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Synthesis and Spectral Studies of Some Novel Derivatives of 1,5-Benzothiazepines

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The title compounds **3a–i**, of potential pharmacological interest, have been obtained by condensation of ring substituted propane-1-(1,3-benzodioxol-5-yl)-3-phenyl-1,3-diones **2a–i** with 2-amino-benzenethiols **1a–b**, in pyridine. Compounds were analyzed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies.

Key Words: 1,5-Benzothiazepines-1,3-diones, Spectral analysis.

INTRODUCTION

1,5-Benzothiazepine derivatives are an interesting heterocyclic family due to their diverse applications. Some of them have found use in medicinal area as antibacterial[1], analgesic[2], anticonvulsants[3], antidepressant[4] and antiarrhythmic[5] agents. A number of 1,5-benzothiazepines having phenyl rings at position 2 or 4 show tranquillizing activity[6]. The 1,3-benzodioxole moiety has shown interesting and diversified properties when used to obtain new biologically active drugs[7,8]. As part of our research program on synthesis of novel derivatives 1,5-benzothiazepines[9], some new 2,4-disubstituted-1,5-benzodiazepine having 1,3-benzodioxole unit have been synthesized .

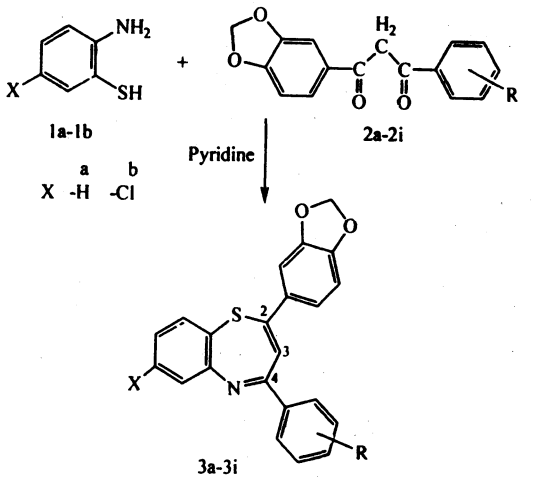
EXPERIMENTAL

All the melting points were uncorrected. The IR spectra were recorded on a Nicolet-Megna FTIR 550 spectrophotometer in KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were scanned in $CDCl_3$ on a DRX 300 spectrometer at 300.13 and 75.48 MHz respectively, using TMS as an internal standard. The mass spectra were recorded on a Jeol D-300 spectrometer. The purity of compounds was checked by TLC.

Preparation of Substituted 1,5-benzothiazepines: 2-aminobenzene thiol/2-amino-5-chlorobenzethiol (0.01 mol) was added to the stirred suspension of β-diketone (0.01 mol) in pyridine and the resulting mixture was refluxed for approx. 4 h. The mixture was cooled and poured onto crushed ice dropwise with vigorous stirring. The pale yellow precipitate formed was filtered, dried and crystallized from methanol. Purity of the compounds was checked by TLC using (CH_3OH : $CHCl_3$, 8 : 2) as mobile phase.

RESULTS AND DISCUSSION

The title compounds **3a–i** have been synthesized by a one-pot reaction involving the condensation of 2-amino benzenethiol/2-amino-5-chlorobenzenethiol **1a–b** with β-diketones **2a–i**, in pyridine. It appears that the reaction is initiated by nucleophilic attack of sulphydryl electrons rather than by lone pair of electrons of amino group, at enolic carbon of β-diketone and then dehydrative cyclization results in 1,5-benzothiazepines. The structures of all the newly synthesized compounds are well supported by spectroscopic data (**Scheme-1**, Table-1).



Scheme-1

	R	X		R	X
(a)	3-Cl	—H	(f)	3,4-OCH_3	—H
(b)	3-NH_2	—H	(g)	4-H	—Cl
(c)	3-NO_2	—H	(h)	4-CH_3	—Cl
(d)	3,4-Cl	—H	(i)	4-Cl	—Cl
(e)	3,4-Br	—H			

The specta of **3a–i** showed absorption in the range 1610–1595 cm^{-1} due to stretching vibration of C=N in benzothiazepine ring. The absorptions at 1270–1235 and 1075–1040 cm^{-1} may be assigned to C—O—C stretching vibrations. In the spectra of **3b**, two bands at 3445–3325 cm^{-1} are due to amino group.

In ^1H NMR, a singlet is obtained for dioxymethylene protons at δ 6.00–6.02. Methine proton at δ 6.67–6.71 as singlet further confirms the formation of seven member heterocyclic ring. A singlet is also observed at δ 3.81 due to protons of —OCH_3 group in the respective compound **3f**. The aromatic protons were indicated at δ 6.79–8.31, as multiplets.

TABLE-1
ELEMENTAL ANALYSIS DATA OF TITLE COMPOUNDS

Compd.	m.f.	m.w.	Elemental analysis %: Calcd. (Found)				m.p. (°C)
			C	H	N	X	
3a	$C_{22}H_{14}SO_2NCl$	391.5	67.43 (67.32)	3.58 (3.39)	3.58 (3.51)	9.07 (8.88)	182
3b	$C_{22}H_{16}SO_2N_2$	372.0	70.97 (70.81)	4.30 (4.14)	7.53 (7.40)	—	205
3c	$C_{22}H_{14}SO_4N_2$	402.0	65.67 (65.49)	3.48 (3.41)	6.97 (6.88)	—	202
3d	$C_{22}H_{13}SO_2NCl_2$	426.0	61.97 (61.83)	3.05 (2.92)	3.29 (3.15)	16.67 (16.58)	172
3e	$C_{22}H_{13}SO_2NBr_2$	513.0	51.46 (51.40)	2.53 (2.48)	2.73 (2.69)	30.80 (30.71)	193
3f	$C_{24}H_{19}SO_4N$	417.0	69.06 (68.97)	4.56 (4.50)	3.36 (3.29)	—	188
3g	$C_{22}H_{14}SO_2NCl$	391.5	67.33 (67.32)	3.58 (3.43)	3.58 (3.54)	9.07 (8.93)	197
3h	$C_{23}H_{16}SO_2NCl$	405.5	68.06 (67.91)	3.94 (3.85)	3.45 (3.37)	8.75 (8.69)	168
3i	$C_{22}H_{13}SO_2N$	426.0	61.97 (61.94)	3.05 (2.99)	3.29 (3.23)	16.67 (16.62)	174

TABLE-2
^{1}H NMR DATA OF TITLE COMPOUNDS (IN δ, PPM)

Compd.	R	X	Ar—R	OCH_2O (2H, s)	Methine (1H, s)	Aromatic protons
3a	3-Cl	H	—	6.00	6.70	6.88–7.99 (11H, m)
3b	3-NH_2	H	2H, 4.39 (b), s	6.02	6.69	6.90–7.90 (11H, m)
3c	3-NO_2	H	—	6.01	6.71	6.96–8.29 (11H, m)
3d	3,4-Cl	H	—	6.00	6.67	6.81–7.92 (10H, m)
3e	3,4-Br	H	—	6.00	6.63	6.84–7.88 (10H, m)
3f	3,4-OCH_3	H	3H, 3.81, s	6.00	6.68	6.80–7.84 (10H, m)
3g	4-H	Cl	—	6.02	6.69	6.90–7.99 (11H, m)
3h	4-CH_3	Cl	3H, 2.43, s	6.02	6.67	6.86–7.66 (10H, m)
3i	4-Cl	Cl	—	6.01	6.69	6.79–8.05 (10H, m)

^{13}C NMR data for the compounds **3a–i** are presented in Table-3 and these data are in good agreement with their structures.

TABLE-3
^{13}C NMR DATA OF TITLE COMPOUNDS (IN δ PPM)

Compd.	Ar—R	O(C)O	C_2	C_3	C_4	Aromatic carbons
3a	—	101.1	138.7	91.9	152.2	150.3–106.3
3b	—	101.0	139.3	92.6	150.9	148.7–106.6
3c	—	101.2	139.0	92.1	151.3	148.0–105.4
3d	—	100.9	138.2	91.7	151.9	149.8–106.1
3e	—	100.9	137.6	93.0	152.0	148.1–105.9
3f	OCH_3-54.9	101.0	138.5	91.9	152.6	162.3–106.4
3g	—	101.4	137.9	92.4	150.6	149.9–106.7
3h	CH_3-21.0	101.2	139.4	93.1	151.3	147.3–105.5
3i	—	100.6	137.1	91.8	152.6	151.3–106.0

Mass spectra of compounds **3a–i** gave the molecular ion peaks (m/z), which corresponded to their molecular weight. A cluster of ion peaks to $[M]^+$, $[M+2]^+$ at 391, 393 were observed in case of **3a.** In case of **3h,** a cluster of ion peaks to $[M]^+$, $[M+2]^+$ at 405, 407 were observed. The presence of isotopic Cl^{37} was indicated by the fact that $[M+2]^+$ peak was nearly one-fourth of $[M]^+$ peak in both the cases (*i.e.*, **3a** and **3h**).

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