

Ylidic polyfunctionalized compounds with a diazinium skeleton

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Dedicated to Kjell Undheim, Oslo, on the occasion of his 70th birthday
(received 16 Feb 01; accepted 19 Mar 02; published on the web 27 Mar 02)

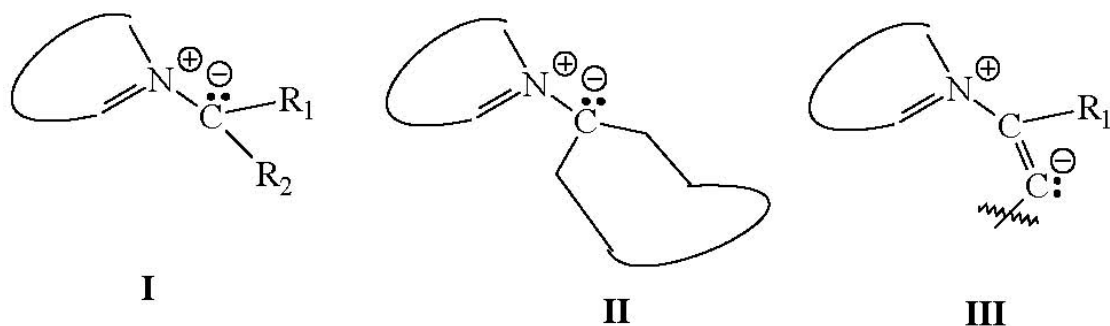
Abstract

For the first time in the cycloimmonium ylide series we have obtained unsaturated styryl carbanion monosubstituted ylides. These ylides, phthalazinium- and 4-methylpyrimidinium-ylides, have polyfunctionalized character: ylide and alkene. In this paper we have exploited only the ylidic character. The ylides **3** and **4** have been proven to have 1,3-dipole characters (**3a** and **4a**), respectively. Thus, the ylides function as 1,3-dipoles in 3+2 dipolar cycloaddition reactions with various dipolarophiles (such as DMAD, NPM). The structure of all the other compounds (salts and cycloadducts) has been proven through elemental and spectral (IR, NMR) analysis. The *in vitro* biological activity of the newly obtained phthalazine and pyrimidine compounds was also tested. Some of them have proved to have a remarkable activity against different microorganisms (germs and fungus). Correlation of the structure-biological activity has been studied.

Keywords : Cycloimmonium ylides, diazine, phthalazine, pyrimidine, cycloaddition, polyfunctionalized compounds, biological activity: antimicrobial and antifungal

Introduction

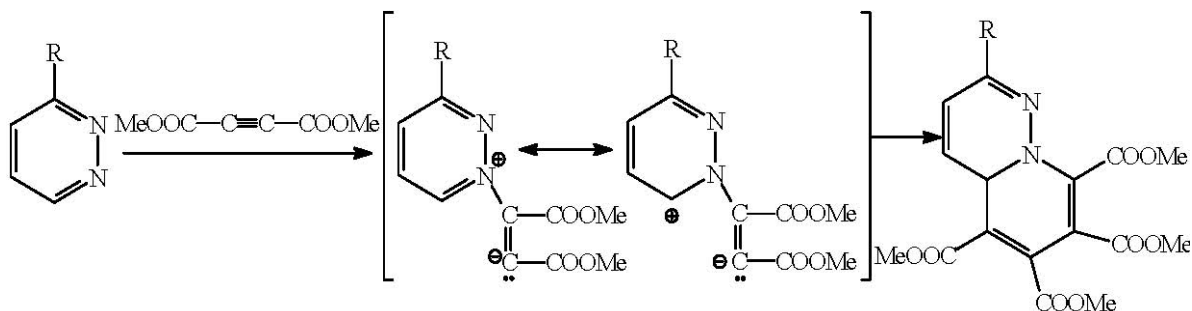
The chemistry of cycloimmonium ylides has been widely discussed.^{1,2,3} The research has focused especially of the ylides of type **I**. Few studies have been done concerning the ylides **II** and **III**.(Scheme 1)



Scheme 1

In the early 70s Acheson and Foxton⁴ assumed, for the first time in the diazine series, the existence of ylides with unsaturated carbanion. (Scheme 2)

Since then no other research has been done in the field of diazinium ylides with unsaturated carbanion although this is a convenient way to access polyfunctionalized compounds with a ylidic skeleton.



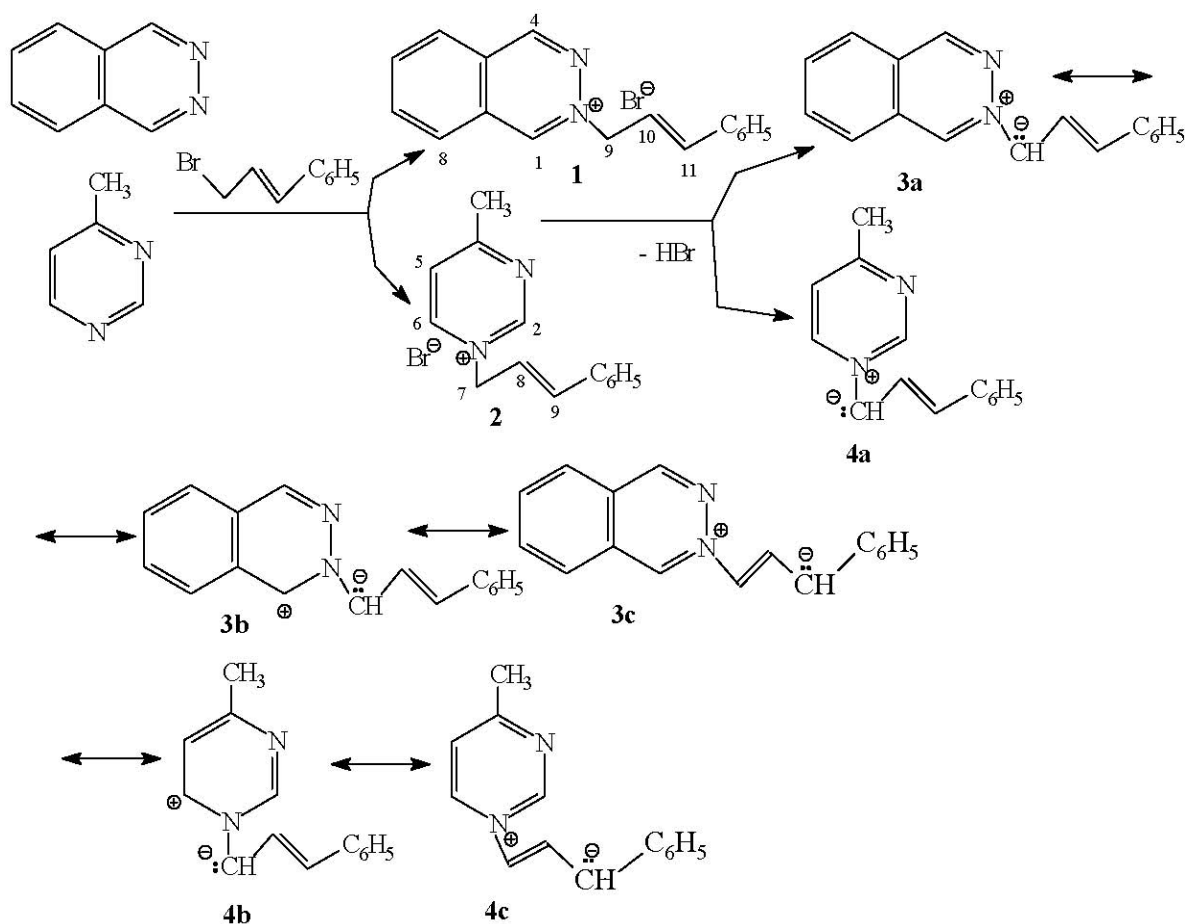
Scheme 2

The emphasis of this work was, on one hand, to get ylides with a new type of unsaturated carbanion (analogous with **III**) and, on the other hand, to get polyfunctionalized compounds with a ylidic skeleton. Another goal was to test the biological activity of the new compounds.

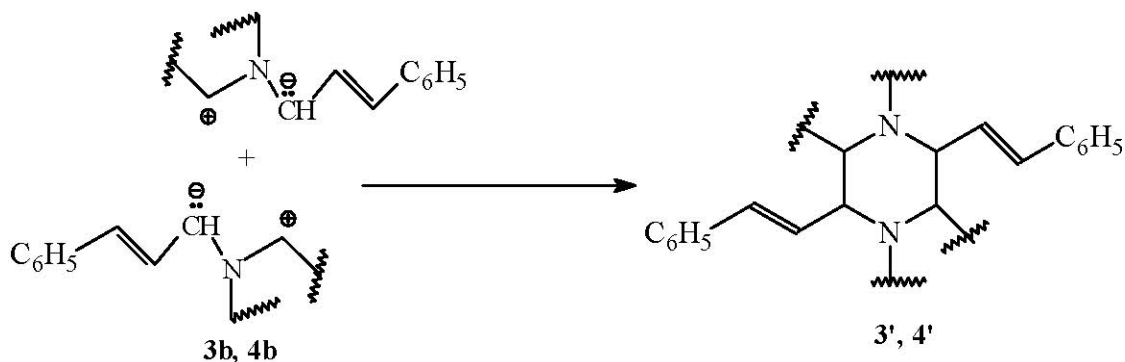
Results and Discussion

In first instance we tried to get phthalazinium- (**3**) and pyrimidinium- (**4**) ylides with unsaturated carbanion, using an adaptation of the Krönke⁵ salts method (Scheme 3). Thus, the reactions of phthalazine and 4-methylpyrimidine with cinnamyl bromide yield to the salts **1** and **2**, respectively. The structures were characterised by elemental and spectral analysis. The dehydrohalogenation of **1** and **2** with 40% aqueous potassium carbonate lead (according to the TLC) to a mixture of two compounds with a structure impossible to be determined through

elemental and spectral analysis. We assumed initially one of the compound to be ylide (**3a** respectively **4a**) and the other one the dimeric structure (**3'** and **4'**) formed via a 3+3 dipolar cycloaddition of **3c** and **4c**, respectively. Scheme 4 (however, further study concerning these compounds remains to be done).



Scheme 3



Scheme 4

Because of the unsatisfactory on the elemental and spectral analysis, in order to elucidate the structure of ylides **3** and **4** (but also in order to get new azabicycles compounds) we underwent chemical proves. Thus, we treated ylides **3** and **4**, generated *in situ*, with different dipolarophiles such as DMAD and N-phenylmaleimide (NPM), Schema **5**. If the ylides have a **3a** respectively **4a** structures (having in view that they could accept the canonical structures **3b** and **4b**), they should function as 1,3-dipoles giving 3+2 dipolar cycloaddition reactions. If the ylides have a **3c** respectively **4c** structure, they should function as 1,5-dipoles giving 5+2 dipolar cycloaddition reactions. Experimentally we have found that styryl ylides **3** and **4**, in reaction with DMAD or/and NPM, give 3+2 cycloadditions reactions. This means that the ylidic structures **3a** respectively **4a** are the real one.

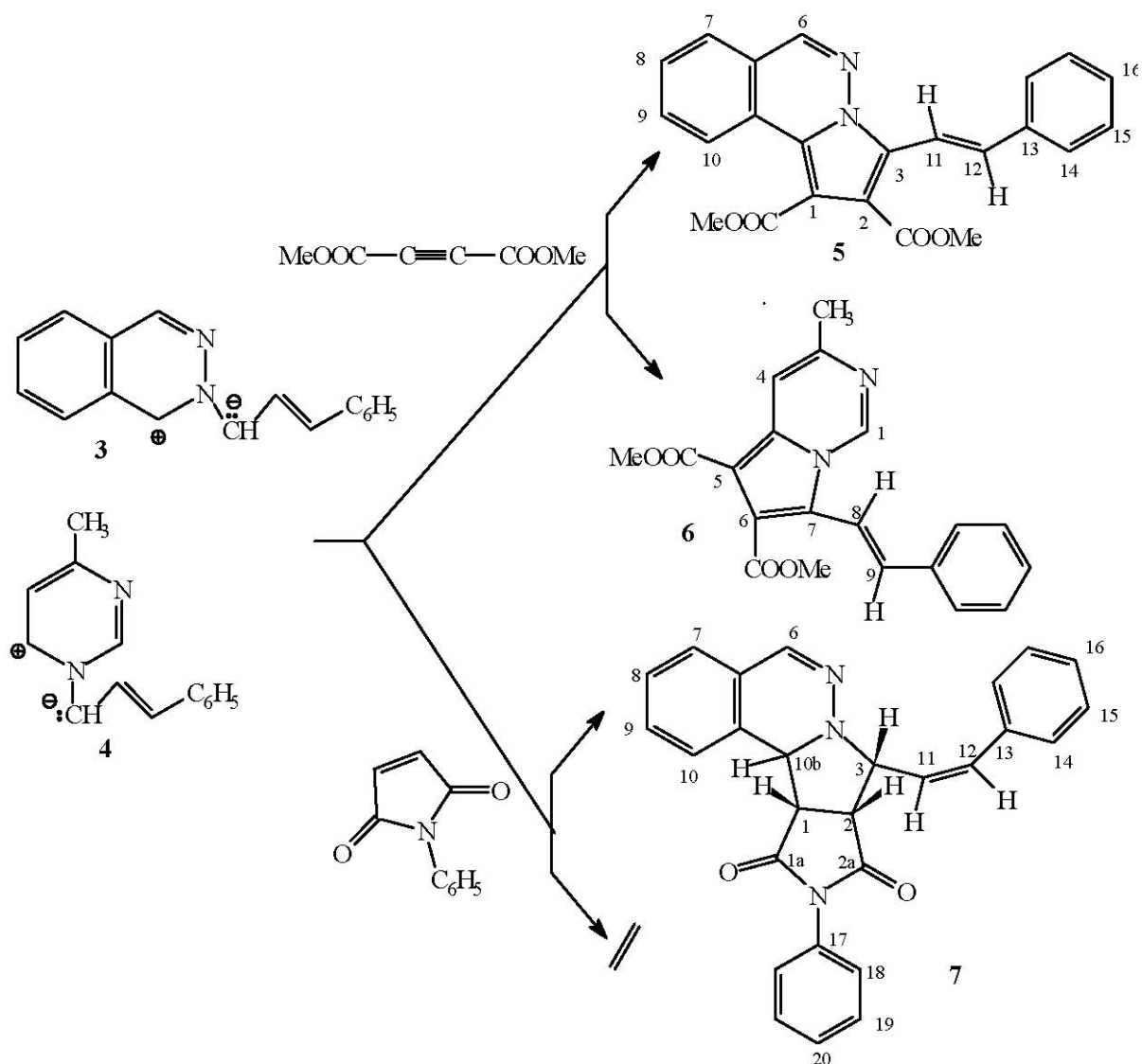
As it can be seen in Scheme **5** in reaction with DMAD we got the 3+2 azabicyclic compounds **5** and **6**. In the case of NPM the reaction took place only with phthalazinium ylide leading to the 3+2 cycloadduct **7** while pyrimidinium ylide did not react (the last one being less reactive⁶).

The structure of the compounds **1,2,5,6,7** has been proven through elemental (N%) and spectral (IR, ¹H-NMR, ¹³C-NMR) analysis.

The salts **1** and **2**: The IR spectra: the most important signals are those of the C=C alkene double bond: $\nu=1630\text{ cm}^{-1}$ (intense) in compound **1** respectively at $\nu=1640\text{ cm}^{-1}$ (intense) in compound **2**. In the ¹H-NMR spectra the most important signals are those of the CH₂ group and ethenyl protons. The CH₂ protons appear at $\delta=5.90\text{-}5.70\text{ ppm}$ (2H, d, J= 5.0 Hz) in **1** respectively at $\delta=5.60\text{-}5.30\text{ ppm}$ (2H, d, J= 5.0 Hz) in **2**. The ethenyl protons appear in compound **1** at $\delta=7.10\text{-}6.70\text{ ppm}$ (1H₁₀, q, J=5.0 Hz, J=10.0 Hz) and $\delta=7.40\text{-}7.10\text{ ppm}$ (H₁₁, d, J=10.0 Hz), respectively in compound **2** at $\delta=6.70\text{-}6.40\text{ ppm}$ (H₈, q, J=5.0 Hz, J=10.0 Hz] and $\delta=7.00\text{-}6.70\text{ ppm}$ (H₉, d, J=10.0 Hz).

Pyrrolo-diazine cycloadducts **5** and **6**: In the IR spectra the signals corresponding to CO ester groups appear at $1750\text{-}1700\text{ cm}^{-1}$. The signals are very strong and broadened with 2 maximum: 1740 cm^{-1} ($\nu_{\text{C=O,Me2}}$) and 1725 cm^{-1} ($\nu_{\text{C=O,Me1}}$) in **5** and respectively at 1735 cm^{-1} ($\nu_{\text{C=O,Me5}}$) and 1720 cm^{-1} ($\nu_{\text{C=O,Me6}}$) in **6**. In the ¹H NMR spectra the most important evidence for pyrrolophthalazine **5** and pyrrolopyrimidine **6** structures are the following : - the rings are aromatized because of the missing signals corresponding to saturated protons; - the ethenyl protons appear at chemical shifts and with coupling constants in accordance with the proposed structures, in *trans*. In compound **5** proton H₁₁ appear at $\delta=4.30\text{-}4.25\text{ ppm}$ (d, J=13.4 Hz) and H₁₂ at $\delta=4.86\text{-}4.82\text{ ppm}$ (d, J=13.4 Hz). In comound **6** proton H₈ appear at $\delta=4.30\text{-}4.10\text{ ppm}$ (d, J=13.0 Hz) and H₉ at $\delta=5.00\text{-}4.80\text{ ppm}$ (d, J=13.0 Hz); - the Me ester groups appear as non equivalent because of the different magnetic vicinity. Thus, in compound **5** the group Me₁ appear at 3.71 ppm (s) and Me₂ at 3.81 ppm (s), while in compound **6** the group Me₅ appear at 3.30 ppm (s) and Me₆ at 3.80 ppm (s). ¹³C NMR spectra of compound **5** confirm also the structure: 175.9 ppm (C_{1a}, ester with conjugation), 174.1 ppm (C_{2a}, ester with conjugation), 52.73 ppm (Me₂ ester), 51.14 ppm (Me₁ ester). These data confirm, as well as the ¹H-NMR, the different magnetic vicinity of the two ester groups. The ethenyl carbons appear at 127.35 ppm (C₁₂)

and 126.26 ppm (C₁₁).



Scheme 5

Cycloadduct 7: In the IR spectra the signals corresponding to CO imide groups appear at 1750-1680 cm^{-1} . The signals are very strong and broadened with 2 maximum: 1735 cm^{-1} and 1715 cm^{-1} . In the $^1\text{H-NMR}$ spectra the most important signals are those of the protons H₁, H₂, H₃, H_{10b}, H₁₁ and H₁₂. The ethenyl protons, H₁₁ and H₁₂, appear with different chemical shifts and coupling constants: H₁₂ at 4.83-4.80 ppm (d, J=7.6 Hz) and H₁₁ at 4.24-4.12 ppm (t, J=7.6 Hz, J=15.2 Hz). These coupling constants prove, on one hand, that the ethenyl protons are in *cis* and, on the other hand, that H₁₁ is in *trans* with H₃ (which appear at 4.41-4.32 ppm, triplet and doublet, J=15.2 Hz, J=7.1 Hz, J=1.8 Hz). Protons H₂ (3.79-3.74 ppm, dd, J=6.5 Hz, J=7.1 Hz), H₁ (3.71-3.65 ppm, triplet and doublet, J=6.5 Hz, J=8.1 Hz, J=1.8 Hz) and H₃ are on the same

side of the pyrrolophthalazine ring. H_{10b} appear at 5.09-5.00 ppm (d, J=8.1 Hz). ¹³C NMR spectra of compound **7** confirm also the structure: 176.84 ppm (C_{2a}, CO imide), 174.76 ppm (C_{1a}, CO imide). The ethenyl carbons appear at 125.53 ppm (C₁₂) and 122.67 ppm (C₁₁).

All the remaining signals from IR and NMR spectra are in accordance with the proposed structure of the compounds **1,2,5,6,7**.

The *in vitro* antimicrobial and antifungal activity of the newly obtained phthalazine and 4-methylpyrimidine compounds was tested having in view that our previous study has proven a certain biological activity in this respect to related compounds.^{7,8,9}

The test was performed using the diffusimetric method¹⁰ with rustlessteel cylinders based on the diffusion of the tested substances on the gelose surface (for bacteria) and *Sabouard* environment (for fungus *Candida albicans*). The cylinders were maintained 24 h at thermostat, at 34 °C for bacteria and at 37 °C for *Candida*. The tested substances were previously dissolved in DMFA 5% (v/v). A witness solvent sample has been done. The inhibition diameter zone, in mm, of development of microbial strain was measured. It is considered active¹¹ a compound for which the difference between the inhibition diameter zone of compound and witness is up to 2 mm (3-4 mm moderate active and up to 5 very active). The results are listed in Table 1.

Table 1. Results of *in vitro* antimicrobial and antifungal activity for some phthalazine and 4-methylpyrimidine derivatives described in the text

Strain→ Product ↓	<i>Staphylococcus aureus</i> <i>Oxford</i>	<i>Escherichia</i> <i>coli</i>	<i>Bacillus</i> <i>subtillis</i>	<i>Bacillus</i> <i>proteus</i>	<i>Candida</i> <i>albicans</i>
Witness	17	18	18	17	18
1	22	23	21	23	17
2	23	21	24	23	20
3	21	17	20	16	21
4	24	22	23	23	24
5	21	20	19	18	15
6	20	20	19	18	16
7	20	15	20	18	15

The comparative analysis of the obtained data (Table 1) leads to the following conclusions concerning the relation between structure and biological activity: - both type of salts, **1** (from phthalazine) and **2**(from pyrimidine), have a remarkable non selective activity against *Gram positive* and *Gram negative* germs; - cycloadducts **5**, **6** and **7** have a moderate activity against germs; - either the salts and cycloadducts are less active or inactive against fungus *Candida*; - we decide to test and the mixture ylides-dimer **3** and **4**. The mixture ylides-dimer **4** from pyrimidine prove to be very, very active having a remarkable non selective activity against germs and also against fungus *Candida*; - if we compare the compounds from the two series, phthalazine and

pyrimidine, we notice that the pyrimidine compounds are more active.

Conclusions

For the first time in the cycloimmonium ylides we have obtained styryl carbanionmonosubstituted ylides. These ylides, phthalazinium- and 4-methylpyrimidinium-ylides, have polyfunctionalized character: ylide and alkene. In this paper we exploited only the ylidic character.

Five new diazine compounds (**1,2,5,6,7**) were synthesized. The structure of these compounds (salts and cycloadducts) has been proven through elemental and spectral analysis. The structure of the ylides **3** and **4** has been proven to be of type **3a** respectively **4a** through chemical ways (however, we classify these compounds as hazardous).

The *in vitro* biological activity of the newly obtained phthalazine and pyrimidine compounds was tested. Some of them proved to have a remarkable activity against different microorganisms (germs and fungus). Correlation of the structure-biological activity has been studied.

Experimental Section

General Procedures. ^1H - and ^{13}C - NMR spectra were run on a Varian Gemini 200 MHz and Bruker 80 MHz spectrometer and were recorded in ppm downfield from an internal standard, SiMe_4 in CDCl_3 . The coupling constants are given in Hz. The IR spectra were recorded with a SPECORD-71 spectrometer in KBr. The melting points are uncorrected.

***N*-Cinnamyl phthalazinium bromide (1).** Phthalazine (10 mmol) was suspended in 30 ml anhydrous benzene and, then, cinnamyl bromide (10 mmol dissolved in 20 ml anhydrous benzene) was added. The solution was stirred at room temperature for 3 h. Recrystallized from acetone-acetonitrile afforded white crystals. Yield 96%, m.p. 179-180 °C. Anal. $\text{C}_{17}\text{H}_{15}\text{BrN}_2$: C: Calcd. 62.38, Found 62.20; H: Calcd. 4.58, Found 4.50; N: Calcd. 8.56, Found 9.00. **IR** (KBr, cm^{-1}): ν : 1630(s), 1600, 1570, 1505, 1470 (s-m), 1290 (s), 2900 (w). **^1H NMR** δ : 10.80 (s, H_1), 10.10 (s, H_4), 8.80-8.35 (m, 4H: H_5 , H_6 , H_7 , H_8), 7.60-7.20 (m, 5H, C_6H_5), 7.40-7.10 (d, H_{11} , $J=10.0$), 7.10-6.60 (q, H_{10} , $J=10.0$, $J=5.0$), 5.90-5.70 (d, H_9 , $J=5.0$).

***N*-Cinnamyl pyrimidinium bromide (2).** 4-Methylpyrimidine (10 mmol) and cinnamyl bromide (10 mmol) was dissolved in 10 ml acetone. The solution was left (stirring intermittently) for 7 days at room temperature, then filtered and washed thoroughly with ethyl ether. Recrystallized from acetone-ethyl ether. Yellow-redish crystals. Yield 89%, m.p. 108-110 °C. Anal. $\text{C}_{14}\text{H}_{15}\text{BrN}_2$: C: Calcd. 57.63, Found 57.60; H: Calcd. 5.15, Found 5.10; N: Calcd. 9.62, Found 9.10. **IR** (KBr, cm^{-1}): ν : 1640(s), 1560, 1505, 1470 (s-m), 1290 (s), 2900 (w), 3100-3000(w). **^1H NMR** δ : 11.80 (s, H_2), 10.10-9.90 (d, H_6 , $J=6.0$), 9.60-9.40 (d, H_5 , $J=6.0$), 7.60-

7.15 (m, 5H, C₆H₅), 7.00-6.70 (d, H₉, J= 10.0), 6.70-6.40 (q, H₈, J= 10.0, J= 5.0), 5.60-5.30 (d, H₇, J= 5.0).

General procedure to obtain diazinium ylides. Salt **1** or **2** (1 mmol) was dissolved in 50 ml water and treated with an aqueous solution of K₂CO₃ 40% when the ylide was obtained. The ylide was filtered to vacuum, washed with a great amount of water and dried to vacuum.

Phthalazinium cinnamyl methylyde (3). *CAUTION: hazardous compound!* According to *General Procedure* using compound **1**. Cream compound. Yield 99%, m.p. 77-80 °C. Anal. C₁₇H₁₄N₂ (for ylide): N: Calcd. 11.02, Found 11.38. **IR** (KBr): v: 1660-1635(s, broaded, with 2 maximum: 1655 and 1645), 1600, 1500, 1465, 1410 (s-m), 1165 (s), 2900 (w).

4-Methylpyrimidinium cinnamyl methylyde (4). *CAUTION: hazardous compound!* According to *General Procedure* using compound **2**. Pink compound. Yield 99%, m.p. 60-65 °C. Anal. C₁₄H₁₄N₂: N: Calcd. 13.46, Found 13.80. **IR** (KBr): v: 1690-1640(s, broaded, with 2 maximum: 1670 and 1650), 1580, 1500, 1470, 1420 (s-m), 1150 (s), 2900 (w), 3100-3000(w).

General procedure to obtain 3+2 cycloadducts. The cycloimmonium salt (10 mmol) and DMAD or NPM (10 mmol) were suspended in 50 ml of benzene. The mixture was heated on a steam bath and triethylamine (10 mmol, dissolved in 30 ml benzene) was then added dropwise in 3 h. The resulting mixture was filtered hot, to eliminate triethylamine bromhydrate. The clear solution was evaporated on a steam bath. The crude products recrystallized from an appropriate solvent for compounds **5** and **7**, and for compound **6** we done and flash chromatography on silica using dichloromethane-methanol 98:2.

1,2-Dicarbomethoxy-3-styryl-pyrrolo[2,1-*b*]phthalazine (5). Recrystallized from methanol. Yellow crystals. Yield 75%, m.p. 122 °C. Anal. C₂₃H₁₈N₂O₄: C: Calcd. 71.50, Found 71.40; H: Calcd. 4.66, Found 4.70; N: Calcd. 7.25, Found 7.00. **IR** (KBr, cm⁻¹): v: 1750-1700(s, brooded, with 2 maximum: 1740 and 1725), 1630(s), 1600, 1570, 1510, 1450 (s-m), 1290 (s), 1230, 1130(s-m), 2900 (w), 3100-3000(w). **¹H NMR** δ : 8.88 (s, H₆), 8.23-8.20 (d, H₇, J= 8.3), 7.96-7.93 (d, H₁₀, J= 8.3), 7.78-7.30 (m, 7H: H₈, H₉, C₆H₅), 4.86-4.82 (d, H₁₂, J= 13.4), 4.30-4.25 (d, H₁₁, J= 13.4), 3.81 (s, 3H: CH₃ from 2 position), 3.71 (s, 3H: CH₃ from position 1). **¹³C NMR** δ : 175.9 (CO, C_{1a}), 174.8 (CO, C_{2a}), 166.27 (C₆), 151.92 (C_{10b}), 141.32 (C_{6a}), 137.62 (C_{10a}), 133.96 (C₁₃), 132.64 (C₉), 131.98 (C₈), 130.01-129.40 (m: C₇, C₁₀, 2C₁₄, 2C₁₅), 128.09 (C₁₆), 127.35 (C₁₂), 126.26 (C₁₁), 123.92 (C₃), 116.16 (C₂), 103.38 (C₁), 52.73 (C, CH₃ from 2 position), 51.14 (C, CH₃ from position 1).

5,6-Dicarbomethoxy-3-methyl-7-styryl-pyrrolo[1,2-*c*]pyrimidine (6). Recrystallized from methanol then flash was doing. Brown-yellow compound. Yield 21%. Anal. C₂₀H₁₈N₂O₄: C: Calcd. 68.57, Found 68.45; H: Calcd. 5.14, Found 5.20; N: Calcd. 8.00, Found 7.60. **IR** (KBr, cm⁻¹): v: 1750-1700(s, brooded, with 2 maximum: 1735 and 1720), 1630(s), 1560, 1505, 1460 (s-m), 1290 (s), 1230, 1130(s-m), 2900 (w), 3100-3000(w). **¹H NMR** δ : 8.05 (s, H₁), 7.60-7.20 (m, 6H: H₄, C₆H₅), 5.00-4.80 (d, H₉, J= 13.0), 4.30-4.10 (d, H₈, J= 13.0), 3.80 (s, 3H: CH₃ from 6

position), 3.60 (s, 3H: CH₃ from 5 position), 2.60 (s, 3H: CH₃ from 3 position).

3-Styryl-10-b-H-pyrrolino[2,1-b]phthalazinium-1,2-dicarboxylic acid N-phenylimide (7).

Recrystallized from methanol. Cream crystals. Yield 79%, m.p. 129-130 °C. Anal. C₂₇H₂₁N₃O₂: C: Calcd. 77.32, Found 77.26; H: Calcd. 5.01, Found 5.10; N: Calcd. 10.02, Found 9.92. **IR** (KBr, cm⁻¹): ν: 1750-1680 (s, brooded, with 2 maximum: 1735 and 1715), 1630(s), 1600, 1500, 1455, 1400 (s-m), 1290 (s), 2900 (w), 3100-3000(w). **¹H NMR** δ : 7.65 (s, H₆), 7.65-7.61 (d, H₇, J= 8.2), 7.55-7.10 (m, 8H: H₈, H₉, H₁₀, C₆H₅), 5.09-5.03 (d, H_{10b}, J= 8.1), 4.83-4.80 (d, H₁₂, J= 7.6), 4.41-4.32 (t and d, H₃, J= 15.2, J= 7.1, J= 1.8), 4.24-4.19 (t, H₁₁, J= 15.2, J= 7.6), 3.79-3.74 (dd, H₂, J= 7.1, J= 6.5), 3.71-3.65 (t and d, H₁, J= 8.1, J= 6.5, J= 1.8). **¹³C NMR** δ : 176.84 (CO, C_{2a}), 174.76 (CO, C_{1a}), 139.94 (C₁₇), 138.99 (C₆), 137.81 (C₉), 136.20 (C_{10a}), 133.51 (C₁₃), 132.45 (C_{6a}), 130.47 (C₇), 129.29-128.52 (m: C₈, C₁₀, 2C₁₉), 128.19-127.41 (m: 2C₁₄, 2C₁₅), 126.64 (C₁₆), 126.27 (C₂₀), 125.53 (C₁₂), 124.86 (2C₁₈), 122.67 (C₁₁), 78.98 (C_{10b}), 72.86 (C₃), 50.62 (C₁), 49.59 (C₂).

Acknowledgements

To CNCSIS Bucuresti for financial support.

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