

Preparation of Some 1,3,4,5-Tetrahydro-2H, 1,5- Benzodiazepines and Study of their Physical and Spectral Properties

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(Received 21st September, 1989, revised 15 March, 1990)

Summary: Preparation of 4-methyl-(1), 3-methyl-(2), 2,2- dimethyl-(3) and unsubstituted -(4), 1,3,4,5-tetrahydro-2H-1:5- benzodiazepines has been accomplished by LiAlH_4 reduction of corresponding 1,3,4,5-tetrahydro-2H-1:5-benzodiazepin-2-ones (5- 8). Physical properties, mass and ^1H n.m.r. spectral properties of 1 - 4 have been described, whereas those of 5 - 8 are being published elsewhere. Carbon-13 n.m.r spectral properties of 1 - 8 are included in this paper. All these compounds will be subjected to dynamic ^1H n.m.r. spectral studies in order to obtain information regarding the effect of methyl- and carbonyl - substitution on the solution conformation of medicinally important 1,3,4,5-tetrahydro-2H 1:5-benzodiazepine ring.

In view of the medicinal importance of benzodiazepines [1-6], a massive research effort has been directed towards the preparation and study of their properties, specially solution conformation [7,8] of this class of compounds. Preparation of 2-methyl-(1), 3- methyl-(2), 2,2-dimethyl-(3) and unsubstituted-(4), 1,3,4,5-tetrahydro-2H-1:5-benzodiazepines has been accomplished by LiAlH_4 reduction of 4-methyl (5), 3-methyl-(6), 4,4-diethyl-(7) and unsubstituted-(8) 1,3,4,5-tetrahydro-2H-1:5-benzodiazepin-2-ones. Compounds (5), (6), (7) and (8) have been obtained by the reaction of [10,11] o-phenylenediamine with α,β -unsaturated acids, namely crotonic, methacrylic, methacrylonic and

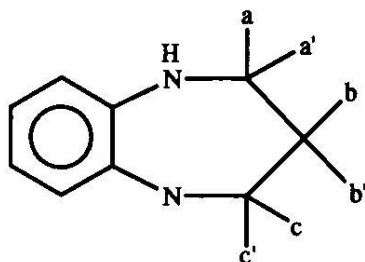
acrylic acids respectively. Synthesis of 1,3,4,5-tetrahydro-2H-1,5-benzodiazepines by this method has not been previously reported in literature. Compound 4 was prepared by another method [9]. Compounds 1, 2 and 3 have not been located by us in previous work. Preparation of all these compounds was undertaken in order to subject them later on to the study of their stereochemistry using mainly dynamic proton n.m.r technique. Compound (5) and its 7-substituted derivatives have already been subjected to such studies [8]. It has been found that this compound and its derivatives exist mainly in boat conformation in solution. Such studies, when carried out with all these compounds

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Table-1

Compound No.	M.P. ^a /C/Solvent for Cryst.	R _f x 10 ² Chloroform/ Methanol 9:1	% Yield	Mass Spectral Fragmentation
1	90-91 Pet.ether	57	40	162(base peak) 147, 132,119,106,92
2	83.5/ Pet.ether	60	30	162, 145, 132,119 (base peak), 197, 92.
3	63-64/ Pet.ether	59	35	176,161,(base peak), 133,119,92.
4	101-102/ Pet.ether	52	25	148,130,119 (base peak), 106, 92

Table-2:



1 a = a¹ = b = b¹ = c = H; c¹ = CH₃.

2 a = a¹ = b = c = c¹ = H; b¹ = CH₃

3 a = a¹ = b = b¹ = H; c = c¹ = CH₃.

4 a = a¹ = b = b¹ = c = c¹ = H

Chemical Shifts (ppm) and Peak Pattern of different Protons

Compound	a	a ¹	b	b ¹	c	c ¹
1	3.30(m)		1.70(m)		2.8(m)	1.30(d)
2	3.27(dd)		1.96(m)	0.94(d)	3.27(dd)	
3	3.09(m)		1.76(m)		1.21(s)	
4	3.05(t)		1.82(m)		3.05(t)	

(1 - 8) will reveal the effect of degree and position of methyl substitution as well as of carbonyl group on the conformation of this mobile ring system. Present paper describes the preparation, physical, mass- and ¹H, C-13 n.m.r.- spectral properties of 1 - 4 and C-13 n.m.r. data of 5 - 8. Proton n.m.r. data of 5 - 8 are being published elsewhere [11].

Table I shows percentage yield, melting point, R_f value in thin layer chromatography and mass

spectral fragmentation of compounds 1 - 4. All these compounds exhibit much lower melting points as compared to the corresponding benzodiazepinones [10,11]. Elemental analysis confirms the molecular formulae of these compounds. Proton nuclear magnetic resonance data of these compounds are shown in Table-2. These data confirm the expected structure of the reduced products 1 - 4. Since ¹H n.m.r. spectra of all compounds (1 - 8) have been measured under similar conditions, comparison of the peak pattern of 3-methylene protons in 1 and 5 indicate that conformational mobility of two ring systems is different. These protons appear as multiplet at 1.7 ppm in 1, whereas in 5 they are resolved into two definite double doublets at 2.42 and 2.63 ppm. Similarly 2 and 4-methylene protons appear as two well defined double doublets at 3.27 and 2.58 ppm in 2, whereas in 6 [11] 4-methylene protons show unresolved multiplet at 3.5 ppm. There is therefore a need to carry out similar ¹H dynamic n.m.r. studies with 1 - 4 and 6 - 8 as have been carried out with 5 and its derivatives. Off resonance C-13 nuclear magnetic resonance data of compounds 1 - 8 shown in Table-3 are also in agreement with their expected structure. As far as our knowledge is concerned, no C-13 n.m.r. data for 1,3,4,5-tetrahydro-2H-1,5-benzodiazepines have been published.

Experimental

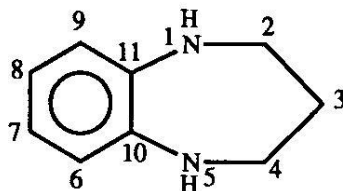
Reduction of compounds 5 - 8 was carried out using 1 mole each of the compound and 0.5 mole of lithium aluminium hydride in ether. The results of elemental analysis of 1 - 4 which were carried out in W. Germany are as follows:

Anal		C	H	N
1 and 2	Calc. for C ₁₀ H ₁₄ N ₂	74.07	8.64	17.28
1	Found **	74.09	8.62	17.30
2	Found **	74.06	8.66	17.29
3	Calc. for C ₁₀ H ₁₆ N ₂	74.95	9.15	5.90
	Found **	74.89	9.14	5.88
4	Calcd. for C ₉ H ₁₂ N ₂	72.94	8.16	18.90
	Found **	72.90	8.18	18.88

Mass spectra of compounds 1 - 4 were taken in H.E.J. Research Institute of Chemistry, Univer-

sity of Karachi, Karachi-75270, Pakistan. Proton magnetic resonance spectra of 1 - 4 were measured in deuterated chloroform using 100 MHz Jeol nuclear magnetic resonance spectrometer. C-13 Magnetic resonance spectra of 1 - 4 and 6 - 8 were measured in dimethylsulfoxide-D₆ using Jeol 67.0 MHz nuclear magnetic resonance spectrometer, whereas that of 5 was measured in deuterated chloroform. M.H. is grateful to University Grants Commission, Islamabad, Pakistan for providing financial support for this work.

Table-3: Chemical Shifts ppm and Peak Pattern of Different Carbons in 1 - 8.



Compound No	C-2	C-3	C-4	C-10	C-6	C-7	C-8	C-9	C-11	3CH ₃	2CH ₃	4CH ₃
1	45.84 t	40.00 t	51.86 d	139.43 s	119.36 s	119.0 d	118.78 d	119.78 d	141.09 d	-	22.68 s	-
2	52.54 t	35.72 d	52.54 t	140.6 s	118.92* s	118.37* d	118.37* d	118.92** d	140.6 d	16.47 s	-	-
3	42.71* t	43.55* t	51.71 t	137.38 s	121.88 s	121.75 s	119.46 d	121.79 d	141.49 d	-	29.16 s	-
4	46.34 t	32.26 t	46.34 t	140.76 s	118.95 s	11.95 d	118.95 d	118.95 d	140.76 d	-	-	-
5	172.43 s	53.70 t	41.47 d	141.71 s	38.27 s	120.85* d	121.8* d	125.54 d	121.94 d	127.7 d	-	23.54 q
6	174.60 s	37.77 d	52.37 t	139.91 s	118.22* s	118.20* d	124.18 d	121.90 d	126.16 d	13.75 s	-	-
7	171.15 s	46.15 t	60.27 s	139.14 s	120.85* s	121.18* d	125.52 d	121.94 d	130.62 d	-	-	29.46 q
8	172.70 s	44.24 t	36.56 t	139.53 t	118.88* t	118.06* d	124.05 d	121.77 d	125.77 d	-	-	-

* can be interchanged between them ** can be interchanged between them

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