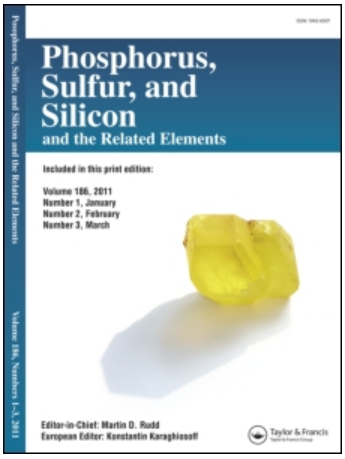

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SYNTHESIS OF DIHYDRO-2-(2-PHENYL-INDOLE-3-YL)-4-ARYL-1,5-BENZOTHIAZEPINES

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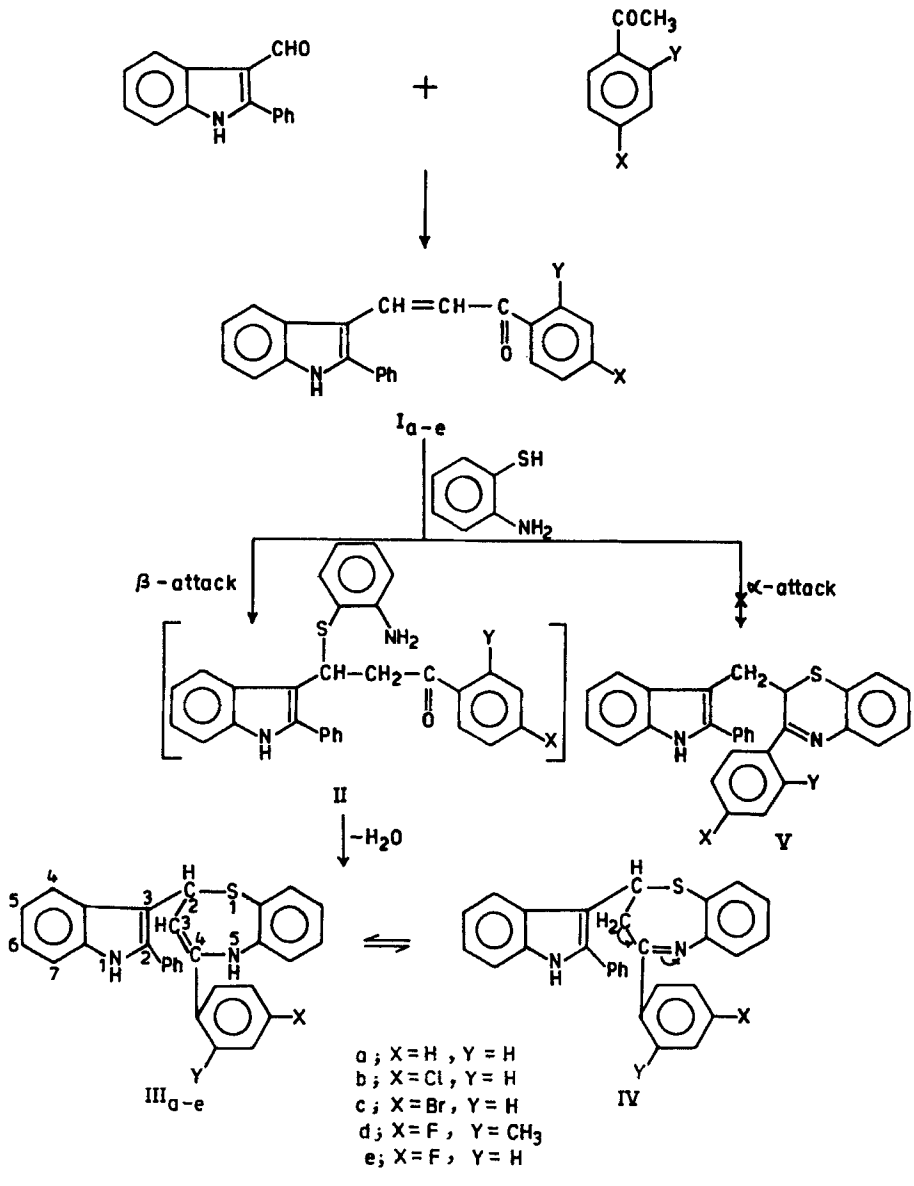
A series of novel dihydro-2-(2-phenyl-indole-3-yl)-4-aryl-1,5-benzothiazepines (**III**) have been synthesized by the reaction of 2-aminothiophenol with 2-phenyl-3-(3-aryl-3-oxo-propen-1-yl)-indoles (**I**) in ethanol and gl. acetic acid mixture. Chalcones (**I**) were prepared by the reaction of 2-phenyl-1H-indole-3-carboxaldehyde with substituted acetophenones in ethanolic sodium hydroxide. The compounds have been characterized on the basis of elemental and spectral studies and were screened for their antifungal and antibacterial activities.

Key words: Benzothiazepines, antibacterial activity, biological activity, IR, NMR, mass spectra.

The importance of the benzothiazepine class of compounds having antihypertensive, cerebral or coronary vasodilating activity[1] is well known. The interesting biological activity shown by diltiazem,[2] and thiazesim[3] stimulated great interest and enthusiasm to synthesize a large number of 1,5-benzothiazepine derivatives having different substituents at different positions. One of the most recent cardiovascular and psychopharmacological drugs belonging to the 1,5-benzothiazepine class is diltiazem,[4] which possesses *p*-anisyl group at position-2. The presence of a methoxyl group in the phenyl ring located at position-2 in 1,5-benzothiazepine in the popular drug, 'diltiazem' attracted our attention to synthesize 1,5-benzothiazepines having a substituted penyl/aryl ring at position-2, alone, or along with other groups. The indole nucleus also possesses diverse biological activities such as antibacterial[5] antiviral,[6,7] antimicrobial,[8] amoebicidal,[9] fungicidal,[10] etc. Indoles are also used as drug intermediates[11,12] and antirheumatic[13] and antitumor agents.[14] Indole-3-carboxaldehyde derivatives are commonly used as intermediates for pharmaceuticals[15,16] and as agrochemicals.[17] We were surprised to note from perusal of the literature that dihydro-1,5-benzothiazepines incorporating an indole moiety have not been synthesized so far. Hence we tried to synthesize dihydro-2-(2-phenyl-indole-3yl)-4-aryl-1,5-benzothiazepine by introducing indole ring at position-2 of 1,5-benzothiazepine. In continuation of our earlier interest on the synthesis of bioactive sulfur- and nitrogen-containing heterocycles,[18–22] we now report the synthesis and characterization of some novel 2-phenyl-3-(3-aryl-3-oxo-propen-1-yl)-indoles 2,3-dihydro-2-(2-phenyl-indole-3-yl)-4-aryl-1,5-benzothiazepines.

DISCUSSION

2,3-dihydro-2-(2-phenyl-indole-3-yl)-4-aryl-1,5-benzothiazepines were prepared in one step by the reaction of 2-aminothiophenol with 2-phenyl-3-(3-aryl-3-oxo-propen-1-yl)-indole (**I**) in ethanol and gl. acetic acid mixture. The compounds (**I**) were



SCHEME I

synthesized by the reaction of 2-phenyl-1H-indole-3-carboxaldehyde with substituted acetophenones in ethanolic sodium hydroxide.

The title reaction appeared interesting in view of the fact that compound **I** having an α, β-unsaturated system might react in different fashions as observed in analogous type of reactions[23-27] yielding a variety of products (**III**, **IV**, **V**). The nucleophilic attack of the electrons of the sulphhydryl group of 2-aminothiophenol at β-position of the α,β-unsaturated chalcone (**I**), as expected, may result in the formation of the dehydro type of products (**III**).

The structure of the synthesized compounds were further established by IR, PMR and mass spectra studies. Elemental and physical data are given in Table I. The synthesized compounds have been screened for their antifungal activity against *Rhizoctonia solani* and antibacterial activity against gram negative bacteria *Escherichia coli* and gram positive bacterial *Staphylococcus albus*. Table II includes the spectra data of the synthesized compounds whereas results of antifungal and antibacterial activities are reported in Tables III and IV.

IR Spectra

The IR spectra of chalcones **I** showed characteristic absorption bands at 3300–3100 (N—H) and 1620 cm^{-1} (conjugated keto group). Formation of compounds **IIIa–e** instead of **IV** may depend on the electron withdrawing effect of the substituent present. The formation of compounds **IIIa–e** were confirmed by the disappearance of carbonyl absorptions at 1620 cm^{-1} and appearance of C=C absorptions at 1600 cm^{-1}. Further, NH stretching was observed at 3250–3100 cm^{-1}, while C=N stretching did not appear.

TABLE I

Physical and analytical data of the compounds **Ia–e** and **IIIa–e**

S.No.	Compounds X	Y	M.P. (°C)	% (yield)	Molecular Formula	Anals. % Found (Cal) C	N	S
Ia	H	H	235	80	$C_{23}H_{17}ON$	85.22 (85.44)	4.56 (4.33)	–
Ib	Cl	H	239	75	$C_{23}H_{16}ONCl$	77.00 (77.20)	3.61 (3.92)	–
Ic	Br	H	230	82	$C_{23}H_{16}ONBr$	68.62 (68.82)	3.67 (3.49)	–
Id	F	CH_3	239	76	$C_{24}H_{18}ONF$	81.24 (81.12)	4.06 (3.94)	–
Ie	F	H	235	78	$C_{23}H_{16}ONF$	80.78 (80.93)	4.02 (4.10)	–
IIIa	H	H	260	37	$C_{29}H_{22}N_2S$	81.02 (80.93)	6.20 (6.51)	7.90 (7.44)
IIIb	Cl	H	>360	40	$C_{29}H_{21}N_2ClS$	75.14 (75.00)	5.85 (6.03)	6.55 (6.89)
IIIc	Br	H	>360	35	$C_{29}H_{21}N_2BrS$	68.12 (68.50)	5.10 (5.51)	6.50 (6.29)
IIId	F	CH_3	>360	42	$C_{30}H_{23}N_2FS$	77.49 (77.92)	6.02 (6.06)	6.78 (6.92)
IIIe	F	H	>360	40	$C_{29}H_{21}N_2FS$	77.42 (77.67)	6.05 (6.25)	7.26 (7.14)

TABLE II

IR and NMR data of the compounds **IIIa–e**

Compound No.	IR (cm^{-1})	^1H NMR (δppm)			
		-CH	Ar-H and =CH	NH (indole)	NH
IIIa	3250-3150,1600,1550,1420,1350, 1300,1220,1150,1060,1010,900	2.54 (d,1H)	7.16-7.97 (m,18H)	10.05 (s,1H)	12.19 (s,1H)
IIIb	3250-3100,1600,1550,1420,1360, 1300,1210,1150,1060,1000,900	2.58 (d,1H)	7.14-7.98 (m,18H)	10.05 (s,1H)	12.19 (s,1H)
IIIc	3240-3140,1600,1550,1410,1350, 1300,1210,1150,1050,1000,900	2.54 (d,1H)	7.16-7.98 (m,18H)	10.05 (s,1H)	12.18 (s,1H)
IIId	3250-3100,1600,1550,1420,1350, 1300,1210,1150,1060,1010,900	2.56 (d,1H)	7.16-7.97 (m,17H)	10.05 (s,1H)	12.19 (s,1H)
IIIe	3250-3120,1600,1550,1410,1360, 1300,1210,1150,1060,1010,900	2.56 (d,1H)	7.16-7.97 (m,18H)	10.05 (s,1H)	12.19 (s,1H)

TABLE III

Antifungal activity of compounds **I** and **III**

Compound	Growth of Fungi	Growth of Check	A.I.*
Ia	0.71 mm	3.21 mm	0.22
Ib	0.24 mm	1.39 mm	0.17
Id	0.91 mm	3.10 mm	0.29
Ie	0.18 mm	0.98 mm	0.18
IIIa	0.68 mm	3.10 mm	0.21
IIIb	0.11 mm	1.92 mm	0.05
IIId	0.71 mm	3.48 mm	0.20
IIIe	0.15 mm	1.85 mm	0.08

* AI (Activity Index) = Growth of fungi/Growth of Check

TABLE IV

Compound	E.Coli	S.Albus	Standard Strain for comparison (NCTC 6571)
Ia	R	10 mm (P.S.)	8 mm (P.S)
Ib	R	10 mm (P.S.)	8 mm (P.S.)
Ic	10 mm (P.S.)	8 mm (P.S.)	10 mm (P.S.)
Id	12 mm (P.S.)	12 mm (P.S.)	8 mm (P.S.)
IIIe	10 mm (P.S.)	12 mm (P.S.)	10 mm (P.S.)
IIIa	10 mm (P.S.)	8 mm (P.S.)	10 mm (P.S.)
IIIb	14 mm (S.)	14 mm (S.)	10 mm (P.S.)
IIIc	12 mm (P.S.)	12 mm (P.S.)	12 mm (P.S.)
IIIe	14 mm (S.)	12 mm (P.S.)	10 mm (P.S.)

R = Resistant range < 8 mm per disc

P.S. = Partial sensitive range 8 mm to 12 mm per disc

S. = Sensitive range > 12 mm per disc

^1H and ^{19}F NMR Spectra

The PMR spectra of compounds **I**, the trans-olefinic α- and β-protons of chalcones absorbed as a pair of widely spaced doublets (J = 15 Hz each) at δ7.0 and 7.9, respectively. However, these doublets are coalesced with aromatic protons. The aromatic protons appeared as complex multiplets in the region δ7.4–8.2 and NH protons observed around 10.05 ppm.

In compounds (**IIIa–e**), the —C—H proton signal was clearly observed in the region δ2.54–2.58 ppm. The doublet signal for =C—H proton merged with aromatic protons in the region δ7.14–7.98 ppm. The indole NH signal is observed in the region at 10.05 ppm[28,29] along with the benzothiazepine NH in the region at 12.19 ppm.[30,31] The absence of —CH_2 protons signal and the presence of thiazepine NH signals not only rule out the probability of structure **IV** and **V** but expediently substantiate the structure **III**. The single fluorine attached to the aryl ring in compound (**IIId**, **IIIe**) appeared as a single at δ − 110.10 ppm.

Mass Spectra

The mass spectrum of the compound **Ia** has shown a molecular ion peak M^+ at 323 (45%) corresponding to its molecular mass. In compound **IIIa**, molecular ion peak was not observed but a characteristic peak was observed at 353 $(M\text{-}77)^+$ (40%) by the loss of a phenyl ring. The peaks at M/Z 220 (100%) and 42 (100%) form the base peaks in the spectra respectively.

EXPERIMENTAL

Melting points were determined on a Toshniwal melting point apparatus, (capillary method) are uncorrected. The purity of the synthesized compounds was tested by thin layer chromatography on silica gel in various non-aqueous solvents. IR spectra were recorded in KBr on a Perkin Elmer 577 granting spectrometer (ν max in cm^{-1}), PMR spectra in $CDCl_3$ and TFA on a Jeol FX 90 Q (89.55 MHZ) using TMS as internal reference (^{19}F NMR on the same instrument) and mass spectra were recorded on a Kratz 30 and 50 mass spectrometer at 70 eV.

(i) 2-phenyl-3-(3-aryl-3-oxo-propen-1-yl)-indoles (**Ia–e**): A mixture of 2-phenyl-1H-indole-3-carboxaldehyde[32] (0.01 mole) and the appropriate acetophenone[33] (0.01 mole) was dissolved in ethanol (50 ml). To this mixture 40% NaOH (10 ml) was added to make the solution alkaline. The solution was stirred for 12 hrs. at room temperature. This was further diluted with H_2O (50 ml) to get the yellow precipitate which was filtered, dried and recrystallized from ethanol to give compounds (**Ia–e**).

(ii) 2,3-Dihydro-2-(2-phenyl-indole-3-yl)-4-aryl-1,5-benzothiazepine (**IIIa–e**): A mixture of **I** (0.01 mole) and 2-aminothiophenol (0.01 mole) in ab. ethanol (30 ml) and one drop of glacial acetic acid was refluxed for 20 days. The solid thus separated out was filtered, dried and recrystallized from benzene to give title compounds (**IIIa–e**).

Antifungal Activity

Synthesized compounds were dissolved in 20% alcohol and compounds were prepared in 500 ppm concentration. These concentrations were screened against the fungus *Rhizoctonia solani* in three replications by 'bit' method. Standard checks were also prepared by inoculating fungi in potato dextrose media for comparison. After 4–5 days, areas of fungal colony were recorded, which are given in Table III.

Antibacterial Activity

The Kirby-Bauer method[34] was used in screening the ethanolic solution of compounds for the antibacterial activity. Ethanolic solutions of the compounds were screened against the gram negative bacteria *Escherichia coli* and gram positive bacteria *Staphylococcus albus* by the whatmann filter paper discs. The areas of inhibition of the growth of bacteria, produced by diffusion of compounds from discs into the surrounding medium were measured. The Oxford strain of Staphylococcus albus (NCTC 6571) was used as standard strain for comparison. The results obtained are given in Table IV.

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