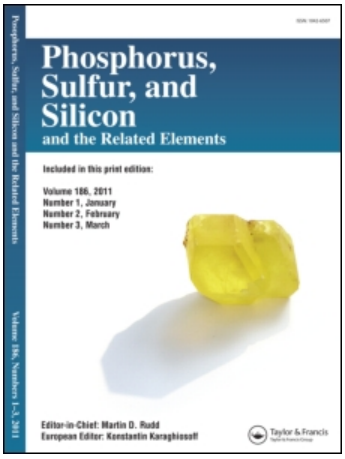

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESES OF 8-SUBSTITUTED-2- CARBOXY-4-(4-HALOPHENYL)-2,3-DIHYDRO-1,5-BENZOTHIAZEPINES

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To cite this Article Sharma, Anita , Pant, Seema , Sharma, C. K. and Pant, Umesh C.(1996) 'SYNTHESES OF 8-SUBSTITUTED-2- CARBOXY-4-(4-HALOPHENYL)-2,3-DIHYDRO-1,5-BENZOTHIAZEPINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 117: 1, 121 — 128
To link to this Article: DOI: 10.1080/10426509608038779
URL: http://dx.doi.org/10.1080/10426509608038779

Phosphorus, Sulfur, and Silicon, 1996, Vol. 117, pp. 121–128
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SYNTHESES OF 8-SUBSTITUTED-2-CARBOXY-4-(4-HALOPHENYL)-2,3-DIHYDRO-1,5-BENZOTHIAZEPINES

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(Received 2 April 1996; Revised 13 June 1996; In final form 13 June 1996)

The reactions of 5-substituted-2-aminobenzenethiols with β-(4-chlorobenzoyl)- and β-(4-bromobenzoyl)acrylic acids have been carried out in methanol containing traces of glacial acetic acid to yield in a single step, 8-substituted-2-carboxy-4-(4-chlorophenyl and 4-bromophenyl)-2,3-dihydro-1,5-benzothiazepines, the substituents being Cl, Br as halogen; CH_3 as alkyl, and OCH_3 and OC_2H_5 as alkoxyl. The structural assignments have been made by a study of microanalyses of the elements and IR, ^1H NMR and mass spectral studies of the title compounds.

Keywords: Chemotherapeutic; 1,5-benzothiazepine; vasodilators; benzothiazepines

Many chemotherapeutic applications of 1,5-benzothiazepine derivatives as calcium antagonists,[1] coronary vasodilators,[2] antiischemics,[3] antihypertensives,[4] antiarrhythmics,[5] blood platelet aggregation inhibitors,[6] antiarteriosclerotics[7] etc. and comparison of their chemical structures with analogous classical psychopharmacological agents such as diazepams,[8] clobazam[9] etc. interested us on synthesizing a series of new 1,5-benzothiazepines having primarily a substituent at position-8 in addition to substituents at position-2 and -4. It is observed that all the patented drugs from among the 1,4- and 1,5-benzothiazepine classes possess a substituent in the fused benzene ring whereas the most commonly used CVS drug, diltiazem,[8] has no substituent in the benzene ring fused with thiazepine ring. In continuation of our work[10] and with the aim of having a halophenyl group at position-4, a carboxyl at position-2 and substituents like halogens—Cl, Br, alkyl—CH_3; alkoxyl—OCH_3 and OC_2H_5 at position-8, the precursors,

*Corresponding author.

5-substituted-2-aminobenzenethiols were treated with β-(4-chlorobenzoyl- and 4-bromobenzoyl)acrylic acids to obtain the title compounds, 8-substituted-2-carboxy-4-(*p*-chlorophenyl or *p*-bromophenyl)-2,3-dihydro-1,5-benzothiazepines. 1,5-Benzothiazepines possessing such structures are expected to possess possible pharmacological potential due to the presence of a probable pharmacophore (i) a substituent in the fused benzene ring, (ii) a carboxyl function at position-2, and (iii) a halophenyl group at position-4.

RESULTS AND DISCUSSION

5-Substituted-2-aminobenzenethiols having the substituents as Cl, Br, CH_3, OCH_3 and OC_2H_5 (**1a–e**) were prepared by literature[11] methods and the β-(4-chlorobenzoyl- and 4-bromobenzoyl)acrylic acids[12] (**2a,b**) were prepared by the application of the Friedel Craft's reaction by reacting maleic anhydride with chlorobenzene or bromobenzene in dry carbon disulphide, and the melting points of 2a,b were tallied with literature.[12]

Equimolar quantities of the two reactants **1a–e** and **2a,b** were taken in dry methanol containing glacial acetic acid as the catalyst. The reaction mixture was refluxed for 3 hrs, cooled, and concentrated. The solid obtained from the cold concentrate was crystallized from benzene to obtain the pure title compounds, 8-substituted-2-carboxy-4-(4-chlorophenyl and 4-bromophenyl)-2,3-dihydro-1,5-benzothiazepine series **3a–j**. The products were obtained in a single step and the yields were found to be satisfactory.

It has been found that 4-aryl-2-carboxy-2,3-dihydro-1,5-benzothiazepines are obtained by single step reactions, but in some cases[13–15] intermediates have also been isolated,[16] under reaction conditions such as using toluene or methanol with piperidine. The isolation and characterization of intermediates, followed by their cyclization, in some cases, affirm that the reaction is initiated by the attack of sulphydryl electrons[17] of 5-substituted-2-aminobenzenethiols on electrophilic carbon in α, β-unsaturated aroyl acrylic acids.[18] This is accompanied by dehydrative cyclization to yield the final products in single-pot synthesis.

The products gave effervescence with sodium bicarbonate indicating the presence of a carboxyl group. Reaction with 2,4-dinitrophenylhydrazine did not give the yellow colored hydrazones, showing the absence of carbonyl group and thereby indicating that the intermediate had been converted to the final cyclised product.

In the IR spectra, all compounds showed the absorption bands in the region 1700–1680 cm^{-1} corresponding to C═O stretching vibrations, very broad ab-

TABLE I Physical Constants and Analytical Data of 8-Substituted -2-Carboxy-4-(4-Chlorophenyl or 4-Bromophenyl)-2,3-Dihydro-1,5-Benzothiazepines (**3a–j**)

Compound No.	*X*	*R*	*mp (°C)*	R_f	*Yield (%)*	*Molecular formula* $[M]^+$,$[M+2]^+[M+4]^+$	*Elemental Analysis for N Found (Calcd.) (%)*
3a	Cl	Cl	217	0.72	38	$C_{16}H_{11}NO_2SCl_2$ (351, 353, 355)	3.46 (3.98)
3b	Br	Cl	194	0.68	43	$C_{16}H_{11}NO_2SClBr$ (395, 397, 399)	3.70 (3.54)
3c	CH_3	Cl	235	0.62	47	$C_{17}H_{14}NO_2SCl_2$	4.95 (4.22)
3d	OCH_3	Cl	216	0.66	45	$C_{17}H_{14}NO_3SCl$	4.53 (4.03)
3f	Cl	Br	210	0.64	40	$C_{16}H_{11}NO_2SBrCl$ (395, 397, 399)	3.50 (3.54)
3g	Br	Br	123	0.70	35	$C_{16}H_{11}NO_2SBr$	3.28 (3.17)
3h	CH_3	Br	220	0.78	42	$C_{17}H_{14}NO_2SBr$	3.94 (3.72)
3i	OCH_3	Br	202	0.70	46	$C_{17}H_{14}NO_3SBr$ (391, 393, 395)	3.80 (3.58)
3j	OC_2H_5	Br	198	0.78	40	$C_{18}H_{16}NO_3SBr$	3.70 (3.45)

sorptions in the region 3150–2880 cm^{-1} due to O-H stretching vibrations, and sharp absorption at 1420–1390 cm^{-1} due to the deformation vibrations of C-O-H moiety which affirm the presence of carboxyl group. In addition, a broad intense absorption in the region 1610–1602 cm^{-1}, characteristic of ν C=N in seven membered heterocyclic compounds,[19] was observed. Moreover, C-Cl and C-Br stretching vibrations were characterised in the frequency region 1095–1085 and 1230–1220 cm^{-1}, respectively.

Absorption at 3000–2900 cm^{-1} and around 3050 cm^{-1} may be assigned to aliphatic and aromatic C-H stretching vibrations, respectively. Absorptions around 1600 and 1470 cm^{-1} were assigned to aromatic skeletal in-plane vibrations while the aromatic C-H deformation vibrations were observed in the frequency region 760–730 cm^{-1} (Table II).

In the ^1H NMR spectra, sharp absorptions were observed at δ 2.85–3.05, 3.40–3.65, 3.85–4.03, 6.10–7.20 and one broad absorption at δ 8.00–8.45. The signals corresponding to the methylene and methine protons at C-3 and C-2, respectively, were found to occur as double doublets in the ABX pattern. Each of the three double doublets were found to integrate for one proton. The two methylene protons gem-couple and give rise to a doublet with $^1J_{HH}$ of 15–16 Hz. Each of the two methylene protons also couple with the methine proton, and therefore the doublet signal again splits, this time, with a vicinal coupling con-

TABLE II Characteristic IR Absorption Bands of 8-Substituted-2-Carboxy-4-(4-Chlorophenyl or 4-Bromophenyl)-2,3-Dihydro-1,5-Benzothiazepines (**3a–j**)

Compd. No.	*IR absorption (cm^{-1})*							
	COOH absorptions				*Saturated*		*Aromatic*	
	ν(C=O)	*ν(O-H)*	*ν(C=N)*	*ν(C-Cl/Br)*	*ν(C-H)*	*δ(C-H)*	*ν(C-H)*	*δ(C-H)*
3a	1680s	3150b	1610s	1095s	3000w	1370w	3045w	760w
	1300w	3050						
3b	1685s	3050b	1600s	1085s	2950w	1375w	3100w	750w
	1310w	2980						
3c	1690s	3000b	1605s	1090s	2900w	1365w	3025w	745w
	1290w	2950						
3d	1685s	3010b	1602s	1085s	2980w	1375w	3050w	750w
	1305w	2890						
3f	1682s	3145b	1620s	1230s	2985w	1365w	3040w	765w
	1270w	3040						
3g	1685s	3010b	1608s	1225s	2980w	1362w	3030w	750w
	1275w	2890						
3h	1690s	3050b	1602s	1220s	2985w	1370w	3050w	740w
	1350w	2980						
3i	1690s	3140b	1610s	1224s	2955w	1365w	3040w	760w
	1310w	3045						
3j	1687s	3120b	1608s	1225s	2900w	1375w	3100w	735w
	1300w	2900						

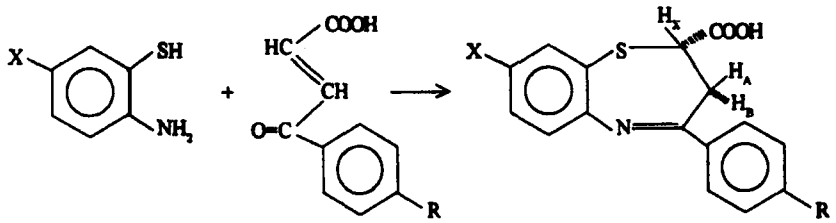
stant of 7–9 Hz, resulting into the formation of two almost identical double doublets. Out of these two double doublets, the one upfield, i.e. centering at δ 2.85–3.05, may be assigned to H_A (which is axial) while the other double doublet at δ 3.40–3.65 may be assigned to H_B (an equatorial one). The methine proton signal at δ 3.85–4.03 also occurs as a double doublet as it possesses two vicinal protons, the different values of coupling constants J_{AX} and J_{BX} may arise due to the axial and equatorial conformations of H_A and H_B (Table III). The absorption signal in the region δ 6.10–7.20 occurred as multiplets corresponding to the aromatic protons while the broad signal at δ 8.00–8.45, integrating for one proton was assigned to the carboxylic acid proton. The characteristic signals at δ 2.08 (s, 3 H, C-8-, CH_3); δ 3.56 (s, 3 H, C-8-OCH_3) and δ 1.22 (t, J = 8 Hz, 3 H), 3.46 (q, J = 8 Hz, 2 H) in the spectra of 3h, 3d and 3j, respectively, were distinctly identified (Table III). These observations correspond to our earlier reportings[10,20] observed in similar compounds structurally related to **3a–j**.

The mass spectrum of **3a** showed $[M]^+$, $[M + 2]^+$, and $[M + 4]^+$ as a cluster of ion peaks at 351, 353 and 355. The $[M]^+$, $[M + 2]^+$ and $[M + 4]^+$ cluster of mass ion peaks of almost equal intensity at 439, 441 and 443 were observed in

E III Characteristic ^1H NMR Spectral Data of 8-Substituted-2-Carboxy-2,3-Dihydro-4-(4-Chlorophenyl or 4-Bromophenyl)-1,5-Benzothia

	δ *in ppm, J in Hz*					
X	*COOH*	*C-2-H$_X$*	*C-3-H*		*C-8-X*	*AR*
			H$_A$	*H$_B$*		
Cl	8.44	4.04 (J_{AX} = 9,J_{BX} = 8)	2.92 (J_{AB} = 16,J_{AX} = 9)	3.44 (J_{AB} = 16,J_{BX} = 8)	–	6.32- (M,
Br	8.40	3.84 (J_{AX} = 9,J_{BX} = 8)	2.84 (J_{AB} = 16,J_{AX} = 9)	3.48 (J_{AB} = 16,J_{BX} = 8)	–	6.68- (M,
CH_3	8.00	4.84 (J_{AX} = 9,J_{BX} = 8)	2.88 (J_{AB} = 16,J_{AX} = 9)	3.36 (J_{AB} = 16,J_{BX} = 8)	2.26 (s,3 H)	6.48- (M,
OCH_3	8.48	4.00 (J_{AX} = 9,J_{BX} = 8)	2.96 (J_{AB} = 16,J_{AX} = 9)	3.40 (J_{AB} = 16,J_{BX} = 8)	3.56 (s,3 H)	6.20- (M,
Cl	8.40	3.84 (J_{AX} = 9,J_{BX} = 8)	2.80 (J_{AB} = 16,J_{AX} = 9)	3.20 (J_{AB} = 16,J_{BX} = 8)	–	6.00- (M,
Br	8.10	3.82 (J_{AX} = 9,J_{BX} = 8)	2.86 (J_{AB} = 16,J_{AX} = 9)	3.28 (J_{AB} = 16,J_{BX} = 8)	–	6.00- (M,
CH_3	7.25	3.89 (J_{AX} = 9,J_{BX} = 8)	2.80 (J_{AB} = 16,J_{AX} = 9)	3.41 (J_{AB} = 16,J_{BX} = 8)	2.08 (s,3 H)	6.10- (M,
OCH_3	8.20	3.85 (J_{AX} = 9,J_{BX} = 8)	2.81 (J_{AB} = 16,J_{AX} = 9)	3.30 (J_{AB} = 16,J_{BX} = 8)	3.41 (s,3 H)	6.15- (M,
OC_2H_5	7.50	3.82 (J_{AX} = 9,J_{BX} = 8)	2.82 (J_{AB} = 16,J_{AX} = 9)	3.30 (J_{AB} = 16,J_{BX} = 8)	1.22 (T,J8,3 H) 3.46 (Q,J8,2 H)	6.15- (M,

the mass spectrum of **3g** (Table I). The molecular ion peaks m/z ($[M]^+$ at 351 and 439 correspond to the molecular weight and affirm the presence of Cl and Br in **3a** and **3g**, respectively.



1 (a-e) **2 (a, b)** **(a, R = Cl; b, R = Br)** **3 (a-j)**

Compd. No.

3	*a*	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*
X	Cl	Br	CH_3	OCH_3	OC_2H_5	Cl	Br	CH_3	OCH_3	OC_2H_5
R	Cl	Cl	Cl	Cl	Cl	Br	Br	Br	Br	Br

EXPERIMENTAL

The melting points are uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer Infracord 881 spectrometer. ^1H NMR spectra were recorded in $CDCl_3$ on a Jeol 90 MHz. F.T. NMR spectrometer using tetramethylsilane as internal standard, while the mass spectra were recorded on a Varian Match-7 instrument at 70 eV. Microestimations for carbon, hydrogen and nitrogen were carried out at Central Drug Research Institute, Lucknow.

1. Preparation of 5-Substituted-2-Aminobenzenethiols (1a–e) was carried out in the laboratory using the literature methods.[11]

2. Preparation of (4-Chloro and 4-Bromobenzoyl)Acrylic Acids (2a,b)

Freshly distilled bromobenzene and chlorobenzene (31.4 ml and 22.5 ml; 0.20 mol), powdered maleic anhydride (20.6 g, 0.21 mol) and dry carbon disulfide (300 ml) were taken in a flask equipped with a mechanical stirrer and a dropping

funnel and cooled below 5°C by using an ice-bath. To the reaction mixture was added in small lots with stirring anhydrous aluminium chloride (56.0 g, 0.42 mol). After the addition of anhydrous aluminium chloride had been completed, the ice-bath temperature was maintained and stirring was continued for an additional 20 minutes. The ice bath was removed, and the stirring was continued for 4 hrs at room temperature. The flask was then warmed gently, and the stirring was continued for 2 hrs. The reaction mixture was cooled and then decomposed by the addition of 300 g of ice and 12% hydrochloric acid (10 ml). The resulting mixture was steam distilled, and the yellow residue obtained was extracted with diethyl ether, and crystallized from hot benzene to yield yellow crystals of (4-chloro- and 4-bromobenzoyl)acrylic acids (**2a**, m.p. 156°, lit.[12] 156–157°, yield, 21.54 g. 50% and **2b**, m.p. 158°, lit.[12] 158–159°, yield, 50%).

3. Synthesis of 2-Carboxy-4-(4-Chlorophenyl)-8-Ethoxy-2,3-Dihydro-1,5-Benzothiazepine (3e)

A mixture of 2-amino-5-ethoxybenzenethiol (**1e**: 0.169 g: 0.001 mol), and β-(4-chlorobenzoyl)acrylic acid (**2a**; 0.210 g; 0.001 mol) in dry methanol (10 ml) containing traces of glacial acetic acid (1 ml) were refluxed for 3 hrs. The resulting solution was cooled and concentrated. The residue obtained from the cool concentrate on crystallization from benzene afforded colorless crystals of 2-carboxy-4-(4-chlorophenyl)-8-ethoxy-2,3-dihydro-1,5-benzothiazepine (**3e**, yield, 0.187 g, 52%, m.p. 221°C. TLC, R_f, 0.75. Found: N, 4.33, $C_{18}H_{16}NO_3SCl$ requires N, 3.87%). IR: 3100–2900 cm^{-1}. ν (OH), 1690, ν (C═O), 1610, ν (C═N), 1090, ν (C-Cl). ^1H NMR: δ 2.92 (dd, J_{AB} = 16 Hz, J_{AX} = 9 Hz, H_A), 3.48 (dd, J_{AB} = 16 Hz, J_{BX} = 8 Hz, H_B), 3.88 (dd, J_{AX} = 9 Hz, J_{BX} = 8 Hz, H_X), 1.24 (3 H, t, J = 8 Hz, $OCH_2C\underline{H}_3$), 3.58 (2 H, q, J = 8 Hz, $OC\underline{H}_2CH_3$), 8.36 (b, COO$\underline{H}$). 6.52–7.48 (m, 7 H, Ar-H). MS: Calcd: 361; Found: m/z 361 $[M]^+$, 363 $[M + 2]^+$.

On similar lines, compounds **3a–d** and **3f–j** were prepared and characterized (Table I–III).

Acknowledgement

The authors are grateful for financial assistance received from U.G.C. and C.S.I.R. New Delhi. One of us (AS) is thankful to U.G.C. for the award of project assistantship. Thanks are also due to C.D.R.I. Lucknow for providing IR, mass spectra, and the analytical data.

References

[1] K. Akiyoshi, I. Hirozumi, N. Hiroshi, N. Taku, (Tanabe Seiyaku Co. Ltd.) *Eur. Pat. Appl.* EP416, 479 (1992) (Cl. CO&D 281/10), 13 Mar (1991); *JP. Appd.* 89/226, 506, 31 Aug (1989); *Chem. Abstr.*, **116**, 59415f.

[2] I. Hirozumi, K. Mikihiko, H. Iomiki, O. Hisao and T. Mikio, (Org. Chem. Res. Lab., Tanabe Seiyaku Co. Ltd., Toda Japan 335) *J. Med. Chem.* **3H(2)**, 675–87 (Eng) (1991).

[3] L. Alistair, M. J. Claude, H. Christian and D. Colombe, (Synthelabo S.A.) *Fur. Pat. Appl.* EP 320, 362 (1990) (Cl A61 K31/55), 14 Jan (1989); *Chem. Abstr.*, **112**, 172330e .

[4] N. Hiroshi and N. Hiroshi, (Tanabe Seiyaku Co. Ltd.) Jpn. Kokai Tokkyo Koho JP 03, 258, 721 (1992) [91, 258, 721] (Cl. A.61 K31/55), 19 No. (1991); *Chem. Abstr.*, **116**, 136275q.

[5] C. Francois, F. Daniel, H. Gilles and J. Simone, (Roussel - UCLAF) *Eur. Pat. Appl.* EP 394, 101 (1991) [Cl CO7 D281/10], 24 Oct. (1990); *Chem. Abstr.*, **114**, 164292v.

[6] I. Hirozummi and H. Trunehiro, (Tanabe Seiyaku Co. Ltd.) Fr. Demande FR 2, 623, 192 (1990) [Cl CO7D 281/10), 19 May (1989); Chem. Abstr., **112**, 55929w.

[7] I. Hitoshi, K. Kazuyuki and O. Akio, (Tanabe, Seiyaku, Co. Ltd.) Austrian AT 390, 880 (1991) (Cl. A61 K31/55), 10 Jul (1990); *Chem. Abstr.*, **115**, 22228a .

[8] R. M. Freidinger, M. G. Bock and B. E. Evans, (Merck & Co. Inc.) *Eur Pat. Appl.* EP 167, 919 (1987) [Cl. COTD 243/18] (1986); *Chem. Abstr.* **106**, 67359z; Z. Veidelek, M. Provita, Czech. CS 232, 783 (1987) [Cl. COTD 243/22] (1986), *Chem. Abstr.*, **106**, 84663m.

[9] R. N. Brogden, R. C. Heel, T. M. Speight and G. S. Avery, *Drugs*, **20(3)**, 161–78 (1980).

[10] U. C. Pant, B. S. Gaur and M. Chugh, *Indian J. Chem.*, **26B** 947 (1987); U. C. Pant and M. Chugh, *Indian J. Chem.*, **28B**, 435 (1987); U. C. Pant, S. Pant, A. Bhatia and A. Sharma, *Indian J. Chem.*, **33B**, 885 (1994).

[11] R. Q. Brevster and F. B. Dains, *J. Am. Chem. Soc.*, **58**, 1364 (1936).

[12] K. Kirchner, *J. Am. Chem. Soc.*, **81**, 1721 (1959).

[13] L. K. Mushkalo, *Zhur. Obscheikhim*, **28**, 507 (1958): *Chem. Abstr.*, **52**, 14627g.

[14] W. D. Stephens and L. Field, *J. Org. Chem.* **24**, 1576 (1959).

[15] A. Levai and R. Bogner, *Acta Chim. Acad. Sci.* (Hung) **92(4)**, 415 (1977).

[16] C. H. Hankovszky and K. Hideg, *Acta. Chim. Acad. Sci. Hung.*, **68**, 403 (1971).

[17] A. K. Gupta, V. K. Singh and U. C. Pant, *Indian J. Chem.*, **22B**, 1057 (1983) and references therein.

[18] A. Levai and H. Duddeck, *Pharmazie*, **38** 827 (1983).

[19] A. Levai and R. Bogner, *Acta Chim. Acad. Sci. Hung.*, **92**, 415; (1976) **88**, 293 (1976).

[20] U. C. Pant and M. Chugh, *Indian J. Chem.*, **28B**, 437 (1989) and references therein.