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PROTON SPONGES CONDENSED WITH PYRIDAZINE AND PYRROLE NUCLEI

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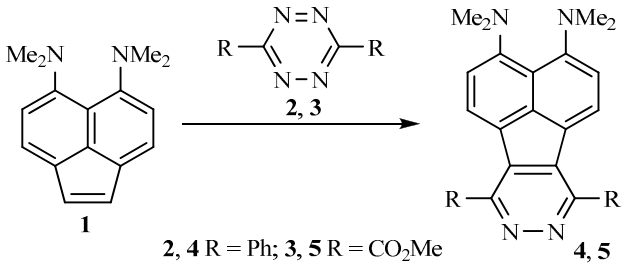
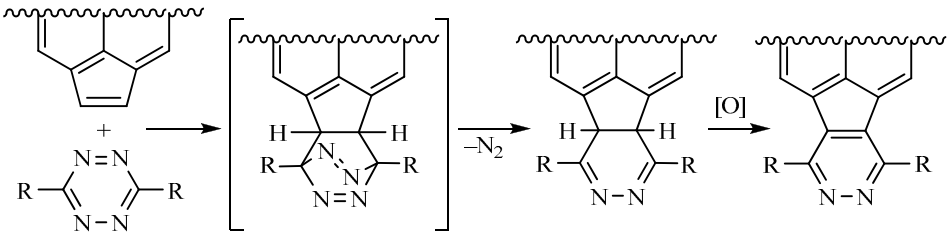
A series of 5,6-bis(dimethylamino)acenaphthylene derivatives fused with pyridazine and pyrrole rings in positions 1 and 2 has been synthesized. The latter are of interest for constructing porphyrin-containing systems with highly basic fragments.

Keywords: acenaphthylene, 8,9-diazafluoranthene, pyridazine, pyrrole, proton sponge, chlorination, cycloaddition.

In the year 2000, we obtained 5,6-bis(dimethylamino)acenaphthylene (acenaphthylene proton sponge) (**1**) for the first time [1]. It was shown that this compound had a highly reactive double bond, which was readily reduced [1], underwent electrophilic substitution [2] and [4+2] cycloaddition with reversed electron demand [3]. In particular, diazafluoranthenes **4** and **5** were formed in high yield [3] by the action of *sym*-tetrazines **2** and **3** on compound **1**.





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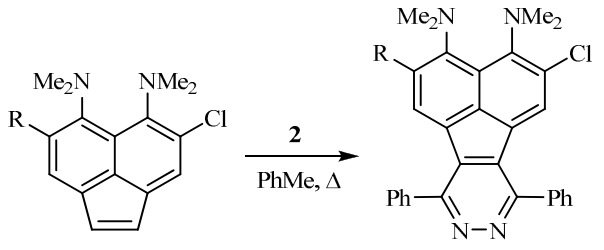
The mechanism of this conversion is known to involve elimination of a nitrogen molecule from the [4+2] adduct and subsequent oxidation of the resulting dihydropyridazine either by air oxygen or by the initial tetrazine [3, 4].

In the present work, we wanted to revisit the synthetic potential of compound **1**. In particular, annelation of a pyridazine ring to compound **1** with further transformation of the former into pyrrole made possible the subsequent synthesis of porphyrin proton sponges (cf. with the analogous approach described in [5]).

First of all, we introduced the recently synthesized chlorine-containing acenaphthylenes **6** and **7** [6] into a [4+2] cycloaddition reaction. It was assumed that the introduction of chlorine atoms into positions 2 and 7 of the acenaphthylene system may lead to twisting of the NMe_2 groups relative to the ring plane, decreasing their +*M* effect, and thereby reducing the reactivity of the double bond. Pyridazines **8, 9** were obtained in high yield by the action of an equivalent quantity of tetrazine **2** on compounds **6** and **7** in refluxing toluene for 15 h. Thus, the reaction in this case required more forcing conditions than with compound **1**, which reacted with diphenyltetrazine (**2**) in refluxing benzene for 10 h [3].

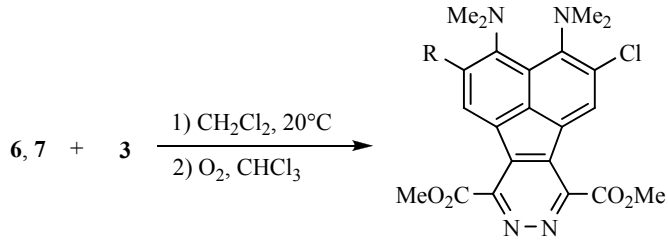


6, 7 **8** (91%), **9** (96%)

6, 8 R = H; **7, 9** R = Cl

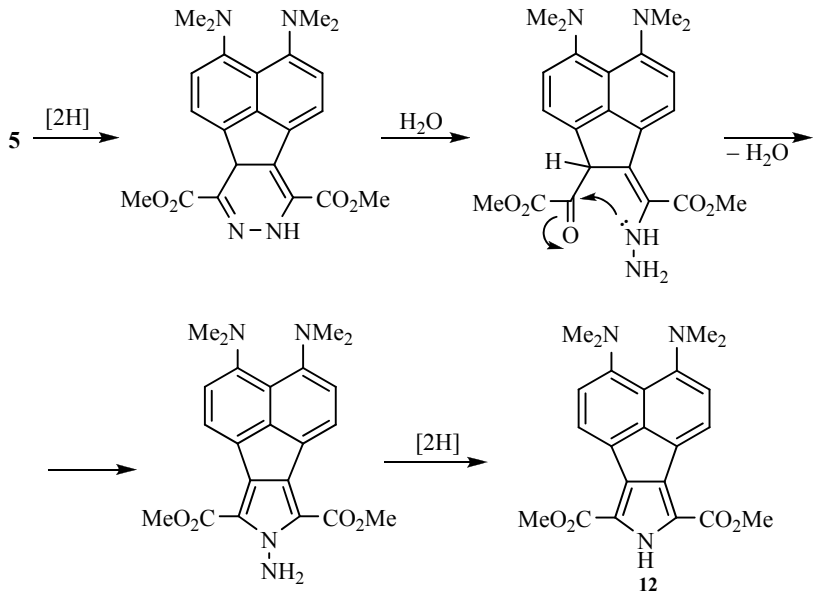
It is remarkable that the dichloride **9** could also be obtained by treating the pyridazine **4** with *N*-chlorosuccinimide (NCS). However, in comparison with the chlorination of substrate **1**, the reaction in this case proceeded with more difficulty (refluxing in chloroform for 8 h, yield 39%) and was accompanied by resin formation. It was not possible to stop the conversion at the stage of monochloride **8**, in contrast to the chlorination of compound **1** where the monochloride was obtained in 80% yield [6].

We further found that the acenaphthylenes **6** and **7** reacted with tetrazine **3** and formed diazafluoranthenes **10** and **11** in high yields. The reactions were carried out in dichloromethane at room temperature with the participation of equimolar quantities of starting materials. The cycloaddition process was rapid (<1 min) and was accompanied by vigorous evolution of nitrogen, which was used for qualitative assessment of the substrate reactivity: **1** > **6** > **7**. However, the subsequent aromatization of the resulting (dihydro)pyridazine in the presence of air in chloroform medium required about 1 day.



10 R = H (97%)
11 R = Cl (82%)

We established further that reduction of the pyridazine **5** with zinc in acetic acid (20°C, 48 h) gave the pyrrole **12** in 57% yield (for the mechanism of similar reactions, see [5]).



Compound **12** forms yellow crystals, readily soluble in organic solvents. In its ^{1}H NMR spectrum the NH proton was displayed as a singlet at 9.31 ppm. Such a small chemical shift clearly indicated against the formation in solution of a bipolar ion with a chelated proton (cf. with the spectra of protonated acenaphthylene sponge salts, where the chelated proton usually had δ_{NH} values of 15.5-18.5 ppm [6]). The pK_a of pyrrole **12** in DMSO, determined by the competitive transprotonation method, was equal to 12.5 (22°C, relative to 1,8-bis-(dimethylamino)-2,7-dimethoxynaphthalene, pK_a 11.5 in DMSO [7]). An X-ray structural investigation of compound **12** revealed molecular pairing in the crystal lattice by intermolecular hydrogen bonds between the pyrrole NH group and the carbonyl oxygen of the substituent. The main geometric parameters are given in Fig. 1.

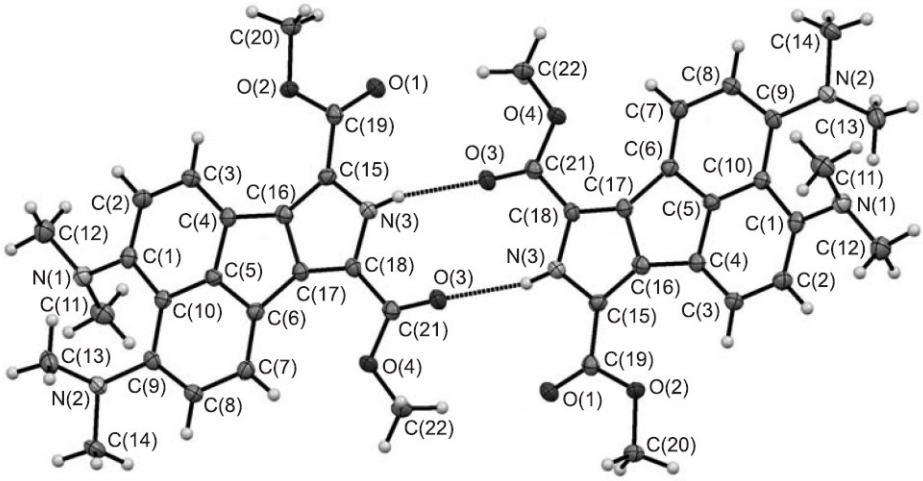
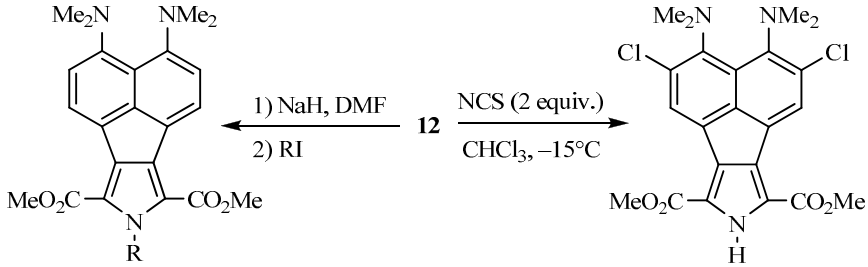


Fig. 1. Molecular structure of proton sponge **12**, in which atoms are represented by thermal vibration ellipsoids of 50% probability, showing the intermolecular H-bonding in crystals. Key distances (Å) and angles (deg.): N(1)···N(2) 2.918, N(3)–H 0.89, O(3)···H(N(3)) 2.10, N(3)–H···O(3) 153.

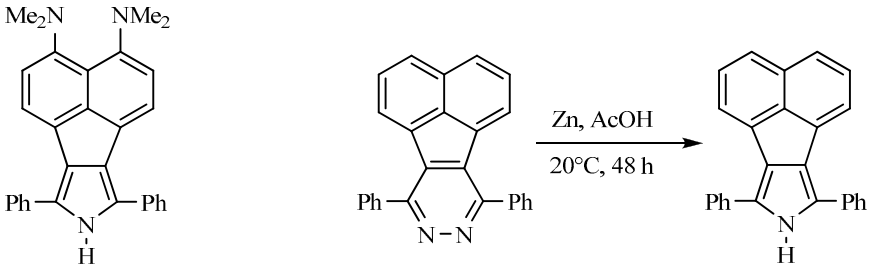
Compound **12** readily formed an anion on treatment with an equivalent amount of sodium hydride in DMF. Its subsequent alkylation (MeI or EtI) gave the corresponding *N*-alkyl derivative **13** in good yield. The pyrrole **12** was chlorinated with *N*-chlorosuccinimide in chloroform with the formation of the dichloro derivative **14**. The reaction was accompanied by strong tarring even at -15°C. The yield of compound **14** did not exceed 11%.



13 a R = Me (56%), **b** R = Et (71%)

14 (11%)

Attempts to affect a synthesis of pyrrole **15** from pyridazine **4** by the action of zinc in acetic acid did not succeed. The yellow fluorescent substance formed in the course of the reaction gave a very complex ^{1}H NMR spectrum and decomposed on adsorbents (Al_2O_3, SiO_2) after a few minutes (eluents were chloroform or toluene). Such behavior was apparently caused by the π-electron rich nature of compound **15**. This view was supported by our observation that the pyrrole **17**, which contained no π-donating NMe_2 groups, was relatively stable. Pyrrole **17** is a pale-yellow fluorescent substance, which was obtained by us from the previously described diazafluoranthene **16** in 14% yield [4, 8].



15 **16** **17** (14%)

In conclusion it must be said that the 3,4-bis(dimethylamino)-8*H*-acenaphtho[1,2-*c*]pyrrole-7,9-dicarboxylates obtained by us may serve as starting materials for preparing new porphyrin derivatives containing proton sponge residues as substituents. The high basicity of such molecular ensembles may exert a large influence on complex formation, proton dynamics, sensor properties, and many other features of these compounds.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-71 instrument and the UV spectra on a Varian Cary 100 instrument ($c = 5 \cdot 10^{-5}$ M). The ^{1}H NMR spectra were recorded on a Bruker DPX-250 instrument (250 MHz) at 20°C, internal standard was TMS. The mass spectra were recorded on a Finnigan MAT Incos 50 instrument with a direct insertion probe, at 70 eV accelerating voltage. Elemental analysis was carried out on a PerkinElmer 2400 analyzer. Melting points were determined by the capillary method on a PTP instrument.

Acenaphthylenes **1**, **6**, and **7** were obtained by the procedures of [1, 6]. Synthesis of the tetrazines **2**, **3** [9, 10] and pyridazines **4**, **5** [3] was carried out by the indicated procedures.

2-Chloro-3,4-bis(dimethylamino)-7,10-diphenyl-8,9-diazafluoranthene (8). A mixture of chloroacenaphthylene **6** (0.109 g, 0.4 mmol) and diphenyltetrazine **2** (0.096 g, 0.4 mmol) in absolute toluene (10 ml) was refluxed for 15 h. The solvent was removed, and the residue was chromatographed on Al_2O_3 (eluent – chloroform), collecting the main red fraction of R_f 0.25. Yield 0.173 g (91%). Red crystals; mp 255-256°C (C_6H_6). UV spectrum (MeCN), λ_{max}, nm (log ε): 285 (4.41), 500 (4.23), longest wavelength of absorption at 600 nm. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.92 (6H, s, 4-N(CH_3)$_2$); 3.09 (6H, s, 3-N(CH_3)$_2$); 6.90 (1H, d, $J_{5,6}$ = 8.4, H-5); 7.55-7.64 (7H, m, H-6, H Ph); 7.72 (1H, s, H-1); 7.89-7.94 (4H, m, H Ph). Found, %: C 75.58; H 5.20; Cl 7.12. $C_{30}H_{25}ClN_4$. Calculated, %: C 75.55; H 5.25; Cl 7.45.

2,5-Dichloro-3,4-bis(dimethylamino)-7,10-diphenyl-8,9-diazafluoranthene (9) was obtained analogously from substrate **7** (0.120 g, 0.4 mmol) and tetrazine **2** (0.096 g, 0.4 mmol). Red fraction with R_f 0.25. Yield 0.196 g (96%). Red crystals; mp 304-305°C (decomp., benzene). UV spectrum (EtOH), λ_{max}, nm (log ε): 271 (4.49), 342 (3.79), 459 (4.05), longest wavelength of absorption at 650 nm. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.05 (12H, s, 2N(CH_3)$_2$); 7.61-7.64 (8H, m, H-1,6, H Ph); 7.88-7.91 (4H, m, H Ph). Found, %: C 70.02; H 4.71; Cl 13.50. $C_{30}H_{24}Cl_2N_4$. Calculated, %: C 70.45; H 4.73; Cl 13.86.

Chlorination of 3,4-Bis(dimethylamino)-7,10-diphenyl-8,9-diazafluoranthene (4). A solution of compound **4** (0.030 g, 0.06 mmol) and NCS (0.017 g, 0.12 mmol) in chloroform (10 ml) was refluxed for 8 h. The mixture was treated with water (20 ml), the organic layer was evaporated, and the residue chromatographed on Al_2O_3 (eluent was chloroform). The red fraction of R_f 0.25 gave compound **9** (0.020 g, 39%), the physicochemical characteristics of which were in agreement with those given above.

Dimethyl 2-Chloro-3,4-bis(dimethylamino)-8,9-diazafluoranthene-7,10-dicarboxylate (10). A solution of tetrazine **3** (0.039 g, 0.2 mmol) in dichloromethane (4 ml) was added in portions to a solution of compound **6** (0.055 g, 0.2 mmol) in dichloromethane (4 ml), with evolution of gas. After 5 min, the solvent was evaporated, the residue was dissolved in chloroform (5 ml), and the obtained solution was allowed to slowly evaporate in ambient conditions to complete the aromatization. The residue was recrystallized from toluene. Yield 0.085 g (97%). Red crystals; mp 212-213°C (decomp.). UV spectrum ($CHCl_3$), λ_{max}, nm (log ε): 245 (4.95), 285 (sh, 4.56), 400 (4.30), 540 (4.51). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.02 (6H, s, 4-N(CH_3)$_2$); 3.19 (6H, s, 3-N(CH_3)$_2$); 4.17 (3H, s) and 4.19 (3H, s, 2CO_2CH_3); 7.11 (1H, d, $J_{5,6}$ = 8.2, H-5); 8.72 (1H, d, $J_{5,6}$ = 8.2, H-6); 8.91 (1H, s, H-1). Found, %: C 60.00; H 4.70; Cl 8.12. $C_{22}H_{21}ClN_4O_4$. Calculated, %: C 59.93; H 4.80; Cl 8.04.

Dimethyl 2,5-Dichloro-3,4-bis(dimethylamino)-8,9-diazafluoranthene-7,10-dicarboxylate (11) was obtained analogously from substrate **7** (0.061 g, 0.2 mmol) and tetrazine **3** (0.039 g, 0.2 mmol), and was recrystallized from toluene. Yield 0.078 g (82%). Dark-red crystals; mp 235-236°C (decomp.). IR spectrum (nujol), ν, cm^{-1} 1710 (CO). UV spectrum ($CHCl_3$), λ_{max}, nm (log ε): 247 (4.68), 280 (sh, 4.56), 400 (4.08), 535 (4.30). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm; 3.15 (12H, s, 2N(CH_3)$_2$); 4.19 (6H, s, 2CO_2CH_3); 8.83 (2H, s, H-1,6). Found, %: C 55.48; H 4.20; Cl 14.88. $C_{22}H_{20}Cl_2N_4O_4$. Calculated, %: C 55.59; H 4.21; Cl 14.95.

Dimethyl 3,4-Bis(dimethylamino)-8*H*-acenaphtho[1,2-*c*]pyrrole-7,9-dicarboxylate (12). A suspension of diazafluoranthene **5** (0.150 g, 0.37 mmol) and zinc dust (0.100 g, 1.54 mmol) in acetic acid (4 ml) was stirred at room temperature for 48 h. The unreacted zinc was filtered off. The remainder, after dilution with water (5 ml), was neutralized with concentrated aqueous ammonia to pH 7-8. The reaction products were extracted with $CHCl_3$ (3×4 ml), the extract was evaporated to minimum volume and chromatographed on Al_2O_3 (eluent was $CHCl_3$). The main yellow fraction had R_f 0.35. Yield 0.082 g (57%). Yellow crystals; mp 202-203°C (MeOH–$CHCl_3$, 16:1). IR spectrum (nujol), ν, cm^{-1}: 3285 (NH), 1720 (C=O), 1565 (ring), 1260 (C–O–C). UV spectrum (EtOH), λ_{max}, nm (log ε): 255 (4.52), 278 (sh, 4.16), 352 (4.21), 404 (sh, 4.10), longest wavelength of absorption at 500 nm. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.91 (12H, s, 2N(CH_3)$_2$); 4.03 (6H, s, 2CO_2CH_3); 6.99 (2H, d, *J* = 7.7, H-2,5); 8.03 (2H, d, *J* = 7.7, H-1,6); 9.31 (1H, br. s, NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.84 (12H, s, 2N(CH_3)$_2$); 3.92 (6H, s, 2CO_2CH_3); 7.01 (2H, d, *J* = 7.9,

H-2,5); 7.97 (2H, d, J = 7.9, H-1,6); 12.1 (1H, br. s, NH). Mass spectrum, m/z (I_{rel}, %): 393 $[M]^+$ (76), 379 (24), 349 (39), 347 (33), 331 (74), 315 (18), 244 (45), 230 (25), 216 (28), 189 (30), 181 (22), 164 (37), 150 (52), 143 (41), 136 (90), 129 (57), 122 (84), 115 (32), 109 (23), 101 (26), 95 (18), 88 (21), 58 (100), 44 (94), 42 (68). Found, %: C 67.10; H 6.00. $C_{22}H_{23}N_3O_4$. Calculated, %: C 67.17; H 5.89.

Dimethyl 3,4-Bis(dimethylamino)-8-methyl-8*H*-acenaphtho[1,2-*c*]pyrrole-7,9-dicarboxylate (13a). Sodium hydride (0.003 g, 0.1 mmol, as 60% suspension in mineral oil) was added to a solution of pyrrole **12** (0.039 g, 0.1 mmol) in dry DMF (4 ml). The obtained mixture was stirred at 20°C for 20 min, after which iodomethane (6 μl, 0.1 mmol) was added. The mixture was stirred for a further 20 min, water (4 ml) was added, and the reaction products were extracted with toluene (1×4 ml). Toluene was removed from the extract, and the residue was chromatographed on Al_2O_3 (eluent was chloroform). The main yellow fraction had R_f 0.90. Yield 0.023 g (56%). Yellow crystals; mp 115-116°C (MeOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.90 (12H, s, $2N(CH_3)_2$); 4.04 (6H, s, $2CO_2CH_3$); 4.34 (3H, s, NCH_3); 6.98 (2H, d, J = 7.9, H-2,5); 7.99 (2H, d, J = 7.9, H-1,6). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 2.84 (12H, s, $2N(CH_3)_2$); 3.98 (6H, s, $2CO_2CH_3$); 4.22 (3H, s, NCH_3); 7.01 (2H, d, J = 7.9, H-2,5); 7.97 (2H, d, J = 7.9, H-1,6). Found, %: C 67.80; H 6.00. $C_{23}H_{25}N_3O_4$. Calculated, %: C 67.81; H 6.14.

Dimethyl 8-Ethyl-3,4-bis(dimethylamino)-8*H*-acenaphtho[1,2-*c*]pyrrole-7,9-dicarboxylate (13b) was obtained analogously from substrate **12** (0.039 g, 0.1 mmol), sodium hydride (0.003 g, 0.1 mmol, as 60% suspension in mineral oil), and EtI (9.3 μl, 0.1 mmol). The yellow fraction had R_f 0.93. Yield 0.034 g (71%). Yellow crystals; mp 181-182°C (MeOH–PhMe, 3:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.43 (3H, t, J = 6.9, $CH_2C\underline{H}_3$); 2.90 (12H, s, $2N(CH_3)_2$); 4.05 (6H, s, $2CO_2CH_3$); 4.95 (2H, q, J = 6.9, $C\underline{H}_2CH_3$); 6.98 (2H, d, J = 7.9, H-2,5); 7.99 (2H, d, J = 7.9, H-1,6). Found, %: C 68.50; H 6.50. $C_{24}H_{27}N_3O_4$. Calculated, %: C 68.39; H 6.46.

Dimethyl 2,5-Dichloro-3,4-bis(dimethylamino)-8*H*-acenaphtho[1,2-*c*]pyrrole-7,9-dicarboxylate (14). A solution of *N*-chlorosuccinimide (0.068 g, 0.50 mmol) in $CHCl_3$ (10 ml) was added at -15°C with vigorous stirring over 15 min to a solution of compound **12** (0.100 g, 0.25 mmol) in $CHCl_3$ (10 ml). The reaction mixture was washed with water (20 ml), the organic phase was evaporated to dryness, and the residue was chromatographed on Al_2O_3 (eluent was ethyl acetate). The yellow fraction had R_f 0.85. Yield 0.013 g (11%). Yellow crystals; mp 267-270°C ($CHCl_3$). IR spectrum (nujol), ν, cm^{-1}: 3290 (NH), 1700 (C=O), 1450 (ring), 1250 (C–O–C). UV spectrum ($CHCl_3$), λ_{max}, nm (log ε): 240 (4.82), 265 (sh, 4.80), 380 (4.30), longest wavelength of absorption at 500 nm. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.99 (12H, s, $2N(CH_3)_2$); 3.96 (6H, s, $2CO_2CH_3$); 7.89 (2H, s, H-1,6); 12.71 (1H, br. s, NH). Found, %: C 57.10; H 4.50. $C_{22}H_{21}Cl_2N_3O_4$. Calculated, %: C 57.14; H 4.58.

7,9-Diphenyl-8*H*-acenaphtho[1,2-*c*]pyrrole (17) was obtained analogously to compound **12** from diazafluoranthene **16** (0.132 g, 0.37 mmol) and zinc (0.100 g, 1.54 mmol). The yellow main fraction had R_f 0.92. Yield 0.018 g (14%). Light-yellow crystals; mp 193-194°C (MeOH) (mp 223-224°C, CH_2Cl_2–hexane [8]; IR and NMR spectra have not been published). IR spectrum (nujol), ν, cm^{-1}: 3410 (NH). UV spectrum (MeCN), λ_{max}, nm (log ε): 249 (4.30), 270 (sh, 4.23), 340 (4.06), 405 (3.91), longest wavelength of absorption at 440 nm. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 7.40 (2H, t, J = 7.6, H-2,5); 7.52-7.63 (6H, m, H Ph); 7.72 (2H, d, J = 8.1, H-1,6): 7.07 (2H, d, J = 7.1, H-3,4); 7.94-7.98 (4H, m, H Ph); 11.43 (1H, br. s, NH).

X-Ray Structural Investigation of Acenaphthopyrrole 12 Monocrystal (yellow plates from MeCN) was carried out at 100 K on a Bruker APEX II diffractometer (λ 0.71073 Å, MoK_α radiation, ω scanning). Crystals of compound **12**, $C_{22}H_{23}N_3O_4$, M 393.43, were monoclinic, space group $C2/c$, a 40.151(9), b 6.3252(13), c 15.390(3) Å, β 102.972(7)º, V 3808.8(14) $Å^3$, Z 8, d_{calc} 1.372 $g \cdot cm^{-3}$, μ 0.096 mm^{-1}, F(000) 1664. The structure was solved by the direct method and refined by the least squares method in a full-matrix anisotropic approximation using the Bruker SHELXTL set of programs. The H(N) hydrogen atom in the structure **12** was revealed by a Fourier difference synthesis and refined isotropically. The results of the investigation have been deposited in the Cambridge Crystallographic Data Center (deposit number CCDC 907661).

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