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Condensed heterocyclic systems containing bridgehead nitrogen atom: Synthesis and antimicrobial activity of *s*-triazolo[3, 4-*b*][1, 3, 4] thiadiazines, thiazolo[3, 2-*b*]-*s*-triazoles and isomeric thiazolo[2, 3-*c*]-*s*-triazoles

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The synthesis of 2-*p*-fluorophenyl-5-*p*-bromophenylthiazolo[3, 2-*b*]-*s*-triazole **5** has been achieved starting from 3-*p*-fluorophenyl-5-mercapto-*s*-triazole **3**. Compound **3** on condensation with *p*-bromophenacyl bromide gave the ketone **4** which on cyclization with PPA affords thiazolo[3, 2-*b*]-*s*-triazole **5** and not the isomeric thiazolo[2, 3-*c*]-*s*-triazole **7**. This has been established by an unequivocal synthesis of **7** through $POCl_3$ cyclization of 2-*p*-fluorobenzoylhydrazino-4-*p*-bromophenyl thiazole hydrobromide **6**. However the condensation of 4-amino-5-mercapto-3-*p*-fluorophenyl-*s*-triazole **8** with *p*-chlorophenacyl bromide furnishes 7H-6-*p*-chlorophenyl-3-*p*-fluorophenyl-*s*-triazolo[3, 4, -*b*][1, 3, 4] thiadiazine **9** in one step only. The diuretic, antibacterial and antifungal activities of these compounds have also been evaluated.

Yale and Piala[1] have reported that s-triazole systems, i.e. 5-(*p*-aminophenyl)-*s*-triazolo-3-thiol, exhibit diuretic and natri-uretic activity in rats when administered intraperitoneally. Also the compounds containing a thiadiazine nucleus (i.e. chlorothiazide and hydrochlorothiazide) are used as diuretics.

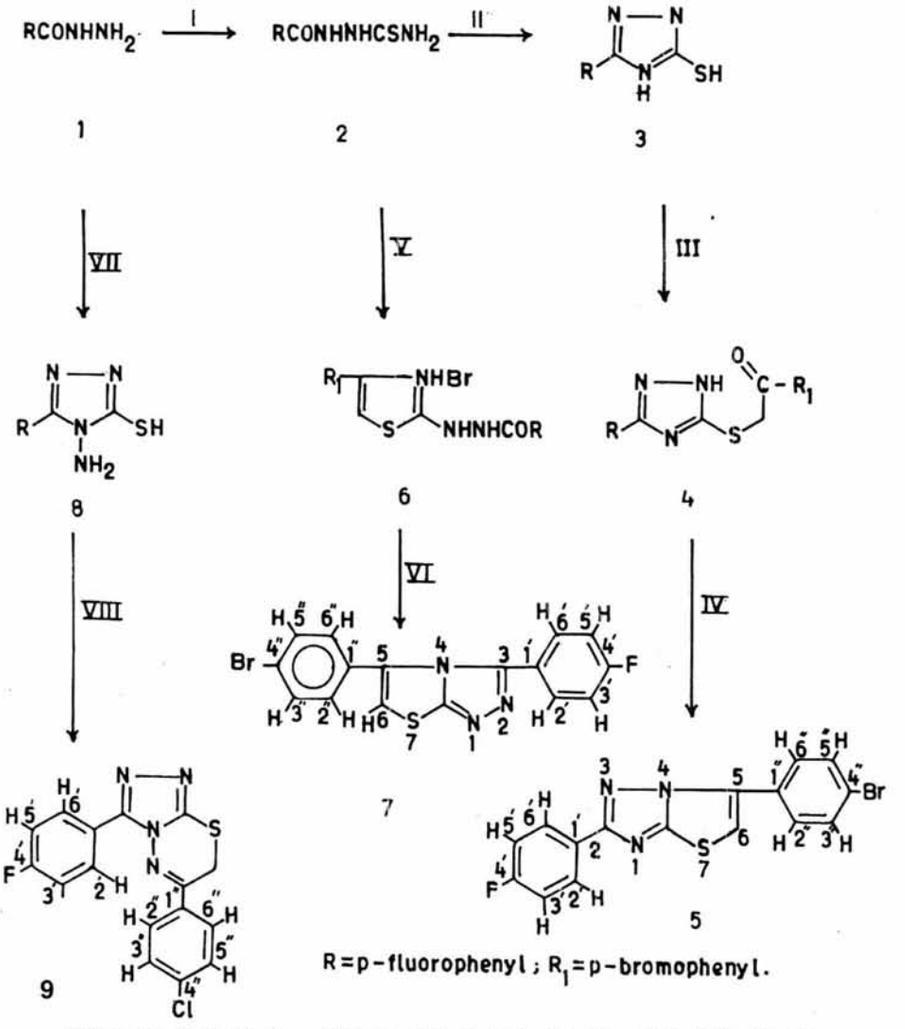
In continuation of our earlier work on the synthesis of biologically active bridgehead nitrogen heterocyclic systems[2-7], the author reports in this paper the synthesis of 5-*p*-bromophenyl-2-*p*-fluorophenyl thiazolo[3, 2-*b*]-*s*-triazole **5**, 5-*p*-bromophenyl-3-*p*-fluorophenylthiazolo[2, 3-*c*]-*s*-triazole **7** and 7*H*-6-*p*-chlorophenyl-3-*p*-fluorophenyl-*s*-triazolo[3, 4-*b*][1, 3, 4] thiadiazine **9** and the biological activity associated with them.

A one step synthesis of 5-substituted thiazolo[3,2-*b*]-2-*p*-tolyl-*s*-triazoles has been reported by the author[8] earlier. In the present paper, a two step synthesis of 5-thiazolo [3, 2-*b*]-2-*p*-fluorophenyl-*s*-triazole is described.

3-*p*-Fluorophenyl-5-mercapto-*s*-trioazole **3** when heated with *p*-bromophenacyl bromide in anhydrous ethanol under reflux for **4** hr. gave uncyclized ketone **4** which underwent PPA cyclization giving thiazolo [3, 2-*b*]-*s*-triazole **5** and not thiazolo [2, 3-*c*]-*s*-triazole **7.** The ketone **4** being unsymmetrical, on PPA cyclization is expected to give thiazolo[3, 2-*b*]-*s*-triazole **5** or thiazolo [2, 3-*c*]-*s*-triazole **7** or both, depending on the mode of cyclization. The ketone **4**, however, on cyclization gave only one product (TLC). The NMR spectral data of the cyclized product was not of much help in deciding its structure **5** or **7**. Hence **7** was synthesized by an unequivocal method. Condensation of *p*-fluorobenzoylthiosemicarbazide **2** with *p*-bromophenacyl bromide yielded 2-*p*-fluorophenylhydrazino-4-*p*-bromophenylthiazolo hydrobromide **6** which on cyclization with $POCl_3$ provided 3-*p*-fluorophenyl-5-*p*-bromophenylthiazolo [2, 3-*c*]-*s*-triazole **7**. The compound **7** was not identical with the cyclized product obtained by the condensation of **3** with *p*-bromophenacyl bromide followed by cyclization of ketone **4** with PPA. This suggests that the cyclized product obtained from **4** should have the structure 5. The structures **4-7** have been supported by IR and PMR spectral data. **4** and **6** exhibit a band in the region 1690-1710 cm^{-1} (C=O), whereas absence of this band in the IR spectra of **5** and **7** shows the absence of a carbonyl group, thereby suggesting their cyclic structures. The signals at δ 6.92 (1H, s, C-6-H) and at 7.18 (1H, s, C-6-H) in PMR spectra of **5** and **7** respectively corroborated the cyclic structures of these compounds. However, the reaction of 4-amino-3-*p*-fluorophenyl-5-mercapto-*s*-triazole **8** with *p*-chlorophenacyl bromide afforded 7*H*-6-*p*-chlorophenyl-3-*p*-fluorophenyl-*s*-triazolo [3, 4-*b*][1, 3, 4] thiadiazine **9** in one step. The absence of a band in the region 1690-1710 cm^{-1} in its IR spectrum and the presence of a signal at δ 4.0 ppm (2H, s, $S-CH_2$) in its PMR spectrum corroborated the cyclic structure for the compound **9 (Scheme I)**.

Antimicrobial activity

The compounds **5**, **7** and **9** were evaluated for their antimicrobial activity against gram-positive *Staphylo-*



i. KSCN;HCl; ii. KOH; iii, v, viii, R_1COCH_2Br; iv PPA; vi $POCl_3$; vii CS_2, KOH–NH_2NH_2.

Scheme I

*coccus aureus*_gram-negative *Escherichia coil* and *Pseudomonas aeruginosa* and the fungus *Candida albicans* by neat sample and serial plate dilution method[9]. The MIC of compound **9** against *Pseudomonas aeruginosa* and *Staphylococcus aureus* was found to be 500μg/mL and against *Candida albicans* was 800μg/mL. The compounds **5** and **7** showed activity against *C. albicans*, when tested as neat samples.

Diuretic testing in rats

Burn's method[10], as recorded by Heller[11], was used. Albine rats of both sexes, weighing between 150-200 g. were used. The animals were fasted overnight but allowed water ad. lib. for determining the diuretic activity. Groups of eight rats were used. Test compounds were administrated in volumes of 10% alcohol lead which amounted to 5% of the body weight of rats. The control groups was given the solvent only. Four rats were placed together in the metabolic cages, resting on a glass funnel. Cross over tests were performed after 48 hr. Urine volumes were measured after every 30 minutes for five hours. The diuresis was calculated by comparing the urine volumes of control and experimental groups. The compounds **5** and **9** were tested for diuretic activity against the dose 50mg, 100 mg and **1** g/kg and found to possess no appreciable diuretic activity of these concentrations.

Experimental Section

TLC was run on silica gel plates using acetone-benzene (1:3) as irrigant. Melting points are uncorrected. IR (KBr) and ^{1}HNMR spectra (chemical shift

in δ ppm) were recorded on a Hitachi 215 and varian VXR-200 MHz spectrometers respectively.

***p*-Fluorobenzoylthiosemicarbazide 2.** This was prepared by the reaction of *p*-fluorobenzoyl hydrazide **1** with potassium thiocyanate, under acidic conditions, according to the method of Dhaka et al[12] in 70% yield, m.p. 165°C [Found: N, 19.98; S, 15.27; $C_8H_8N_3$ SOF requires N, 19.72; S, 15.02%].

5-Mercapto-3-*p*-fluorophenyl-*s*-triazole 3. *p*-Fluorobenzoyl thiosemicarbazide (21.3g, 0.1 mole) in 8% sodium hydroxide (300ml) was heated under reflux for **3** hr. The reaction mixture was cooled to room temperature and acidified with dil. acetic acid. The product separated was filtered, washed with water and crystallized from methanol as colourless crystals, m.p. 240°C, yield 10.72 g (55%). (Found: N, 3.27; S, 16.67. Calcd For C_8 H_6 N_3 FSN: N, 3.08; S, 16.41%). IR: 840 (1, 4-Disubstituted benzene ring); 2590 (S-H stretching); 1620 (C=N); 3040 cm^{-1} (aromatic C-H stretching).

5-*p*-Bromobenzoylmethylmercapto-3-*p*-fluorophenyl-*s*-triazole 4. A mixture of **3** (1.95g, 0.01 mole) and *p*-bromophenacyl bromide(2.78g, 0.01 mole) in dry methanol (100mL) was heated under reflux on steam bath for **3** hr, cooled to room temperature, neutralized with aqueous potassium carbonate solution. The solid thus separated was filtered, washed with water and crystallized from ethanol as cream coloured crystals, m.p. 175^0, yield 2.34g(60%). [Found: N, 10.56; S, 8.32. $C_{16}H_{11}N_3SOBrF$ requires N, 10.71; S, 8.16%]. IR: 835, 845 (1, 4-disubstituted benzene rings), 1520 (C-N stretching); 1695 (C=O); 3410 (N-H stretching).

5-*p*-Bromophenylthiazolo[3, 2-*b*]-2-*p*-fluoro-phenyl-*s*-triazole 5. A mixture of **4** (1g), P_2O_5 (4.0g) and H_3 PO_4 (3mL) was heated in an oil bath at 150^{0}c for about **3** hr. The reaction mixture was cooled, poured into water, neutralized with potassium carbonate solution and the solid thus obtained crystallized from ethanol as colourless crystals, m.p. 185°C, yield 0.4g (48%) [Found: C, 51.58; H, 2.62; N, 11.51; S, 8.27. $C_{16}H_9N_3S$ BrF requires C, 51.34; H, 2.41; N, 11.23; S, 8.56%].IR: 820, 835 (1, 4-Disubstituted benzene rings), 1510 cm^{-1} (C-N stretching). PMR ($CDCl_3$): 6.92 (1H, *s*, C-6-H); 7.20-8.40 (8H, m, aromatic protons).

2-*p*-Fluorophenylhydrazino-4-*p*-bromophenylthiazole hydrobromide 6. A mixture of **2** (1.06g, 0.005mole) and *p*-bromophenacyl bromide (1.39g, 0.005 mole) in dry methanol (100mL) was heated under reflux on a steam bath for **5** hr. The reaction mixture was cooled to room temperature and the solid thus separated was crystallized from ethanol affording light green crystals, m.p. 180^0, yield 1.3g (55%). [Found: N, 9.21; S, 6.52. $C_{16}H_{11}N_3OFBr_2S$ requires N, 8.90; S, 6.78%]. IR: 830, 840 (1, 4-Disubstituted benzene rings); 1510 (C-N stretching); 1600, 1620 (C=C & C=N); 1700 (C=O), 3120, 3450 (N-H stretching).

5-*p*-Bromophenyl-3-*p*-fluorophenylthiazolo[2, 3-*c*]-*s*-triazole 7. A mixture of **6** (1g) and $POCl_3$ (10 mL) was heated in an oil bath (120-130°C) for **3** hr. The reaction mixture was cooled, poured into water and neutralized with an aqueous potassium carbonate solution. The solid thus separated was filtered, washed with water and crystallized from ethanol giving brown crystals, m.p. 168°C, yield 0.3g (42%). [Found: C, 51.53; H, 2.74; N, 11.18; S, 8.81. Calcd for $C_{16}H_9N_3S$ FBr: C, 51.34; H, 2.41; N, 11.23; S, 8.56%]. IR: 830, 840 (1, 4-disubstituted benzene rings); 1525 cm^{-1} (C-N stretching); 1610, 1620 (C=C & C=N), 3040 (aromatic C-H stretching). PMR ($CDCl_3$ + TFA); 7.18 (1 H, *s*, C-6-H); 7.1-8.1 (8 H, *m*, aromatic protons).

3-*p*-Fluorophenyl-4-amino-5-mercapto-*s*-triazole 8. This was prepared from *p*-fluorobenzoyl hydrazide according to the method of Reid and Heindel[13] in 75% yield, m.p. 221^0 (lit[13] m.p. 223°C).

6-*p*-Chlorophenyl-3-*p*-fluorophenyl-7*H*-*s*-triazolo [3, 4-*b*][1, 3, 4] thiadiazine 9. A mixture of **8** (1.05g, 0.005 mole) and *p*-chlorophenacyl bromide (1.16 g, 0.005 mole) in anhydrous ethanol (40mL) was heated under reflux for **5** hr. on a steam bath. The reaction mixture was cooled and basified with an aqueous potassium carbonate solution. The solid, thus separated was filtered, washed well with water and crystallized from ethanol as colourless crystals, m.p 190°C, yield 0.8 g (46%) [Found: C, 55.47; H, 2.68; N, 16.44; S, 9.42. $C_{16}H_{10}N_4$ SCIF requires C, 55.73; H, 2.90; N, 16.26; S, 9.30%]. IR: 835, 845 (1,4-disubstituted benzene rings); 1510 (C-N stretching); 1620 (C=N), 3030 cm^{-1} (aromatic C - H stretching); PMR ($CDCl_3$): 4.0 (2H, s, SCH_2); 7.2-8.4 (8H, m, aromatic protons).

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