A NEW METHOD FOR SYNTHESIZING 1H-1-BENZAZEPINE-2,5-DIONE DERIVATIVES FROM N,N-SUBSTITUTED MALEAMIC ACIDS

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Abstract : N,N-Substituted maleamic acids have been found to be converted, via the corresponding acid chlorides, through an intramolecular Friedel-Crafts reaction to 1H-1-benzazepine-2,5-dione derivatives in good overall yields.

Some years ago, considerable interest had been focused on the development of new construction methods for the benzazepine skeletons which are common structural moieties of pharmacologically active alkaloids.[1a,b] Benzazepinone-based structures specifically have been successfully employed by several groups as peptide mimetics and constrains, and in the development of new central nervous system active agents.[2-8] The observation[9] that introduction of a carbonyl group in position 5 of a tetrahydro-benzo[b]azepine-2-one dramatically improved both the dopamine D_3 affinity and selectivity in connection with the substitution effect on the fused benzo- ring within this series appeared to be well tolerated in terms of D_3 affinity and selectivity versus dopamine D_2 receptors. The significant effect from the introduction, of two methoxy-moieties, on the reactivity of the same derivative was very characteristic. On the other hand 3-hydroxy-1H-1-benzazepine-2,5-dione derivatives were also synthesized and evaluated[10] as antagonists at *N*-methyl-D-aspartate receptor glycine sites, among them 1H-1-benzazepine-2,5-dione-8-chloro-3-hydroxy which is of interest as potential drug for the treatment of stroke.[11] It is worth to notice the observation[10] that on a series of 3-hydroxy-1H-1-benzazepine-2,5-diones the substituted at the 8-position possessed the highest potency with the 8-methyl being among the most active. Analogous observations have been also reported[12] for tetrahydro-derivatives of 3-hydroxy-1H-1-benzazepine-2,5-diones for which substitution at C(6), C(7) and C(8), with methyl groups gives 6-18-fold increase in the potency comparatively to non substituted analogous.

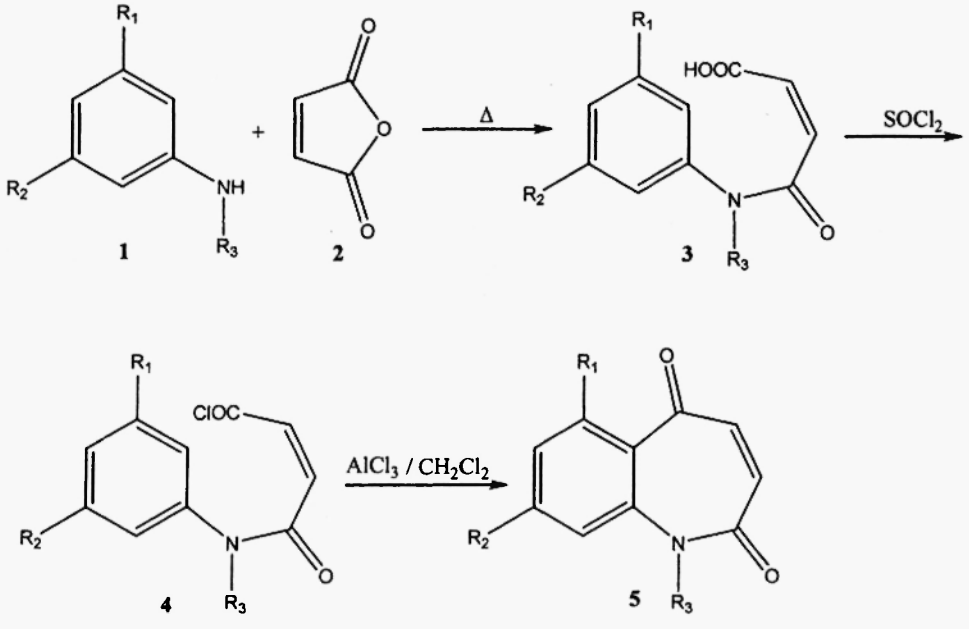
Aromatic and azepine ring-modified analogs of this series were prepared via a Schmidt reaction on substituted naphthalene-1,4-diones, which in turn were prepared via a Diels-Alder reaction of substituted benzoquinones with butadienes, following the long ago known reaction on alkyl-subsituted quinones and naphthoquinones with sodium azide in concentrated sulfuric acid to the formation 2,5-azepinediones.[13,14] These reactions are essentially the application of the Schmidt rearrangement on quinones instead of the more commonly used carbonyl compounds.

Here, we are interested to report a new method for synthesizing 1,8- and 1,6,8-substituted-1H-1-benzazepine-2,5-diones **5** starting from the appropriate secondary amines **1** and maleic anhydride **2**. The resulting maleamic acids **3** after conversion to the corresponding maleamic acid chlorides **4** were transformed to the desired benzazepinediones **5**, via an intramolecular Friedel-Crafts reaction using as catalyst anhydrous aluminium chloride, in yields 57-76 %, Scheme 1. This method we believe that offers a new route to the synthesis of new 1H-1-benzazepine-2,5-dione derivatives via simple reaction conditions using easily prepared and/or commercial starting materials, resulting furthermore to easily separated final products. The (Z)-

configuration of the double bond for the products **3** and **4** was assigned on the basis of their two vinylic protons coupling constant, J=12.80 Hz, given that in the crude products of **3** the observed, low intensity dd, J=16 Hz, that disappeared after recrystallization, must be attributed to the presence of the respective (E)-diastereomers.

Conclusively, we have developed a facile and efficient synthesis of 1H-1-benzazepine-2,5-dione derivatives, by three steps from the starting materials. The intramolecular Friedel-Crafts reaction of maleamic acid chlorides **4**, obtained from the corresponding maleamic acids **3**, which in turn were prepared from the reaction of the appropriate secondary N-arylamines with maleic anhydride, proceeded to produce the target benzazepine-2,5-diones **5**. Currently, efforts to expand the scope of the method in combination with its application to the synthesis of useful prodrugs are ongoing in our laboratory.

Scheme 1



(a) R_1=H, R_2=R_3=Me; (b) R_1=H, R_2=Me, R_3=Ph; (c) R_1=H, R_2=MeO, R_3=Me; (d) R_1=H, R_2=MeO, R_3=Ph; (e) R_1= R_2= R_3=Me; (f) R_1=R_2=Me, R_3=Ph; (g) R_1= R_2=MeO, R_3=Me; (h) R_1= R_2=MeO, R_3=Ph

Experimental

General. NMR spectra were recorded, at ambient temperature using a Varian Gemini 2000 300 MHz spectrometer in $CDCl_3$ or in DMSO-d_6. The data are reported as follows: chemical shift are quoted in ppm on the δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in (Hz). Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer (in KBr pellets).

General procedure for the preparation of maleamic acids **3**. An equimolar mixture, 0.105 mol of each, of the appropriate secondary amine and maleic anhydride was warmed in a round bottom flask, under stirring, in an oil bath at 130-140 ^{0}C for 2-2.5 h. The resulting melt, was solidified after cooling to room temperature, the solid was dissolved in ethyl acetate and washed with a dilute solution of hydrochloric acid and water. The organic layer after the usual work up concentrated under vacuum to give a crude solid which after recrystallization from ethanol gave the analytical pure maleamic acid **3**, in yields 73-87 %.

(Z)-2-Butenoic acid-4[(3-methylphenyl)methylamino]-4-oxo 3a: yield 87 %, mp 117-118 ^{0}C. Anal Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.85; H, 6.11; N, 6.30. IR: 2954, 1714, 1630, 1587. ^{1}H NMR (DMSO-d_6): 2.31 (s, 3H, CH_3Ar), 3.23 (s, 3H, CH_3N), 6.35 (d, J=12.80, 1H, 3-CH=), 6.72 (d, J=12.80, 1H, 2-CH=), 6.95-7.48 (m, 4H, arom.), 14.58 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): 21.43, 37.15, 118.47, 121.30, 124.61, 128.85, 132.11, 133.50, 138.60, 165.10, 166.70.
(Z)-2-Butenoic acid-4[(3-methylphenyl)phenylamino]-4-oxo 3b: yield 73 %, mp 143-144 ^{0}C. Anal Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.44; H, 5.50; N, 5.11. IR: 2939, 1712, 1633, 1595. ^{1}H NMR (DMSO-d_6): 2.33 (s, 3H, CH_3Ar), 6.33 (d, J=12.80, 1H, 3-CH=), 6.70 (d, J=12.80, 1H, 2-CH=), 6.94-7.70 (m, 9H, arom.), 14.23 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): 21.20, 116.10, 118.31, 119.22, 129.33, 132.10, 133.45, 139.20, 140.61, 165.25, 166.90.
(Z)-2-Butenoic acid-4[(3-methoxylphenyl)methylamino]-4-oxo 3c: yield 76 %, mp 120-121 ^{0}C. Anal Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.15; H, 5.64; N, 6.18. IR: 2948, 1715, 1627, 1586. ^{1}H NMR (DMSO-d_6): 3.25 (s, 3H, CH_3N), 3.73 (s, 3H, CH_3O), 6.34 (d, J=12.80, 1H, 3-CH=), 6.94-7.70 (m, 5H: 4H, arom. plus 1H, 2-CH=), 15.10 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): 37.20, 54.85, 104.95, 110.11, 114.00, 118.53, 118.80, 129.51, 130.21, 132.10, 133.55, 148.21, 160.70, 165.36, 167.70.
(Z)-2-Butenoic acid-4[(3-methoxylphenyl)phenylamino]-4-oxo 3d: yield 71 %, mp 147-148 ^{0}C. Anal Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.08; N, 4.71. Found: C, 68.40; H, 5.21; N, 4.93. IR: 2955, 1710, 1630, 1595. ^{1}H NMR (DMSO-d_6): 3.75 (s, 3H, CH_3O), 6.36 (d, J=12.80, 1H, 3-CH=), 6.75 (d, J=12.80, 1H, 2-CH=), 6.90-7.68 (m, 9H, arom.) 13.85 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): 54.93, 102.22, 103.85, 111.43, 118.31, 119.10, 129.70, 130.65, 130.68, 132.40, 133.60, 148.13, 160.80, 165.47, 167.73.
(Z)-2-Butenoic acid-4[(3,5-dimethylphenyl)methylamino]-4-oxo 3e: yield 77 %, mp 133-134 ^{0}C. Anal Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.13; H, 6.34; N, 6.21. IR: 2963, 1713, 1632, 1595. ^{1}H NMR (DMSO-d_6): 2.30 (s, 6H, two CH_3Ar), 3.24 (s, 3H, CH_3N), 6.37 (d, J=12.80, 1H, 3-CH=), 6.74 (d, J=12.80, 1H, 2-CH=), 6.90-7.42 (m, 3H, arom.) 14.20 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): 21.53, 37.20, 118.33, 126.67, 132.10, 133.90, 138.44, 144.43, 164.20, 166.33.
(Z)-2-Butenoic acid-4[(3,5-dimethylphenyl)phenylamino]-4-oxo 3f: yield 73 %, mp 151-153 ^{0}C. Anal Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.45; H, 5.64; N, 4.88. IR: 2950, 1717, 1630, 1590. ^{1}H NMR (DMSO-d_6): 2.32 (s, 6H, two CH_3Ar), 6.34 (d, J=12.80, 1H, 3-CH=), 6.76 (d, J=12.80, 1H, 2-CH=), 6.86-7.60 (m, 8H, arom.) 13.85 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): 21.65, 115.67, 118.32, 119.13, 129.65, 120.42, 132.21, 133.14, 139.23, 140.64, 144.53, 164.33, 166.40.
(Z)-2-Butenoic acid-4[(3,5-dimethoxylphenyl)methylamino]-4-oxo 3g: yield 81 %, mp 146-147 ^{0}C. Anal Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C,

58.70; H, 5.91; N, 5.47. IR: 2955, 1718, 1631, 1588. ^{1}H NMR (DMSO-d_6): 3.28 (s, 3H, CH_3N), 3.75 (s, 6H, two CH_3O), 6.40 (d, J=12.80, 1H, 3-CH=), 6.21-6.97 (m, 4H: 3H, arom. plus 1H, 2-CH=), 15.22 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): 37.71, 54.50, 94.33, 129.33, 132.10, 133.60, 148.10, 161.30, 164.23, 166.10.

(Z)-2-Butenoic acid-4[(3,5-dimethoxylphenyl)phenylamino]-4-oxo 3h: yield 74 %, mp 161-162 ^{0}C. Anal Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.27; H, 4.98; N, 4.40. IR: 2963, 1716, 1635, 1590. ^{1}H NMR (DMSO-d_6): 3.78 (s, 6H, two CH_3O), 6.34 (d, J=12.80, 1H, 3-CH=), 6.73 (d, J=12.80, 1H, 2-CH=), 6.18-7.67 (m, 8H, arom.) 14.81 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): 54.81, 90.47, 94.60, 118.31, 119.20, 129.67, 132.15, 133.73, 140.60, 142.76, 162.31, 164.30, 166.20.

General procedure for the preparation of maleamic acid chlorides **4**. A mixture of maleamic acid **3**, 50 mmol, and freshly distilled thionyl chloride, 30 ml, was stirred at room temperature for 3 h. The resulting solution was concentrated under vacuum to a resinous mass which proved to be an almost pure, ^{1}H NMR, maleamic acid chloride **4**. These chlorides were used for further reaction without additional purification.

(Z)-2-Butenoic acid chloride-4[(3-methylphenyl)methylamino]-4-oxo 4a: ^{1}H NMR ($CDCl_3$): 2.33 (s, 3H, CH_3Ar), 3.28 (s, 3H, CH_3N), 6.63 (d, J=12.80, 1H, 3-CH=), 6.95-7.48 (m, 5H: 4H arom. plus 1H, 2-CH=). **(Z)-2-Butenoic acid chloride-4[(3-methylphenyl)phenylamino]-4-oxo 4b**: ^{1}H NMR ($CDCl_3$): 2.35 (s, 3H, CH_3Ar), 6.67 (d, J=12.80, 1H, 3-CH=), 6.94-7.70 (m, 10H: 9 arom.plus 1H, 2-CH=).

(Z)-2-Butenoic acid chloride-4[(3-methoxylphenyl)methylamino]-4-oxo 4c: ^{1}H NMR ($CDCl_3$): 3.27 (s, 3H, CH_3N), 3.76 (s, 3H, CH_3O), 6.67 (d, J=12.80, 1H, 3-CH=), 6.63-7.31 (m, 5H: 4H, arom. plus 1H, 2-CH=). **(Z)-2-Butenoic acid chloride-4[(3-methoxyphenyl)-phenylamino]-4-oxo 4d**: ^{1}H NMR ($CDCl_3$): 3.77 (s, 3H, CH_3O), 6.64 (d, J=12.80, 1H, 3-CH=), 6.23-7.67 (m, 10H: 9H arom. plus 1H, 2-CH=).

(Z)-2-Butenoic acid chloride-4[(3,5-dimethylphenyl)methylamino]-4-oxo 4e: ^{1}H NMR ($CDCl_3$): 2.31 (s, 6H, two CH_3Ar), 3.27 (s, 3H, CH_3N), 6.65 (d, J=12.80, 1H, 3-CH=), 6.85-7.39 (m, 4H: 3H, arom. plus 1H, 2-CH=). **(Z)-2-Butenoic acid chloride-4[(3,5-dimethylphenyl)phenylamino]-4-oxo 4f**: ^{1}H NMR ($CDCl_3$): 2.33 (s, 6H, two CH_3Ar), 6.63 (d, J=12.80, 1H, 3-CH=), 6.80-7.63 (m, 9H: 8H arom. plus 1H, 2-CH=).

(Z)-2-Butenoic acid chloride-4[(3,5-dimethoxylphenyl)methylamino]-4-oxo 4g: ^{1}H NMR ($CDCl_3$): 3.29 (s, 3H, CH_3N), 3.75 (s, 6H, two CH_3O), 6.69 (d, J=12.80, 1H, 3-CH=), 6.21-7.35 (m, 4H: 3H, arom. plus 1H, 2-CH=). **(Z)-2-Butenoic acid chloride-4[(3,5-dimethoxylphenyl)phenylamino]-4-oxo 4h**: ^{1}H NMR ($CDCl_3$): 3.79 (s, 6H, two CH_3O), 6.63 (d, J=12.80, 1H, 3-CH=), 6.20-7.70 (m, 9H: 8H arom. plus 1H, 2-CH=).

General procedure for the preparation of 1H-1-benzazepine-2,5-diones **5**. To a solution of the crude maleamic acid chloride **4**, 50 mmol, in dichloromethane, 100 ml, maintained at 5-10 ^{0}C, anhydrous aluminium chloride (13.4 g, 100 mmol) was added under stirring so that the temperature did not exceed the above range. Stirring was continued for about 1 h at this temperature and then to room temperature for 3 h. The complex at 0-5 ^{0}C was hydrolysed by addition of cold dilute hydrochloric acid, the organic phase was washed repeatedly with saturated sodium bicarbonate and water, dried over ($MgSO_4$) and the solvent was concentrated under reduced pressure, yielding, (after recrystallization, of the resulting solid, from ethanol), the

benzazepinedione **5** in yields 57-76 %, (the yields are based on the starting maleamic acid).

1H-1-Benzazepine-2,5-dione-1,8-dimethyl 5a: yield 70 %, mp 168-169 ^{0}C. Anal Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.39; H, 5.67; N, 7.14. IR: 1676, 1647. ^{1}H NMR (DMSO-d_6): 2.33 (s, 3H, CH_3Ar), 3.59 (s, 3H, CH_3N), 6.68 (d, J=12, 1H, 3-CH=), 7.07 (d, J=12, 1H, 4-CH=), 7.55-7.75 (m, 3H, arom.). ^{13}C NMR (DMSO-d_6): 21.48, 31.45, 121.80, 125.15, 130.20, 132.31, 134.80, 138.65, 142.20, 144.45, 162.40, 189.45.

1H-1-Benzazepine-2,5-dione-8-methyl-1-phenyl 5b: yield 57 %, mp 191-192 ^{0}C. Anal Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.29; H, 5.11; N, 5.44. IR: 1674, 1640. ^{1}H NMR (DMSO-d_6): 2.31 (s, 3H, CH_3Ar), 6.73 (d, J=12, 1H, 3-CH=), 6.95-7.70 (m, 911: 8 arom. plus 1H, 4-CH=). ^{13}C NMR (DMSO-d_6): 21.53, 118.15, 119.10, 119.20, 119.42, 129.70, 130.65, 132.40, 134.45, 140.51, 142.33, 145.15, 162.23, 189.70.

1H-1-Benzazepine-2,5-dione-1-methyl-8-methoxy 5c: yield 67 %, mp 159-160 ^{0}C. Anal Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.57; H, 5.05; N, 6.60. IR: 1678, 1645. ^{1}H NMR (DMSO-d_6): 3.55 (s, 3H, CH_3N), 3.74 (s, 3H, CH_3O), 6.71 (d, J=12, 1H, 3-CH=), 7.11 (d, J=12, 1H, 4-CH=), 7.35-7.70 (m, 3H, arom.). ^{13}C NMR (DMSO-d_6): 37.23, 54.78, 105.22, 110.44, 127.50, 130.60, 131.11, 134.53, 139.70, 142.20, 162.35, 165.35, 189.67.

1H-1-Benzazepine-2,5-dione-8-methoxy-1-phenyl 5d: yield 59 %, mp 203-205 ^{0}C. Anal Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.01. Found: C, 72.87; H, 4.73; N, 5.24. IR: 1675, 1645. ^{1}H NMR (DMSO-d_6): 3.75 (s, 3H, CH_3O), 6.70-7.70 (m, 10H: 8H, arom. plus 2H, -CH=CH-). ^{13}C NMR (DMSO-d_6): 54.70, 102.67, 104.35, 118.13, 119.11, 125.10, 129.75, 131.70, 134.47, 140.60, 141.54, 141.63, 162.37, 167.25, 189.70.

1H-1-Benzazepine-2,5-dione-1,6,8-trimethyl 5e: yield 76 %, mp 181-183 ^{0}C. Anal Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.80; H, 6.21; N, 6.43. IR: 1678, 1646. ^{1}H NMR (DMSO-d_6): 2.32 (s, 3H, 8-CH_3Ar), 2.34 (s, 3H, 6-CH_3Ar), 3.57 (s, 3H, CH_3N), 6.67 (d, J=12, 1H, 3-CH=), 7.10 (d, J=12, 1H, 4-CH=), 6.80 and 7.45 (two d, J=3, 2H, arom.). ^{13}C NMR (DMSO-d_6): 21.43, 21.57, 31.47, 118.50, 125.33, 127.00, 134.28, 138.50, 139.62, 142.35, 144.30, 162.20, 189.66.

1H-1-Benzazepine-2,5-dione-6,8-dimethyl-1-phenyl 5f: yield 59 %, mp 213-215 ^{0}C. Anal Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.69; H, 5.26; N, 5.27. IR: 1674, 1643. ^{1}H NMR (DMSO-d_6): 2.33 (s, 3H, 8-CH_3Ar), 2.35 (s, 3H, 6-CH_3Ar), 6.65 (d, J=12, 1H, 3-CH=), 6.81-7.68 (m, 8H: 7H, arom. plus 1H, 4-CH=.). ^{13}C NMR (DMSO-d_6): 21.45, 21.60, 116.28, 118.33, 119.10, 120.85, 122.70, 129.67, 134.20, 140.31, 140.47, 140.62, 144.33, 145.11, 162.10, 189.80.

1H-1-Benzazepine-2,5-dione-6,8-dimethoxy-1-methyl 5g: yield 69 %, mp 178-179 ^{0}C. Anal Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.23; H, 5.17; N, 5.87. IR: 1676, 1648. ^{1}H NMR (DMSO-d_6): 3.53 (s, 3H, CH_3N), 3.74 (s, 3H, 8-CH_3O), 3.76 (s, 3H, 6-CH_3O), 6.70 (d, J=12, 1H, 3-CH=), 7.12 (d, J=12, 1H, 4-CH=), 6.51 and 6.92 (two d, J=3, 2H, arom.). ^{13}C NMR (DMSO-d_6): 37.23, 54.67, 54.81, 96.53, 97.48, 118.11, 134.40, 140.71, 141.60, 162.32, 162.54, 167.60, 189.73.

1H-1-Benzazepine-2,5-dione-6,8-dimethoxy-1-phenyl 5h: yield 60 %, mp 214-215 ^{0}C. Anal Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.13; H, 4.63; N, 4.70. IR: 1675, 1645. ^{1}H NMR (DMSO-d_6): 3.73 (s, 3H, 8-CH_3O), 3.75 (s, 3H, 6-CH_3O), 6.49-7.69 (m, 9H: 7H, arom. plus 2H, -CH=CH-). ^{13}C NMR (DMSO-d_6): 54.70, 54.87, 90.41, 95.21, 115.11, 118.23, 118.32, 119.31, 129.70, 132.40, 141.75, 142.60, 162.54, 163.00, 168.47, 189.90.

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