

Note

Novel bridgehead nitrogen bisheterocyclic systems: Synthesis, stereochemistry and antimicrobial activity of *p*-bis[2*H*, 5*H*-4-oxo-thiazol-3-yl]phenylenes and *p*-bis[*cis*-5*H*-3,3a-dihydropyrazolo[3,4-*d*]thiazol-6-yl]phenylenes

Jag Mohan* & Ashok Kumar

Department of Chemistry, Maharshi Dayanand University,
Rohtak 124 001, India

Received 19 June 2003; accepted (revised) 5 April 2004

The facile synthesis of *p*-bis[*cis*-3,3a-dihydro-5*H*-pyrazolo[3,4-*d*]thiazol-6-yl]phenylenes **4** has been achieved by the condensation of *p*-bis[4-substituted phenylimine]phenylenes **1** with thioglycollic acid in toluene, using Dean-Stark water separator, to give *p*-bis[2*H*,5*H*-4-oxo-2-(*p*-substituted phenyl)-thiazol-3-yl]phenylene **2**, which on condensation with arylaldehydes furnishes 5-arylidene derivatives **3** followed by treatment with 2,4-dinitrophenylhydrazine. The antibacterial and antifungal activities of some of the compounds have also been evaluated.

IPC: Int.Cl.⁷ C 07 D // A 61 P 31/04, 31/10

In continuation of our earlier work on the synthesis of novel bridgehead nitrogen heterocyclic systems¹⁻¹⁰ and in view of the reported biological activity of thiazole systems¹¹⁻¹⁵ together with antimicrobial activity exhibited by alkylpyrazoles¹⁶⁻¹⁷, we report herein the synthesis of *p*-bis[*cis*-3,3a-dihydro-5*H*-pyrazolo[3,4-*d*]thiazol-6-yl]phenylene system and the associated bioactivity.

Condensation of *p*-phenylenediamine with arylaldehydes in aqueous ethanol gave *p*-bis[4-substituted phenylimine]phenylene **1**, which on condensation with thioglycollic acid furnished *p*-bis[2*H*, 5*H*-4-oxo-2-(*p*-substituted phenyl)thiazol-3-yl]phenylene **2**. Condensation of **2** with arylaldehydes yielded 5-arylidene derivatives **3** which when treated with 2,4-dinitrophenylhydrazine gave the cyclized product, *p*-bis[*cis*-3,3a-dihydro-5*H*-pyrazolo[3,4-*d*]thiazol-6-yl]phenylenes **4**, in one step (Scheme I). The structures **2** and **3** were supported by their IR spectra. The parent thiazolidinone **2** showed a peak at 1725 cm⁻¹ (>N-C=O) but the exocyclic double bond at 5-position in **3** being in conjugation with the carbonyl

group at 4-position produced a bathochromic shift¹⁸. The structures **4** were supported by their ¹H NMR spectral data (vide Experimental). The appearance of two doublets at δ 7.05 and 7.75 ($J=8.4$ Hz) respectively for the protons at **3a** and **3** positions corroborated the cyclic structure and *cis* configuration¹⁹.

Antimicrobial activity

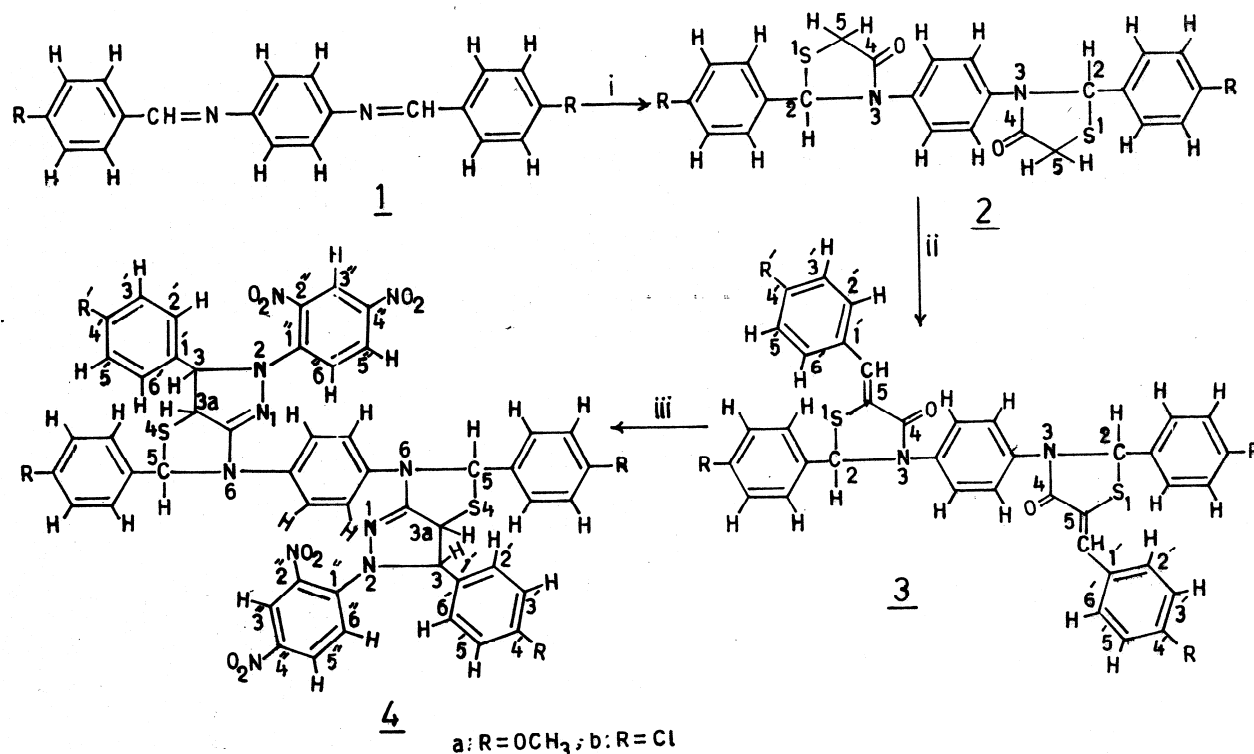
The compounds **4a**₁ (R=OCH₃; R'=Cl) and **4b**₁ (R=Cl; R'=OCH₃) were evaluated for their antimicrobial activity against the gram-positive *Staphylococcus aureus*, the gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* and the fungus *Candida albicans* by neat samples and serial plate dilution method²⁰.

Both the compounds were found to be active against *E. coli*, *S. aureus* and *P. aeruginosa*, when tested as neat samples and may be used for local application in the form of powder or ointment provided further studies indicate the absence of toxicity following local application.

Experimental Section

TLC was run on silica gel G plates using acetone-benzene (1:3) as eluant. Melting points are uncorrected. IR(KBr)($\nu_{\max}$ in cm⁻¹) and ¹H NMR (DMSO-*d*₆) (δ , ppm downfield from TMS) spectra were recorded on a Hitachi-215 and Varian VXR-200 MHz spectrometers, respectively. C,H,N and S analysis were carried out on a Yanaco MT-3 (Japan) analyser.

***p*-Bis[4-methoxyphenylimine]phenylene 1a (R = OCH₃).** A mixture of *p*-phenylenediamine (5.4 g, 0.05 mole) and *p*-anisaldehyde (13.6 g, 0.1 mole) in a mixture of alcohol and water (3:1) was refluxed on a steam-bath for 30 min. The reaction mixture was concentrated and cooled. After standing for a few hours at room temperature, golden yellow shining flakes separated out, filtered, washed with water and recrystallized from toluene as golden yellow shining flakes, m.p. 200°C, yield 15.0 g (87.21%) (Found: C, 76.45; H, 5.98; N, 8.45. Calcd for C₂₂H₂₀N₂O₂: C, 76.74; H, 5.81; N, 8.14%).



(i) HSCH₂COOH; (ii) ArCHO, anhyd. NaOAc, EtOH; (iii) 2,4-Dinitrophenylhydrazine; anhyd. NaOAc, gl. AcOH.

Scheme I

Similarly, **1b** (R=Cl) was obtained from *p*-phenylenediamine and *p*-chlorobenzaldehyde, having m.p. 195°C, yield 15.5 g (88.07%) (Found: C, 68.50; H, 3.80; N, 7.68. Calcd for C₂₀H₁₄N₂Cl₂: C, 68.18; H, 3.98; N, 7.95%).

***p*-Bis[2*H*,5*H*-4-oxo-2-(*p*-methoxyphenyl)thiazol-3-yl]phenylene 2a (R=OCH₃).** A mixture of **1a** (3.44 g, 0.01 mole) and thioglycolic acid (0.92 g, 0.01 mole) in freshly distilled toluene (100 mL) was refluxed on heating mantle using Dean-Stark water separator for 16 hr. Toluene was removed under reduced pressure. The light brown solid, thus separated, was washed well with water, crystallized from ethanol to give colourless crystals, m.p. 148°C, yield 3.5 g (71.44%) (Found: C, 63.70; H, 4.72; N, 5.95; S, 12.74. Calcd for C₂₆H₂₄N₂S₂O₄: C, 63.41; H, 4.88; N, 5.69; S, 13.00%; IR: 810, 830 (1,4-disubstituted benzene rings), 1515 (C-N stretching), 1600, 1620 (C=C and C=N), 1725 (C=O), 3040 (aromatic C-H stretching).

Similarly, **2b** (R=Cl) was obtained having m.p. 205°C, yield 64.00% (Found: C, 57.98; H, 3.42; N, 5.34; S, 13.05. Calcd for C₂₄H₁₈N₂S₂O₂Cl₂: C, 57.60; H, 3.60; N, 5.60; S, 12.80%; IR: 820, 840 (1,4-disubstituted benzene rings), 1520 (C-N stretching),

1610, 1625 (C=C and C=N), 1725 (C=O), 3050 (aromatic C-H stretching).

***p*-Bis[2*H*-2-(*p*-methoxyphenyl)-5-(*p*-chlorobenzylidene)-4-oxo-5*H*-thiazol-3-yl]phenylene 3a₁ (R = OCH₃; R'=Cl).** A mixture of **2a** (2.46 g, 0.005 mole), *p*-chlorobenzaldehyde (1.40 g, 0.01 mole) and anhydrous sodium acetate (0.82 g, 0.01 mole) in absolute ethanol (100 mL) in the presence of a few drops of glacial acetic acid was heated under reflux on heating mantle for 6 hr. The reaction mixture was concentrated, cooled and poured into ice-cold water. The light brown solid, thus separated, was filtered, washed well with water and recrystallized from ethanol to give colourless crystals, m.p. 190°C, yield 2.25 g (61.14%) (Found: C, 65.50; H, 4.25; N, 3.54; S, 8.44. Calcd for C₄₀H₃₀N₂S₂O₄Cl₂: C, 65.22; H, 4.08; N, 3.80; S, 8.69%; IR: 820, 835 (1,4-disubstituted benzene rings), 1525 (C-N stretching), 1610, 1625 (C=C and C=N), 1700 (C=O), 3050 (aromatic protons).

Similarly, the other compounds **3a₂-a₄** and **3b₁-b₄** were prepared and their characterization data are given in Table I.

***p*-Bis[2-(2'',4''-dinitrophenyl)-3-(*p*-chlorophenyl)-5-(*p*-methoxyphenyl)-cis-3a-dihydro-5*H*-pyrazolo-**

Table I—Characterization data of compounds **3**

Compd	R'	Mol. formula	m.p. °C	Yield (%)	Found (Calcd) (%)			
					C	H	N	S
3a₂	-OCH ₃	C ₄₂ H ₃₆ N ₂ S ₂ O ₆	182	54.95	69.55 (69.23)	4.81 4.95	4.12 3.85	8.53 8.79
3a₃	-N(CH ₃) ₂	C ₄₄ H ₄₂ N ₄ S ₂ O ₄	231	58.36	69.75 (70.03)	5.74 5.57	7.16 7.43	8.77 8.49
3a₄	-NO ₂	C ₄₀ H ₃₀ N ₄ S ₂ O ₈	222	54.09	63.61 (63.32)	4.18 3.95	- -	8.15 8.44
3b₁	-Cl	C ₃₈ H ₂₄ N ₂ S ₂ O ₂ Cl ₄	235	64.52	61.00 (61.29)	3.38 3.23	3.51 3.76	8.91 8.60
3b₂	-OCH ₃	C ₄₀ H ₃₀ N ₂ S ₂ O ₄ Cl ₂	230	58.42	65.51 (65.22)	4.25 4.08	3.55 3.80	8.44 8.69
3b₃	-N(CH ₃) ₂	C ₄₂ H ₃₆ N ₄ S ₂ O ₂ Cl ₂	>250	53.81	66.45 (66.14)	4.55 4.72	7.10 7.35	8.65 8.39
3b₄	-NO ₂	C ₃₈ H ₂₄ N ₄ S ₂ O ₆ Cl ₂	248	58.75	59.25 (59.53)	3.29 3.13	- -	8.62 8.36

Table II—Characterization data of compounds **4**

Compd	R	Mol. formula	m.p. °C	Yield (%)	Found (Calcd) (%)		
					C	H	S
4a₂	-OCH ₃	C ₅₄ H ₄₄ N ₁₀ S ₂ O ₁₂	226	56.98	59.85 (59.56)	4.19 4.04	5.60 5.88
4a₃	-N(CH ₃) ₂	C ₅₆ H ₅₀ N ₁₂ S ₂ O ₁₀	241	57.45	60.05 (60.32)	4.62 4.49	5.99 5.74
4a₄	-NO ₂	C ₅₂ H ₃₈ N ₁₂ S ₂ O ₁₄	248	55.46	55.52 (55.81)	3.26 3.40	5.47 5.72
4b₁	-Cl	C ₅₀ H ₃₂ N ₁₀ S ₂ O ₈ Cl ₄	240	54.35	54.64 (54.35)	2.75 2.89	5.52 5.79
4b₂	-OCH ₃	C ₅₂ H ₃₈ N ₁₀ S ₂ O ₁₀ Cl ₂	238	59.31	56.66 (56.93)	3.63 3.47	6.11 5.84
4b₃	-N(CH ₃) ₂	C ₅₄ H ₄₄ N ₁₂ S ₂ O ₈ Cl ₂	>250	57.04	57.99 (57.75)	4.07 3.92	5.42 5.70
4b₄	-NO ₂	C ₅₀ H ₃₂ N ₁₂ S ₂ O ₁₂ Cl ₂	>250	55.95	53.55 (53.28)	2.70 2.84	5.41 5.68

[3,4-*d*]thiazol-6-yl]phenylene 4a₁ (R=OCH₃; R' = Cl). A mixture of **3a₁** (1.84 g, 0.0025 mole), 2,4-dinitrophenylhydrazine (0.99g, 0.005 mole) and anhydrous sodium acetate (0.82 g, 0.01 mole) in glacial acetic acid (50 mL) was heated under reflux on a heating mantle for 5 hr, concentrated, cooled and poured into ice-cold water. The red coloured solid thus separated, was filtered, washed well with water and crystallized from gl. acetic acid to red coloured crystals, m.p. 255°C, yield 1.5 g (54.74%) (Found: C, 57.25; H, 3.32; S, 6.12. C₅₂H₃₈N₁₀S₂O₁₀Cl₂ requires C,

56.93; H, 3.47; S, 5.84%); IR: 700, 820, 835, 870 (1,4-di- and 1,2,4-trisubstituted benzene rings), 1510 (C-N stretching), 1350, 1555 (NO₂ group), 1600, 1620 (C=C and C=N), 3040, 3090 (aromatic C-H stretching); ¹H NMR (DMSO-*d*₆): 3.82 (6H, s, OCH₃ protons), 7.05 (1H, d, *J*=8.4 Hz, C-3a-H), 7.75 (1H, d, *J*=8.4 Hz, C-3-H), 7.47 (2H, s, C-5-H), 7.0-9.0 (26H, m, aromatic protons).

Similarly, the other compounds **4a₂-a₄** and **4b₁-b₄** were prepared and their characterization data are given in **Table II**.

Acknowledgement

The authors are thankful to Dr Jacob Klug of Ben Gurion University of the Negev Israel for IR, ^1H NMR and elemental analysis, to Dr D R Arora, Department of Microbiology, Medical College, Rohtak for biological screening, to CSIR for the award of JRF to Ashok Kumar and to Head of the Chemistry Department, M.D. University, Rohtak for providing laboratory facilities.

References

- 1 Jag Mohan & Kiran, *Indian J Chem*, 30B, **1991**, 75.
- 2 Jag Mohan, Anjaneyulu G S R & Verma P, *Indian J Chem*, 30B, **1991**, 624.
- 3 Jag Mohan, *Organic Preparation and procedures (International Briefs, USA)*, 24, **1992**, 523.
- 4 Jag Mohan & Singh V, *Indian J Chem*, 31B, **1992**, 786.
- 5 Jag Mohan, Singh V & Kumar V, *Indian J Chem*, 32B, **1993**, 953.
- 6 Jag Mohan & Verma P, *Indian J Chem*, 32B, **1993**, 986.
- 7 Jag Mohan & Kataria S, *Indian J Chem*, 33B, **1994**, 196.
- 8 Jag Mohan, Singh V & Malik N, *Indian J Chem*, 34B, **1995**, 1105.
- 9 Jag Mohan, *Indian J Chem*, 37B, **1998**, 953.
- 10 Jag Mohan & Anupama, *Indian J Chem*, 40B, **2001**, 303.
- 11 Jungphaehnel R, Renckhoff G & Thewalt K, *Fr Pat*, 1 585, 632 (**1970**); *Chem Abstr*, 74, **1971**, 41427r.
- 12 Mazzone G, Bonina F, Puglisi G, Arrigo R R, Cosentino C & Blandino G, *Farmaco Ed Sci*, 37, **1982**, 685; *Chem Abstr*, 98, **1983**, 100754r.
- 13 Farge D, Jossin A, Ponsint G & Reisdorf D, *Ger offen*, 2, 802, **1978**, 520; *Chem Abstr*, 89, **1978**, 197532s.
- 14 Miyamatsu H, Ueno S, Shimizu M, Tomari M & Kiyota K, *Japan Kokai*, 74 81, 366 and 81, 367, **1974**; *Chem Abstr*, 82, **1975**, 16823, 24 .
- 15 Kubo K, Itoh N, Sohzu I, Somura Y & Honma H, *Japan Kokai Tokkyo Koho*, 79 05, 997, (**1979**); *Chem Abstr*, 91, **1978**, 57008s.
- 16 Herrman E & Cabliks J, *Cancer Chemotherapy Rept*, 14, **1961**, 85.
- 17 Rich S & Horsfall JG, *Phytopathology*, 42, **1962**, 457.
- 18 Randall H M, Fowler R G, Fusin H & Dangle J R, *Infrared determination of Organic Structures*, (Van Nostrand, New York), **1949**.
- 19 Jag Mohan, *Organic Spectroscopy*, 2nd edn (Narosa Publishing House, New Delhi, India), **2004**, 221.
- 20 Nakahara H, Ishikawa T, Sarai Y, Kondo T & Mitsuhashi S, *Nature*, 266, **1977**, 165.