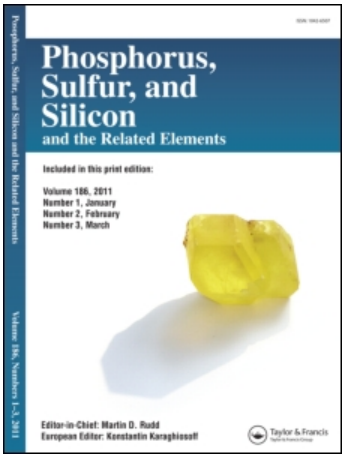

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Syntheses of 1,5-Benzothiazepines: Part XXIV- Syntheses of 4-(4-Chlorophenyl)-2-(4-Dimethyl-Aminophenyl)-2,5-Dihydro-8-Substituted-1,5-Benzothiazepines

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SYNTHESES OF 1,5-BENZOTHIAZEPINES: PART XXIV - SYNTHESES OF 4-(4-CHLOROPHENYL)-2-(4-DIMETHYL-AMINOPHENYL)-2,5-DIHYDRO-8-SUBSTITUTED-1,5-BENZOTHIAZEPINES

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Single step syntheses of 4-(4-chlorophenyl)-2-(4-dimethylaminophenyl)-2,5-dihydro-8-substituted-1,5- benzothiazepines have been achieved by the reactions of five 5-substituted-2-aminobenzenethiols with 4-dimethyl aminobenzal-4′-chloroacetophenone in ethanol saturated with HCl gas. The structural assignments of the final products are based on the results of elemental analyses, IR, ^{1}H NMR and mass spectral studies.

Keywords: Chemotherapeutic; 1; 5-benzothiazepine; cardiovascular

The successful chemotherapeutic applications of diltiazem[1,2] [(+)-cis-(2S, 3S)-3-acetoxy-2-(4-methoxyphenyl)-5-(2-dimethylaminoethyl)-1,5-benzothiazepin-4(5H)-one hydrochloride, CRD-401], especially in cardiovascular ailments prompted us to look for different parameters in 1,5-benzothiazepine nucleus, which are responsible for imparting pharmacological activity. While carrying out drug designing, the introduction of halogens in analogous 1,4- and 1,5-benzodiazepine nucleus resulted into the discovery of most effective CNS drugs, chlordiazepoxide[3], triflubazam[4,5], clobazam[6], flurazepam[7], flunitrazepam[8]. In 1,5-benzothiazepine class of compounds, clentiazem[9], having chlorine at position-8 in 1,5-benzothiazepine nucleus, has also been found more effective than diltiazem. These observations led us to the synthesis of 4-(4-chlorophe-

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nyl)-8-ethoxy-2,5-dihydro-2-(4-dimethylaminophenyl)-1,5-benzothiazepine which has been found to possess anti-inflammatory activity[10]. It was, therefore, thought useful to synthesise a series of compounds having 4-chlorophenyl and 4-dimethylaminophenyl group in 2,5-dihydro-1,5-benzothiazepine series having substituents like alkoxyl-methoxyl, alkyl-methyl and halogeno-fluoro, chloro, bromo at position-8 which are described here.

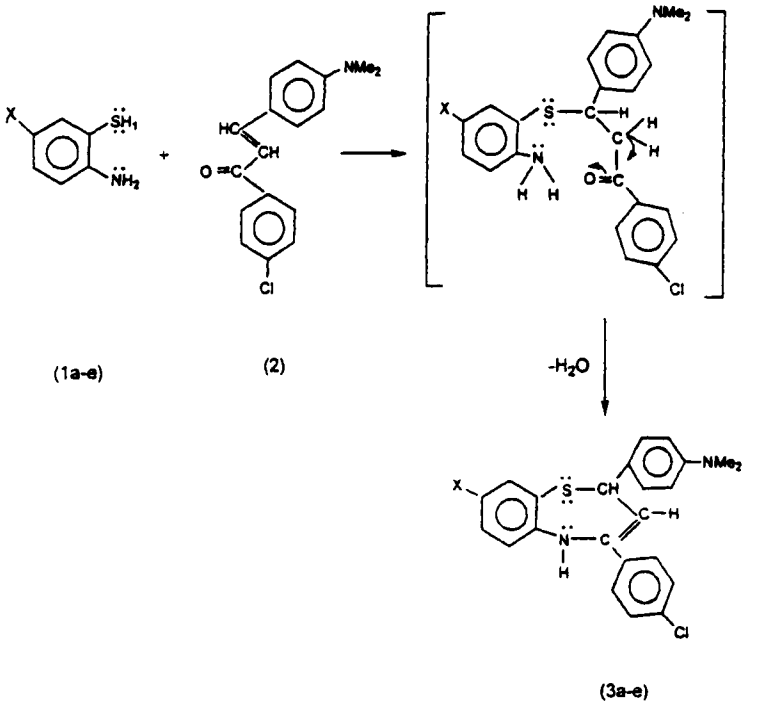
In order to obtain 8-substituted-1,5-benzothiazepines, 5-substituted-2-aminobenzenethiols[11,12](1a-e) having substituents as fluoro, chloro, bromo, methyl and methoxyl were reacted with the chalcone, 4-dimethylaminobenzal-4'-chloroacetophenone[13] in ethnaol saturated with hydrogen chloride gas. The reaction mixture was refluxed for nearly 3 hrs on a water-bath and then concentrated under reduced pressure to give a solid which was recrystallized from ethanol.

The purity of the products was tested by tlc using Silica Gel 'G' coated glass plates and solvent system, benzene : ethanol : ammonia (7:2:1, upper layer). The structure of the products were ascertained by microanalysis of elements and IR, ^{1}H NMR and mass spectral studies. In a study of reactions of chalcones with 5-substituted-2-aminobenzenethiols, it has already been established[14,15] that in the first step, Michael type addition takes place initiated by the nucleophilic attack[16,17] by the lone pair of sulfhydryl electrons[14] on the activated β-carbon atom of chalcones to give a ketoamine, a type of Michael adduct (intermediate)[18,19]. The ketone group undergoes 1,2-addition followed by dehydrative cyclization[14,16–19] resulting into the formation of products, 4-(4 chlorophenyl)-2-(4-dimethylaminophenyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines (3a-e) (Scheme 1).

The values of % of elements, C, H and N were found to be satisfactorily within the permissible limit of error of the calculated values and are given alongwith physical constants in table I.

IR SPECTRAL STUDIES

The IR spectra of the final products were diagnostic of the fact that the reaction between 5-substituted-2-aminobenzenethiols (1a-e) and the chalcone (2) had taken place as no absorption bands at 3445–3200 cm^{-1} and



1,3	a	b	c	d	e
X	F,	Cl,	Br,	Me,	OMe

SCHEME I

1690–1650 cm^{-1}, characteristic of NH_2 and>C = O respectively, were present. However, presence of a broad absorption at 3150–3140 cm^{-1} indicated secondary amino absorption. Absorption at around 3100–3000, 1600–1590, 1550 and 1460–1440 cm^{-1} could be assigned to aromatic skeletal vibrations and the absorption in the region 2900–2870 cm^{-1}, 1390–1375 cm^{-1} indicated the presence of aliphatic C-H absorption. Bands at 795–785 cm^{-1} may be assigned to C-Cl stretching and absorptions at 1275–1230 cm^{-1} and 1190–1160 cm^{-1} to C-O-C system (table II).

TABLE I Physical constants and microanalytical data of 4-(4-chlorophenyl)-2-(4-dimethylaminophenyl)-2,5-dihydro-8- substituted-1,5-benzothiazepines (3a-d)

Compd. No.	*X*	*m.p. (°C)*	R_f	*Yield %*	*Molecular formula (Mol. wt.)*	*Elemental Analysis* *Found (Calcd.)*		
						C	*H*	*N*
3a	F	122	0.87	62	$C_{23}H_{20}N_2SClF$	66.95	4.66	6.86
					(410.5)	(67.23)	(4.80)	(6.82)
3b	Cl	128	0.85	59	$C_{23}H_{20}N_2SCl_2$	64.69	4.53	6.72
					(427)	(64.63)	(4.68)	(6.55)
3c	Br	126	0.80	62	$C_{23}H_{20}N_2SClBr$	58.68	4.09	-
					(470.5)	(58.74)	(4.24)	(5.93)
3d	CH_3	124	0.78	67	$C_{24}H_{23}N_2SCl$	69.98	5.72	6.90
					(406.5)	(70.84)	(5.65)	(6.82)

TABLE II Characteristic IR absorption bands (cm^{-1}) of 4-(4-chlorophenyl)-2-(4-dimethylaminophenyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines (3a-d)

Compd.	*X*	$\nu_{(N-H)}$ (cm^{-1})	$\nu_{(C-Cl)}$ (cm^{-1})	*Aromatic*		*Aliphatic*	
				$\nu_{(C-H)}$ (cm^{-1})	*Skeletal* (cm^{-1})	$\nu_{(C-H)}$ (cm^{-1})	$\delta_{(C-H)}$ (cm^{-1})
3a	F	3090	795	3045	1595,1540,1445	2900	1380
3b	Cl	3055	790	3010	1590,1545,1440	2875	1375
3c	Br	3085	785	3095	1595,1540,1450	2880	1385
3d	Me	3090	780	3100	1580,1490,1440	2885	1390

TABLE III Characteristic ^1H NMR signals of 4-(4 chlorophenyl)-2-(4 dimethylaminophenyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines [(3a-d); solvent $CDCl_3$; δ Scale; J in Hz)

Compd. No.	*X*	*C-2-H (d,J=7,1H)*	*C-3-H*	*$N(CH_3)_2$ (s, 6H)*	*CH_3*	*Aromatic (m, 11H)*
3a	F	6.04	7.24	2.80	–	6.06 – 7.18
3b	Cl	5.98	7.36	2.78	–	6.04 – 7.34
3c	Br	6.24	7.40	2.76	–	6.26 – 7.36
3d	Me	6.02	7.22	2.82	1.90 (3H, s)	6.04 – 7.18

^{1}H NMR SPECTRA

The ^{1}H NMR spectra of 3e gave characteristic 3H singlet at δ3.60 which is assigned to three protons of the methoxyl group. In the spectra of all the compounds (3a-e) absorption as a singlet equivalent to 6H at δ2.76 to 2.82 is assigned to six protons of dimethylamino group. A broad singlet at around δ 4.00 to 4.22 may be assigned to 1H proton of NH. Signals at δ 5.98 to 6.24 as doublets (J = 7 Hz) may be assigned to C-2-H. Another doublet with the coupling constant J = 7 Hz at δ 7.22 to 7.40 may be assigned to C-3-H. It is interesting to find that the PMR spectral pattern, having a methine and a methylene protons at position-2 and 3 respectively in 2,3-dihydro-1,5-benzothiazepines[20,21] exhibit three double doublets in the ABX pattern. The absence of this pattern rules out 2,3-dihydro form of 1,5-benzothiazepine structure. The presence of 1H at C-2 and the presence of N-H is indicative of its 2,5-dihydro structure. The aromatic protons show multiplets in the region δ 6.06 to 7.36 (table III).

The mass spectra of 3c gave $[M]^+$, $[M+2]^+$ peaks of nearly equal heights at 470, 472 and a shorter $[M+4]^+$ peak at 474 which indicate the presence of bromine in the molecule and the even mass numbers obtained are according to the nitrogen rule.

EXPERIMENTAL

All the recorded melting points are uncorrected. Progress of the reaction was monitored by using tlc on silica gel 'G' coated plates using benzene: ethanol: ammonia (7 : 2 : 1, upper layer). IR spectra were recorded in KBr pellets on Perkin Elmer Infracord-577 and Magna FTIR-557 spectrophotometers. Mass spectra were taken on Jeol D-300 (El/Cl) instrument at 70 eV and PMR spectra were recorded in $CDCl_3$ on Jeol 90 MHz FT NMR spectrometer using TMS as internal standard.

5-Substituted-2-aminobenzenethiols (1a-e) were prepared by reported methods[11,12].

4-dimethylaminobenzal-4'-chloroacetophenone (2)

To an equimolar quantities of p-dimethylamino-benzaldehyde (1.49g, 0.01 mole) and p-chloroacetophenone (1.54 g, 0.01 mole) in ethanol (7.0 ml),

50% solution of NaOH was added with vigorous shaking and warmed on a water-bath to obtain the orange coloured precipitate. The crude product was recrystallized from ethanol to obtain orange granular crystals of 4-dimethylaminobenzal-4'-chloroacetophenone; m.p. 138°C, lit[13] 140°C, yield, 2.02 g.

4-(4-Chlorophenyl)-2-(4-dimethylaminophenyl)-2,5-dihydro-8-methoxy-1,5-benzothiazepine (3e)

2-Amino-5-methoxybenzenethiol (0.155g; 0.001 mole) and 4-dimethylaminobenzal-4'-chloroacetophenone (0.285g; 0.001 mole) in dry ethanol (10 ml) were saturated with dry hydrogen chloride gas, refluxed for three hrs on a water bath and then concentrated by distillation under reduced pressure and cooled to obtain orange crude product which was recrystallized from dry ethanol to afford orange crystals of 4-(4-chlorophenyl)-8-methoxy-2-(4-dimethylaminophenyl)-2,5-dihydro-1,5-benzothiazepine (3e), m.p. 110°C, yield, 0.27 g (66%), TLC, R_f 0.72,

Found: C, 68.07, H, 5.38 and N, 6.69, $C_{24}H_{23}N_2SOCl$ requires C, 68.16: H, 5.44; N, 6.62 %, IR: 3095 cm^{-1}(N-H), 785 cm^{-1} (C-Cl); ^1H NMR : δ 6.02 (1H, d, J = 7 Hz, C-2-H), δ 7.24 (1H, d, J = 7 Hz, C-3-H), δ 2.76 (6H, s, $N(CH_3)_2$), δ 3.56 (3H, s, 8-OCH_3), δ 6.06 – 7.22 (11H, m ArH).

Following the same procedure, the compounds (3a-d) were prepared. Their characterization data are recorded in table-1, 2 and 3.

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