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Condensed bridgehead nitrogen heterocyclic systems: Synthesis and antimicrobial activity of thiazolo[3′,2′:2,3]-*as*-triazino[5,6-*b*]indoles and isomeric thiazolo[2′,3′:3,4]-*as*-triazino[5,6-*b*]indoles

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2,3-Dihydro-7-methyl-5*H*-*as*-triazino[5,6-*b*]indole-3-thione **4** on condensation with α-haloketones gives 3-aroylmethylthio-7-methyl-5*H*-*as*-triazino[5,6-*b*]indole hydrobromides **5** which on PPA catalysed cyclisation furnishes 3-aryl-8-methylthiazolo[3′,2′:2,3]-*as*-triazino[5,6-*b*]indoles **6** and not the angular isomer, 1-aryl-8-methylthiazolo[2′,3′:3,4]-*as*-triazino[5,6-*b*]indoles **8**. The unequivocal synthesis of **8** has also been accomplished. The antibacterial and antifungal activities of some of the representative compounds have also been evaluated.

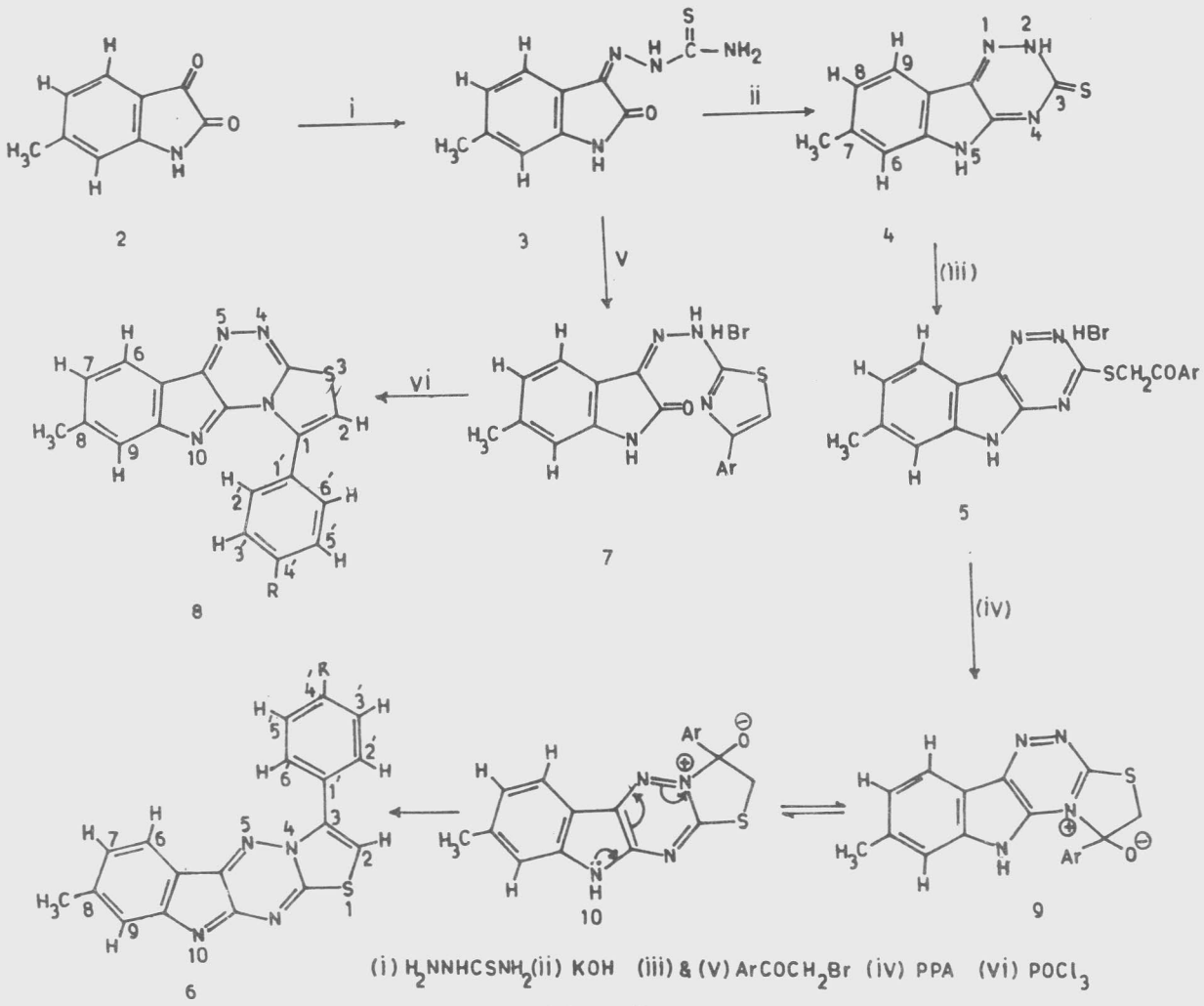
In continuation of our earlier studies[1-9] on the orientation of cyclization in the reaction of unsymmetrical mercaptazoles with bifunctional compounds, we report herein the synthesis of two isomeric condensed bridgehead nitrogen heterocyclic systems derived from unsymmetrical azine (mercapto indole triazine) and the biological activity associated with them.

2, 3-Dihydro-7-methyl-5*H*-*as*-triazino[5, 6-*b*]indole-3-thione **4** was obtained by the condensation of 6-methylisatin **2** with thiosemicarbazide followed by base catalysed cyclization. The reaction of **3** with α-haloketone gave 3-aroylmethylthio-7-methyl-5*H*-2, 3-dihydro-*as*-triazino[5,6-*b*]indole hydrobromide **5**. The ketone **4** being unsymmetrical, on cyclization was expected to yield 3-aryl-8-methylthiazolo[3′,2′:2,3]-*as*-triazino[5, 6-*b*]indole **6** or 3-aryl-8-methylthiazolo-[2′, 3′:3, 4]-*as*-triazino[5,6-*b*]indole **8** or both depending upon the mode of cyclization. The ketone **5**, however, on treatment with PPA underwent cyclization giving only a single product (TLC), which was confirmed by IR and ^{1}H NMR spectral data. The ketones **5a,b** exhibit band at 1680-1690 cm^{-1} (C=O) whereas the absence of this band in the IR spectrum of **6a,b** shows the absence of a carbonyl group, thereby suggesting cyclic structure for **5**. The signal at δ 7.55, (1H, s, C_2-H) in the ^{1}H NMR spectrum of **6a** (R=Cl) corroborated the cyclic structure. However, the spectral data were not of much help in deciding in favour of either the linear product **6** or the angular product **8** (Scheme I).

The mode of cyclization in **5** will be governed by the stability of cyclic transition state **9** or **10**. In structure **5**, nitrogen at N-4, being more nucleophilic than nitrogen at N-2 which is directly attached to N-1, will attack the carbonyl carbon of the ketone giving **9**. There exists a steric repulsion between NH of pyrrole ring and aryl moiety of the ketosulphide chain in **5** and this crowding would render the transition state **9**, comparatively unstable.

Thus intermediate **9**, being energetically more active opens up and closes at N-2 to give energetically less active intermediate **10** in which there would be no such steric crowding. The intermediate **10** finally undergoes prototropic change followed by the loss of a water molecule to give **6** (Scheme I).

The unequivocal synthesis of the angular isomer **8** was achieved by condensation of **3** with α-haloketone followed by cyclization in the presence of $POCl_3$. The amide carbonyl (>N-CO-) absorption between 1680-1710 cm^{-1} in the IR spectrum of **7a,b** was found to be absent in the IR spectrum of **8a,b** suggesting the cyclic srtructure for **8**. Further confirmation for the cyclic structure for this TLC-pure compound forthcame from ^{1}H NMR spectra (vide Experimental).



Scheme I

Antimicrobial activity

The compounds **6a** (R=Cl) and **7a** (R=Cl) were evaluated for their antibacterial activity against the gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* bacteria and the fungus *Candida albicans* by neat samples and serial plate dilution method[10].

Both the compounds showed activity against *S. aureus* and *C. albicans* when treated as neat samples and may be used for local application in the form of powder or ointment provided further studies is indicate the absence of toxicity following local application.

Experimental Section

TLC was run on silica gel G plates using acetonebenzene (1:3) as irrigant. Melting points are uncorrected. IR (KBr) (ν_{max} in cm^{-1}) and ^1H NMR (DMSO-d_6) spectra (δ, ppm downfield from TMS) were recorded on a Hitachi-215 and Varian VXR-200 MHz spectrometers respectively.

***m*-Mehylisonitrosoacetanilide 1**. It was obtained from *m*-toluidine, hydroxylamine and chloral hydrate following the method of Marvel and Hiers[11], yield 50%, m.p. 130°. IR 725, 775, 890 (*m*-disubstituted benzene ring); 930 (N-O stretching); 1555 (C-N stretching); 1500, 1610, 1620 (skeletal vibrations of the aromatic ring); 1660 (–NHCO–); 3150 (N-H stretching) (Found: C, 60.38; H, 5.76. $C_9H_{10}N_2O_2$ requires C, 60.67; H, 5.62%).

6-Methylisatin 2. Compound **1** (4.45 g, 0.025 mole) was added in small lots to H_2SO_4 (67%, 27 mL). The mixture was warmed for 10 min at 50-60°, cooled and poured into ice-water. The solid thus separated was filtered, washed well with

water and crystallised from ethanol as orange crystals, yield 1.61 g (40%), m.p. 180°. IR: 720, 790, 890 (*m*-disubstituted benzene ring); 1500, 1600, 1620 (skeletal vibrations of the aromatic ring); 1730 (–NHCO–), 1750 (C=O); 3060 (aromatic C-H stretching); 3300 (N-H stretching) (Found: C, 66.87; H, 4.44; N, 8.52. $C_9H_7O_2N$ requires C, 67.08; H, 4.35; N, 8.70%).

6-Methylisatin-3-thiosemicarbazone 3. It was prepared by heating for one hour a mixture of 6-methylisatin and thiosemicarbazide in water and glacial acetic acid (instead of aqueous potassium carbonate) following the method of Gladych *et al.*[12], m.p. >250°, yield 70%. IR: 830, 865 (1,2,4-trisubstituted benzene ring); 1120 (C=S); 1610 (C=N); 1690 (C=O); 3180, 3300, 3420 (NH, NH_2) (Found: N, 23.61, S, 13.86. $C_{10}H_{10}ON$ S requires N, 23.93; S, 13.68%).

2, 3-Dihydro-7-methyl-5*H*-*as*-triazino[5, 6-*b*]-indole-3-thione 4. It was obtained from base catalysed cyclization of **3** according to method of Vishnu *et al.*[13], yield 51%, m.p. >250°. IR: 825, 870 (1,2,4-trisubstituted benzene ring), 1140 (C=S), 1600, 1620 (C=N); 3220 (N-H stretching) (Found: C, 55.47; H, 3.58; N, 26.20, S, 14.56. $C_{10}H_8N_4S$ requires C, 55.56; H, 3.70; N, 25.93; S, 14.81%).

3-(*p*-Chlorophenacylthio)- 7-methyl-5*H*-*as*-triazino[5, 6-*b*]indole hydrobromide (5a, Ar=*p*-ClC_6H_4–). A mixture of **4** (2.16 g, 0.01 mole) and *p*-chlorophenacyl bromide (2.34 g, 0.01 mole) in DMF (60 mL) was heated under reflux on a heating mantle for 3 hr, cooled to room temperature and poured into ice-water. The solid, thus separated was filtered, washed with water and crystallised from aq. DMF to give **5a** as orange red crystals, yield, 2.0 g (45%),m.p. >250°. IR: 825, 835, 890 (*p*-disubstituted and 1,2,4-trisubstituted benzene rings); 1585, 1610 (C=N); 1700 (C=O); 3200 (N-H stretching) (Found: N, 12.72; S, 7.38. $C_{18}H_{14}ON_4SClBr$ requires N, 12.47; S, 7.13%).

A similar procedure was adopted to synthesize **5b** (Ar=*p*-BrC_6H_4–), yield 2 g (40%), m.p. >250°. IR: 830, 840, 875 (*p*-disubstituted and 1,2,4-trisubstituted benzene ring); 1600, 1615 (C=N); 1690 (C=O); 3210 (N-H stretching) (Found: N, 11.12; S, 6.34. $C_{18}H_{14}ON_4SBr_2$ requires N, 11.34; S, 6.48%).

3-*p*-Chlorophenyl-8-methylthiazolo[3′,2′:2,3]-*as*-triazino[5,6-*b*]indole (6a, R=Cl). Ketone **5a** (1.0 g) and a mixture of H_3PO_4 (3.0 mL) and P_2O_5 (4.0 g) were heated on an oil-bath at 150° for 3 hr. The reaction mixture was cooled to room temperature, poured into water and neutralised with aq. K_2CO_3 solution. The solid, thus separated was filtered, washed well with water and crystallised from DMF-alcohol mixture (4:1) to furnish **6a** as dark red crystals, yield 0.35 g (45%), m.p. >250°. IR: 1515 (C-N stretching); 1610 (C=N); ^1H NMR (DMSO-d_6); 2.51 (3H, s, C_8-CH_3); 7.55 (1H, s, C_2-H); 7.2-8.0 (7H, m, ArH) (Found: C, 61.49; H, 3.04; N, 16.28; S, 9.18. $C_{18}H_{11}N_4SCl$ requires C, 61.71; H, 3.14; N, 16.0; S, 9.14%).

A similar procedure was adopted to prepare **6b** (R=Br), yield 0.4 g (50%), m.p. >250° (Found: N, 13.87; S, 8.42. $C_{18}H_{11}N_4SBr$ requires N, 14.18; S, 8.10%).

6-Methylisatin- 3 -[(*p*-chlorophenyl)- 2′ -thiazolyl]-hydrazone hydrobromide (7a, Ar=*p*-ClC_6H_4–). A mixture of **3** (2.34 g; 0.01 mole) and *p*-chlorophenacyl bromide (2.34 g, 0.01 mole) in anhydrous ethanol (50 mL) and DMF (50 mL) was heated under reflux on a heating mantle for 3 hr. The reaction mixture was concentrated, cooled to room temperature and poured into ice-water. The solid thus separated was filtered, washed well with water and crystallised from alcohol-DMF mixture (1:1) to furnish **7a** as yellow crystals, yield 1.84 g (41%), m.p. >250°. IR: 810, 835, 860 (*p*-disubstituted and 1,2,4-trisubstituted benzene ring); 1600, 1620 (C=N); 1700 (C=O); 3170, 3420 (N-H stretching) (Found: N, 12.21; S, 6.80. $C_{18}H_{14}ON_4ClBr$ requires N, 12.47; S, 7.13%).

7b: (Ar=*p*-BrC_6H_4–): yield 2.22 g (45%), m.p. >250°. IR: 815, 835, 890 (*p*-disubstituted and 1,2,4-trisubstituted benzene ring); 1600, 1620 (C=N); 1690 (C=O); 3180 (N-H stretching) (Found: N, 11.64; S, 6.27. $C_{18}H_{14}N_4OSBr_2$ requires N, 11.34; S, 6.48%).

1-(*p*-Chlorophenyl)-8-methylthiazolo[2′, 3′: 3, 4]-*as*-triazino[5, 6-*b*]indole (8a, R=Cl). Compound **7a** (1.0 g) in $POCl_3$ (10 mL) was heated in an oil-bath at 125° for 3 hr. The reaction mixture was cooled to room temperature and poured into cold water and neutralised with potassium carbonate solution. The solid, thus separated was filtered, washed well with water and crystallised from DMF to furnish **8a** as orange red crystals, yield 0.35 g (45%), m.p. >250°. IR: 1520 (C-N stretching); 1600 and 1620 (C=C & C=N); ^1H

NMR (DMSO-d_6): 2.51 (3H, s, C_8-CH_3); 6.79 (2H, d, J=7.6 Hz, H-3′ and H-5′); 6.90 (2H, d, J=7.6 Hz, H-2′ and H-6′); 7.66 (1H, s, C_2-H); 7.2-8.0 (3H, m, aromatic protons of indole moiety) (Found: C, 61.54, H, 3.06; N, 16.32: S, 8.84. $C_{18}H_{11}N_4SCl$ requires C, 61.71; H, 3.14; N, 16.0; S, 9.14%).

8b: (R=Br): yield 0.4 g (50%), m.p. >250° (Found: C, 55.15; H, 2.67; N, 13.96; S, 8.30. $C_{18}H_{11}N_4SBr$ requires C, 54.68; H, 2.78; N, 14.18; S, 8.10%).

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