

New Conjugated Systems Derived from Piperazine-2,5-dione

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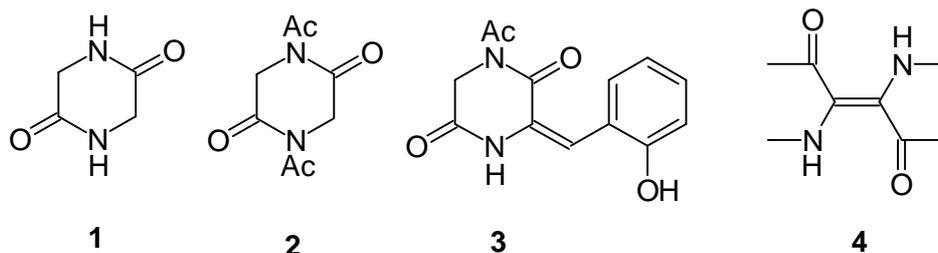
Abstract: The preparation of monoarylidene and both symmetrical and unsymmetrical bisarylidene derivatives of piperazine-2,5-dione is described. The use of 1,4-diacetyl-piperazine-2,5-dione make it possible to prepare unsymmetrical bisarylidenes. The introduction of a dicyanomethylene moiety into the para position of one of the arylidene groups gave a remarkable deepening in the colour of the resulting compounds **11** and **16**.

Keywords: Piperazine-2,5-dione, arylidene, bisarylidene, dicyanomethylene.

Introduction

The chemistry of piperazine-2,5-dione **1** is of great interest since many natural products contain this ring system[1-3]. Derivatives of **1** are useful in peptide synthesis [4], in the synthesis of pyrazines [5,6], and in Diels-Alder reactions as a 4π component [7]. Recent studies showed that 3-salicylidene-piperazine-2,5-dione **3** was supposed to be the most promising precursor for the synthesis of spiro[benzofuran-2(3H)-2'-piperazine]-3',6'-dione as a main skeleton of aspirochlorine [8-9].

The structural similarity of derivative **3** to the chromophore of indigo **4**, led us to assume that if the arylidene(piperazine-2,5-dione) system could be obtained with donor-acceptor substituents, then merostabilization of the excited state [10] should occur to give deeply coloured compounds that might be novel dyestuffs. This paper deals with the synthesis of mono- and bisarylidene derivatives possessing such donor and acceptor substituents.

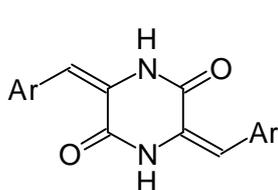


Results and Discussion

Piperazine-2,5-dione **1** was prepared by self condensation of glycine according to the literature [4]. 1,4-Diacetylpiperazine-2,5-dione **2** was prepared by treating compound **1** with acetyl chloride at room temperature [11].

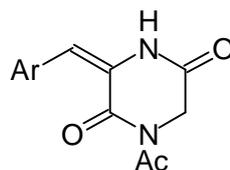
Symmetrical Bis-arylidene Derivatives

Condensation of compound **1** with two equivalents of thiophene-3-carboxaldehyde and indole-3-carboxaldehyde afforded the corresponding bis-arylidenes **5** and **6** respectively. Compound **5** showed an NH absorption at 3266 cm^{-1} , a band at 1683 cm^{-1} for the carbonyl group and 1625 cm^{-1} for C=C (See Table 2).



5 ; Ar = 3-thienyl

6; Ar = 3-indolyl



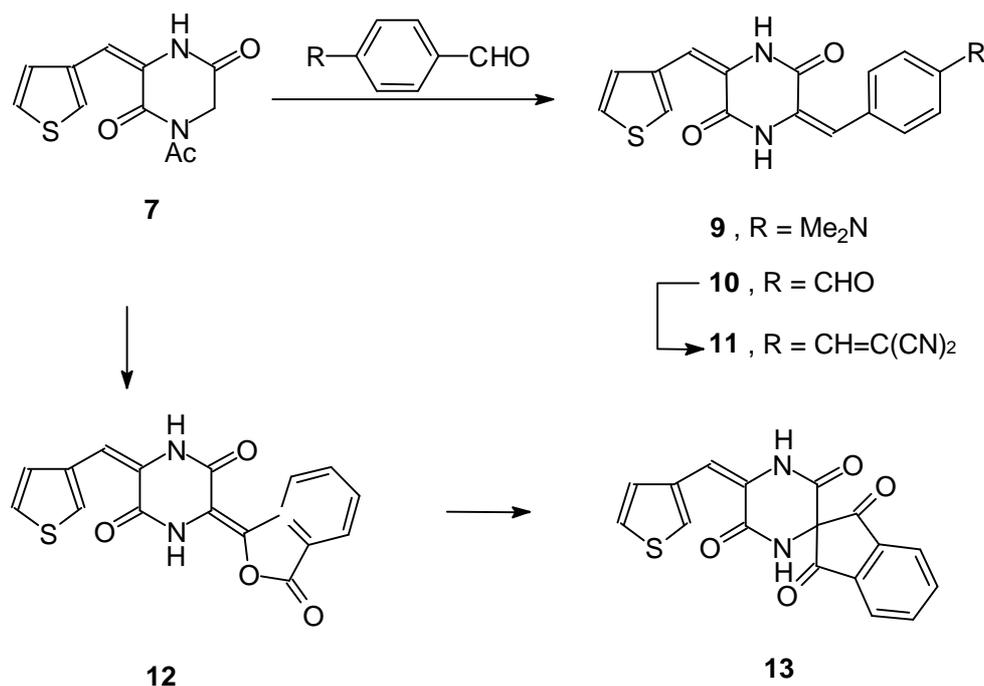
7; Ar = 3-C₄H₃S

8; Ar = 4-Me₂NC₆H₄

Mono Arylidene and Unsymmetrical Bis-arylidene Derivatives

Condensation of piperazine-2,5-dione **1** with aromatic aldehydes always afforded symmetrical bis-arylidene derivatives. However, condensation using 1,4-diacetylpiperazine-2,5-dione **2** with aldehydes could be controlled to occur in a stepwise fashion. Two novel monoarylidenes **7** and **8** were synthesized from the reaction of equal molar quantities of **2** and the appropriate aldehyde.

The ¹H-NMR spectrum of compound **7** showed a singlet at δ 4.5 ppm attributed to the methylene signal, indicative of a monoarylidene derivative. Its IR spectrum showed an NH absorption band at 3255 cm^{-1} and broad bands at 1693 cm^{-1} and 1661 cm^{-1} for the two C=O groups. The unsymmetrical diarylidene derivatives were prepared from the monoarylidene derivatives **7** and **8**, as shown in Scheme 1.



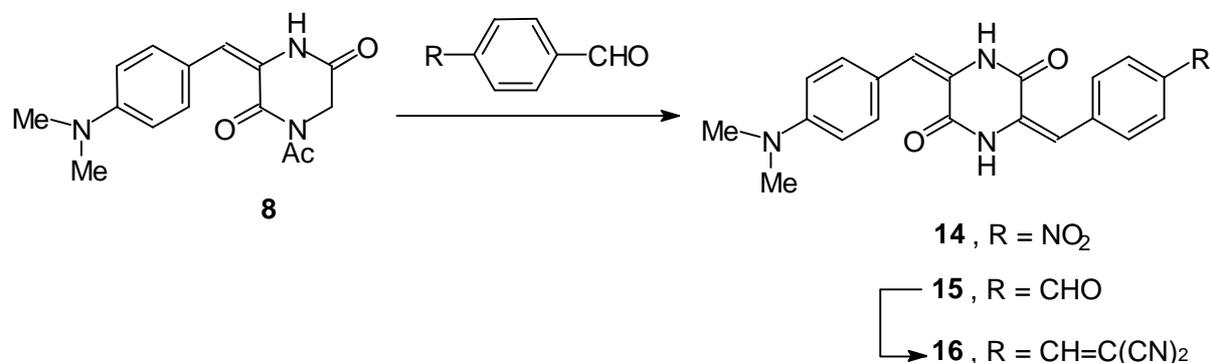
Scheme 1.

Compound **10** was synthesized by condensing one equivalent of compound **7** with an equivalent amount of terephthalic aldehyde in dimethylformamide (DMF) at room temperature. The IR spectrum of compound **10** showed an absorption band at 1705 cm^{-1} for the aldehydic C=O group. Compound **10** readily undergoes a Knoevenagel condensation with malononitrile, using piperidine as a base, to afford the red dicyanomethylene adduct **11** in good yield. The IR spectrum of the latter showed a CN absorption band at 2197 cm^{-1} . The introduction of the powerful electron withdrawing group $\text{CH}=\text{C}(\text{CN})_2$ into the para position of the phenyl group in compound **11** gave a remarkable deepening in colour when compared with the yellow compound **10**.

To get a clear insight into this colour change we synthesized the bisarylidene derivative **13** which contains a donor group on one arylidene ring and an acceptor on the other one. Compound **13** was prepared from the monoarylidene **7** and phthalic anhydride in good yield. The formation of the 1,3-dione derivative **13** is believed to occur via the intermediate **12**. The structure of compound **13** was deduced from its IR spectrum which showed an absorption of the carbonyl groups of the 1,3-diketone moiety at 1670 cm^{-1} , at a higher wavenumber than the 1750 cm^{-1} expected for compound **12**. In the case of compound **13**, despite the fact that it possesses the thienylidene donor moiety, the compound is yellow and no red shift was observed.

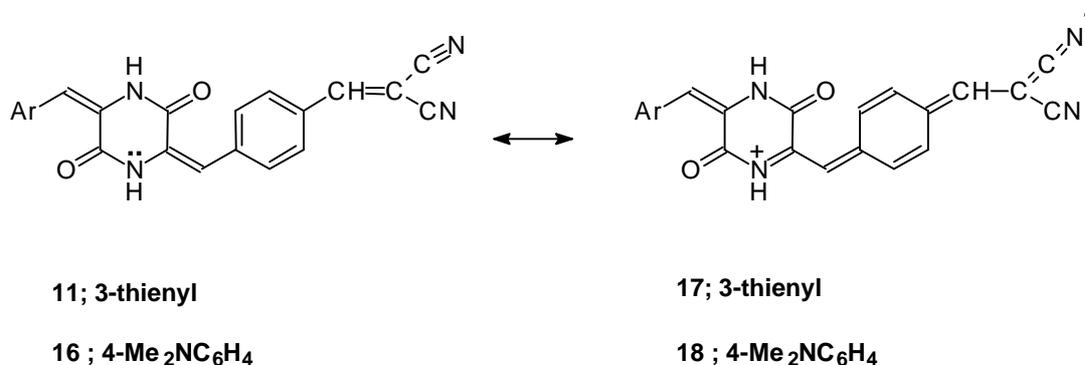
It was of interest to examine the effect of changing the electron donating arylidene moiety from 3-thienylidene to 4-dimethylaminobenzylidene on the colour of compound **11**. Thus, we prepared compounds **14** and **15** by condensing compound **8** with 4-nitrobenzaldehyde and terephthalic aldehyde respectively (Scheme 2). In the event, despite having arylidene substituents with a donor and acceptor

group present, no absorption shift to the red region was observed, the compound **14** was yellow in colour. This suggests that in this system, the amide bond is not an efficient transmitter of the electronic effects and merostabilisation is not observed.



Scheme 2.

Compound **15** undergoes a Knoevenagel condensation with malononitrile, in the same manner used to prepare its analogue **11**, to give compound **16** as dark red crystals. Changing the donor moiety from a thienyl ring to 4-dimethylaminobenzylidene resulted in a noticeable red shift as the compound **16** is dark red in colour. The deepening of the colour observed in the case of compounds **11** and **16** is believed to be due to the stabilization of half of the molecule brought about by the hybrid resonance structures **17** and **18** (Scheme 3).



Scheme 3.

Experimental

General

Melting points were recorded on a Thomas-Hoover capillary melting apparatus and are uncorrected. IR spectra were taken as KBr disks on a Nicolet Magna 520 FT IR spectrometer, ¹H-NMR were recorded as CDCl₃ solutions on a Bruker DPX 400 MHz spectrometer using TMS as the internal stan-

standard. Microanalyses were carried out using a Perkin Elmer 240B Analyzer. The following compounds were prepared by the previously reported literature methods: Piperazine-2,5-dione **1**, m.p. > 300 °C [lit.[4], m.p. > 300 °C]; 1,4-diacetylpiperazine-2,5-dione **2**, m.p. 98-100 °C [lit.[11], m.p. 99-100.5 °C]

3,6-Di(3-thienylidene)piperazine-2,5-dione 5 and 3,6-Di(3-indolylidene)piperazine-2,5-dione 6

A mixture of piperazine-2,5-dione **1** (0.01 mol), the appropriate aldehyde (0.02 mol) and anhydrous sodium acetate (0.04 mol) in acetic anhydride (15 ml) was refluxed for 5 hrs. The mixture was cooled, filtered and the solid washed with small amount of ether (see Tables 1 & 2).

1-Acetyl-3-(3-thienylidene)piperazine-2,5-dione 7 and 1-Acetyl-3-(4-dimethylaminobenzylidene)piperazine-2,5-dione 8

A mixture of 1,4-diacetylpiperazine-2,5-dione **2** (0.01 mole), the appropriate aldehyde (0.01 mole) and triethylamine (0.01 mole) was stirred at room temperature for 12 hrs. The resulting precipitate was filtered off and washed with water. Recrystallization from ethanol gave the pure monosubstituted derivatives **7** and **8** (see Tables 1 & 2).

General procedure for the preparation of unsymmetrical bisarylidenes: 3-(3-Thienylmethylidene)-6-(4-dimethylaminobenzylidene)piperazine-2,5-dione 9, 3-(3-Thienylmethylidene)-6-(4-formylbenzylidene)piperazine-2,5-dione 10, and 3-(3-Thienylmethylidene)-6-(1,3-dioxo-2-indanylidene)piperazine-2,5-dione 13

A solution of 1-acetyl-3-(3-thienylmethylidene)piperazine-2,5-dione **7** (0.01 moles), an aldehyde (0.01 moles) and triethylamine (0.01 moles) in DMF (25 ml) was stirred at 25 °C for 12 hrs. The precipitate was filtered off and washed with water and a small amount of cooled ethanol (10 ml). The pure samples were obtained after recrystallization from dimethylformamide (see Tables 1 & 2).

3-(4-Dimethylaminobenzylidene)-6-(4-nitrobenzylidene)piperazine-2,5-dione 14

This material was prepared from 1-acetyl-3-(4-dimethylaminobenzylidene) piperazine-2,5-dione **8** (1.0 mmole) and 4-nitrobenzaldehyde (1.0 mmole) using the same general procedure mentioned above (Tables 1 & 2).

3-(3-Thienylmethylidene)-6-[4-(1,1-dicyanovinylbenzylidene)]piperazine-2,5-dione 11

Piperidine (0.5 ml) was added dropwise to a warm solution of the aldehyde **10** (0.5 g, 1.5 mmole) and malononitrile (0.1 g, 1.5 mmole) in ethanol (20 ml). A deepening in the colour of the solution was observed. The reaction mixture was refluxed for 3 hrs, then cooled. A dark red solid precipitated,

which was filtered off and washed with cold ethanol and dried (see Tables 1 & 2).

3-(4-Dimethylaminobenzylidene)-6-(4-formylbenzylidene)piperazine-2,5-dione 15

This compound was prepared from of 1-acetyl-3-(4-dimethylaminobenzylidene) piperazine-2,5-dione **8** (0.50g, 1.73 mmole), terephthalic aldehyde (0.23g, 1.73 mmole) and triethylamine (1.0 ml) in DMF (25 ml) using the same procedure employed to prepare compound **10** (Tables 1 & 2).

3-[4-(1,1-Dicyanocinyl)benzylidene]-6-(4-dimethylaminobenzylidene)piperazine-2,5-dione 16

This compound was prepared from the aldehyde **15** (0.25 g, 0.7 mmole), malononitrile (0.05 g, 0.7 mmole) and piperidine (0.5 ml) in DMF (10 ml) using the same procedure described for preparation of compound **11** (see Tables 1 & 2).

Table 1. Physical and analytical data of synthesized compounds.

Comp No.	Yield (%)	M.p. (°C)	Colour of crystals	Molecular formula	Calculated (%)			Found (%)		
					C	H	N	C	H	N
5	73	> 340	Yellow	C ₁₄ H ₁₀ N ₂ O ₂ S ₂	55.63	3.31	9.27	55.35	3.52	9.52
6	85	> 340	Yellow	C ₂₂ H ₁₄ N ₄ O ₂	72.13	3.83	15.3	71.88	3.94	15.5
7	86	> 320	Yellow	C ₁₁ H ₁₀ N ₂ O ₃ S	52.80	4.00	11.2	52.65	3.85	11.1
8	80	> 320	Yellow	C ₁₅ H ₁₇ N ₃ O ₃	62.72	5.92	14.6	62.54	6.11	14.8
9	92	> 320	Yellow	C ₁₈ H ₁₇ N ₃ O ₂ S	63.71	5.01	12.4	63.66	5.33	12.11
10	89	> 300	Yellow	C ₁₇ H ₁₂ N ₂ O ₃ S	62.96	3.70	8.64	62.75	3.86	8.75
11	87	> 340	Dark Red	C ₂₀ H ₁₂ N ₄ O ₂ S	64.52	3.22	15.05	64.32	3.42	15.38
13	92	> 340	Yellow	C ₁₇ H ₁₀ N ₂ O ₄ S	60.36	2.96	8.28	60.22	3.12	8.42
14	94	> 340	Yellow	C ₂₀ H ₁₈ N ₄ O ₄	63.49	4.76	14.82	63.22	4.85	14.95
15	75	> 320	Orange	C ₂₁ H ₁₉ N ₃ O ₃	69.82	5.26	11.63	69.59	5.41	11.75
16	52	>340	Dark Red	C ₂₄ H ₁₉ N ₅ O ₂	70.42	4.64	17.12	70.21	4.71	17.41

Table 2. IR and ¹H-NMR data of synthesized compounds.

Comp No.	δ			ν _{max} /cm ⁻¹			
	NH	Ar-H + -CH=C-	Other	NH	C=O	C=C	Other
5	10.34	6.70-7.90		3266	1683	1625	
6	10.84	7.10-8.40		3220	1702, 1665	1640	
7	11.11	6.82-7.61	4.50 (s, 2H, CH ₂), 2.43 (s, 3H, CH ₃ CO)	3255	1693, 1661	1625	
8	10.34	7.00-7.55	4.42 (s, 2H, CH ₂), 3.01 (s, 6H, (CH ₃) ₂ N), 2.49 (s, 3H, CH ₃ CO)	3320	1693, 1651	1609	
9	10.72	6.88-7.60	3.07 (s, 6H, (CH ₃) ₂ N)	3200	1683	1611	1705 (C=O)
10	11.85	6.95-7.60	9.80 (s, 1H, CHO)	3165	1694, 1682	1612	1705 (C=O)
11	10.72	6.81-7.90	8.3 (s, 1H, CH=C(CN) ₂)	3193	1688	1605	2197 (CN)
13	10.85	6.66-8.20		3205	1670	1603	1695 (C=O)
14	10.89	6.82-8.60	3.1 (s, 6H, (CH ₃) ₂ N)	3225	1698, 1645		
15	8.11	6.70-8.36	9.5 (s, 1H, CHO)	3195	1687, 1652	1611	1698 (C=O)
16	8.24	6.65-8.0	8.14 (s, 1H, CH=C(CN) ₂)	3211	1682, 1650	1625	2197 (CN)

References and Notes

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Samples Availability: Available from the authors.

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