D) situated in the 161st position in the D_2 protein which is located on the donor side of photosystem (PS) 2 and due to this interaction, the photosynthetic electron transport between photosystem 2 and photosystem 1 is interrupted [16].

We synthesized twelve new *N,N'*-diphenylalkanediamides by the reactions of alkanedioyl dichlorides with appropriate anilines (Scheme 1) and investigated their effects on oxygen evolution rate (OER) in spinach chloroplasts.

Of the studied derivatives of *N,N'*-diphenylbutanediamide (*Ia—Ih*), only *N,N'*-bis(3,4-dichlorophenyl)-butanediamide (*Ia*) inhibited photosynthetic electron transport in spinach chloroplasts (IC_{50} = 22 μmol dm^{-3}). The prolongation of the connecting alkane chain did not improve the photosynthesis-inhibiting activity. The OER inhibiting activity of *N,N'*-bis(3,4-dichlorophenyl)alkanediamides showed a linear decrease with increasing lipophilicity of the studied compounds (IC_{50} = 22 (*Ia*; *m* = 2), 46.4 (*IIa*; *m* = 3), 45.2 (*IIIa*; *m* = 4), 204.4 (*IVa*; *m* = 6), and 368.4 μmol



m = 2 (*Ia*—*Ih*), 3 (*IIa*), 4 (*IIIa*), 6 (*IVa*), 7 (*Va*)

	R		R		R
a	3,4-Cl_2	*d*	3-NO_2	*g*	4-C_4H_9
b	3-F	*e*	3,4-$(CH_3)_2$	*h*	4-sC_4H_9
c	4-F	*f*	4-iC_3H_7		

Scheme 1

dm^{-3} (*Va*; $m = 7$)), and the structure—activity relationship could be expressed by the following regression equation

$$\log(1/IC_{50}) = -[0.241\ (\pm 0.026)]m + 5.154\ (\pm 0.125)$$

$$r = 0.983 \quad s = 0.108 \quad F = 85.6 \quad n = 5$$

where m is the number of CH_2 groups in the connecting chain. The decrease in biological activity with increasing lipophilicity of the compounds is connected with their lowered aqueous solubility. This is in accord with the restricted passage of the inhibitor through the hydrophilic regions of thylakoid membranes.

EXPERIMENTAL

The melting points were determined on a Kofler apparatus. After drying of compounds over P_2O_5 at 61 °C and 66 Pa for 24 h, elemental analyses were performed on a C,H,N analyzer (Laboratorní přístroje, Prague). Infrared spectra were measured on a Nicolet Impact 400 spectrometer using KBr discs. The purity of the products was checked by TLC on Silufol UV 254/366 plates (Kavalier, Votice) using chloroform—acetone ($\varphi_r = 9 : 1$) or light petroleum—ethyl acetate ($\varphi_r = 1 : 1$). ^{1}H NMR spectra were recorded for dimethyl sulfoxide ($(CD_3)_2SO$) solutions at ambient temperature on a Varian Mercury-Vx BB 300 spectrometer (operating at 300 MHz). Chemical shifts were indirectly referenced to tetramethylsilane *via* the solvent signal ($\delta = 2.49$ for ^{1}H).

N,*N*′-Diphenylalkanediamides

Alkanedioyl dichloride (16 mmol) was added dropwise to a stirred solution of aniline (32 mmol) in pyridine (20 cm^3) at 0 °C. The reaction mixture was allowed to stand at ambient temperature for 24 h and then poured into water (100 cm^3). The product was filtered off and crystallized from ethanol.

N,*N*′-Bis(3,4-dichlorophenyl)butanediamide (*Ia*), yield = 93 %, m.p. = 258—259 °C. For $C_{16}H_{12}Cl_4N_2O_2$ (M_r = 406.10) w_i(calc.): 47.32 % C, 2.98 % H, 6.90 % N; w_i(found): 47.08 % C, 3.04 % H, 6.65 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1659 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 2.67 (s, 4H, CH_2), 7.47 (dd, J = 8.8 Hz, J = 2.5 Hz, 2H, H_{arom}-6,6′), 7.54 (d, J = 8.8 Hz, 2H, H_{arom}-5,5′), 7.99 (d, J = 2.5 Hz, 2H, H_{arom}-2,2′), 10.32 (s, 2H, NH).

N,*N*′-Bis(3-fluorophenyl)butanediamide (*Ib*), yield = 89 %, m.p. = 206—207 °C. For $C_{16}H_{14}F_2N_2O_2$ (M_r = 304.30) w_i(calc.): 63.15 % C, 4.64 % H, 9.21 % N; w_i(found): 62.88 % C, 4.49 % H, 9.02 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1663 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 2.65 (s, 4H, CH_2), 6.78—6.88 (m, 2H, H_{arom}-4,4′), 7.22—7.36 (m, 4H, H_{arom}-5,5′, H_{arom}-6,6′), 7.53—7.62 (m, 2H, H_{arom}-2,2′), 10.23 (s, 2H, NH).

N,*N*′-Bis(4-fluorophenyl)butanediamide (*Ic*), yield = 92 %, m.p. = 244—245 °C. For $C_{16}H_{14}F_2N_2O_2$ (M_r = 304.30) w_i(calc.): 63.15 % C, 4.64 % H, 9.21 % N; w_i(found): 62.78 % C, 4.50 % H, 9.13 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1651 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 2.62 (s, 4H, CH_2), 7.05—7.15 (m, 4H, H_{arom}-3,3′, H_{arom}-5,5′), 7.53—7.63 (m, 4H, H_{arom}-2,2′, H_{arom}-6,6′), 10.05 (s, 2H, NH).

N,*N*′-Bis(3-nitrophenyl)butanediamide (*Id*), yield = 88 %, m.p. = 228—230 °C. For $C_{16}H_{14}N_4O_6$ (M_r = 358.31) w_i(calc.): 53.63 % C, 3.94 % H, 15.64 % N; w_i(found): 53.22 % C, 3.96 % H, 15.78 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1675 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 2.72 (s, 4H, CH_2), 7.57 (t, J = 8.2 Hz, 2H, H_{arom}-5,5′), 7.82—7.90 (m, 4H, H_{arom}-4,4′, H_{arom}-6,6′), 8.63 (t, J = 2.1 Hz, 2H, H_{arom}-2,2′), 10.53 (s, 2H, NH).

N,*N*′-Bis(3,4-dimethylphenyl)butanediamide (*Ie*), yield = 85 %, m.p. = 231—232 °C. For $C_{20}H_{24}N_2O_2$ (M_r = 324.42) w_i(calc.): 74.05 % C, 7.46 % H, 8.63 % N; w_i(found): 73.84 % C, 7.37 % H, 8.77 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1651 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 2.12 (s, 6H, CH_3), 2.14 (s,

6H, CH_3), 2.58 (bs, 4H, CH_2), 6.99 (d, J = 8.2 Hz, 2H, H_{arom}-5,5'), 7.27 (dd, J = 8.2 Hz, J = 2.1 Hz, 2H, H_{arom}-6,6'), 7.34 (d, J = 2.1 Hz, 2H, H_{arom}-2,2'), 9.80 (s, 2H, NH).

N,N'-Bis(4-isopropylphenyl)butanediamide (*If*), yield = 83 %, m.p. = 234—236 °C. For $C_{22}H_{28}N_2O_2$ (M_r = 352.48) w_i(calc.): 74.97 % C, 8.01 % H, 7.97 % N; w_i(found): 74.93 % C, 8.03 % H, 7.97 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1656 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 1.13 (d, J = 6.9 Hz, 12H, CH_3), 2.60 (s, 4H, CH_2), 2.73—2.85 (m, 2H, CH), 7.08—7.16 (m, 4H, H_{arom}-3,3', H_{arom}-5,5'), 7.42—7.50 (m, 4H, H_{arom}-2,2', H_{arom}-6,6'), 9.89 (s, 2H, NH).

N,N'-Bis(4-butylphenyl)butanediamide (*Ig*), yield = 81 %, m.p. = 232—234 °C. For $C_{24}H_{32}N_2O_2$ (M_r = 380.53) w_i(calc.): 75.75 % C, 8.48 % H, 7.36 % N; w_i(found): 76.07 % C, 8.16 % H, 7.47 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1659 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 0.85 (t, J = 7.3 Hz, 6H, CH_3), 1.18—1.33 (m, 4H, CH_2), 1.42—1.55 (m, 4H, CH_2), 2.45—2.52 (signal overlapped by solvent, 4H, CH_2), 2.60 (s, 4H, CH_2), 7.03—7.11 (m, 4H, H_{arom}-3,3', H_{arom}-5,5'), 7.42—7.50 (m, 4H, H_{arom}-2,2', H_{arom}-6,6'), 9.90 (s, 2H, NH).

N,N'-Bis(4-*sec*-butylphenyl)butanediamide (*Ih*), yield = 81 %, m.p. = 178—179 °C. For $C_{24}H_{32}N_2O_2$ (M_r = 380.53) w_i(calc.): 75.75 % C, 8.48 % H, 7.36 % N; w_i(found): 75.80 % C, 8.48 % H, 7.28 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1655 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 0.72 (t, J = 7.1 Hz, 6H, CH_3), 1.13 (d, J = 7.1 Hz, 6H, CH_3), 1.40—1.57 (m, 4H, CH_2), 2.45—2.55 (signal overlapped by solvent, 2H, CH), 2.60 (s, 4H, CH_2), 7.05—7.11 (m, 4H, H_{arom}-3,3', H_{arom}-5,5'), 7.44—7.50 (m, 4H, H_{arom}-2,2', H_{arom}-6,6'), 9.91 (s, 2H, NH).

N,N'-Bis(3,4-dichlorophenyl)pentanediamide (*IIa*), yield = 63 %, m.p. = 267 °C. For $C_{17}H_{14}Cl_4N_2O_2$ (M_r = 420.12) w_i(calc.): 48.60 % C, 3.36 % H, 6.67 % N; w_i(found): 48.79 % C, 3.27 % H, 6.75 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1679 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 1.8—1.9 (m, J = 7.4 Hz, 2H, CH_2), 2.38 (t, J = 7.4 Hz, 4H, CH_2), 7.44 (dd, J = 8.8 Hz, J = 2.5 Hz, 2H, H_{arom}-6,6'), 7.56 (d, J = 8.8 Hz, 2H, H_{arom}-5,5'), 7.99 (d, J = 2.5 Hz, 2H, H_{arom}-2,2'), 10.20 (s, 2H, NH).

N,N'-Bis(3,4-dichlorophenyl)hexanediamide (*IIIa*), yield = 58 %, m.p. = 277 °C. For $C_{18}H_{16}Cl_4N_2O_2$ (M_r = 434.15) w_i(calc.): 49.80 % C, 3.71 % H, 6.45 % N; w_i(found): 50.03 % C, 3.68 % H, 6.60 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1670 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 1.54—1.65 (m, 4H, CH_2), 2.30—2.35 (m, 4H, CH_2), 7.44 (dd, J = 9.1 Hz, J = 2.4 Hz, 2H, H_{arom}-6,6'), 7.52 (d, J = 9.0 Hz, 2H, H_{arom}-5,5'), 7.9 (d, J = 2.4 Hz, 2H, H_{arom}-2,2'), 10.18 (s, 2H, NH).

N,N'-Bis(3,4-dichlorophenyl)octanediamide (*IVa*), yield = 35 %, m.p. = 167—168 °C. For $C_{20}H_{20}Cl_4N_2O_2$ (M_r = 462.20) w_i(calc.): 51.99 % C, 4.33 % H, 6.06 % N; w_i(found): 51.79 % C, 4.44 % H, 6.11 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1671 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 1.28—1.35 (m, 4H, CH_2), 1.56—1.61 (m, 4H, CH_2), 2.29 (t, J = 7.4 Hz, 4H, CH_2), 7.44 (dd, J = 8.8 Hz, J = 2.5 Hz, 2H, H_{arom}-6,6'), 7.53 (d, J = 8.8 Hz, 2H, H_{arom}-5,5'), 7.99 (d, J = 2.5 Hz, 2H, H_{arom}-2,2'), 10.16 (s, 2H, NH).

N,N'-Bis(3,4-dichlorophenyl)nonanediamide (*Va*), yield = 52 %, m.p. = 170—171 °C. For $C_{21}H_{22}Cl_4N_2O_2$ (M_r = 476.23) w_i(calc.): 52.96 % C, 4.66 % H, 5.88 % N; w_i(found): 52.99 % C, 4.64 % H, 6.08 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 1680 ν(C=O). ^{1}H NMR spectrum ($(CD_3)_2SO$), δ: 1.28—1.35 (m, 6H, CH_2), 1.51—1.63 (m, 4H, CH_2), 2.28 (t, J = 7.4 Hz, 4H, CH_2), 7.47 (dd, J = 8.8 Hz, J = 2.2 Hz, 2H, H_{arom}-6,6'), 7.53 (d, J = 8.8 Hz, 2H, H_{arom}-5,5'), 7.99 (d, J = 2.2 Hz, 2H, H_{arom}-2,2'), 10.16 (s, 2H, NH).

Photosynthesis-Inhibiting Activity

The inhibition of oxygen evolution rate (OER) in spinach chloroplasts was investigated spectrophotometrically, using 2,6-dichlorophenol—indophenol (DPIP) as an electron acceptor [17]. Because of an insufficient solubility of the tested compounds in water these were dissolved in dimethyl sulfoxide.

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