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BRIDGEHEAD NITROGEN HETEROCYCLIC SYSTEMS: SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SPIRO [2, 6-di-*p*-ANISYL PIPERIDINE-3', 4(4'-*H*)-[2*H*] THIAZOLO [3, 2-*b*]-*s*-TETRAZINE]

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ABSTRACT

The reaction of spiro[2,6-di-*p*-anisylpiperidine-3',4-1', 2', 4', 5'-tetrahydro-*s*-tetrazine-6'-thione] **1** obtained from 2,6-di-*p*-anisylpiperidin-4-one and thiocarbohydrazide, with chloroacetic acid results in the facile synthesis of 6'-(7'*H*)-oxospiro[2,6-di-*p*-anisylpiperidin-3',4(4'*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] **2.** 7'-arylidene derivatives **3a-b** have been prepared by the condensation of thiazolidinone **2** with aldehydes. Condensation of **3a** with hydrazine hydrate yielded 3, 3a-dihydro-2H-3-aryl-2', 6'-di-*p*-anisylspiropiperidin-4', 7(8*H*)-[6*H*] pyrazolo [3,4-*d*]thiazolo[3,2-*b*]-*s*-tetrazine**4.** The antibacterial activity of some of the compounds have been evaluated.

KEYWORDS

spiro[2,6-di-*p*-anisylpiperidine-3',4-1', 2', 4', 5'-tetrahydro-*s*-tetrazine-6'-thione], 2,6-di-*p*-anisylpiperidin-4-one, 6'-(7'*H*)-oxospiro[2,6-di-*p*-anisylpiperidin-3',4(4'*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] , 3, 3a-dihydro-2H-3-aryl-2', 6'-di-*p*-anisylspiropiperidin-4', 7(8*H*)-[6*H*] pyrazolo [3,4-*d*]thiazolo[3,2-*b*]-*s*-tetrazine

INTRODUCTION

In continuation of my earlier studies on the synthesis of biologically active bridgehead nitrogen heterocyclic systems[i-x], I report herein the synthesis of novel thiazolo-*s*-tetrazine and the antibacterial properties associated with them.

The required compound spiro[2,6-di-*p*-anisyl piperidine-3',4-1',2',4',5'-tetrahydro-*s*-tetrazine-6'-thione] **1** was obtained by the reaction of 2,6-di-*p*-anisylpiperidin-4-one[xi] withthiocarbohydrazide following the method of Lamon[xii]. Condensation of compound **1** with chloroacetic acid furnished the compound **2.** 7'-Arylidene-6'-(7'*H*)-oxospiro[2,6-di-*p*-anisylpiperidine-3',4(4'*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] **3** were prepared by the condensation of thiazolidinone **2** with aldehydes. Condensation of compound **3a** with hydrazine hydrate yielded in one step the cyclized product 3, 3a-dihydro-2-H-3-aryl-2', 6'-di-

p-anisylspiropiperidine-4', 7(8*H*)-[6*H*]-pyrazolo[3,4-*d*]thiazolo[3,2-*b*]-*s*-tetrazine **4.** The structures of compounds **1, 2, 3a-b&4** were established by their IR and PMR spectral data.

The parent thiazolidinone**2** showed a carbonyl absorption at 1728 cm^{-1} but the unsaturation at 7'-position being conjugated with the carbonyl group at 6'-position as in arylidenethiazolidinones**(3a-b)** produced a bathochromic shift[xiii] as expected. The carbonyl absorption appeared at 1702 cm^{-1} for compound **3a,** 1704 cm^{-1} for compound **3b.** Lack of absorption in the spectra of compound **4** at 1700-1728cm^{-1} showed the absence of a carbonyl group thereby suggesting the cyclic structure.

ANTIBACTERIAL ACTIVITY

The compounds **1** and **3b** were evaluated for their antibacterial activity (in vitro) against the gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli, Pseudomonas aeruginosa* and *Bacillus subtilis* by neat samples & serial plate dilution method[xiv]. Compound **1** is sufficiently active against all the four organisms while the compound **3b** is active against both *E. coli* and *S. aureus.* The concentration of the compounds used was 125µg/ml.

EXPERIMENTAL AND RESULTS

TLC was run on silica gel G plates using acetone-benzene (1:3) as irrigant. Melting points are uncorrected. IR (KBr)(cm^{-1}) and ^1H NMR ($CDCl_3$) (δppm downfield from TMS) spectra were recorded on a Hitachi-215 and Varian VXR-200 MHz spectrometers respectively. C, H and N analyses were carried out on a Yanaco MT-3 (Japan) analyser.

Spiro[2,6-di-*p*-anisylpiperidine-3',4-1',2',4',5'-tetrahydro-*s*-tetrazine-6'-thione]1a

It was prepared in 65% yield by the reaction of 2,6-di-*p*-anisylpiperidine-4-one with thiocarbohydrazide according to the method of Lamon, m.p. 130°C. (Found : C, 60.74; H, 5.91; N, 17.43; S, 8.38. $C_{20}H_{23}N_5SO_2$ requires C, 60.45; H, 5.79; N, 17.63; S, 8.06%); IR : 840 (1,4-disubstituted benzene rings), 1220 (C=S), 1520 (C-N stretching), 3375 (N-H stretching).

Similarly spiro [2,6-diphenylpiperidine-3', 4-1',2',4',5'-tetrahydro-*s*-tetrazine-6'-thione] **1b** was prepared in 61% yield by the reaction of 2,6-diphenylpiperidin-4-one with thiocarbohydrazide having m.p. 157°C. (Found : C, 63.48; H, 6.40; N, 20.36; S, 9.27. $C_{18}H_{21}N_5S$ requires C, 63.71; H, 6.19; N, 20.64; S, 9.43%); IR : 710, 755 (mono-substituted benzene ring), 1225 (C=S), 1520 (C-N stretching), 3340 (N-H stretching), 3030 (aromatic C-H stretching).

6'-(7'*H*)-oxospiro[2,6-di-*p*-anisylpiperidine-3', 4(4'*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] 2a

A mixture of compound **1a** (5.0g, .012 mole), chloroaceticacid (1.19g, 0.012 mole), anhyd sodium acetate (0.984g, 0.012 mole) in absolute ethanol was refluxed for 6 hr on steam bath, cooled and allowed to stand overnight. The solid, thus obtained was filtered, washed well with water and recrystallized from alcohol, yield 3.0g (54.54%), m.p. 120°C. (Found : C, 60.27; H, 5.48; N, 16.32; S, 7.58. $C_{22}H_{23}N_5SO_3$ requires C, 60.41; H, 5.26; N, 16.01; S, 7.32%); IR : 835(1, 4-disubstituted benzene ring), 1525 (C-N stretching), 1600, 1620 (C=C & C=N), 1725 (C=O), 3040 (aromatic C-H Stretching).

Similarly 6'-(7'*H*)-oxospiro[2,6-diphenylpiperidine-3',4(4'*H*)-[2*H*]thiazolo [3,2-*b*]-*s*-tetrazine] **2b** was prepared from **1b** having m.p. 172°C, yield 3.0g (53.76%). (Found :C, 63.61; H, 5.28; N, 18.67; S, 8.70%. $C_{20}H_{21}N_5SO$ requires C, 63.32; H, 5.54; N, 18.46; S, 8.44%); IR:700, 755 (monosubstituted benzene ring), 1520 (C-N stretching), 1590, 1610 (C=C & C=N), 1720 (C=O), 3040 (aromatic C-H stretching).

7'-Arylidene-6'-(7'*H*)-oxospiro[2,6-di-*p*-anisylpiperidine-3',4(4'*H*)-[2*H*]thiazolo[3,2-*b*]-*s*-tetrazine] 3a$_1$

A mixture of compound **2a** (1.5g, .0034 mole), *p*-chlorobenzaldehyde (0.477g, .0034 mole), anhyd. sodium acetate (0.278g, .0034 mole) in gl acetic acid (30 ml) was heated under reflux for 3 hr. The reaction mixture was half concentrated, poured into cold water. The solid thus separated was filtered and recrystallized from ethanol, m.p. 115^{o}C, yield .700g (37.43%). (Found: C, 61.53; H, 4.56; N, 12.91; S, 5.67. $C_{28}H_{26}N_5SO_3Cl$ requires C, 61.36; H, 4.74; N, 12.78; S, 5.84%); IR : 840 (1,4-disubstituted benzene rings), 1515 (C-N stretching), 1600, 1625 (C=C & C=N), 1700 (C=O), 3030 (aromatic C-H stretching); ^{1}H NMR ($CDCl_3$) : 1.64 (1 H, s, -NH group at N-1), 2.03 (2H, s, -NH group at N-2' & N-4'), 3.72 (6H, s, OCH_3 group), 7.19 (1H, s, = CHAr), 7.29- 7.68 (12H, m, ArH).

A similar method was adopted for the synthesis of compounds **3a**$_2$, **3b**$_1$**&3b**$_2$, their characterization data are given in Table-1.

3, 3a-dihydro-2*H*-3-aryl-2', 6'-di-*p*-anisyl spiropiperidine-4', 7-(8*H*)-[6*H*]-pyrazolo[3,4-*d*]thiazolo[3,2-*b*]-*s*-tetrazine 4a$_1$(Ar=*p*-Cl-C$_6$H$_4$)

A mixture of compound **3a**$_1$ (.500g, .0009 mole), hydrazine hydrate (0.045g, .0009 mole), anhyd. sodium acetate (.073g, .0009 mole) in gl acetic acid (30ml) was heated under reflux for 6hr. The reaction mixture was half concentrated, cooled and poured into cold water. The solid thus obtained was filtered and recrystallized from gl acetic acid,m.p. 160^{o}C, yield .300g (56.60%). (Found: C, 61.24; H, 4.51; N, 16.49; S, 5.29. $C_{30}H_{28}N_7SClO_2$ requires C, 61.48; H, 4.78; N, 16.73; S, 5.46%); IR : 835, 840(1, 4-disubstituted benzene rings), 1520 (C-N stretching), 1600, 1620 (C=C & C=N), 3040 (aromatic C-H stretching), 3320 (N-H stretching); ^{1}H NMR ($CDCl_3$) : 1.80 (1H, s, -NH group at N-1'), 2.26(2H, s, -NH group at N-6 & N-8), 3.39(6H, s, -OCH_3 group), 1.17 (4H, d , $C_{3'}$-H&$C_{5'}$-H), 3.56(2H, t, $C_{2'}$-H &$C_{6'}$-H),7.06 (1H,d (J=8.0 Hz), C_{3a}-H) ,7.34 (1H,d (J=8.0 Hz), C_3-H) , 7.18(1H,s, -NH at N-2), 6.71-7.40 (12H, m, aromatic protons).

A similar method was adopted for the synthesis of compound **4a**$_2$ (Ar=*p*-H_3CO-C_6H_4), the characterization data of which is given in Table 2.

3,3a-dihydro-2*H*-3-aryl-2',6'-diphenylspiropiperidine-4',7-(8*H*)-[6*H*]-pyrazolo[3,4-*d*]thiazolo[3,2-*b*]-*s*-tetrazine 4b$_1$ (Ar=*p*-Cl-C$_6$H$_4$)

A mixture of compound **3b$_1$** (.500g, .0009mole), hydrazinehydrate (.045g, .0009 mole), anhyd. sodium acetate (.045g, .0009 mole), anhyd. sodium acetate (.073g, .0009 mole) in gl acetic acid (30 ml) was heated under reflux for 6 hr. The reaction mixture was half concentrated, cooled and poured into cold water. The solid thus obtained was filtered and recrystallized from gl. acetic acid, m.p. 175°C, yield .250g (48.73%). (Found: C, 62.63; H, 5.38; N, 18.79; S, 6.42. $C_{27}H_{26}N_7SC1$ requires C, 62.85; H, 5.04; N, 19.01; S, 6.20%); IR : 700, 755, 830, 840 (monosubstituted and 1, 4-disubstituted benzene rings), 1520 (C-N stretching), 1600, 1620 (C=C &C=N), 3030 (aromatic C-H stretching), 3280,3300 (N-H stretching); ^{1}H NMR (DMSO) : 1.22(1H, s, -NH group at N-1'), 2.23 (2H, s, -NH grp at N-6 & N-8), 1.14 (4H,d, C_3-H & C_5-H), 3.54 (2H, t, C_2-H & C_6-H), 6.58 (1H, d (J=7.0Hz), C_{3a}-H), 7.87 (1H, d (J=7.0Hz), C_3 - H), 6.93-7.89 (14H, m, Ar-H) , 7.19 (1H,s, -NH at N-2).

A similar procedure was adopted for the synthesis of compound 4b$_2$(Ar=p-H_3CO-C_6H_4), the characterization data is given in Table-2.

6'-(p-chlorophenyl)-7'*H*-spiro[2,6-di-p-anisyl piperidine-3', 4(4'H)-[2H]thiazolo[3,2-*b*]-s-tetrazine]hydrobromide 5a (R=C1)

A mixture of compound **la**(1.0g, 0.0025 mole), p-chlorophenacyl bromide (0.583g, 0.0025 mole), absolute alcohol (40ml) was heated under reflux for 3 hr on steam bath. The reaction mixture was half concentrated, cooled. The solid thus separated was filtered and recrystallized from alcohol, yield 0.500g (37.59%), m.p. 95°C. (Found : C, 63.42; H, 4.68; N, 13.43; S, 6.38. $C_{28}H_{26}N_5SO_2C1$ requires C, 63.21; H, 4.89; N, 13.17; S, 6.02%); IR : 830, 842 (1, 4-disubstituted benzenerings), 1515 (C-N stretching), 1615, 1625

(C=C&C=N), 3040 (aromatic C-H stretching); ^{1}H NMR ($CDC1_3$):1.25(1H, s, -NH group at N-1), 1.62(2H, s, -NH group at N-2' & N-4'), 3.83 (6H, s, OCH_3 group), 7.26(1H, s, C-7'-H), 7.54-7.69 (12H, m, ArH).

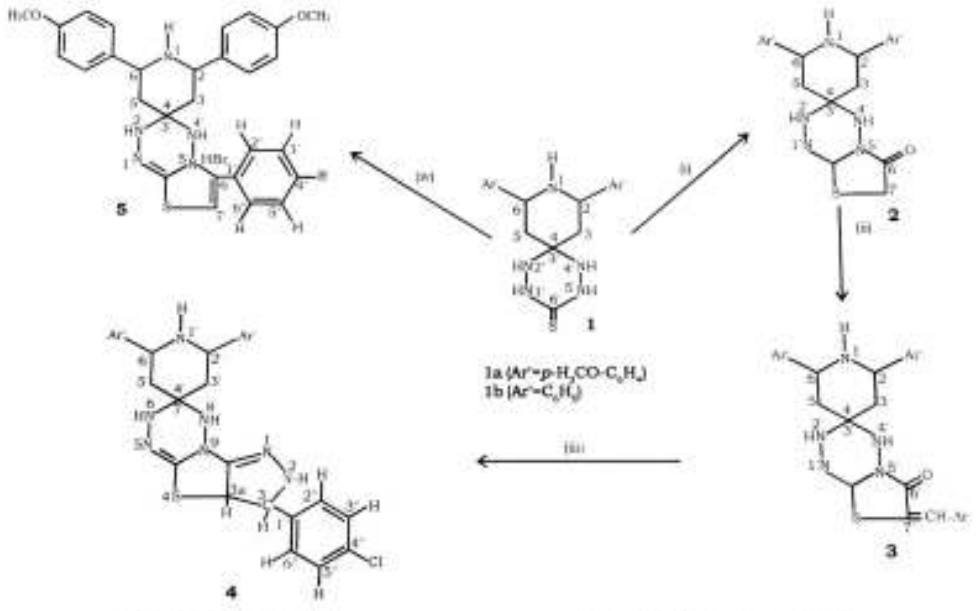
A similar procedure was adopted for the synthesis of compd. 5b (R=Br) having m.p. 100°C, yield 0.500g (34.48%). (Found : C, 58.57; H, 4.29; N, 12.36; S, 5.31. $C_{28}H_{26}N_5SO_2Br$ requires C, 58.33; H, 4.51; N, 12.15; S, 5.55%); IR : 835, 840 (1, 4-disubstituted benzene rings), 1510 (C-N stretching), 1600, 1625 (C=C & C=N), 3040 (aromatic C-H stretching).

TABLE-1 Characterization data of compounds $3a_2$, $3b_1$& $3b_2$

Compd.	Ar	m.p. °C	Yield %	Mol. Formula	Found (%)/Calcd.			
					C	H	N	S
3a$_2$	*p*-H_3CO-C_6H_4	110	32.25	$C_{30}H_{29}N_5SO_4$	64.27 (64.08	5.12 5.34	12.65 12.89	5.71 5.89)
3b$_1$	*p*-Cl-C_6H_4	160	37.00	$C_{27}H_{24}N_5SOCl$	64.81 (64.60	4.89 4.78	13.73 13.95	6.09 6.38)
3b$_2$	*p*-H_3CO-C_6H_4	150	51.00	$C_{28}H_{27}N_5O_2S$	67.47 (67.60	5.17 5.43	14.29 14.08	6.13 6.43)

TABLE-2 Characterization data of compounds $4a_2$& $4b_2$

Compd.	Ar	m.p. °C	Yield %	Mol. Formula	Found (%)/Calcd.			
					C	H	N	S
4a$_2$	*p*-H_3CO-C_6H_4	145	39.00	$C_{30}H_{31}N_7SO_3$	64.28 (64.02	5.12 5.33	16.98 16.86	5.21 5.50)
4b$_2$	*p*-H_3CO-C_6H_4	165	38.91	$C_{28}H_{29}N_7SO$	62.58 (62.75	5.79 5.67	19.41 19.17	6.43 6.26)



SCHEME-1

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