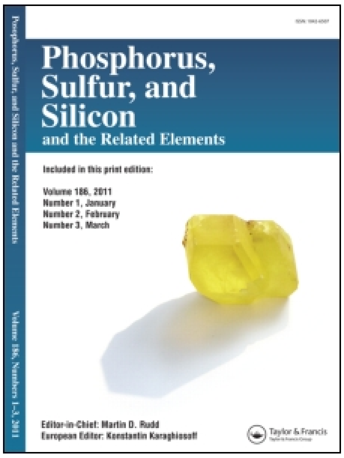

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Stereochemistry of Thiapyranothiazoles as Diels-Alder Adducts Obtained from Spirodimers of 1,3-Thiazolidines with Cinnamic Acid and its Ester

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To cite this Article Omar, M. T. , El-Khamry, A. , Youssef, Ali M. and Ramadan, S.(2003) 'Synthesis and Stereochemistry of Thiapyranothiazoles as Diels-Alder Adducts Obtained from Spirodimers of 1,3-Thiazolidines with Cinnamic Acid and its Ester', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 4, 721 — 735

To link to this Article: DOI: 10.1080/10426500307800

URL: http://dx.doi.org/10.1080/10426500307800

Phosphorus, Sulfur and Silicon, 2003, Vol. 178:721–735
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1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390197931

SYNTHESIS AND STEREOCHEMISTRY OF THIAPYRANOTHIAZOLES AS DIELS-ALDER ADDUCTS OBTAINED FROM SPIRODIMERS OF 1,3-THIAZOLIDINES WITH CINNAMIC ACID AND ITS ESTER

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(Received August 7, 2001; accepted January 17, 2002)

*Thiation of 5-Arylmethylene-3-phenyl-2-thioxo-1,3-thiazolidin-4-ones (**1a** and **b**) with either P_4S_{10}[1] or Lawesson's reagent[2], gave mainly the spirodimers 3′phenyl-2′-thoxo-1′,3′-thiazolidino[2,3-d]-spiro[6′,7′ diaryl-5,5′-perhydrothiapyrano]-3-phenyl-1,3-thiazolidin-4-thiones (**3a** and **b**) beside, 5-(3-bromo-4-methoxyphenylmethylene)-3-phenyl-1,3-thiazolidin-2,4-dithione (**2b**) as a mixture with **3b**. **2b** was allowed to react with ethyl cinnamate as a dienophile producing **4b** and **5b**. Moreover, prolonged heating of either **3b** or **3a** with ethyl cinnamate gave a mixture contains 40% of **4b** and a mixture of **4a** and **5a** respectively. Furthermore, the dimer **3b** reacted with cinnamic acid in glacial acetic acid to give the Diels-Alder-adduct **6b** and **7b**. Structures and stereochemistry of obtained compounds have been studied.*

Keywords: Spiro[thiapyrano-thiazolidines]; thiapyranothiazoles; thiation of 1,3-thiazolidines

Thiation of 5-phenylmethylene-3-phenyl-(**1a**), and 5-(3-bromo-4-methoxyphenylmethylene)-3-phenyl-(1b)-2-thioxo-1,3-thiazolidin-4-one with either tetraphosphorous decasulfide or Lawesson's reagent in xylene yielded the unexpected hitherto unknown spirodimer; 3′-phenyl-2′ thioxo-1′,3′-thiazoldino[2,3-d]-spiro[5,5′-perhydro-3-3′,6′,7′-tetraphenylthia-pyrano]-1,3-thiazolidin-4-thione (**3a**) as the sole product in the former case, and in the latter case, 3′-phenyl-2′-thioxo-1′, 3′-thiazolidino[2,3-d]-spiro[6,7′-di-(3-bromo-4-methoxyphenyl)-5,5′-perhydrothiapyrano]-3-phenyl-1,3-thiazolidin-4-thione (**3b**) which was mixed with ≈30% of the expected 5-(3-bromo-4-methoxy-phenylmethylene)-3-phenyl-1,3-thiazolidine-2,4-dithione (**2b**).

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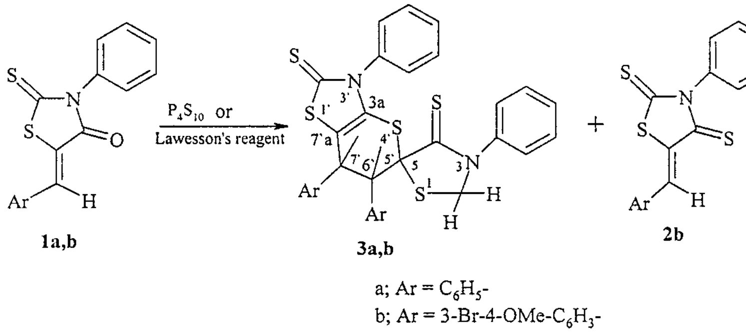


The structure of **3a** and **b** was deduced from microanalytical as well as spectroscopic data. The infrared spectroscopic data (Table I) are devoid of any absorption which could be correlated with a $\nu_{C=O}$ group, while, exhibiting stretching vibration absorptions of ν_{C-H}, $\nu_{=C-H}$, and ν_{SCSN}, which are consistent with the proposed structure.

Apart from the aromatic protons, the ^{1}H-NMR spectra of **3a**,**b** (Figure 1) shown from low to high field a partially splitted doublet (H-6′) a doublet (H-7′, j = 7.6 Hz) and two central peaks of an ABq (H_2C-2) with the integrated proton ratios of 1:1:2 respectively. Existence of two doublets (j = 6.5 Hz) is in harmony with the presence of two vicinal protons and location of two central peaks corresponding to the two protons of ABq at $\delta = 5.5$ ppm is consistent with a methylene group substituted with two electron attracting groups.

Existence of the spiro (C-5), C-2, C-6′, and C-7′ as well as the quaternary carbon atoms [C-4, C-2′, C3a, and C-7′a) is confirmed by ^{13}C-NMR spectroscopy (Figure 1). Moreover, the easy decomposition of **3a**,**b** to give fragments [A] and [B] is evidenced by mass spectroscopy. Fragment [A] is the ion radical of **2a**, whereas, fragment [B] is analogous to **2a** in which a methylene group displaces the C=S group at position-2, Figure 2.

The structure of **2b** was confirmed by microanalytical as well as spectroscopic data. The infrared spectrum of **2b** (Table I) lacks any absorbance to be correlated with a $\nu_{C=O}$ group, and shows the presence

TABLE I Infrared Spectroscopic Data of Compounds **3a**,**b** and **2b**

	TR (cm^{-1})				
Comp.	ν =CH	ν C—H	ν SCSN	δ 2H	δ 5H
3a	3060	2840, 2920	1240	—	700, 760
3b	3060	2860, 2920	1220	810	700, 760
2b	3060	2860, 2920	1220	810	600, 760

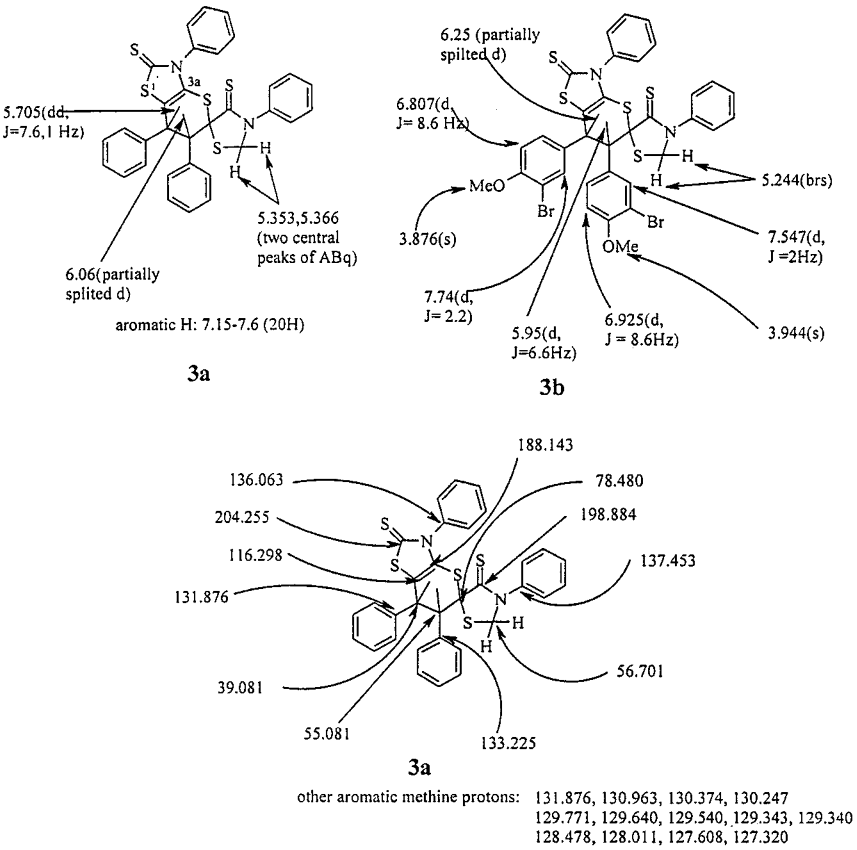
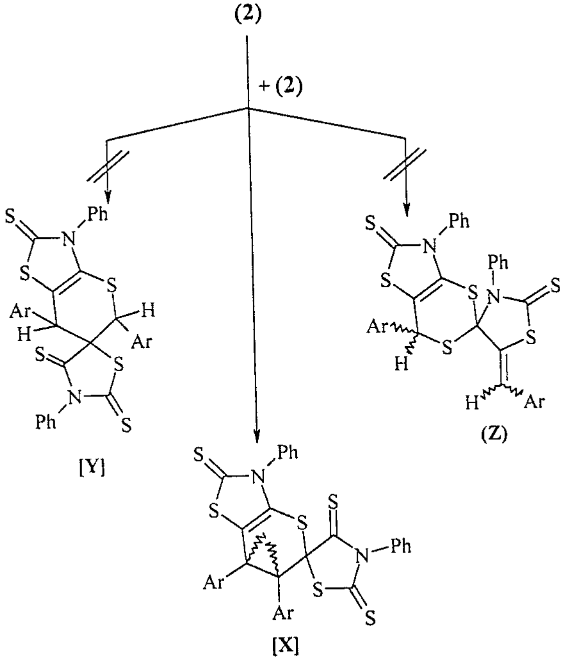


FIGURE 1 ^{13}C-NMR spectroscopic data of compound **3a** and ^{1}H-NMR spectroscopic data of compounds **3a** and **3b**.

of ν_{SCNS}. The ^{1}H-NMR spectrum of **2b** exhibits a singlet consistent with the olefinic proton, aromatic protons and a singlet consistent with the three protons of the methoxy group (Figure 3). Moreover, the EI-MS of **2b** shows the correct molecular ion peak and was fragmented as presented in Figure 4.

Formation of **2** was expected as reported previously by V'yunov et al.[3] Formation of the unexpected spirodimers **3a,b** could be understood taking into consideration the high reactivity of **2** (which is formed first upon treatment of **1** with either P_4S_{10} or Lawesson's reagent) as a heterodiene system. Thus, formation of **3a,b** could be visualized as represented in Scheme 1, in which two molecules of **2** interact; one as a heterodiene, whereas, the other acts as a dienophile either by using the π-electrons of the exocycle double bond or of the 4-thioxo group.

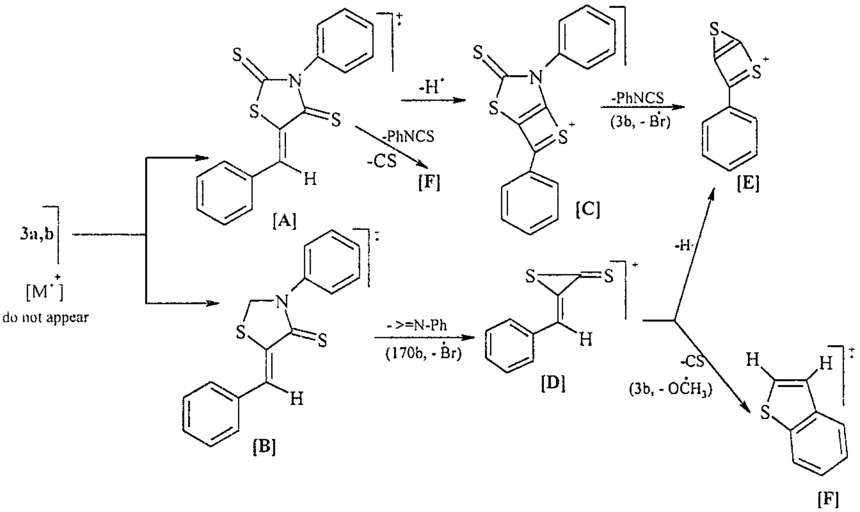


SCHEME 1 Conversion of the 2,4-dithioxothiazolidines (**1a**,**b**) into the respective dimer products **3a**,**b**.

The dimeric product actually isolated (**3a**,**b**), undoubtedly exhibits the skeleton [X] as it allows for the vicinal couplings observed in the ^{1}H-NMR spectrum. Structures [Y] and [Z], would each have two singlets. There still remains the problem of existence of four tetrahedral carbon atoms observed in the ^{13}C-NMR spectrum of **3a**. As structure [X] has only three of such carbon atoms (C-5, C-6′, C-7) a new sp3 carbon atom is expected to be formed through the reaction, most likely via reduction at the 2-thioxo group to a methylene group.[4]

As a chemical evidence for the reactivity of **2** as a heterodiene, the toluene solution of **2b** was treated with ethyl cinnamate and a mixture of ethyl(5**S***, 6**S***, 7**S***)-7-(3-bromo-4-methoxyphenyl)-5,6-dihydro-3,5-diphenyl-2-thioxo-thiopyranol[2,3-d] thiazolidine-6-carboxylate (**4b**) and the (5**S***, 6**S***, 7**R***) analogue (**5b**), in 4:1 ratio respectively was obtained.

The structure of **4b** and **5b** was deduced from the following spectral evidence. Their infrared spectra (Table II) exhibit ν_{C-H}, $\nu_{C=O}$ and $\nu_{C=S}$. The ^{1}H-NMR spectra (Figure 5) display, besides the aromatic and ethoxycarbonyl proton resonances, two doublets (H-5 and H-7) as well

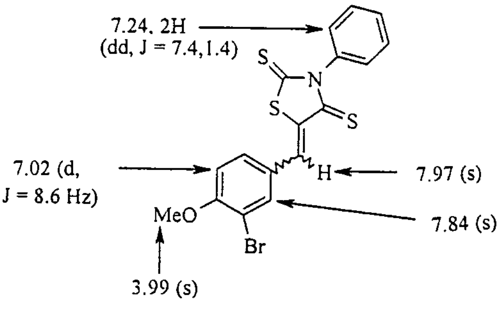


	Fragments m/e (% abundance)					
Comp.	[A]	[B]	[C]	[D]	[E]	[F]
3a	313 (83.5)	283 (0.2)	312 (100)	178 (8.9)	177 (40.3)	134 (61.6)
3b	421 (35.2)	39 (0.2)	420 (32.3)	207 (54.5)	206 (45.5)	134 (20.2)

FIGURE 2 Fragmentation pathway of **3a**,**b**.

as an apparent triplet (H-6 of **4b**) and a doublet of doublets (H-6 of **5b**). EI-MS of **4a**,**b** and **5a**,**b** are presented in Figure 6.

The reaction is proved to be of high regioselectivity, although minor amounts of more isomers were detected in the crude reaction mixture by



The rest of aromatic H = 7.5-7.65 (m, 4H)

FIGURE 3 ^{1}H-NMR spectroscopic data of compound **2b**.

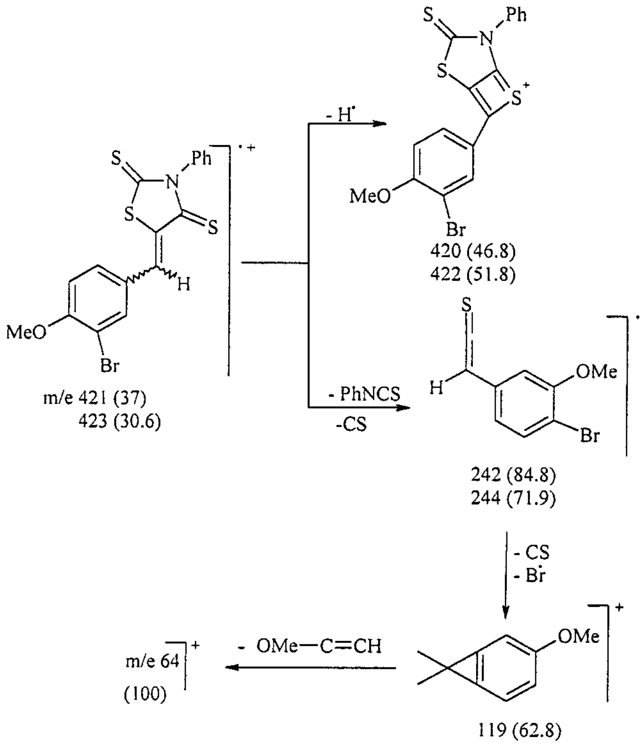


FIGURE 4 EI-MS fragmentation pattern of **2b**.

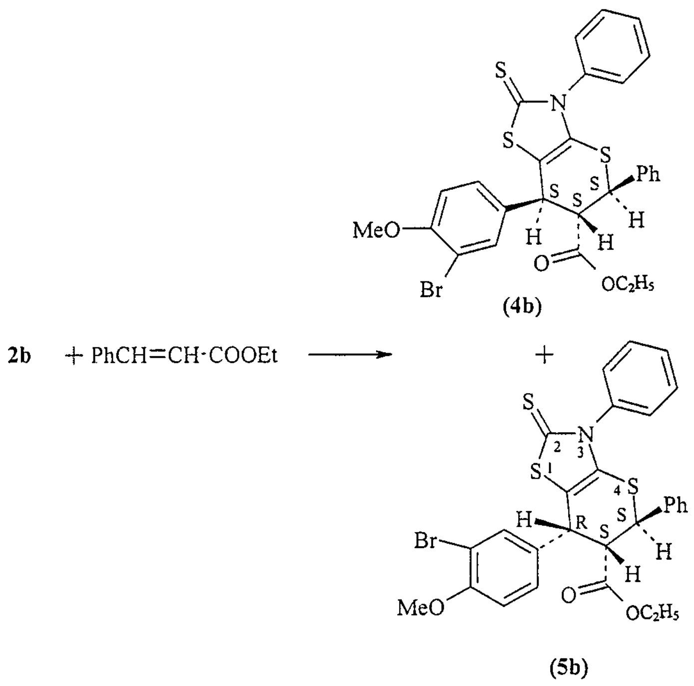
^{1}H-NMR spectroscopy. The major products obtained are in agreement with the favorable interaction between the sulphur atom of the hetero-diene components, C=C—C=S and β-carbon atom of the dienophile.[5]

The problem of configurational assignment of the three chiral centers (C-5, C-6 and C-7) has been solved by ^{1}H-NMR spectroscopy via

TABLE II Infrared Spectroscopic Data of Compounds **4a**,**b**, **5a**,**b**, **6b**, and **7b**

Compound	IR (cm)$^{-1}$				
	ν =CH	ν C—H	ν C=O	ν C=S	δ 2H
4b, **5b**	3060	2950 (br)	1735	1185	820
4a, **5a**	2900–3009 (br)		1735	1185	700–750[a]
6b, **7b**	2900–3700 (br)[b]		1700 (br)	1190	700–750[a]

[a] Characteristic of the bending frequency of aromatic 5-adjacent hydrogens.
[b] Including interbonded ν —OH of —COOH group.



analyses of the AMX pattern and extracting of the coupling constants. Table III shows the coupling constants of H-5, H-6, and H-7 of compounds **4b** and **5b**.

Taking into consideration the fact that the thiapyrene ring acquires the halfchair conformation and therefore, H-5, H-6, and H-7, must

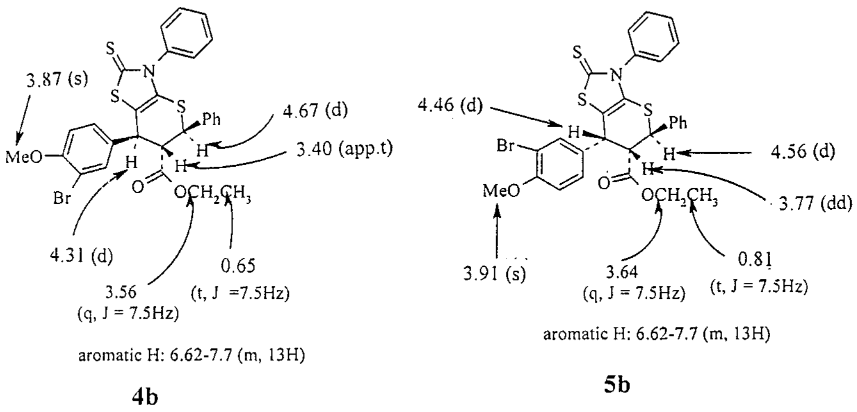
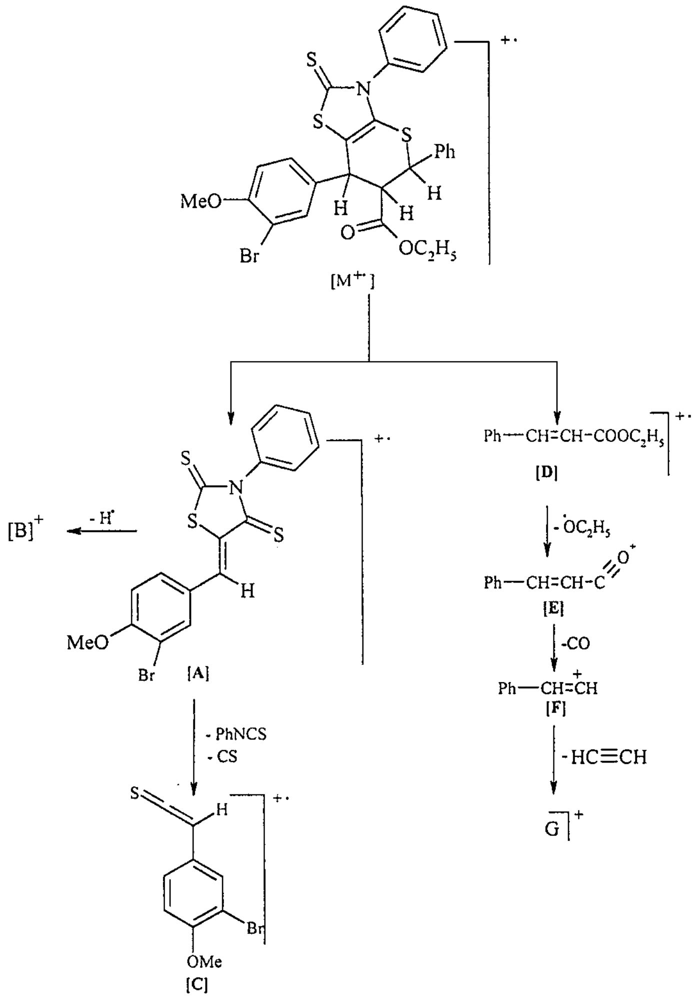


FIGURE 5 The ^{1}H-NMR spectroscopic data of compounds **4b** and **5b** in ($CDCl_3$).



	Fragments (abundance %)							
Compd.	[M]	[A]	[B]	[C]	[D]	[E]	[F]	[G]
4a, **5a**	489	313	312	134	176	131	103	77
	(30)	(35)	(100)	(30)	(29.5)	(25)	(23)	(30)
4b, **5b**	597	421	420	242	176	131	103	77
	(9)	(42.1)	(33.4)	(59.5)	(12)	(50)	(39.6)	(100)
	599*	423*	422*	244*				
	(6.7)	(40.2)	(52.5)	(57.8)				

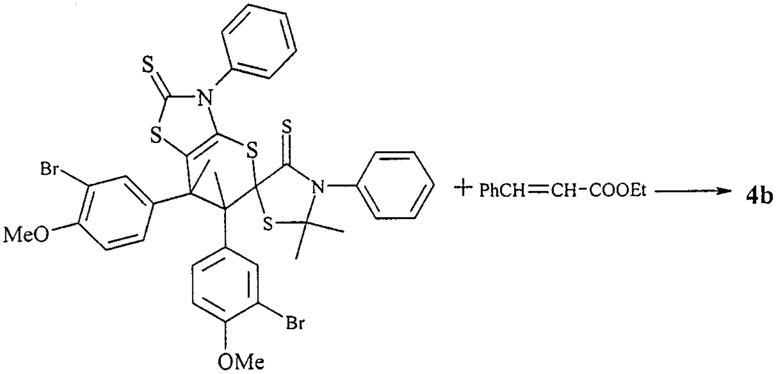
*p + 2 peaks

FIGURE 6 EI-MS spectroscopic data of **4a**,**b** and **5a**,**b**.

acquire pseudoaxial or pseudoequatorial positions and that the coupling constant between two pseudoaxial protons is ≈10 Hz and that between pseudoaxial and pseudoequatorial protons is ≈5.0 Hz. The measured coupling constants (Table II) reaveled that, H-5, H-6, and H-7 of **4b** acquire the pseudoaxial conformation, but in **5b** H-5 and H-6 acquire the pseudoaxial conformation whereas H-7 acquires the pseudoequatorial position.

Consulting the computer software program (*Alchemy III, 1992*) infers that the energy optimized molecule in which H-5, H-6, and H-7 acquire the pseudoaxial conformations will have the (5**S***, 6**S***, and 7**S*** configurations, whereas, the compound having equatorial H-7 must acquire the (5**S***, 6**S***, 7**R***) configuration.

The easy decomposition of the dimeric products (**3a**,**b**) during volatilization in the mass spectrometry has prompted us to check the possibility of participation of these compounds as heterodiene precursors in Diels-Alder reactions. The results obtained are quite interesting and worthy to be discussed. Thus, treating **3b** with ethyl cinnamate under the same conditions as applied with **2b** produced unreacted starting materials. However, refluxing the reactants for 15 h gave a mixture of products from which the (5**S***, 6**S***, 7**S***) derivative (**4b**) was isolated in 40% yield.



3b

Similar treatment of **3a** with ethyl cinnamate gave a mixture of **4a** and **5a** in an overall yield of 70% and in the ratio 5:1, respectively, whose structures were evidenced exclusively by their ^{1}H-NMR spectra, Figure 7.

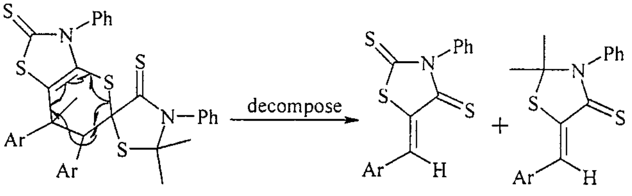
Configurational assignments for **4a** and **5a** are based solely on ^{1}H-NMR spectroscopy and the coupling constants are represented in

TABLE III ^{1}H-NMR ($CDCl_3$) Coupling Constants of H-5, H-6, and H-7

Comp.	$^3J_{5,6}$(H-5_{sx},H-6_{sx})	^3J6,7(H-6_{sx}, H-7_{sx})	^3J6,7(H-6_{sx}, H-7_{sx})
4b	10.6	10.6	
5b	11.6		5.0
4a	11.0	10.8	
5a	11.8		5.5
6b	11.0	10.6	
7b	11.8		5.2

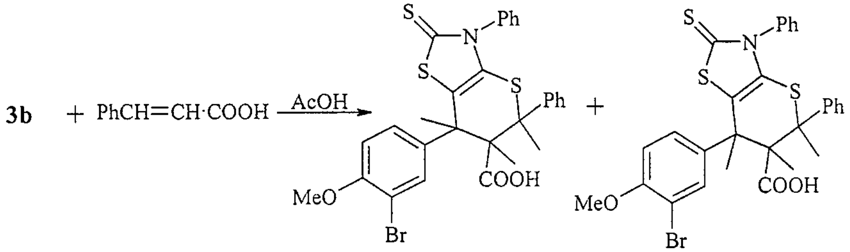
Table III. According to the data, **4a** has pseudoaxial H-5, H-6, H-7, whereas **5a** has H-5, and H-6 pseudoaxial but H-7 is pseudoequatorial.

Formation of compounds **4** and **5** by prolonged heating of **3** with ethyl cinnamate is visualized to occur through reaction of the fraction of **2**, which is believed to be formed at first via decomposition of **3**, with ethyl cinnamate.



3 **2**

Furthermore, the dimer (**3b**) reacts with cinnamic acid in glacial acetic acid solution to afford a mixture of the Diels-Alder adducts **6b** and **7b**, in an overall yield of 60% and in the ratio of 2:1, respectively.



6b **7b**

The structures of **6b** and **7b** are deduced from spectral evidence. The ^{1}H-NMR spectra exhibit the pattern of splitting and coupling constants similar to the respective ester (Figure 8). The mass spectrum (Figure 9) do not show the molecular ion peak due to easy elimination of CO_2.

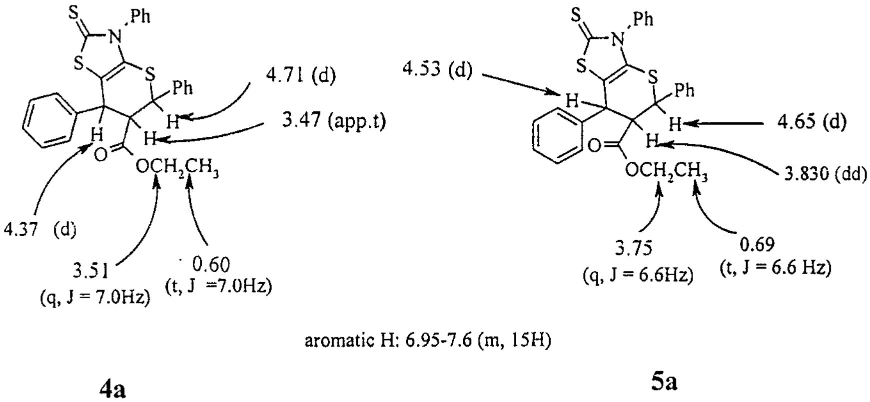


FIGURE 7 ^{1}H-NMR spectroscopic data of compounds **4a** and **5a**.

Subsequent elimination of styrene produced the ion radical of **2b**. The base peak is located at m/e 64.

Configurational assignment to C-5, C-6, and C-7 is based exclusively on ^{1}H-NMR spectral data. The coupling constants, which are represented in Table III, infer that H-5, H-6, and H-7 protons of **7b** acquire pseudoaxial positions, whereas in **8b**, H-5 and H-6 acquire the pseudoaxial conformation whereas H-7 acquires the pseudoequatorial position.

CONCLUSION

Ethyl cinnamate and cinnamic acid cycloadded to compound **2** and **3** in a regioselective reaction. The reaction most likely occurs via a non-concerted reaction and rotation around the bond (a) of the zwitterion (**8**), which is believed to be formed first, and would lead to configurational changes at C-7.

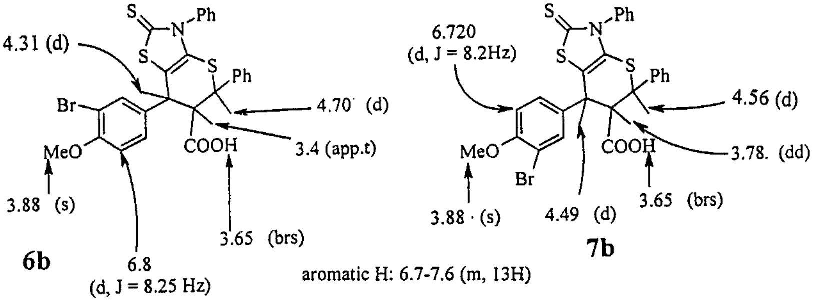
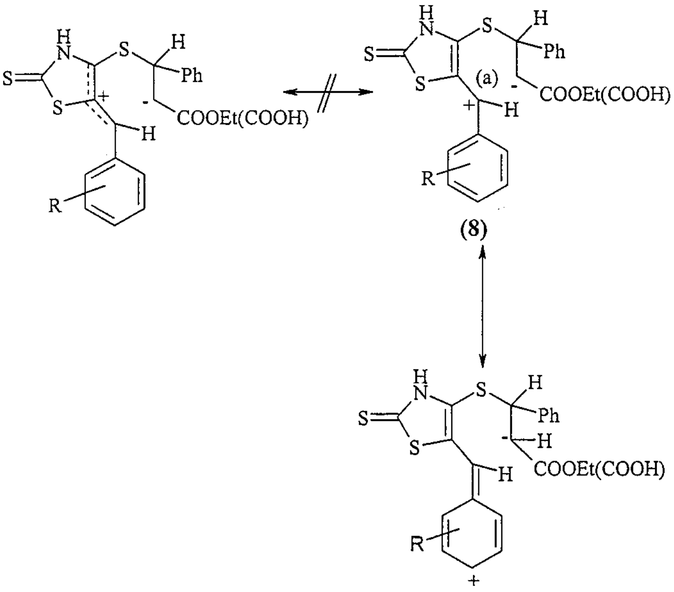


FIGURE 8 The ^{1}H-NMR spectroscopic data of **6b** and **7b**.



(8)

Experimental

Synthesis of 5-Arylmethylene-1,3-thiazolidine-2,4-dithione(2b) and the Corresponding Spirodimers (3a,b)

General procedure.

Using half mole of thiating agent. A mixture of **1a** or **b** (10 mmol), tetraphosphorus decasulfide or Lawesson's reagent (5 mmol) is refluxed in dry xylene (75 ml) for 2 h. The dark wine red solution is washed successively with water, sodium carbonate solution (10%) then with water and dried (anhydrous sodium sulphate). Xylene is concentrated (25 ml), treated with 20 ml of light petroleum (b.p. 40–60°), the precipitated dark red solid is filtered off, air dried and chromatographed over silica gel.

The crude product obtained from **1a** (3.5 g) is chromatographed over silica gel and eluted with a mixture of light petroleum (b.p. 60–80°)/ether (V/V 90:10) to give **3a** as lemon yellow needles.

3′-phenyl-2′thioxo-1′,3′-thiazoldino[2,3-d]-spiro[5,5′-perhydrothiapyrano-6′-7′-diphenyl]3-phenyl-1,3-thiazolidin-4-thione (3a): m.p. 230–2°C; yield, 83%. Calcd, for $C_{32}H_{24}N_2S_5$ (596): C, 64.43; H, 4.17; N, 4.70. Found: C, 64.25; H, 4.15; N, 4.56.

The crude product obtained from **1b** (3.5 g) is chromatographed over silica gel and eluted with a mixture of light petroleum (b.p. 60–80°)/ether (V/V 95.5) to yield **2b** as dark red needles. Further elution

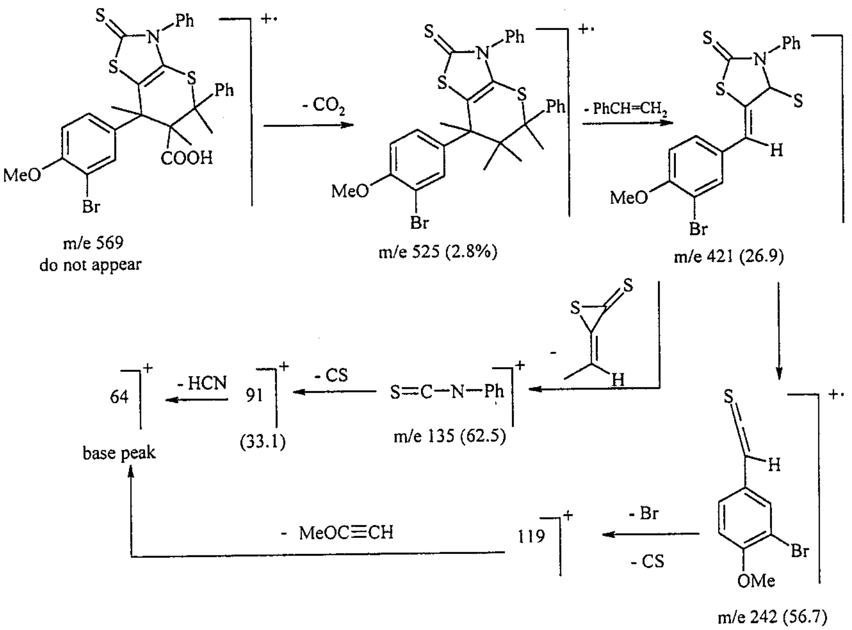


FIGURE 9 The EI-MS of compounds **6b** and **7b**.

with a mixture of light petroleum (b.p. 60–80°)/ether (V/V 90:10 provides **3b**).

5-(3-Bromo-4-methoxyphenylmethylene)-1,3-thiazolidine-2,4-dithione (2b): R_i = 0.68 (eluent: light petroleum b.p. 60–80°/ether V/V 7/3), m.p. 222–224°C; yield, 65%. Calcd. for $C_{17}H_{12}BrNOS_3$ (422): C, 48.34; H, 2.84; N, 3.32% Found C, 48.31; H, 2.67; N, 3.21%.

3-phenyl-2′-thioxo-1′,3′-thiazolidino[2,3-d]-spiro[6,7′-di(3-bromo-4-methoxyphenyl)-5,5′-perhydrothiapyrano]-3-phenyl-1,3-thiazolidin-4-thione (3b): R_i = 0.28 (eluent; light petroleum b.p. 60–80°/ether V/V 7/3), m.p. 232–234°C; yield 35%. Calcd. for $C_{34}H_{26}Br_2N_2$ O_2S_5 (814); C, 50.12; H, 3.19: N, 3.44%. Found: C, 50.26; H, 3.15; N, 3.41%.

Using two moles of thiating agent. Reflux a mixture **1b** (10 mmol) and Lawesson's reagent (20 mmol) in 75 ml xylene for 5 h. Then the reaction mixture is worked up as in the previous experiment. The crude product (3.5 g) is chromatographed over silica gel and eluted successively with light petroleum (b.p. 60–80°)/ether (V/V 95/5) then with light petroleum (b.p. 60–80°)/ether (V/V 90/10)to give **2b**, m.p. 222–4°C; yield 20% and 3b, m.p. 232–234°C; yield 70% respectively.

Synthesis of 4b and 5b

General procedure.

Reflux time two hours. Ethyl cinnamate (1.2 mmol) is added to a solution of **2b** (1 mmol) in dry xylene (20 ml) and the whole mixture is refluxed for 2 h during which the red color fades away. The mixture is concentrated to 10 ml, light petroleum (b.p. 60–80°) is added and the precipitated solid (0.3 g), m.p. 110–113°C is filtered off, air dried, and recrystallized from ethanol to give a mixture of ethyl (5**S***, 6**S***, 7**S***) 7-(3-bromo-4-methoxyphenyl)-5,6-dihydro-3,5-diphenyl-3-thioxo-thiopyrano[2,3-d]thiazolidin-6-carboxylate (**4b**) and the (5**S***, 6**S***, 7**R***) analogue (**5b**) in the ratio 4:1 respectively.

Working out the reaction mixture obtained from ethyl cinnamate (1.2 mmol) and **3b** (1 mmol) yields 0.4 g of unreacted starting material (**3b**), m.p. 232–234°C.

Reflux time 15 h. A mixture of ethyl cinnamate (1.2 mmol) and **3b** or **3a** (1.0 mmol) is refluxed in dry xylene (20 ml) for 15 h and the concentrated xylene solution (10 ml) is treated with 5 ml light petroleum (b.p. 60–80°). The precipitated solid is filtered off and air dried (0.2 g). The crude product obtained from **3b** is repeatedly recrystallized from ethanol to give; ethyl (5**S***, 6**S***, 7**S***) 7-(3-bromo-4-methoxyphenyl)-5,6-dihydro-3,5-diphenyl-3-thioxo-thiopyrano[2,3-d]-thiazolidine-6-carboxylate (**4b**): m.p. 110–112°C; yield 40%. Calcd for $C_{28}H_{24}BrNO_3S_3$ (598); C, 56.19; H, 4.01; N, 2.34%. Found; C, 56.21, H, 3.95; N, 2.31%.

The crude product obtained from **2a** (0.3 g), m.p. 120–130°C is boiled with 50 ml light petroleum (b.p. 80–100°) to afford a mixture of **4a** and **5a**.

Diels-Alder Reaction of 3b with Cinnamic Acid: Synthesis of 7b

General procedure. A mixture of **3b** (1 mmol) and glacial acetic acid (15 ml) is refluxed for 15 h. The concentrated reaction mixture (5 ml) is poured onto ice-cold water (100 ml) and the precipitated solid is filtered off, air dried (0.35 g), and boiled with 50 ml of light petroleum (b.p. 80–100°). The insoluble product (0.23 g) is recrystallized from ethanol to give **6b**. The product which is precipitated from light petroleum (b.p. 80–100°) is recrystallized from the same solvent to afford **7b**.

REFERENCES

[1] M. M. Orlinsky and B. S. Zimenkovsky, *Farm. Zh.* (Kiev.), **4,** 64 (1995); *Chem. Abst.*, **125,** 221684s (1996).

[2] M. P. Cava and M. I. Levinson, *Tetrahedron*, **41**(22), 5061 (1968).

[3] K. A. V'yunov, A. I. Ginak, and E. G. Sochilin, *Khim. Geterotsikl. Soedin*, **7**(2), 192 (1971); *Chem. Abst.*, **75,** 35863.

[4] H. U. Kibbel, H. Blödorn, R. Ketcham, and E. Schaumann, *Chem. Ber.*, **126,** 2079 (1993).

[5] J. S. A. Brunskill, De. Asish, and D. F. Ewing, *J Chem. Soc.*, 629 (1978).