Microwave assisted synthesis for dimers *via* [3+3] dipolar cycloadditions

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Dedicated to Prof. Alexandru Balaban on his 75th anniversary
(received 29 Mar 05; accepted 09 Jun 05; published on the web 17 Jun 05)

Abstract
[3+3] Dipolar cycloaddition reactions of phthalazinium ylides are described. For the first time in the cycloimmonium ylides series, a study concerning the [3+3] dipolar cycloaddition under microwave irradiation (in liquid and solid phase) is reported. A comparative study classical / microwave heating was performed and a feasible explication for the efficiency of microwave heating in [3+3] dipolar cycloadditions reactions of cycloimmonium ylides is presented. For the obtained dimers, a tetrahydropyrazino-diphthalazine structure was assigned. The [3+3] dipolar cycloadditions occur in a highly *cis* selective fashion and ten new compounds (**4a-j)** were obtained.

Keywords: Ylides, cycloadditions, dimers, liquid and solid phase reactions, microwave

Introduction

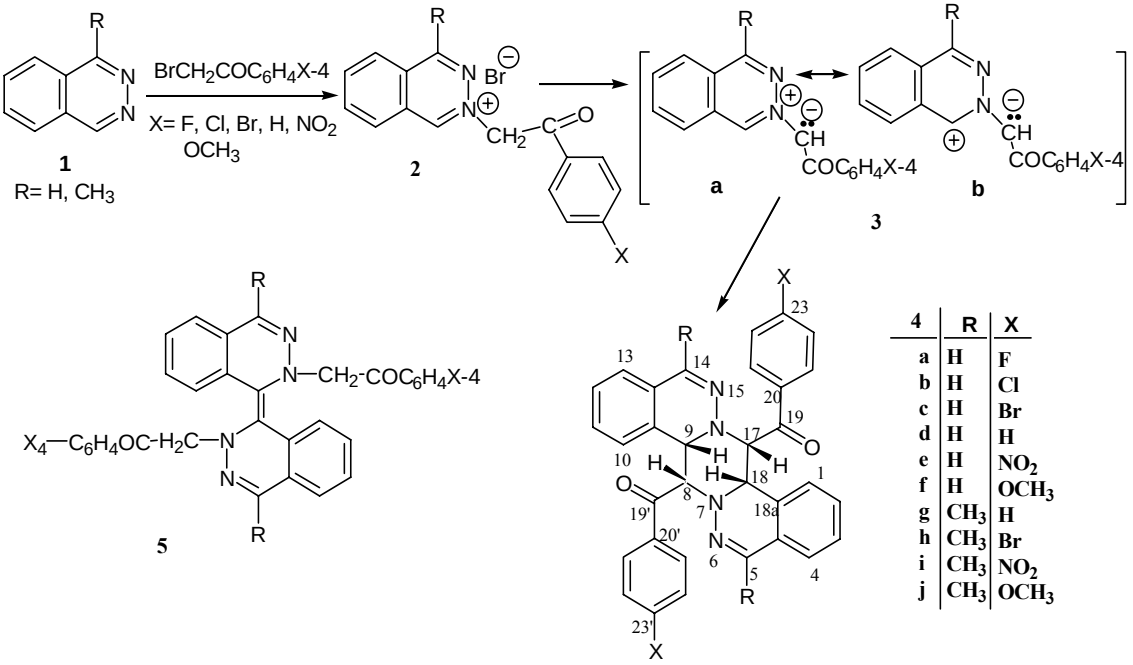
According to the literature,[1-11] the chemistry of cycloimmonium ylides is widely discussed, either because of their theoretical importance[1-7] or because of their practical applications [drugs (antituberculosis,[8] antimicrobial[9]) acid-base indicators,[10] electrical (semiconducting properties[11]) etc.]. In most cases, the ylides react with a large variety of dipolarophiles (with double or triple bonds) *via* a [3+2] dipolar cycloaddition. Depending on the reactivity and stability of ylides, an undesirable competitive [3+3] dipolar cycloaddition of two molecules of the ylide can take place, leading to dimers.[1-3] The structures of these dimers were often established only through IR, UV-VIS or 60-80 MHz ^{1}H-NMR spectra and, accordingly, may be uncertain.[1-3, 16, 19] Further, classical heating was employed for the reported cycloadditions; however, in recent years,

microwave heating[12-15, 17] has become a versatile alternative to classical heating. Also, reactions in the solid phase under microwave heating have the great advantage of requiring no solvent.

Taking into account the above considerations, we decided to clarify the aspects concerning the structure of the dimers and to study the influence of microwave heating upon these [3+3] dipolar cycloaddition reactions, both in the liquid and solid phases.

Results and Discussion

In order to conduct the experiments, we synthesized phthalazinium salts **2**, according to the literature procedure under classical heating[18] or by using an adaptation from the literature[17] under microwave irradiation. In an alkaline medium (Et_3N in liquid phase and $KF–Al_2O_3$ in solid phase), the cycloimmonium salts **2**, generate the ylides **3** *in situ*. Under the conditions we employed, the ylides **3** underwent a [3+3] dipolar cycloaddition reaction with each other leading to the dimers **4** with a tetrahydropyrazino-diphthalazine structure, as shown in Scheme 1.

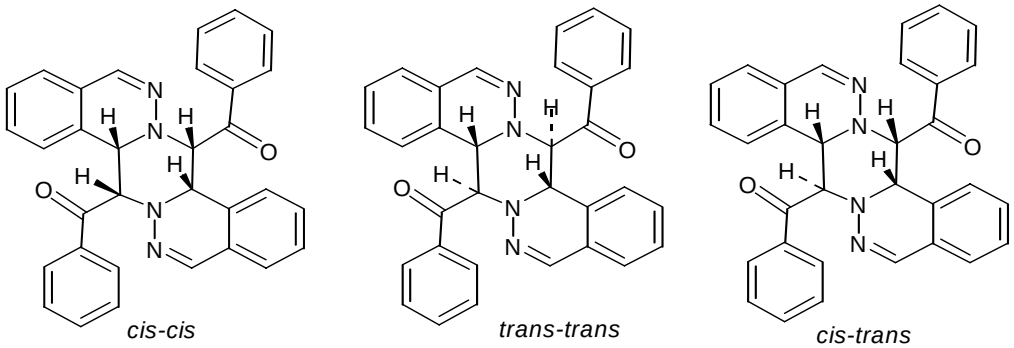


Scheme 1

Concerning the structure of the dimers, the literature data are controversial. In the early 1970's, a structure of type **5** (a phthalazinylidene) was assigned for compound **4g** (and later for **4d**)[19]. In the 1990's some of us,[16] using a 80 MHz NMR machine, assumed a tetrahydropyrazino-diphthalazine structure for compounds **4h-j**. Taking into account the data furnished by elemental and spectral analysis (IR, ^{1}H-NMR, ^{13}C-NMR, COSY, HMQC, HMBC), we question now that all the dimers **4a-j** have a tetrahydropyrazino-diphthalazine structure. In the ^{1}H-NMR spectra,

the most important signals are those of the protons $H_{8\equiv17}$ and $H_{9\equiv18}$. These protons appear in compounds **4a-j** with different chemical shifts and with the same coupling constant: $H_{8\equiv17}$ around 5.50 ppm and $H_{9\equiv18}$ around 5.40 ppm, both as doublets, having a coupling constant around 10.0 Hz. The corresponding carbons, $C_{8\equiv17}$ and $C_{9\equiv18}$, appear in ^{13}C-NMR spectra around 65.00 ppm and 45.00 ppm, respectively, which also confirms the structure. On a 60 MHz NMR[19] the signal from around 5.00 ppm appeared broadened and looked like a CH_2, that is why we believe that the researcher from the 70's assigned a phthalazinylidene structure for dimer **4g**.

The [3+3] dipolar cycloadditions occur in a highly *cis* selective fashion. The stereochemistry of the resulting adducts **4** was assigned using the value of the coupling constant (around 10.0 Hz, characteristic value for *cis*- adducts) and NOE experiments, as well as by the value of the heat of formation of stereoisomers (calculated using a MOPAC protocol, Scheme 2).



Scheme 2

Unfortunately, the NOE experiments did not supply significant information concerning *cis-cis* stereochemistry. Thus, in the case of compound **4e** for instance, we could not asses the NOE effect of the irradiation of the peak from 5.28-5.31 ppm ($H_{9\equiv18}$) over the proton from 5.44-5.47 ppm ($H_{8\equiv17}$ protons), because the signals appear too close in the NMR spectrum and the irradiation is not selective enough, thus producing also a small negative peak on 5.44-5.47 ppm. It is of interest, however, that irradiation of the peak from 5.28-5.31 ppm ($H_{8\equiv17}$ protons) caused significant increase of the positive signal from 7.17-7.18 ppm (corresponding to $H_{1\equiv10}$ protons).

As shown in Scheme 2, the isomer *cis-cis* has the lowest heat of formation (168.31 kcal/mol) and, thus, has the greatest probability of formation from a thermodynamic point of view. In view of all the information above, we conclude that the stereochemistry of the resulting adducts **4** is *cis-cis*.

No matter the conditions we employed, synthesis of tetrahydropyrazino-diphthalazine **4** *via* [3+3] dipolar cycloadditions under classical heating (refluxing in a solvent) presents some major disadvantages: long reactions time (2-6 hours), low yields (below 40%), high energy

consumption, difficulty in purifications (often, dimers **4** undergo an oxidative dehydrogenation leading to a complex mixture of saturated, unsaturated and aromatized compounds), etc. Taking into account the above consideration, and the fact that we did not find any literature indications concerning dimerisation under microwave conditions, we decided to study the [3+3] dipolar cycloadditions of phthalazinium ylides under microwave irradiation. In Table 1 and 2 are listed the best results obtained under microwave and classical heating, in liquid phase (benzene) and solid phase ($KF–Al_2O_3$ support), respectively. In addition, some other conditions were tested (in liquid phase: different solvents, various times of reaction, different amounts of solvent; in solid phase: different reaction temperature, various times of reaction).

Table 1. [3+3] Dipolar cycloaddition reactions of phthalazinium ylides under microwave and classical heating conditions in the liquid phase

Comp.	Microwaves			Classical		
	Time, min.	Temperature, ^oC	Yield, %	Time, min.	Temperature, ^oC	Yield, %
4a	5	70	63	180	80	32
4b	5	70	65	180	80	43
4c	5	70	63	180	80	41
4d	5	70	62	180-240	80	41-44
4e	5	70	61	120	80	32
4f	5	70	71	120	80	35
4g	5	70	66	120	80	32
4h	5	70	63	120	80	38
4i	5	70	60	120	80	31
4j	5	70	72	120	80	35

The data from Table 1 reveal some interesting facets concerning the behaviour of cycloaddition in the liquid phase. Thus, under microwave irradiation the yields are much higher (by about 25%), reaction times decrease dramatically (from hours to 5 min.), and the amount of solvent used is halved (see experimental).

Table 2. [3+3] Dipolar cycloaddition reactions of phthalazinium ylides under microwave and classical heating in the solid phase (on solid support $KF–Al_2O_3$)

Comp.	Microwaves			Classical		
	Time, min.	Temperature, ^oC	Yield, %	Time, min.	Temperature, ^oC	Yield, %
4a	15	150	79	15-240	100-200	trace
4b	15	150	78	15-240	100-200	trace
4c	15	150	83	15-240	100-200	trace
4d	15	150	76	15-240	100-200	trace
4e	15	150	71	15-240	100-200	trace
4f	15	150	82	15-240	100-200	trace
4g	15	150	79	15-240	100-200	trace
4h	15	150	78	15-240	100-200	trace
4i	15	150	72	15-240	100-200	trace
4j	15	150	82	15-240	100-200	trace

In the solid state, Table 2, the results are even more spectacular: while under classical heating (oil bath) we obtained a trace of dimers, under microwave heating we got excellent yields, between 70 to 80%. Also, if we compare the yields for the liquid phase/ solid phase under microwave irradiation, it has to be pointed out that in the solid state these are higher by about 15%.

We believe that the microwave heating approach is so effective in [3+3] dipolar cycloaddition reactions due to two factors: the microwave mechanism of action and the structure of the ylide. It is well know that the magnetic field component of microwave radiation is responsible for the microwave dielectric heating. The greater the dipole moment of the molecule, the higher the effect of microwaves will be. The ylides, having a 1,2- dipolar structure are excellent dipoles and, therefore, the efficiency of microwave heating increases considerably as compared with classical heating.

Conclusions

For the first time in the cycloimmonium ylides series, a general and facile way for dimer synthesis under microwave irradiation is reported. The [3+3] dipolar cycloadditions occur in a highly *cis* selective fashion. Both in the liquid and solid phase, under microwave irradiation the yields are much higher, reaction times decrease dramatically, and the compounds are much more pure (compared with classical heating). Under microwave irradiation in the solid state, the yields are higher than in the liquid phase. A feasible explication for the efficiency of microwave heating in [3+3] dipolar cycloadditions reactions of cycloimmonium ylides has been presented. For the

obtained dimers, a tetrahydropyrazino-diphthalazine structure was assigned and ten new compounds (**4a-j)** were obtained.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance instrument (400 MHz) downfield from an internal standard, $SiMe_4$ in $CDCl_3$. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra were recorded with a JASCO V-570 spectrometer in KBr. For the microwave irradiation we used a monomode reactor STAR-2, CHEM corporation (50 W). Melting points were determined on a MELTEMP II apparatus and are uncorrected.

General procedure for [3+3] dipolar cycloaddition in the liquid phase
Phthalazinium bromide (1 mMol) was suspended in 10 mL of anhydrous benzene (under classical heating) and 5 mL of anhydrous benzene (under microwave heating). Then, triethylamine (1.1 mMol) was added. Under classical conditions, the solution was refluxed (water bath) for 2-4 h. Under microwave heating, the solution was exposed to microwave for 5 min. The resulting mixture was filtered hot to remove triethylamine hydrobromide and the clear solution was evaporated. The crude product was crystallized from an appropriate solvent.

General procedure for [3+3] dipolar cycloaddition in the solid phase
Phthalazinium bromide (2 mMol) and 15 g of mineral support ($KF-Al_2O_3$) were ground in an agate mortar until a fine homogeneous mixture was obtained. The mixture was heated under classical conditions (oil bath) or exposed to microwaves (see Table 2). The activated solid was cooled, then washed four times: three times with 10 mL of acetone and once with 10 mL of dimethylacetamide (DMA). The acetone was then evaporated and the product was crystallized from an appropriate solvent. In the DMA case, the solution was precipitated with water, filtered, dried and then recrystallized from an appropriate solvent.
8,17-(4-Fluorobenzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-a;4,5-a′]-diphthalazine (4a). White pale crystals from methanol, mp 241-242° C. IR (KBr, ν, cm^{-1}): 3067 w (C-Harom.), 2923 w (C-Haliph.), 1697 s (CO), 1587, 1498, 1453, 1431 s-m(C=N, C=C). ^{1}H NMR: 5.35-5.38 (2H, d, 1-H_9, 1-H_{18}, J = 10.0), 5.41-5.44 (2H, d, 1-H_8, 1-H_{17}, J = 10.0), 7.00-7.07 (6H, m (overlapped peaks), 1-H_1, 1-H_{10}, 2-H_{22}, 2-$H_{22'}$, $J_{22,21}$ = 8.8, $J_{22,F}$ = 9.0), 7.23-7.26 (2H, t, 1-H_3, 1-H_{12}, J = 7.6, J = 7.2), 7.30-7.34 (2H, t, 1-H_2, 1-H_{11}, J = 8.0, J = 7.2), 7.42-7.44 (2H, d, 1-H_4, 1-H_{13}, J = 7.6), 7.58 (2H, s, 1-H_5, 1-H_{14}), 7.99-8.03 (4H, dd, 2-H_{21}, 2-$H_{21'}$, $J_{21,22}$ = 8.8, $J_{21,F}$ = 5.6); ^{13}C NMR: 56.39 (C_9, C_{18}), 61.39 (C_8, C_{17}), 115.49 (C_{22}, $C_{22'}$), 124.17 (C_{4a}, C_{13a}), 124.46 (C_3, C_{12}), 126.89 (C_1, C_{10}), 128.77 (C_4, C_{13}), 130.76 (C_{9a}, C_{18a}), 130.96 (C_2, C_{11}), 131.42 (C_{20}, $C_{20'}$), 131.69 (C_{21}, $C_{21'}$), 139.86 (C_5, C_{14}), 164.27 (C_{23}, $C_{23'}$), 192.87 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{32}H_{22}F_2N_4O_2$: C, 72.18; H, 4.14; N, 10.52; Found: C, 72.10; H, 4.18; N, 10.35.

8,17-(4-Chlorobenzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-diphthalazine (4b). Yellow crystals from methanol, mp 203-204° C. IR (KBr, ν, cm^{-1}): 3061 w (C-Harom.), 2929 w (C-Haliph.), 1695 s(CO), 1590, 1496, 1452, 1430 s-m (C=N, C=C). ^{1}H NMR: 5.35-5.38 (2H, d, 1-H_9, 1-H_{18}, J = 10.0), 5.42-5.45 (2H, d, 1-H_8, 1-H_{17}, J = 10.0), 7.13-7.14 (2H, d, 1-H_1, 1-H_{10}, J = 8.4), 7.27-7.32 (6H, m (overlapped peaks), 1-H_2, 1-H_{11}, 1-H_3, 1-H_{12}, 1-H_4, 1-H_{13}), 7.48-7.50 (4H, d, 2-H_{22}, 2-$H_{22'}$, J = 8.8), 7.57 (2H, s, 1-H_5, 1-H_{14}), 7.95-7.97 (4H, d, 2-H_{21}, 2-$H_{21'}$, J = 8.8); ^{13}C NMR: 47.71 (C_9, C_{18}), 66.58 (C_8, C_{17}), 124.30 (C_{4a}, C_{13a}), 124.91 (C_3, C_{12}), 126.83 (C_1, C_{10}), 128.74 (C_{22}, $C_{22'}$), 128.81 (C_4, C_{13}), 130.08 (C_{20}, $C_{20'}$), 130.47 (C_2, C_{11}), 130.96 (C_{9a}, C_{18a}), 131.17 (C_{21}, $C_{21'}$), 138.87 (C_{23}, $C_{23'}$), 140.06 (C_5, C_{14}), 193.82 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{32}H_{22}Cl_2N_4O_2$: C, 67.96; H, 3.87; N, 9.91; Found: C, 67.83; H, 3.98; N, 9.83.

8,17-(4-Bromobenzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-diphthalazine (4c). Yellow brown crystals from methanol, mp 209-210° C. IR (KBr, ν, cm^{-1}): 3060 w(C-Harom.), 2930 w(C-Haliph.), 1699 s(CO), 1591, 1497, 1453, 1431 s-m(C=N, C=C). ^{1}H NMR: 5.36-5.39 (2H, d, 1-H_9, 1-H_{18}, J = 10.0), 5.42-5.45 (2H, d, 1-H_8, 1-H_{17}, J = 10.0), 7.14-7.15 (2H, d, 1-H_1, 1-H_{10}, J = 8.4), 7.28-7.33 (6H, m (overlapped peaks), 1-H_2, 1-H_{11}, 1-H_3, 1-H_{12}, 1-H_4, 1-H_{13}), 7.48-7.50 (4H, d, 2-H_{22}, 2-$H_{22'}$, J = 8.8), 7.58 (2H, s, 1-H_5, 1-H_{14}), 7.94-7.96 (4H, d, 2-H_{21}, 2-$H_{21'}$, J = 8.8); ^{13}C NMR: 47.72 (C_9, C_{18}), 66.59 (C_8, C_{17}), 124.31 (C_{4a}, C_{13a}), 124.92 (C_3, C_{12}), 126.85 (C_1, C_{10}), 128.36 (C_{23}, $C_{23'}$), 128.81 (C_4, C_{13}), 130.47 (C_2, C_{11}), 130.98 (C_{9a}, C_{18a}), 131.04 (C_{21}, $C_{21'}$), 131.64 (C_{22}, $C_{22'}$), 134.40 (C_{20}, $C_{20'}$), 140.12 (C_5, C_{14}), 193.86 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{32}H_{22}Br_2N_4O_2$: C, 58.71; H, 3.36; N, 8.56; Found: C, 58.67; H, 3.48; N, 8.21.

8,17-(Benzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-diphthalazine (4d). Yellow crystals from methanol, mp 251-253° C. IR (KBr, ν, cm^{-1}): 3060 w(C-Harom.), 2939 w(C-Haliph.), 1682 s(CO), 1595, 1501, 1452, 1436 s-m(C=N, C=C). ^{1}H NMR: 5.34-5.37 (2H, d, 1-H_9, 1-H_{18}, J = 10.0), 5.40-5.43 (2H, d, 1-H_8, 1-H_{17}, J = 10.0), 7.08-7.11 (2H, d, 1-H_1, 1-H_{10}, J = 8.0), 7.26-7.33 (10H, m (overlapped peaks), 1-H_2, 1-H_{11}, 1-H_3, 1-H_{12}, 1-H_4, 1-H_{13}, 2-H_{22}, 2-$H_{22'}$), 7.39-7.41 (2H, t, 1-H_{23}, 1-$H_{23'}$, J = 7.6), 7.58 (2H, s, 1-H_5, 1-H_{14}), 8.06-8.08 (4H, d, 2-H_{21}, 2-$H_{21'}$, J = 7.6); ^{13}C NMR: 47.69 (C_9, C_{18}), 66.58 (C_8, C_{17}), 124.30 (C_{4a}, C_{13a}), 124.94 (C_3, C_{12}), 126.81 (C_1, C_{10}), 128.26 (C_{22}, $C_{22'}$), 128.80 (C_4, C_{13}), 129.68 (C_{21}, $C_{21'}$), 130.43 (C_2, C_{11}), 130.94 (C_{9a}, C_{18a}), 133.11 (C_{23}, $C_{23'}$), 135.02 (C_{20}, $C_{20'}$), 140.10 (C_5, C_{14}), 193.72 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{32}H_{24}N_4O_2$: C, 77.42; H, 4.84; N, 11.29; Found: C, 77.30; H, 4.98; N, 11.23.

8,17-(4-Nitrobenzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-diphthalazine (4e). Yellow crystals from methanol, mp 210-211° C. IR (KBr, ν, cm^{-1}): 3096 w(C-Harom.), 2929 w(C-Haliph.), 1702 s(CO), 1525, 1345 s(NO_2), 1598, 1456, 1429 s-m(C=N, C=C). ^{1}H NMR: 5.28-5.31 (2H, d, 1-H_9, 1-H_{18}, J = 9.6), 5.44-5.47 (2H, d, 1-H_8, 1-H_{17}, J = 9.6), 7.17-7.18 (2H, d, 1-H_1, 1-H_{10}, J = 8.0), 7.23-7.29 (6H, m (overlapped peaks), 1-H_2, 1-H_{11}, 1-H_3, 1-H_{12}, 1-H_4, 1-H_{13}), 7.53 (2H, s, 1-H_5, 1-H_{14}), 8.22-8.24 (4H, d, 2-H_{21}, 2-$H_{21'}$, J = 8.8), 8.25-8.27 (4H, d, 2-H_{22}, 2-$H_{22'}$, J = 8.8); ^{13}C NMR: 47.60 (C_9, C_{18}), 66.56 (C_8, C_{17}), 123.56 (C_{22}, $C_{22'}$), 124.26 (C_{4a}, C_{13a}), 125.43 (C_3, C_{12}), 126.78 (C_1, C_{10}), 128.77 (C_4, C_{13}), 130.33 (C_{9a}, C_{18a}), 130.58 (C_{21}, $C_{21'}$), 131.04 (C_2, C_{11}), 139.83 (C_{20}, $C_{20'}$), 139.99 (C_5, C_{14}), 150.30 (C_{23}, $C_{23'}$), 192.82 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{32}H_{22}N_6O_6$: C, 65.53; H, 3.75; N, 14.33; Found: C, 65.40; H, 3.87; N, 14.18.

8,17-(4-Methoxybenzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-diphthalazine (4f). Pale yellow crystals from methanol, mp 138-139° C. IR (KBr, ν, cm^{-1}): 3070 w(C-Harom.), 2921 w(C-Haliph.), 1676 s(CO), 1598, 1510, 1456 s-m(C=N, C=C), 1257, 1174 s(C-O-C). ^{1}H NMR: 3.79 (6H, s, 2xOCH_3), 5.38-5.40 (2H, d, 1-H_9, 1-H_{18}, *J* = 10.0), 5.41-5.43 (2H, d, 1-H_8, 1-H_{17}, *J* = 10.0), 6.81-6.84 (4H, d, 2-H_{22}, 2-$H_{22'}$, *J* = 8.8), 7.08-7.10 (2H, d, 1-H_1, 1-H_{10}, *J* = 8.4), 7.12-7.14 (2H, t, 1-H_3, 1-H_{12}, *J* = 7.2, *J* = 6.0), 7.17-7.23 (4H, m (overlapped peaks), 1-H_2, 1-H_{11}, 1-H_4, 1-H_{13}), 7.63 (2H, s, 1-H_5, 1-H_{14}), 8.02-8.04 (4H, d, 2-H_{21}, 2-$H_{21'}$, *J* = 8.8); ^{13}C NMR: 48.12 (C_9, C_{18}), 55.43 (C, OCH_3), 65.96 (C_8, C_{17}), 113.62 (C_{22}, $C_{22'}$), 124.66 (C_{4a}, C_{13a}), 124.85 (C_3, C_{12}), 126.91 (C_1, C_{10}), 128.23 (C_4, C_{13}), 128.79 (C_{20}, $C_{20'}$), 130.54 (C_2, C_{11}), 130.96 (C_{9a}, C_{18a}), 131.82 (C_{21}, $C_{21'}$), 138.57 (C_5, C_{14}), 163.68 (C_{23}, $C_{23'}$), 193.01 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{34}H_{28}N_4O_4$: C, 73.38; H, 5.04; N, 10.07; Found: C, 73.26; H, 5.12; N, 9.96.

8,17-(Benzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-di-(1-methylphthalazine) (4g). Yellow crystals from methanol, mp 216-217° C. IR (KBr, ν, cm^{-1}): 3051 w(C-Harom.), 2941 w(C-Haliph.), 1681 s(CO), 1596, 1485, 1450, 1427 s-m(C=N, C=C). ^{1}H NMR: 2.43 (6H, s, 2xCH_3), 5.28-5.31 (2H, d, 1-H_9, 1-H_{18}, *J* = 9.6), 5.34-5.36 (2H, d, 1-H_8, 1-H_{17}, *J* = 9.6), 7.07-7.09 (2H, d, 1-H_1, 1-H_{10}, *J* = 7.2), 7.15-7.25 (4H, m (overlapped peaks), 1-H_2, 1-H_{11}, 1-H_3, 1-H_{12}), 7.30-7.35 (6H, m (overlapped peaks), 1-H_4, 1-H_{13}, 2-H_{22}, 2-$H_{22'}$), 7.42-7.46 (2H, t, 1-H_{23}, 1-$H_{23'}$, *J* = 7.6), 8.03-8.05 (4H, d, 2-H_{21}, 2-$H_{21'}$, *J* = 7.6); ^{13}C NMR: 18.76 (C, CH_3), 48.25 (C_9, C_{18}), 66.27 (C_8, C_{17}), 123.42 (C_{4a}, C_{13a}), 125.83 (C_3, C_{12}), 126.84 (C_1, C_{10}), 128.01 (C_4, C_{13}), 128.30 (C_{22}, $C_{22'}$), 129.49 (C_{21}, $C_{21'}$), 130.32 (C_2, C_{11}), 132.31 (C_{9a}, C_{18a}), 133.07 (C_{23}, $C_{23'}$), 135.92 (C_{20}, $C_{20'}$), 143.80 (C_5, C_{14}), 194.93 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{34}H_{28}N_4O_2$: C, 77.86; H, 5.34; N, 10.69; Found: C, 77.72; H, 5.43; N, 10.42.

8,17-(4-Bromobenzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-di-(1-methylphthalazine) (4h). Pale yellow crystals from methanol, mp 210-211° C. IR (KBr, ν, cm^{-1}): 3060 w(C-Harom.), 2914 w(C-Haliph.), 1685 s(CO), 1584, 1486, 1450, 1430 s-m(C=N, C=C). ^{1}H NMR: 2.41 (6H, s, 2xCH_3), 5.22 (broaded signal, 4H, 1-H_9, 1-H_{18}, 1-H_8, 1-H_{17}), 7.09-7.11 (2H, d, 1-H_1, 1-H_{10}, *J* = 6.4), 7.20-7.26 (4H, m (overlapped peaks), 1-H_2, 1-H_{11}, 1-H_3, 1-H_{12}), 7.31-7.33 (2H, d, 1-H_4, 1-H_{13}, *J* = 7.2), 7.46-7.48 (4H, d, 2-H_{22}, 2-$H_{22'}$, *J* = 8.4), 7.89-7.91 (4H, d, 2-H_{21}, 2-$H_{21'}$, *J* = 8.4); ^{13}C NMR: 18.78 (C, CH_3), 47.93 (C_9, C_{18}), 66.26 (C_8, C_{17}), 123.55 (C_{4a}, C_{13a}), 125.63 (C_3, C_{12}), 126.77 (C_1, C_{10}), 128.14 (C_4, C_{13}), 128.41 (C_{23}, $C_{23'}$), 130.46 (C_2, C_{11}), 131.01 (C_{21}, $C_{21'}$), 131.59 (C_{22}, $C_{22'}$), 132.05 (C_{9a}, C_{18a}), 134.43 (C_{20}, $C_{20'}$), 144.22 (C_5, C_{14}), 193.97 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{34}H_{26}Br_2N_4O_2$: C, 59.82; H, 3.81; N, 8.21; Found: C, 59.71; H, 3.94; N, 8.01.

8,17-(4-Nitrobenzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-di-(1-methylphthalazine) (4i). Orange crystals from methanol, mp 182-183° C. IR (KBr, ν, cm^{-1}): 3106 w(C-Harom.), 2926 w(C-Haliph.), 1690 s(CO), 1525, 1345 s(NO_2), 1601, 1454, 1427 s-m(C=N, C=C). ^{1}H NMR: 2.45 (6H, s, 2xCH_3), 5.17-5.19 (2H, d, 1-H_9, 1-H_{18}, *J* = 9.6), 5.26-5.28 (2H, d, 1-H_8, 1-H_{17}, *J* = 9.6), 7.14-7.16 (2H, d, 1-H_1, 1-H_{10}, *J* = 6.0), 7.30-7.34 (4H, m (overlapped peaks), 1-H_2, 1-H_{11}, 1-H_3, 1-H_{12}), 7.35-7.37 (2H, d, 1-H_4, 1-H_{13}, *J* = 6.8), 8.16-8.18 (4H, d, 2-H_{21}, 2-$H_{21'}$, *J* = 8.8), 8.21-8.23 (4H, d, 2-H_{22}, 2-$H_{22'}$, *J* = 8.8); ^{13}C NMR: 18.82 (C, CH_3), 47.68 (C_9, C_{18}), 66.68

(C_8, C_{17}), 123.45 (C_{22}, $C_{22'}$), 123.83 (C_{4a}, C_{13a}), 125.49 (C_3, C_{12}), 126.74 (C_1, C_{10}), 128.42 (C_4, C_{13}), 130.54 (C_{21}, $C_{21'}$), 130.70 (C_2, C_{11}), 131.78 (C_{9a}, C_{18a}), 140.11 (C_{20}, $C_{20'}$), 145.16 (C_5, C_{14}), 150.14 (C_{23}, $C_{23'}$), 193.27 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{34}H_{26}N_6O_6$: C, 66.45; H, 4.23; N, 13.68; Found: C, 66.40; H, 4.30; N, 13.51.

8,17-(4-Methoxybenzoyl)-8,9,17,18-tetrahydropyrazino-[2,1-*a*;4,5-*a'*]-di-(1-methylphthalazine) (4j). Brownish crystals from ethanol, mp 266-267° C. IR (KBr, ν, cm^{-1}): 3066 w(C-Harom.), 2914 w(C-Haliph.), 1673 s(CO), 1599, 1509, 1456 s-m(C=N, C=C), 1257, 1174 s(C-O-C). ^{1}H NMR: 2.40 (6H, s, 2xCH_3), 3.78 (2H, s, 2xOCH_3), 5.25-5.27 (2H, d, 1-H_9, 1-H_{18}, J = 9.6), 5.30-5.32 (2H, d, 1-H_8, 1-H_{17}, J = 9.6), 6.79-6.81 (4H, d, 2-H_{22}, 2-$H_{22'}$, J = 8.8), 7.07-7.09 (2H, d, 1-H_1, 1-H_{10}, J = 7.2), 7.14-7.21 (4H, m (overlapped peaks), 1-H_2, 1-H_{11}, 1-H_3, 1-H_{12}), 7.28-7.30 (2H, d, 1-H_4, 1-H_{13}, J = 7.2), 7.99-8.01 (4H, d, 2-H_{21}, 2-$H_{21'}$, J = 8.8); ^{13}C NMR: 18.78 (C, CH_3), 48.32 (C_9, C_{18}), 55.39 (C, OCH_3), 66.04 (C_8, C_{17}), 113.48 (C_{22}, $C_{22'}$), 123.30 (C_{4a}, C_{13a}), 125.83 (C_3, C_{12}), 126.89 (C_1, C_{10}), 127.89 (C_4, C_{13}), 129.01 (C_{20}, $C_{20'}$), 130.23 (C_2, C_{11}), 131.78 (C_{21}, $C_{21'}$), 132.37 (C_{9a}, C_{18a}), 143.50 (C_5, C_{14}), 163.46 (C_{23}, $C_{23'}$), 193.65 (C_{19}, $C_{19'}$, keto). Anal. Calcd. for $C_{36}H_{32}N_4O_4$: C, 73.97; H, 5.48; N, 9.59; Found: C, 73.81; H, 5.60; N, 9.48.

Acknowledgements

CNCSIS Bucuresti, grant no.1322/2004, for financial support.

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