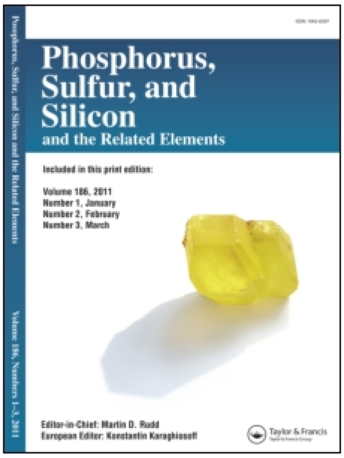

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SYNTHESIS AND CLEAVAGE REACTIONS OF BENZOTHIAZEPINYL CHROMONE DERIVATIVES

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A few benzothiazepinyl chromones (**II** & **IV**) were prepared by the reaction of 2-amino benzenethiol with new types of chromonyl chalcones (**I** & **III**). One representative compound (**IVb**) was cleaved with hydrazine hydrate and with hydroxylamine hydrochloride to afford pyrazole (V) and isoxazole (VI) derivatives. The structures of these compounds were confirmed by their analytical and spectral analysis. Some of the above compounds were screened for their anti-microbial activity.

Key words: Benzothiazepine; diastereotropic; chromonyl chalcones; fungicidal; antibacterial; ethereal oxygen cleavage.

Various derivatives of benzothiazepines are claimed to exhibit antibacterial,[1] anticonvulsant,[2] tranquilising,[1] antispasmodic,[3] neuroleptic,[4] antidepressent[5] and CNS activities.[6] Many chromone systems are reported to be most potent CNS stimulants.[7-10] Various alkoxy chromones are assayed as insecticides,[11] fish poisons[12] and haemostatic agents.[13] The medicinal importance of benzothiazepines and our earlier work on chromone system[14] inspired us to undertake a project on the synthesis of benzothiazepinyl chromones in a facile one step method. A few benzothiazepinyl chromones have been cleaved with hydrazine hydrate and hydroxylamine to form hitherto unknown heterocycles with pyrazole and isoxazole ring systems respectively.

Various chalcones[15] (**I** & **III**) are treated with 2-amino-benzenethiol in dry methanol containing catalytic amount of glacial acetic acid to afford 3-(3-aryl-2,3-dihydro-1,5-benzothiazepin-2-yl)-4H-1-benzopyran-4-ones (**II**) and 8-(2-aryl-2,3-dihydro-1,5-benzothiazepin-4-yl)-7-hydroxy-2,3-dimethyl-4H-1-benzopyran-4-ones (**IV**). All these compounds have been identified by their analytical and spectral data.

All these benzothiazepine derivatives prepared display a strong carbonyl absorption of the chromone ring around 1640 cm^{-1} in their IR spectra. The other IR bands appear at 1600 cm^{-1} (C=N), 1550 cm^{-1} (C=C), 1230–1050 cm^{-1} (C—O—C).

The methine and methylene protons of benzothiazepine nucleus gave an ABX pattern of lines in the PMR spectrum of **IIb**. Non-equivalence of methylene protons due to their diastereotropic nature, owing to the presence of a chiral center bearing the methine hydrogen, render them appear as two double doublets at δ 3.55 and δ 5.3. The downfield signal is attributed to one of the hydrogens of methylene group which assumes an equatorial position with respect to *p*-chlorophenyl group on the adjacent carbon. In contrast with earlier report,[16] the methine proton absorbs at a higher field, δ 2.48 probably due to the shielding effect of chromone carbonyl. The hydrogen on C—2 of chromone nucleus appears as a singlet at δ 8.4. A doublet integrating for two protons at δ 8.25 is assignable to one of the pairs of hydrogens present on *p*-chlorophenyl ring. The other two hydrogens along with rest of the phenyl ring appear as a complex multiplet spreading over in the region of δ 7.1–7.8 for ten protons.

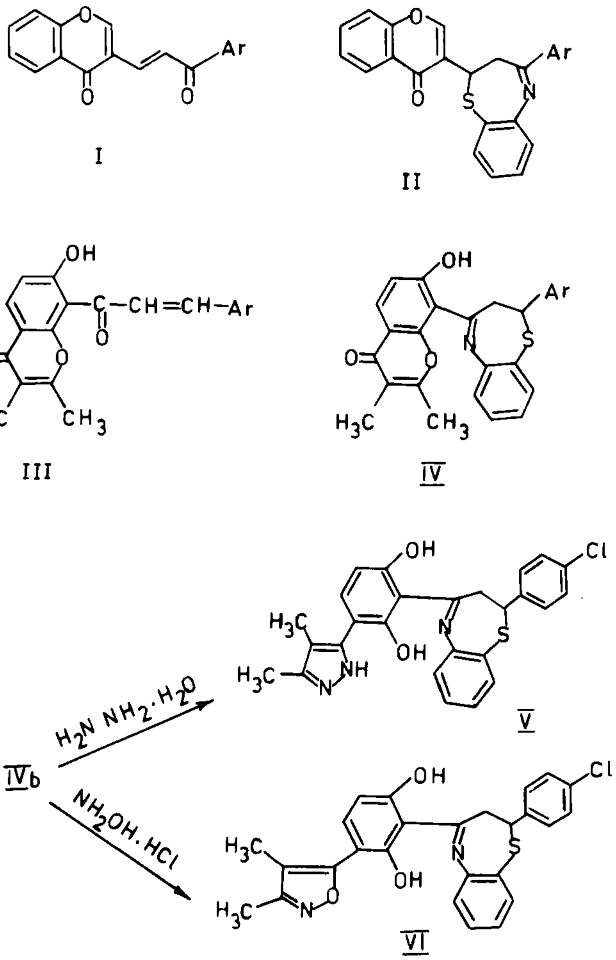
In the PMR spectrum of **IVc**, an upfield signal integrating for three protons at δ 1.9 is observed which may be ascribed to methyl group on phenyl ring. The two sharp signals at δ 2.1 and δ 2.2 are due to the two methyl groups attached to chromone ring. A characteristic ABX pattern of lines are also observed for methine and methylene protons of benzothiazepine nucleus in the aliphatic region, while the former appears as triplet at δ 3.1, the absorption due to methylene hydrogens appear as two double doublets at δ 3.65 and δ 5.0. A doublet integrating for two protons at δ 7.8 is due to two hydrogens present on *p*-tolyl group. A cluster of peaks in the region of δ 6.5 to δ 7.3 arise due to eight phenyl ring hydrogens. However, the absorption of phenolic hydroxylic proton did not appear below δ 10.0.

The structures of the above compounds are also confirmed by their mass spectra. The molecular ion for **IIb** is recorded at *m/z* 417 with M + 2 peak due to the isotopic contributions of chlorine and sulphur. The base peak at *m/z* 245 comes from the loss of chromonylethylene, recorded at *m/z* 172, from M+ ion. The molecular ion also suffers a loss of *p*-chlorobenzonitrile to give a fragment recorded at *m/z* 108. The other peaks of major fragments appear at *m/z* values of 384, 306, 280, 259, 210, 158, 108.

The molecular ion of **IVd** is recorded with appreciable intensity at *m/z* 461. In a similar type of cleavage, as observed in **IIb**, the base peak at *m/z* 324 results from the loss of *o*-chlorophenylethynyl ion, recorded at *m/z* 137, from M+ ion. The fragmentation pattern is very similar to that of **IIb**. The major peaks are at *m/z* values of 336, 308, 272, 252, 246, 215, 195.

To know the nature and reactivity of chromonyl benzothiazepines, one representative compound **IVb** has been reacted with hydrazine hydrate in alcohol. It is interesting to note that the pyrone ring is cleaved at ethereal oxygen to form 2-[2-(4-chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-4-yl]-4-(3,4-dimethyl-1H-pyrazol-5-yl)-1,3-benzenediol (**V**). The same type of cleavage is observed when **IV** is treated with hydroxylamine hydrochloride in pyridine to afford 2-[2-(4-chlorophenyl)-2,3-dihydro-1,5-benzothiazepin-4-yl]-4-(3,4-dimethyl-5-isoxazolyl)-1,3-benzenediol (**VI**) (Scheme 1). Both these products have been identified by their analytical and IR data.

Absence of the carbonyl absorption around 1640 cm^{-1} in the spectra of both the cleaved products (**V** and **VI**) confirms the involvement of chromone carbonyl in the reaction. Very broad absorption in the region of 3400 cm^{-1} indicates the presence of intramolecularly hydrogen bonded hydroxyl groups. Strong peaks at 1590 and 1600 cm^{-1} are due to C═N stretchings. A weak absorption around 1120 cm^{-1} is due to O—N stretchings of isoxazole system of **VI**.



SCHEME 1

BIOLOGICAL SCREENING

Antibacterial activity: A few selected compounds of the type **II** and **IV** are screened against *Bacillus megaterium* and *Proteus vulgaris* by adopting Vincent and Vincent filter paper disc method[17] at 400 and 600 μg/ml concentrations. All the compounds tested, registered a feeble activity against *B. megaterium,* but virtually inactive against *P. vulgaris.*

Antifungal activity: The compounds employed for antibacterial screening are also assayed against fungi. The testing is carried out by following glass-slide humid chamber technique[18] against *Dreschlera speciferum* and *Fusarium solani* at 360, 600 and 840 μg/ml concentrations. The activity is measured as the percentage of spore gemination inhibition. Compounds of the type **II** are found to lack in the fungicidal activity. Compound **IVa** is highly toxic to both the fungi and hence can be exploited for the fungicidal formulation, while **IVb** registered a moderate toxicity towards both the fungi.

EXPERIMENTAL

Melting points were uncorrected. The IR data were obtained for KBr discs with Perkin-Elmer Model-283 instrument. The PMR spectra were measured at 90 MHz on Varian A-90 spectrometer using TMS as internal standard. Mass spectra were recorded on JMS-D 300 mass spectrometer at 70 eV. The physical and analytical data are given in Table I.

Synthesis of benzothiazepinyl chromones: General procedure. 2-Aminobenzenethiol (0.01 mol) and appropriate chalcone (**I** or **III**, 0.01 mol) were dissolved in anhydrous methanol (50 ml) to which glacial acetic acid (3 ml) was added. The mixture was refluxed for 2 hrs and cooled. The solid separated was filtered and washed with fresh methanol. It was purified from a suitable solvent.

TABLE I

Physical and analytical data of the compounds (**II** and **IV**)

Comp. no.	Ar[a]	Mol. formula	M.P. °C	Yield %	Analyses[b] Found (calcd.)		
					C	H	N
IIa	Phenyl	$C_{24}H_{17}NO_2S$	174–5	52	75.20 (75.19)	4.42 (4.43)	3.66 (3.65)
b	*p*-chlorophenyl	$C_{24}H_{16}ClNO_2S$	195–6	56	68.90 (68.98)	3.55 (3.59)	3.34 (3.35)
c	*p*-methylphenyl	$C_{25}H_{19}NO_2S$	82–3	50	75.50 (75.56)	4.75 (4.78)	3.50 (3.52)
d	*p*-methoxyphenyl	$C_{25}H_{19}NO_3S$	186–7	53	72.00 (72.63)	4.55 (4.59)	3.35 (3.38)
IVa	Phenyl	$C_{26}H_{21}NO_3S$	228–9	55	73.00 (73.06)	4.62 (4.69)	3.25 (3.27)
b	*p*-chlorophenyl	$C_{26}H_{20}ClNO_3S$	235–6	54	67.55 (67.60)	4.35 (4.33)	3.00 (3.03)
c	*p*-tolyl	$C_{27}H_{23}NO_3S$	204–5	48	73.41 (73.46)	5.20 (5.21)	3.18 (3.17)
d	*o*-chlorophenyl	$C_{26}H_{20}ClNO_3S$	220–1	55	67.50 (67.60)	4.30 (4.33)	3.00 (3.03)
e	3,4-dimethoxy phenyl	$C_{28}H_{25}NO_5S$	212–3	48	68.90 (68.99)	5.08 (5.13)	2.83 (2.87)
f	*p*-methoxyphenyl	$C_{27}H_{23}NO_4S$	194–5	56	70.83 (70.89)	5.00 (5.03)	3.00 (3.06)
g	*p*-dimethylamino-phenyl	$C_{28}H_{26}N_2O_3S$	208–9	49	71.44 (71.48)	5.51 (5.53)	5.96 (5.95)
h	*o*-hydroxyphenyl	$C_{26}H_{21}NO_4S$	225–6	48	70.38 (70.42)	4.71 (4.73)	3.16 (3.15)
i	2-hydroxy-1-naphthyl	$C_{30}H_{23}NO_4S$	243–4	46	73.00 (73.90)	4.64 (4.66)	2.85 (2.83)

[a] Compounds **IIa–d** are recrystallised from benzene while **IVa–i** are purified from dioxane.

[b] Analysis for sulphur also found satisfactory.

Preparation of cleaved products. (A) Compound **IVb** (4.61 g) was dissolved in ethanol (20 ml) and hydrazine hydrate (1 ml) was added and refluxed for 30 min. The reaction mixture was concentrated and poured over crushed ice to get a milky solution. The compound (**V**) was separated on acidifying the reaction mixture. It was filtered, washed, dried and purified from benzene (2.94 g; 62%). m.p. 178°C. (Found: C, 65.64; H, 4.61; 8.81%. $C_{22}H_{22}ClN_3O_2S$ requires C, 65.68; H, 4.63; N, 8.84%).

(B) Hydroxylamine hydrochloride (1 g) in water (1 ml) was added to a solution of compound **IVb** (4.61 g) in pyridine (20 ml) and the mixture was refluxed for 3 hrs. It was concentrated and diluted with ice cold water. It was neutralised with acetic acid and the colourless mass was filtered, washed, dried and recrystallised from benzene (2.85 g; 60%). m.p. 172°C. (Found: C, 65.44; H, 4.38; N, 5.85%. $C_{26}H_{21}ClN_2O_3S$ requires C, 65.47; H, 4.40; N, 5.87%).

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