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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-6-ethyl-5*H*-*as*-triazino[5, 6-*b*]indole-3-thione **4** on condensation with α-haloketone gives 3-aroylmethylthio-6-ethyl-5*H*-*as*-triazino[5, 6-*b*]indolehydrobromide **5** which on PPA catalyzed cyclization furnishes 3-aryl-9-ethylthiazolo[3', 2': 2, 3]-*as*-triazino[5, 6-*b*]indole **6** and not the isomer, 1-aryl-9-ethylthiazolo[2', 3': 3, 4]-*as*-triazino[5, 6-*b*]indole **8**. The unequivocal synthesis of **8** has also been accomplished. The antibacterial and antifungal activity of the compound **6** has 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 (mercaptoindole triazine) and the biological activity associated with them.

2, 3-Dihydro-6-ethyl-5*H*-*as*-triazino[5, 6-*b*]indole-3-thione **4** was obtained by condensation of 7-ethylisatin **1** with thiosemicarbazide followed by acid catalyzed cyclization. The reaction of **3** with α-haloketone gave 3-aroylmethylthio-6-ethyl-5*H*-*as*-triazino[5, 6-*b*]indolehydrobromide **5**. The ketone **4** being unsymmetrical, on cyclization, was expected to yield 3-aryl-9-ethylthiazolo[3',2':2,3]-*as*-triazino[5,6-*b*]indole **6** or 1-aryl-9-ethyl thiazolo[2',3':3,4]-*as*-triazino[5, 6-*b*]indole **8** or both depending upon the mode of cyclization (**Scheme I**). The ketone **5**, however, on treatment with PPA underwent cyclization giving only a single product (TLC), which was confirmed by IR and PMR spectral data. The ketone **5** exhibits IR band at 1685 cm^{-1} (C=O) whereas absence of this band in the IR spectrum of **6** shows the absence a carbonyl group, thereby suggesting cyclic structure for **6**. The signal at δ7.65 (1H, s, C_2-H) in the PMR spectrum of **6** corroborated the cyclic structure. However the spectral data were not of much help in favour of either **6** or **8**.

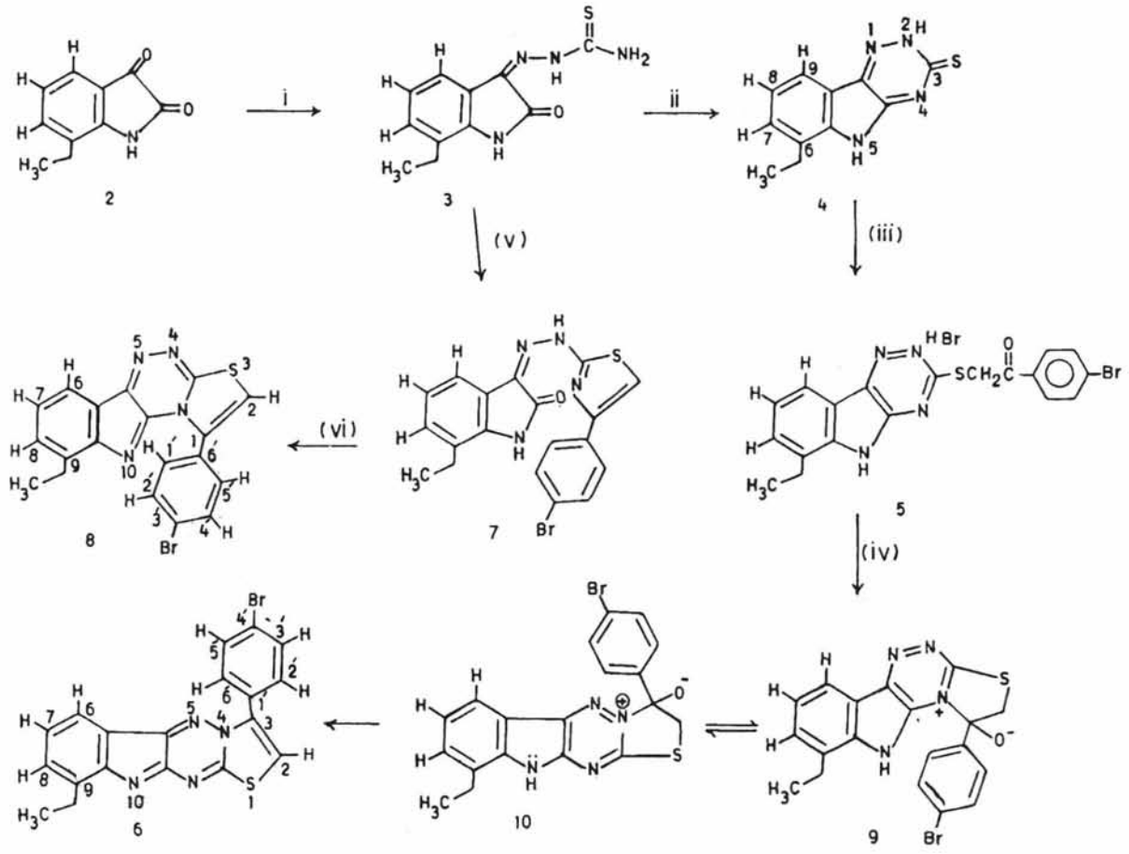
The mode of cyclization in **5** will be governed by the stability of transition state (**9** or **10**). In structure **5**, nitrogen at N-4, being more nucleophillic than nitrogen at N-2 which is directly attached to N-1, will attack the carbonyl carbon of the ketone giving **9**. There exists a steric 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 more favourable intermediate **10** in which there would be no such steric crowding. The intermediate **10** finally undergoes prototropic change followed by loss of a water molecule to give **6**.

The unequivocal synthesis of the angular isomer **8** was achieved by condensation of **3** with α-haloketone followed by cyclization in presence of $POCl_3$. The amide carbonyl (>N-C=O) absorption at 1700 cm^{-1} in **7** was found absent in the IR spectrum of **8**. Further confirmation for the cyclic structure of this TLC-pure compound forthcame from PMR spectra(vide Experimental).

Antimicrobial activity

The compounds **6** and **8** 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 provided further studies indicate absence of toxicity following local application.



(i) $H_2NNHCSNH_2$ (ii) KOH (iii) & (v) *p*-BrC_6H_4-$COCH_2Br$ (iv) PPA (vi) $POCl_3$

Scheme I

Experimental Section

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

o-Ethyl isonitrosoacetanilide 1. It was obtained from *o*-ethylaniline, hydroxylamine and chloral hydrate following the method of Marvel and Heirs[11], yield 39%, m.p. 156^{0}C. IR: 725, 775, 890 (m-disubstituted benzene ring), 930(N-O stretching), 1550(C-N stretching), 1600, 1610, 1620 (skeletal vibrations of the aromatic ring), 1660(-NHCO-), 3150(N-H stretching) (Found: C, 62.63; H, 6.30; N, 14.80. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25;N, 14.58%).**7-Ethylisatin 2. 1**(7.29 g, 0.03 mole) was added in small lots to H_2SO_4 (90%, 15 mL).The mixture was warmed for 30 min. at 90^0 C, cooled and poured into ice cold water. The solid thus separated was filtered, washed well with water and crystallised from ethanol as bright red crystals, yield 5.0 g (78%), m.p.>200^{0}C; IR: 775 (1, 2, 3-trisubstituted benzene ring), 1500, 1600, 1620 (skeletal vibrations of the aromatic ring), 1730 (-NHCO-), 1750 (C=O), 3060 (aromatic C-H stretching), 3300cm^{-1} (N-H stretching)(Found: C, 68.68; H, 5.20; N, 8.13%. Calcd. for $C_{10}H_9NO_2$: C, 68.57; H, 5.14; N, 8.00%).

7-Ethylisatin-3-thiosemicarbazone 3. This compound was prepared by heating for 1hr., a mixture of 7-ethylisatin and thiosemicarbazide in water and glacial acetic acid (instead of aqueous potassium carbonate) following the method of Gladych *et al*[12], yield 1.6 g(46%), m.p.> 250^0 C; IR: 770 (1, 2, 3-trisubstituted benzene ring), 1130 (C=S), 1620 (C=N), 1685 (C=O); 3200, 3320, 3400 cm^{-1} (NH, NH_2) (Found: C, 53.59; H, 4.99; N, 22.76; S, 13.09. Calcd for $C_{11}H_{12}N_4OS$: C, 53.22; H, 4.83; N, 22.58; S, 12.90%).

2, 3-Dihydro-6-ethyl-5*H*-*as*-triazino[5, 6-*b*]indole-3-thione 4. It was obtained from base catalyzed cycli-

zation of 7-ethylisatin-3-thiosemicarbazone **3** according to method of Vishnu *et al*[13], yield 1.2 g (83%), m.p.>200^0 C; IR: 780 (1, 2, 3-trisubstituted benzene ring) 1140 (C=S), 1570 (C-N), 1625 (C=N) and 3320 cm^{-1}(N-H) (Found: C, 57.49; H, 4.53; N, 24.52; S, 14.02. Calcd. for $C_{11}H_{10}N_4S$: C, 57.39; H, 4.34; N, 24.34; S, 13.91%).

3-(*p*-Bromophenacylthio)-6-ethyl-5*H*-*as*-triazino-[5, 6-*b*]indole hydrobromide 5. A mixture of **4** (1.14g, 0.0049 mole) and *p*-bromophenacylbromide (1.36 g, 0.0049 mole) in DMF (30 mL) was heated under reflux on a heating mantle for 3 hr., cooled to room temperature and poured into ice cold water. The solid, thus separated was filtered, washed with water and crystallized from aq. DMF to give 5 as orange coloured crystals, yield 1.1 g (44%), m.p. 225^0(d); IR: 780(1, 2, 3-trisubstituted benzene ring), 830(1, 4-disubstituted benzene ring), 1550(C-N); 1630 (C=N); 1685(C=O) and 3340(N-H) (Found: C, 44.86; H, 3.33; N, 11.22; S, 6.38. Calcd. for $C_{19}H_{16}N_4OSBr_2$: C, 44.94; H, 3.14; N, 11.22; S, 6.29%).

3-*p*-Bromophenyl-9-ethylthiazolo[3', 2': 2, 3]-*as*-triazino[5, 6-*b*]indole 6. Ketone **5** (1.0 g) in a mixture of H_3PO_4 (3.0 mL) and P_2O_5 (4.0 g) was heated in an oil bath at 150^0 for 3 hr. The reaction mixture was cooled to room temperature, poured into water and neutralized with aq. K_2CO_3 solution. The solid, thus separated was filtered, washed well with water and crystallized from DMF to furnish **6** as dark red crystals, yield 0.5 g (63%), m.p.169^{0}C; IR: 775(1, 2, 3-trisubstituted benzene ring) 830 (1, 4-disubstituted benzene ring), 1520 (C-N), 1625cm^{-1}(C=N); PMR($CDCl_3$): 1.40(3H, *t*, CH_3 protons); 3.18 (2H, *q*, CH_2 protons); 7.65 (1H, *s*, C_2-H); 7.20-8.10 (7H, *m*, aromatic protons)(Found: C, 55.85; H, 3.28; N, 13.78; S, 7.77. Calcd. for $C_{19}H_{13}N_4SBr$: C, 55.74; H, 3.17; N, 13.69; S, 7.82%).

7-Ethylisatin-3-[(*p*-bromophenyl)-2'-thiazolyl]-hydrazonehydrobromide 7. A mixture of **3** (1.00 g, 0.004 mole) and *p*-bromophenacyl bromide(1.11 g, 0.004 mole) in dry methanol (12.5 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 crystallized from ethanol to furnish **7** as yellow crystals, yield 1.1 g (54%), m.p.>200^0 C; IR: 770(1, 2, 3-trisubstituted benzene ring), 1540(C-N), 1600 & 1620 (C=C & C=N), 1700 (C=O), 3030 (C-H), 3200cm^{-1}(N-H) (Found: C, 45.00; H, 3.28; N, 11.21; S, 6.38. Calcd. for $C_{19}H_{16}N_4OSBr_2$: C, 44.94; H, 3.14; N, 11.02; S, 6.29%).

1-(*p*-Bromophenyl)-9-ethylthiazolo[3',2' : 2,3]-*as*-triazino[5,6-*b*]indole 8. Compound **7** (1.0 g) in $POCl_3$(10 mL) was heated in an oil bath at 125^0 C for 3 hr. The reaction mixture was cooled to room temperature, poured into water and neutralized with aq. K_2CO_3 solution. The solid, thus separated was filtered, washed well with water and crystallized from DMF to furnish **8** as red crystals, yield 1.0 g(81%), m.p.>250^{0}C; IR: 780(1, 2, 3-trisubstituted benzene ring), 840 (1, 4-disubstituted benzene ring), 1535(C-N), 1625 (C-N); PMR (DMSO-d_6): 1.38(3H, t, CH_3 protons), 3.10 (2H, q, CH_2 protons), 7.60 (1H, s, C2-H) 7.0-8.40 (7H, m, aromatic protons)(Found: C, 57.82; H, 3.29; N, 13.79; S, 7.99. Calcd for $C_{19}H_{13}N_4SBr$: C, 55.74; H, 3.17; N, 13.69; S, 7.82%).

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