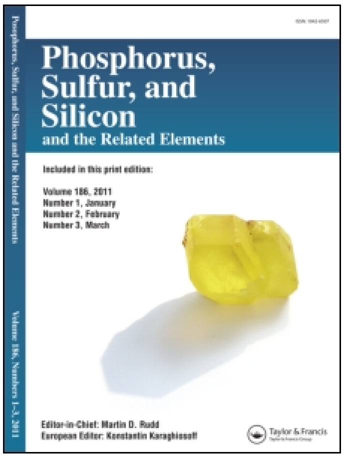


**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# ELEGANT SYNTHESIS OF SOME NOVEL SPIRO [BENZOTHIAZEPINE-INDOLE] DERIVATIVES

Anshu Dandia[a]; Varinder Kaur[a]; Pahup Singh[a]
[a] Department of Chemistry, University of Rajasthan, Jaipur, India

**To cite this Article** Dandia, Anshu , Kaur, Varinder and Singh, Pahup(1992) 'ELEGANT SYNTHESIS OF SOME NOVEL SPIRO [BENZOTHIAZEPINE-INDOLE] DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 69: 3, 277 — 281

**To link to this Article: DOI:** 10.1080/10426509208040647

**URL:** http://dx.doi.org/10.1080/10426509208040647

*Phosphorus, Sulfur, and Silicon,* 1992, Vol. 69, pp. 277–281
Reprints available directly from the publisher
Photocopying permitted by license only

# ELEGANT SYNTHESIS OF SOME NOVEL SPIRO [BENZOTHIAZEPINE-INDOLE] DERIVATIVES

ANSHU DANDIA,* VARINDER KAUR and PAHUP SINGH
*Department of Chemistry, University of Rajasthan, Jaipur 302004, India*

*(Received October 23, 1991; in final form January 2, 1992)*

The synthesis of some novel sulfur-containing spiroindole derivatives is reported, 2,3-Dihydrospiro [cycloalka[3,4][1,5] benzothiazepine-2,3′-[3H]indole]-2′-(1′H)-ones (V) were prepared by the reaction of 1,3-dihydro-3-(2-oxocycloalkylidene)indole-2(1H)-one (II) with 2-aminothiophenol in dry toluene. The compounds have been characterized on the basis of elemental and spectral studies.

*Key words:* Sulfur-containing spiroindoles; benzothiazepine; 3-(2-oxocycloalkylidine) indole; 2-aminothiophenol.

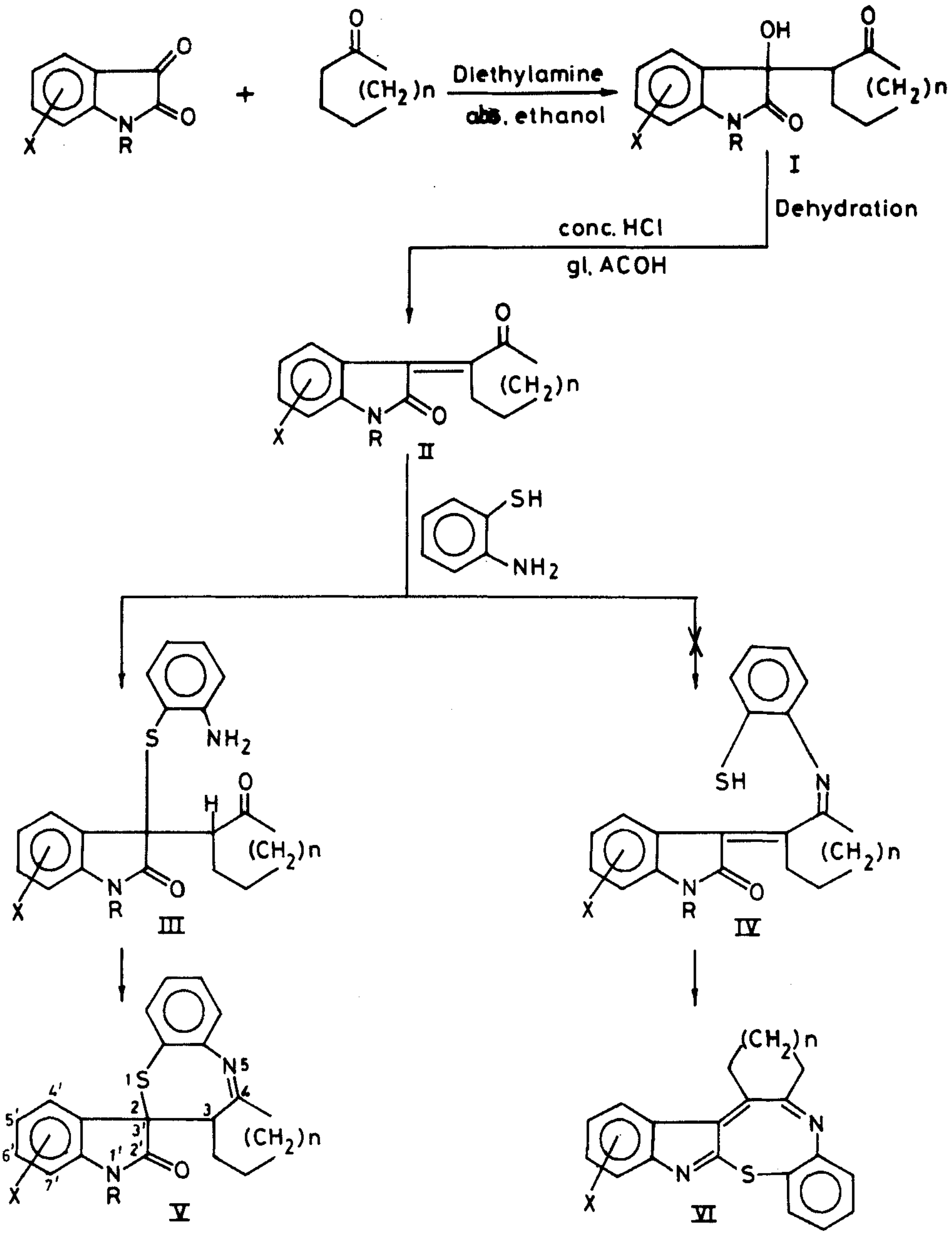
## INTRODUCTION

The successful therapeutic utilization of diltiazem,[1] thiazesim,[2] etc. with superior cardiovascular activity and pharmacological properties to barbiturates, meprobamates, phenothiazines and Raumolfia serpentina (sarpgandha-H) alkaloids[3] attracted the attention of chemists and pharmacologists worldwide to 1,5 and 1,4-benzothiazepine classes of compounds. The indole derivatives[4,5] are also well known potentially bioactive compounds, yet spiroindole derivatives incorporating both thiazepine and indole moieties have not been synthesized. In continuation to our earlier work on the synthesis of spiroindole derivatives,[6–10] we now report in this communication the synthesis and characterization of some spiroindole-benzothiazepines (V); this is the first report of such sulfur-containing spiro indole derivatives.

## DISCUSSION

2,3-Dihydro spiro[cycloalka[3,4][1,5] benzothiazepine-2,3′-[3H] indole]-2′-(1′H)-ones (**Va–e**) were prepared in one step by the reaction of 2-aminothiophenol with equimolar amounts of 1,3-dihydro-3-[2-oxocycloalkylidine] indole-2(1H)-one (**II**) in dry toluene. The compounds (**II**) were synthesized by the Knoevenagel reaction of indole-2,3-diones with cyclic ketones (cyclopentanone/cyclohexanone) in the presence of diethylamine as a basic catalyst, followed by dehydration in concentrated hydrochloric acid and glacial acetic acid medium.

The title reaction appeared interesting in view of the fact that compounds (**II**) having two $\alpha$, $\beta$-unsaturated systems can react in different fashion or may undergo condensation involving both the carbonyl groups, yielding a variety of products (**III, IV, V, VI**). In the present study reaction involves the nucleophilic attack by the sulphhydryl electrons of 2-aminothiophenol, rather than by the lone pair of electrons of the amino group, at the $\beta$-carbon of the $\alpha$, $\beta$-unsaturated carbonyl system of the side chain, leading to the formation of Michael type adducts as



n = 1,2; R = H, $CH_3$; X = H, 5-F.

SCHEME 1

intermediate (**III**) instead of (**IV**). The intermediate **III** then undergo dehydrative cyclization at amino and carbonyl groups to give 2,3-dihydro-1,5-benzothiazepines (**V**).[11-13] The intermediate (**IIIe**) has been isolated in one case and then cyclised to give the final product. In the rest of the cases the final products were directly

TABLE I

Physical and analytical data of the compounds **Va–e***

| S. | Compounds | | | % | Molecular | Anals. % Found (Cal) | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. | R | X | n | Yield | Formula | C | H | N | S |
| Va | H | H | 1 | 55 | $C_{19}H_{16}ON_2S$ | 71.65<br>(71.25) | 5.36<br>(5.00) | 8.88<br>(8.75) | 10.90<br>(10.00) |
| Vb | H | H | 2 | 45 | $C_{20}H_{18}ON_2S$ | 70.98<br>(71.85) | 5.28<br>(5.38) | 8.81<br>(8.38) | 10.00<br>(9.58) |
| Vc | H | 5-F | 1 | 52 | $C_{19}H_{15}ON_2FS$ | 67.89<br>(67.45) | 4.49<br>(4.43) | 8.19<br>(8.26) | 9.58<br>(9.46) |
| Vd | H | 5-F | 2 | 48 | $C_{20}H_{17}ON_2FS$ | 68.71<br>(68.18) | 4.90<br>(4.82) | 7.80<br>(7.95) | 9.42<br>(9.09) |
| Ve | $CH_3$ | H | 2 | 50 | $C_{21}H_{20}ON_2S$ | 72.89<br>(72.41) | 5.69<br>(5.74) | 8.10<br>(8.04) | 9.00<br>(9.19) |

• Melting point of all compounds exceeded 360°C.

TABLE II

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

| | | $^1H$ NMR ($\delta$ ppm) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| S.No. | IR ($cm^{-1}$) | $C\underline{H}_2$-$C\underline{H}_2$/$C\underline{H}_2$ | CH-$C\underline{H}_2$ | N-$C\underline{H}_3$ | N=C-$C\underline{H}_2$ | C-H | Ar-$\underline{H}$ | NH |
| Va | 3390-3350; 1690; 1600 1460; 1300; 1020; 750 | 1.27-1.67 (m, 2H) | 2.81 (m, 2H) | - | 4.42-4.54 (t, 2H) | 4.54-4.62 (dd, 1H) | 6.56-7.40 (m, 8H) | 9.70 (br) |
| Vb | 3410-3380; 1715; 1625; 1490; 1375; 1235; 1108; 800 | 1.26-1.67 (m, 4H) | 2.37 (m, 2H) | - | 3.21-3.50 (t, 2H) | 4.29-4.60 (dd, 1H) | 6.75-7.92 (m, 8H) | 9.12 (br) |
| Vc | 3400-3350; 1700; 1625; 1480; 1330; 1230; 1100; 760 | 1.27-1.70 (m, 2H) | 2.84 (m, 2H) | - | 4.34-4.54 (t, 2H) | 4.54-4.62 (dd, 1H) | 6.68-8.12 (m, 7H) | 9.72 (br) |
| Vd | 3410-3350; 1710; 1625; 1475; 1335; 1235; 1080; 750 | 1.26-1.67 (m, 4H) | 2.34 (m, 2H) | - | 3.31-3.52 (t, 2H) | 4.30-4.59 (dd, 1H) | 6.80-8.32 (m, 7H) | 9.30 (br) |
| Ve | 1707; 1625; 1475; 1335; 1225; 1020; 755 | 1.20-1.60 (m, 4H) | 2.21 (m, 2H) | 2.74 (s, 3H) | 3.28-3.48 (t, 2H) | 4.35-4.62 (dd, 1H) | 7.23-8.17 (m, 8H) | - |

obtained without intermediates being isolated. The structures of the synthesized compounds were further established by IR, PMR and mass spectral studies. Elemental and physical data are given in Table I. The synthesized compounds have been screened for antifungal activity against *Alternaria alternata* at 1000 ppm. None of them showed promising activity. Screening for CNS activity is under progress, and results will be reported elsewhere.

### *IR Spectra*

The IR spectrum of the intermediate ketone **IIIe** (X = H, R = Me) shows absorptions at 3340 (N—H, asym), 3300 (N—H, sym) and both CO absorptions at 1700 and 1670 $cm^{-1}$. Absence of absorption in the region 2650–2550 $cm^{-1}$ indicated the absence of a thiol group.

The IR spectra of compounds **Va–e** show the retention of NHCO absorption at 1715–1690 $cm^{-1}$ and complete disappearance of conjugated C=O absorption of cyclic ketone at 1670 $cm^{-1}$ indicating the participation of the $\alpha$, $\beta$-unsaturated carbonyl system of **II**, thereby leading to the formation of spiroheterocyclic compounds at position-3 of the 2-oxoindoles, as reported earlier.[6] Further, expected NH frequency at ca. 3400 $cm^{-1}$ appeared for **Va–Vd** but not for the NMe compound **Ve**.

### *$^1H$ and $^{19}F$ NMR Spectra*

The PMR spectra of these compounds (**III** and **Va–e**) show characteristic resonance of the corresponding cycloalkyl ring in the region at $\delta$ 1.12–5.38 ppm along with aromatic protons in the region at $\delta$ 6.56–8.32 ppm. All numbers of protons met at expectation in PMR spectra. In compound **IIIe** a broad signal at $\delta$ 10.05 ppm due to the —$NH_2$ group was also observed which disappeared on deuteration, while in compounds (**Va–d**) the indole NH signal is observed in the region at $\delta$ 9.12–9.72 ppm, as reported earlier[6,7] but **Vd** showed singlet at $\delta$ 2.74 ppm due to N—Me protons. The single fluorine attached to the indole ring at position 5 in compound (**Vc**, **Vd**) appeared as a singlet at $\delta$-115 and -112 ppm.

### *Mass Spectra*

The mass spectra of compounds **IIIe**, **Vb** and **Ve** showed molecular ion peaks $M^+$ at 366; 30% (**IIIe**), 334; 28% (**Vb**) and 348; 22% (**Ve**) corresponding to their molecular masses. The characteristic peak was observed at $M^+$-28 in mass spectra of all the compounds either by the loss of neutral CO or the $C_2H_4$ molecule. The peak at m/z, 42 corresponding to the cyclopropyl cation forms the base peak in the spectrum.

## EXPERIMENTAL

Melting points, determined on a Toshniwal melting point apparatus, (capillary method) are uncorrected. The purity of the synthesized compounds was assured by thin layer chromatography on silica gel in various nonaqueous solvents. IR spectra were recorded in KBr on a Perkin-Elmer 577 grating spectrophotometer ($\gamma$ max in $cm^{-1}$), PMR spectra in $CDCl_3$ and Trifluoro acetic acid on Jeol FX 90Q (89.55 MHz) using TMS as internal standard ($^{19}F$ NMR on the same instrument), and mass spectra were recorded on Kratz 30 and 50 mass spectrometer at 70 eV.

(i) 1,3-Dihydro-3-hydroxy-3-(2-oxocycloalkyl)indole-2(1H)-one (**I**) and 1,3-dihydro-3-(2-oxocycloalkylidene)indole-2(1H)-one (**II**). These compounds were synthesized by literature methods.[6,7]

(ii) 2,3-Dihydro spiro[cycloalka[3,4][1,5]benzothiazepine-2,3'-[3H]indole]-2'-(1'H)-ones (**Va–e**). These compounds were synthesized by refluxing the mixture of **II** and 2-aminothiophenol in dry toluene (25 ml) for 20–28 hrs. The progress of reaction is checked by TLC. On cooling, the brownish black solid that separated was filtered, dried and recrystallized from ethanol to give the title compounds (**Va–e**).

The light brown intermediate ketone (**IIIe**) is isolated, when the reaction is stopped after 3 hrs. It is purified by recrystallization from ethanol. Yield 1.68 gm (46%), m.p. > 360°C (Found: C, 73.08; H, 6.19; N, 8.32; S, 9.04. $C_{21}H_{22}O_2N_2S$ requires C, 72.00; H, 6.28; N, 8.00; S, 9.14%.)

IR: 3340, 3300, 1700, 1670, 1600, 1460, 1360, 1250, 1080 and 750 $cm^{-1}$. $^1H$ NMR: 1.12–2.01 (m, $C\underline{H}_2$—$C\underline{H}_2$—$C\underline{H}_2$, 6H); 2.75 (s, N—$C\underline{H}_3$, 3H); 2.9–3.5 (m, CO—$C\underline{H}_2$, 2H); 5.06–5.38 (dd, $C\underline{H}$, 1H); 6.75–7.47 (m, Ar-$\underline{H}$, 8H); and 10.05 ppm (br, $N\underline{H}_2$).

Mass: $M^+$ at 366 (30%), 328 (35%), 286 (25%), 247 (38%), 152 (45%), 138 (100%).

## ACKNOWLEDGEMENT

Financial support from the Department of Science and Technology, New Delhi is gratefully acknowledged.

## REFERENCES

1. (a) K. Hiroshi, T. Satoshi and M. Masanori, Jap. Patent 7208, 544 (1972), *Chem. Abstr.*, **77**, 5554th (1972); (b) K. Hiroshi, T. Satoshi and N. Tako, Jap. Patent 7143784 (1971), *Chem. Abstr.*, **76**, 59676K (1972); (c) I. Hirosumi and I. Munekatsu, Jap. Patent 7116,749 (1971), *Chem. Abstr.*, **75**, 63848b (1971); (d) K. Hiroshi, N. Tako, T. Satoshi and S. Masanori, *Jap. J. Pharmacol.*, **22**, 467 (1972); (e) M. Testsuo, N. Hiromichi and K. Akio, *Jap. J. Pharmacol.*, **27**, 361 (1977).
2. (a) Z. P. Harovitz, *Int. J. Neuropharmacol.*, **5**, 405 (1966), *Chem. Abstr.*, **66**, 9922V (1967); (b) K. Opitz and U. Borchert, *Arzeim-Forsch*, **18**, 316 (1968), *Chem. Abstr.*, **69**, 1620P (1968).
3. H. J. Bein, *Pharmacol. Rev.*, **8**, 435 (1956).
4. C. A. Damerson, L. G. Henber, A. M. Philip and R. P. Martel, *J. Med. Chem.*, **19**, 391 (1976).
5. M. J. Kornet and A. P. Thio, *J. Monatsh Chemie*, **19**, 592 (1976).
6. K. C. Joshi, A. Dandia and S. Sanan, *J. Fluorine Chem.*, **44**, 59 (1989).
7. K. C. Joshi, A. Dandia and S. Sanan, *J. Heterocyclic Chem.*, **26**, 1397 (1989).
8. K. C. Joshi, A. Dandia and N. Ahmed, *Heterocycles*, **24**, 2479 (1986).
9. K. C. Joshi, R. Jain, A. Dandia and V. Sharma, *J. Heterocyclic Chem.*, **23**, 97 (1986).
10. K. C. Joshi, R. Jain, A. Dandia, S. Garg and N. Ahmed, *J. Heterocyclic Chem.*, **26**, 1799 (1989).
11. (a) A. Levai and H. Duddeck, *Acta Chim. Acad. Sci. Hung.*, **112**, 167 (1983); (b) H. Duddeck, M. Kaiser and A. Levai, *Leiberg's Ann.*, 869 (1985); (c) A. Levai and H. Duddeck, *Pharmazie*, **38**, 827 (1983); (d) A. Levai, *Pharmazie*, **35**, 680 (1980).
12. C. H. Hankovszky and K. Hideg, *Acta. Chim. Acad. Sci. Hung.*, **68**, 403 (1971).
13. A. K. Gupta, V. K. Singh and U. C. Pant, *Indian J. Chem.*, **22B**, 1057 (1983) and references therein.