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RESEARCH ARTICLE

Synthesis and Spectral Studies of Novel Diazepine Derivatives and Study in Specific Reference to Tautomerization

R. K. SAINI[a*], Y. C. JOSHI[a] and P. JOSHI[b]

[a]Department of Chemistry, University of Rajasthan, Jaipur-302004, India
[b]S. S. Jain Subodh P. G. College, Jaipur, Rajasthan, India
sainirk97@yahoo.co.in

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Abstract: Condensation of various 1,3-diketone derivatives (**1a-1f**) with ethylene diamine and O-PDA in absolute ethanol led to synthesis of new 1,4-diazepines and 1,5-benzodiazepine derivatives. Structure of newly synthesized 1,4-diazepines (**2a-2f**) and 1,5-benzodiazepine derivatives (**3a-3f**) were established on the spectral studies *viz*: IR,^{1}H NMR,^{13}C NMR.

Keywords: 1,3-Diketone, Ethylene diamine, O-PDA, Diazepine, Benzodiazepine

Introduction

Diazepine and its derivatives are important class of compounds possess various biological activities *viz*: anticancer[1], antibacterial[2], antiemetic[3], anticonvulsant[4], fungicidal, insecticidal and herbicidal[5], antiviral[6], antihypertensive[7], antidepressant[8], antiasthamatic[9], anti-inflammatory agent[10].Benzodiazepines are also used in elderly as community dwelling population[11].

Interestingly, benzothienobenzodiazepine(Y-931), dibenzo [b,f]Diazepine (clozapine) and thienobenzodiazepine (Olanzapine) are known as typical effectiveantipsychotics[12,13]. Naturally occurring benzodiazepines, such as pyrrolo [2, 1-e] 1, 4-benzodiazepines (PBDs) isolated from streptomyces species[14] are found effective as antitumour[15], antibiotics and in DNA probe[16]. Realizing the medicinal important of diazepines derivatives and in continuation of our earlier work[17], in this paper we report the synthesis of some new 1, 4-diazepines and 1, 5-benzodiazepine derivatives.

Experimental

Melting points were uncorrected. The IR spectra were recorded in KBr disks on Nicolet-Megna-FT-IR550 spectrometers. ^{1}H NMR and ^{13}C NMR recorded on model DRX 300 at 300.13 & 75.48 MHz respectively in $CDCl_3$\DMSO-d_6 using TMS as internal standard. The purity of newly synthesized compounds was checked by TLC.

*Generalized preparation of diazepine nucleus (**2a**)*

A mixture of diketones (**1a-1f**, 0.01 M) and ethylenediamine (0.01 M) were refluxed in absolute ethanol (10 mL) by making reaction medium slightly acidic. The reaction mixture was

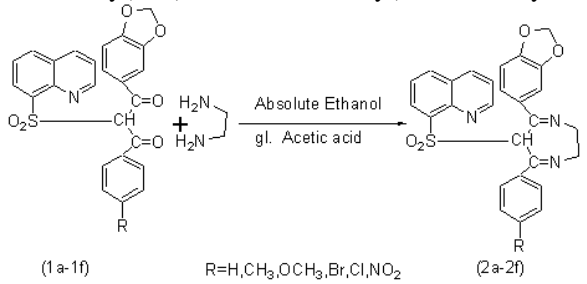
refluxed for 3 hours and then cooled to room temperature. The solid residue was recrystallized from acetone-ethanol mixture yield crystalline product. Purity of compound were checked by TLC using (benzene: ethanol: ammonia: 7: 2: 1) upper layer as mobile phase.

*Generalized preparation of benzodiazepine nucleus (**3a**)*

A mixture of diketones (**1a-1f**, 0.01 M) and O-PDA (0.01 M) were refluxed in absolute ethanol (10 mL) by making reaction medium slightly acidic. The reaction mixture was refluxed for 6-8 hours and then cooled to room temperature. The solid residue was recrystallized from ethanol yield crystalline product. Purity of compound were checked by TLC using (benzene: ethanol: ammonia: 7: 2: 1) upper layer as mobile phase.

Results and Discussion

Condensation of propane-1-(1,3-benzodioxol-5yl)-2-(quinoline-8-sulfonyl)-3-phenyl-1,3-dione(**1a**) or other compounds(**1b-1f**) having various substituent in phenyl ring, with ethylene diamine in absolute ethanol and refluxing for 3 hours results in the formation of 5-substituted phenyl-6-(quinoline-8-sulfonyl)-7-(1,3-benzodioxol-5yl)-6*H*-2,3-dihydro-1,4-diazepine.



Scheme 1

Similarly condensation of propane-1-(1,3-benzodioxol-5yl)-2-(quinoline-8-sulfonyl)-3-phenyl-1,3-dione(**1a**) or other compounds(**1b-1f**) having various substituent in phenyl ring, with ethylene diamine in absolute ethanol and refluxing for 6-8 hours results in the formation of 2-substituted elemental analysis and spectral analysis of title compounds are given in Tables 1 & 2 respectively.

Table 1. Elemental analysis of title compounds

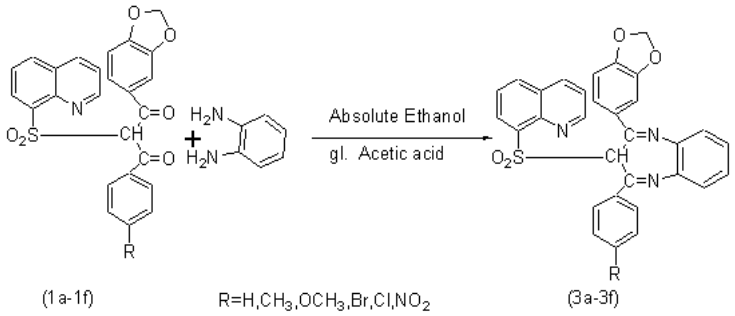
Compd.	Molecular formula	M.P ^{0}C	Yields %	Elemental analysis calculated (found)			
				C	H	N	S
2a	$C_{27}H_{21}O_4N_3S$	187	40	67.08(67.05)	4.34(4.32)	8.69(8.50)	6.62(6.60)
2b	$C_{28}H_{23}O_4N_3S$	176	35	67.60(67.50)	4.62(4.50)	8.45(8.43)	6.43(6.40)
2c	$C_{28}H_{23}O_5N_3S$	150	42	65.49(65.40)	4.48(4.40)	8.18(8.10)	6.23(6.21)
2d	$C_{27}H_{20}O_4N_3SBr$	Oily	47	57.70(57.30)	3.56(3.52)	7.47(7.40)	5.69(5.62)
2e	$C_{27}H_{20}O_4N_3SCl$	210	37	62.60(62.75)	3.86(3.83)	8.11(8.03)	6.18(6.10)
2f	$C_{27}H_{20}O_6N_4S$	Oily	30	61.36(61.25)	3.78(3.70)	10.60(10.5)	6.06(6.01)
3a	$C_{31}H_{21}O_4N_3S$	193	50	70.05(70.01)	3.76(3.70)	7.90(7.87)	6.02(6.11)
3b	$C_{32}H_{23}O_4N_3S$	140	55	70.45(70.62)	4.72(4.65)	7.70(7.65)	5.87(5.81)
3c	$C_{32}H_{23}O_5N_3S$	155	50	68.44(68.14)	4.09(4.14)	7.48(7.40)	5.70(5.74)
3d	$C_{31}H_{21}O_4N_3SBr$	201	45	61.03(61.45)	3.44(3.54)	6.89(6.80)	5.25(5.28)
3e	$C_{31}H_{21}O_4N_3SCl$	Oily	53	65.78(65.70)	3.71(3.65)	7.42(7.36)	5.65(5.61)
3f	$C_{31}H_{21}O_6N_4S$	213	40	64.58(64.51)	3.64(3.73)	9.72(9.65)	5.55(5.50)

Table 2. Spectral analysis of title compounds

Compd	IR(KBr, cm^{-1})	^{1}H NMR($CDCl_3$\DMSO-d_6), (δ ppm)	^{13}C NMR($CDCl_3$\DMSO-d_6), (δ ppm)
2a	3325(N-H), 3040 (Ar-H), 1580(C=N), 2920(C-H), 1320 & 1140(SO_2)	3.30(2H,t,CH_2N=),3.00(2H,t, CH_2NH),8.75(1H,s,NHC=C, inte.0.62),6.02(OCH_2O), 7.01(1H,>CH, inte.0.42), 7.15-8.45 (14H,aromatic)	120-150(twenty one lines, 21aromatic carbon), 164 & 165 (two lines,two C=N), 99(OCH_2O), 45 & 47(two lines,=N-CH_2CH_2-NH),83(>CH)
2b	3320(N-H), 3050 (Ar-H), 1590(C=N), 2924(C-H), 1324 &1135 (SO_2)	3.37(2H,t,CH_2N=),3.15(2H,t,C H_2NH),8.69(1H,s,NHC=C,inte. 0.62),5.94(OCH_2O),7.00(1H,> CH,inte.0.44),7.25-8.54 (13H,aromatic),2.35(3H,s,CH_3)	118-152(twenty one lines, 21aromatic carbon), 162 & 164 (two lines, two C=N) 99(OCH_2O),46 & 48 (two lines, =N-CH_2CH_2-NH), 84(>CH)21(CH_3)
2c	3322(N-H), 3060(Ar-H), 1585(C=N), 2940(C-H), 1327&1130(SO_2)	3.20(2H,t,CH_2N=), 3.00(2H,t,CH_2NH), 8.85(1H,s,NHC=C,inte.0.62)6. 02(OCH_2O),7.00(1H,>CH,inte 0.43),7.15-8.55(13H,aromatic), 3.89(3H,s,OCH_3)	115-150(twenty one lines, 21aromatic carbon), 164 & 166 (two lines, two C=N) 100(OCH_2O),46&47(two lines =N-CH_2CH_2-NH), 84(>CH)56(0CH_3)
2d	3325(N-H), 3056(Ar-H), 1594(C=N), 2930(C-H), 1315 &1120(SO_2)	3.32(2H,t,CH_2N=), 2.98(2H,t,CH_2NH),8.70 (1H,s,NHC=C,inte.0.62), 6.05(OCH_2O), 7.14(1H,>CH,inte.0.38), 7.25-8.45(13H,aromatic)	120-152(twenty one lines, 21aromatic carbon), 163&165(two lines,twoC=N), 100(OCH_2O),45&46(two lines =N-CH_2-CH_2-NH),83(>CH)
2e	3335(N-H), 3052(Ar-H), 1584(C=N), 2910(C-H), 1318&1130(SO_2)	3.25(2H,t,CH_2N=), 3.05(2H,t,CH_2NH), 8.55(1H,s,NHC=C,inte.0.64) 5.98(OCH_2O), 7.00(1H,>CH,inte.0.42), 7.15-8.35(13H,aromatic)	117-156(twenty one lines, 21aromatic carbon), 164&165(two lines,twoC=N), 100.01(OCH_2O),45&47(two lines, =N-CH_2-CH_2-NH), 84(>CH)
2f	3325(NH), 3030(Ar-H), 1588(C=N), 2928(C-H), 1326 &1137(SO_2)	3.33(2H,t,CH_2N=), 3.08(2H,t,CH_2NH), 8.65(1H,s,NHC=C,inte.0.63) 6.00(OCH_2O), 6.96(1H,>CH,inte.0.40), 7.25-8.40 (13H,aromatic)	118-155(twenty one lines, 21aromatic carbon), 162 & 164(two lines,twoC=N), 99.97(OCH_2O),43&44(two lines, =N-CH_2-CH_2-NH),82(>CH)
3a	3030(Ar-H), 1590(C=N), 2930(C-H), 3320(N-H), 1325&1127(SO_2)	6.00(2H,s,OCH_2O), 8.65(1H,s,NH,inte.0.80) 7.2(1H,s,>CH,inte.0.27), 7.34-8.53(18H,aromatic)	118-153(twenty seven lines, 27aromatic carbons), 162&165(two lines,two C=N), 98(OCH_2OCH_2),45 & 47 (=NCH_2CH_2NH),83(>CH)
3b	3035(Ar-H), 1593(C=N), 2938(C-H), 3315(N-H), 1315&1120(SO_2)	6.03(2H,s,OCH_2O), 8.70(1H,s,NH,inte.0.81) 7.15(1H,s,>CH,inte.0.25), 7.24-8.49(17H,aromatic), 2.25(3H,s,CH_3)	119-154(twenty seven lines, 27 aromatic carbons), 162&163(two lines, two C=N), 100(OCH_2OCH_2),45&46 (=NCH_2CH_2NH),83(>CH) 22(CH_3)

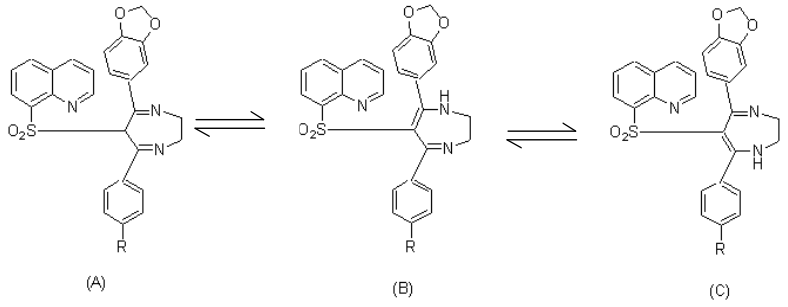
Contd…

3c	3020(Ar-H), 1605(C=N), 2940(C-H), 3324(N-H), 1328&1117(SO_2), 1090(O-C)	6.10(2H,s,OCH_2O), 8.73(1H,s,NH,inte.0.77) 7.2(1H,s,>CH,inte.0.27), 7.34-8.53(17H,aromatic) 3.79(3H,s,OCH_3)	120-155(twenty seven lines, 27aromatic carbons), 163&164(two lines,two C=N), 99(OCH_2OCH_2), 46&47(=NCH_2CH_2NH), 84(>CH)52(0CH_3)
3d	3026(Ar-H), 1600(C=N), 2937(C-H), 3340(N-H), 1317&1117(SO_2)	6.00(2H,s,OCH_2O), 8.62(1H,s,NH,inte.0.78) 7.12(1H,s,>CH,inte.0.23), 7.24-8.55 (17H,aromatic)	121-153(twenty seven lines, 27 aromatic carbons), 164 & 165(two lines, two C=N), 100.02(OCH_2OCH_2),44 & 45(=NCH_2CH_2NH),83(>CH)
3e	3030(Ar-H), 1588(C=N), 2940(C-H), 3340(N-H), 1335&1127(SO_2)	5.98(2H,s,OCH_2O), 8.55(1H,s,NH,inte.0.80) 7.14(1H,s,>CH,inte.0.24), 7.20-8.43(17H,aromatic)	116-151(twenty seven lines, 27aromatic carbons), 163&165(two lines,two C=N), 99.97(OCH_2OCH_2),45&47 (=NCH_2CH_2NH),85(>CH)
3f	3040(Ar-H), 1595(C=N), 2934(C-H), 3330(N-H), 1335&1130(SO_2)	6.01(2H,s,OCH_2O), 8.67(1H,s,NH,inte.0.78) 7.12(1H,s,>CH,inte.0.21), 7.24-8.54(17H,aromatic)	122-156(twenty seven lines, 27 aromatic carbons), 166&168(two lines,two C=N), 100.12(OCH_2OCH_2),47&48 (=NCH_2CH_2NH),84(>CH)



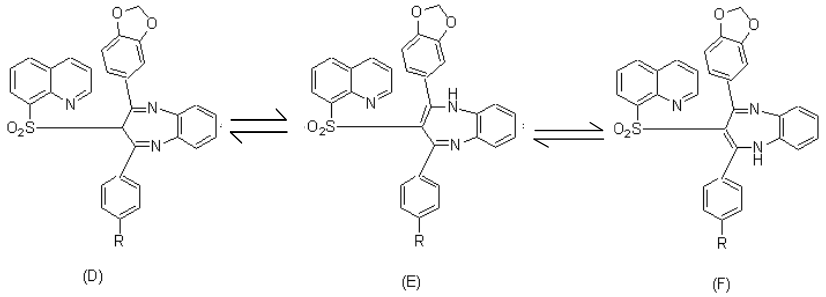
Scheme 2

Tautomerization forms also exist in diazepines and benzodiazepines. On the behalf of integration of NH proton and active CH proton, we have established that A & (B+C) forms are exist in 4:6 ratio. Integration values of NH & CH protons are given in ^{1}H NMR data of Table 2.



Scheme 3. Tautomerization in 1, 4-diazepines

Similarly on the behalf of integration of NH proton and active CH proton, we have established that D & (E+F) forms are existing in 2.5:7.5 ratios. Integration values of NH & CH protons are given in ^{1}H NMR data of Table 2.



Scheme 4. Tautomerization in 1, 5-benzodiazepine

Spectral studies

The IR spectra of compounds (**2a-2f, 3a-3f**) showed a NH stretching vibration around 3320 cm^{-1}, Ar-H stretching vibration around 3040 cm^{-1}, C-H stretching vibration around 2940 cm^{-1} and SO_2 stretching vibrations at 1140 & 1320 cm^{-1} respectively.

The ^{1}H NMR spectra of compounds (**2a-2f, 3a-3f)** showed a multiplet in the range of δ6.75-8.50 ppm due to aromatic protons. A singlet observed around δ6.01ppm is due to presence of dioxymethylene proton, a singlet observed at δ8.75 ppm is due to presence of NH proton and triplet observed around δ3.15 ppm is due to presence of –NCH_2CH_2N- protons.

The ^{13}C NMR spectra of compounds (**2a-2f**) showed 21 lines between region δ120-150 ppm due to aromatic carbon. Two carbon of C=N groups are appeared around δ165 ppm. The carbon of dioxymethylene group appeared at δ100 ppm. Two lines for two carbons of CH_2 attached to nitrogen atoms of diazepine ring appeared around δ47 ppm. Active methylene carbon which appeared in diketones at δ88.13 ppm undergo slightly upward shift and observed at δ85ppm indicating the formation of diazepine ring.

The ^{13}C NMR spectra of compounds (**3a-3f**) showed 27 lines between region δ115-152 ppm due to aromatic carbons. Two carbon of C=N groups are appeared around δ162&165 ppm. The carbon of dioxymethylene group appeared at δ101 ppm. Two lines for two carbons of CH_2 attached to nitrogen atoms of diazepine ring appeared around δ47& δ44 ppm. Active methylene carbon which appeared in diketones at δ88.13 ppm undergo slightly upward shift and observed at δ83 ppm indicating the formation of diazepine nucleus.

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