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Synthesis of spiro thiopyrano[2,3-*d*]thiazolidines

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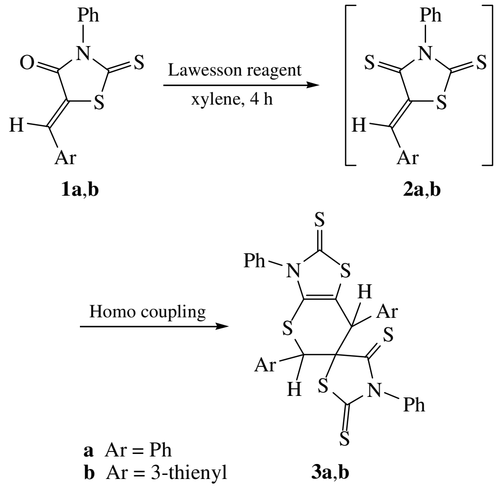
Spiro thiazolidine rings 3a,b are obtained in excellent yields by one-pot reaction of 1a,b with Lawesson reagent *via* [4 + 2] cycloaddition; the X-ray crystallography structure for compound 3a was determined and documented.

Previously, we have paid more attention to the sulfur chemistry of isothiasol and dithiohydantoin.[1–3] The synthesis of 5-(5-nitrofurylidene) Rhodanine or thiazolidine was reported by Sasaki.[4] Owing to its poor water solubility, Rhodanine derivatives or thiazolidines appeared to lack promise as antibacterial agents. However, Koschucharoff[5] found it to be the most active of a series of 5-nitrofurylidene derivatives tested against a variety of fungi, including *Candida albicans*, *Trichophyton*, *Epidermophyton* and *Microspora*. Antibacterial activity of Rhodanine derivatives or thiazolidines against *Escherichia coli* and *Staphylococcus aureus* with dilutions of 1:4000 to 1:8000 was also observed. The evaluation of thiazolidine-2-thiones for hepatoprotective activities against propionibacterium acnes-lipopolysaccharide (P. acnes-LPS)-induced is reported to liver injury in mice and *in vitro* lipid peroxide (LPO) formation in rat liver microsomes.[6] The expected biological importance of the thiopyrano[2,3-*d*]-thiazole ring system might be due to the dual activities of the thiazole and thiopyrano moieties, since the biological and medicinal activities of thiazoles[7,8] and the antimalaria potential of thiopyrano derivatives[9,10] have been well documented. The anti-HIV-1 activity of thiazolidinone derivatives was recently reported.[11] Synthesis of this system has been extensively studied *via* the [4 + 2] cycloaddition of dienophiles such as maleic anhydride,[12–15] ethyl acrylate,[12–16] acrylonitrile,[12–17] nitrostyrene,[9–17] *N*-phenylmaleimide,[9–17] methyl acrylate,[18] alkyl maleate,[18] alkyl fumarate,[12–18] maleonitrile[19] and azodicarboxylate[20] to 5-arylmethylene-2,4-dithioxo-1,3-thiazolidines **2a**,**b**, which represent a hetero diene *via* $C{=}C_5{-}C_4{=}S$. However, thiopyrano[2,3-*d*]-thiazoles **3a**,**b** with a spiro-thiazolidine ring have not been reported yet. It has been previously reported[12–20] that 3-substituted or unsubstituted 5-arylmethylene-4-oxo-2-thioxo-1,3-thiazolidines react with either tetraphosphorous decasulfide or Lawesson reagent to give corresponding 2,4-dithioxo derivatives. The formation of the thiono dimers from the reaction of 1,3-diphenyl-2-propen-1-one (chalcone) and phenylmethylene-1-tetralone with Lawesson reagent has also been reported.[21] Here, we report the novel synthesis of thiono dimers **3a**,**b** by refluxing 3-phenyl-5-arylmethylene-4-oxo-2-thioxo-1,3-thiazolidine **1a**,**b** prepared with Lawesson reagent in dry xylene for 4 h, as shown in Scheme 1.[†]

The reaction of **1a**,**b** with two equivalents of Lawesson reagent and 2–4 h of reaction were applied and speculated under these conditions. The product was isolated in excellent yield after column chromatography and the preparation of **2a**,**b** was consistent with results described by Nishio *et al.*,[22] who established that the amide group tends to be more active to Lawesson reagent than ketones. The mechanism of this thionation was speculated and outlined in Scheme 2.

This synthesis affords thione dimer **3a** as the sole product (90% yield) and **3b** as the major product (78% yield) rather than corresponding 2,4-dithioxo derivatives **2a**,**b**. The formation of thiono dimers **3a**,**b** can be visualised in Scheme 3, two molecules of **2a**,**b** interact together, one acting as a hetero diene *via* C=C(5)–C(4)=S, whereas the other acting as a dienophile using either the π-electron of the exocyclic double bond or of the 4-thioxo group. Formation of the mono cycloadduct is consistent with the region-chemical assignment, which has been reported previously.[23] This is in accordance with the favourable interactions between the sulfur atom of the hetero diene component and the β-carbon atom of the dienophile. Theoretically, however, attack at the exocyclic double bond could form a skeleton of either [X] or [Y], whereas attack at the 4-thioxo group would produce a skeleton of [Z].



Scheme 1

The elucidation of the structure of the thiono dimers **3a**,**b** is based on CHN, spectral and X-ray data.[‡] Elemental analysis shows good agreement between the calculated and experimental values. The IR spectra are devoid of any carbonyl absorption, which could be correlated to C=O groups and exhibit $\nu_{\text{C–H}}$, $\nu_{\text{=C–H}}$ and ν_{SCSN} bands consistent with the proposed structure. The ^{1}H NMR spectra of **3a** show two singlets at δ 5.359 and 5.346 for the two different protons and two doublets at different chemical shifts δ 5.70 and 6.06 are splitting part of the shielded two different *ortho* protons of one of the phenyl rings at the same coupling

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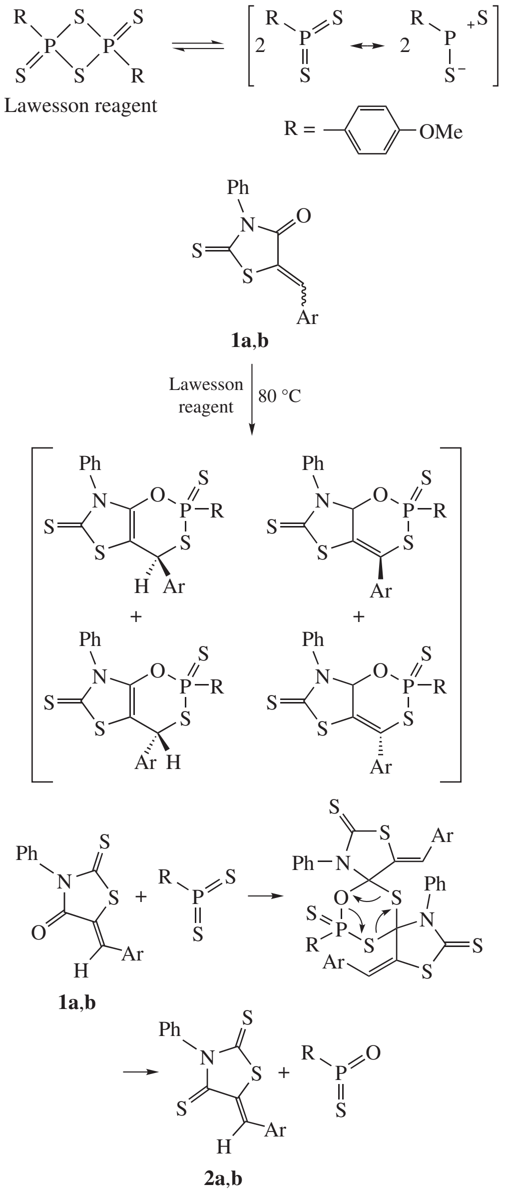
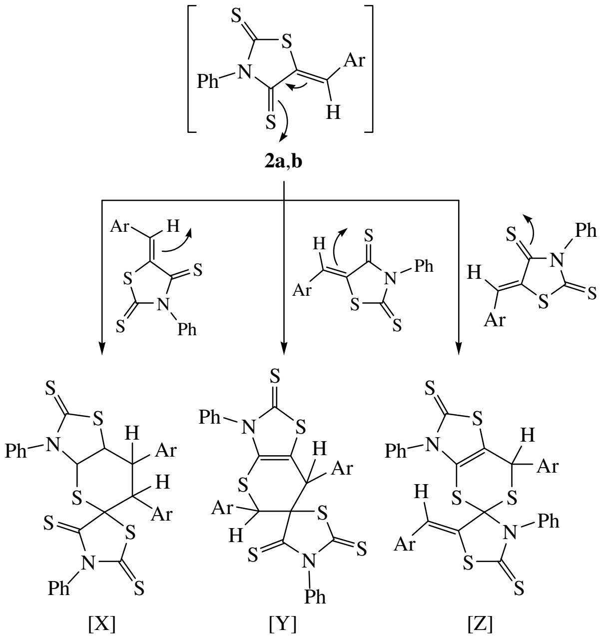
[†] The melting points were measured using an MPD350.BM2.5 Gallenkamp melting point apparatus and are uncorrected. CHN analyses were carried out at Ain Shams University, Cairo, Egypt. Flash column chromatography was performed on silica gel 60 (70–230 mesh).[31] The IR spectra were recorded in KBr discs on a Shimadzu DR-8001 spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a FT-NMR JEOL JNM-LA 300 MHz spectrometer at room temperature using $CDCl_3$ solutions with TMS as an internal standard, EI-MS were measured on a GC/MS JEOL AX 500 instrument operating at 70 eV.

General procedure. A mixture of 3-phenyl-5-arylmethylene-4-oxo-thioxo-1,3-thiazolidine **1a**,**b** (10 mmol) and Lawesson reagent (10 mmol) were refluxed in dry xylene (75 ml) for 4 h, the dark wine red solution was filtered, washed successively with an aqueous sodium carbonate solution (10%), then with water and dried over anhydrous sodium sulfate. The solution was concentrated under vaccum (15 ml), and treated with 20 ml of light petroleum (bp 40–60 °C). The dark red precipitated solid was filtered off, air dried and chromatographed over silica gel using cyclohexane–diethyl ether (9:1, v/v). Compounds **3a**,**b** were isolated as lemon yellow needles.

constant J 7.6 Hz. The ^{1}H NMR spectra of **3b** show two singlets at δ 5.42 and 5.51 for the two different protons and two doublet of doublets at different chemical shifts δ 5.95–5.98 and 6.23–6.27 are splitting part of the shielded two different thiophene protons at the different coupling constants $^4J_{HH}$ 1.11 and $^3J_{HH}$ 7.71 Hz, thienyl-H$_\beta$ and $^4J_{HH}$ 2.22 and $^3J_{HH}$ 4.95 Hz, thienyl-H$_\alpha$, respectively, which augment skeleton [Y] rather than skeleton [X]. The existence of three C=S groups at δ 188.24, 199.11 and 204.47 for **3a** and 188.28, 199.29 and 205.93 for **3b** is confirmed by ^{13}C NMR spectroscopy, which eliminates skeleton [Z] as a possible structure and substitutes the region-selectivity of this cyclization. The HyperChem 6.03 software was used to calculate the minimum energies of the skeletons [X] and [Y]. The calcula-tions show that there is a slight difference in energy between them: 59.291 kcal mol^{-1} for skeleton [X] and 60.236 kcal mol^{-1} for skeleton [Y], due to the case decomposition of Diels–Alder adducts **3a**,**b** the molecular ion peaks of **3a**,**b** were not observed in Gc/Ms. The *m*/*z* values of the fragments are shown in Table 1. The fragmentation pathways of the thiono dimers **3a**,**b** are outlined in Scheme 3. According to the NMR spectra of **3a**,**b** and the X-ray analysis of **3a**, the products show only one stereo-isomer of [Y]. The existence of two singlet signals at different chemical shifts in the ^{1}H NMR spectrum of **3a**,**b** confirmed only the structure [Y] rather than [X].



Scheme 2



Scheme 3

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‡ *3,3′,5′,7′-Tetraphenylspiro(2,4-dithioxo-1,3-thiazolidine-5,6′-perhydro-thiopyrano[2,3-*d*]-1′,3′-thiazolidine)-2′-thione* **3a**: yield 90%, mp 230–232 °C. IR (ν/cm^{-1}): 3060 ($\nu_{=C-H}$), 2930 (ν_{C-H}), 1265, 1212 ($\nu_{C=S}$), 751, 697 (ν_{Ph-H}). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.35 (s, 1H), 5.36 (s, 1H), 5.70 (d, 1H, *o*-H$_{Ph}$, J 7.86 Hz), 6.06 (d, 1H, *o*-H$_{Ph}$, J 7.14 Hz), 7.16–7.57 (m, 18H, H$_{Ar}$). ^{13}C NMR (125 MHz, CDCl$_3$), see Figure 2. Found (%): C, 61.28; H, 3.49; N, 4.39; S, 30.72. Calc. for $C_{32}H_{22}N_2S_6$ (626.90) (%): C, 61.31; H, 3.54; N, 4.47; S, 30.68; LRMS (EI), *m*/*z*: 648 ([M$^+$ – 22], 1.11), 630 (0.63), 605 (3.05), 543 (2.3), 504 (1.86), 431 (2.51), 405 (2.18), 381 (3.72), 313 (12.42), 281 (11.75), 231 (10.63), 181 (10.02), 169 (28.68), 134 (13.32), 131 (30.30), 122 (14.21), 120 (48.38), 119 (25.90), 118 (41.17), 117 (19.34), 91 (10.77), 87 (100), 86 (23.15), 85 (12.60), 84 (69.06), 82 (60.08), 72 (11.21), 71 (15.12), 69 (14.29), 53 (21.42), 51 (10.42). GC, t_R = 1.56 min; column, DB-5 6 m × 0.01 mm + 1 m guard column. Temperature programming, 25.2 °C/2 min/20 °C/1 min/25.2 °C/43 min. Bp; *m*/*z* 87; Scan (30).

*3,3′-Diphenyl-5′,7′-bis(3-thienyl)spiro(2,4-dithioxo-1,3-thiazolidine-5,6′-perhydrothiopyrano[2,3-*d*]-1′,3′-thiazolidine)-2′-thione* **3b**: yield 78%, mp 216–218 °C. IR (ν/cm^{-1}): 3080 ($\nu_{=C-H}$), 2905 (ν_{C-H}), 1263, 1215 ($\nu_{C=S}$), 757, 691 ($\nu_{Ph\text{-}H_5}$), 780, 620 ($\nu_{Ph\text{-}H_3}$). LRMS (EI), *m*/*z*: 516 ([M$^+$ – 122], 5), 417 (> 5), 393 (> 5), 357 (> 5), 319 (45), 303 (> 5), 274 (> 5), 242 (> 10), 210 (15), 197 (> 5), 184 (35), 140 (100), 108 (25), 96 (50), 77 (80), 69 (75), 61 (25), 53 (35). GC, t_R = 5.56 min; column, DB-5 6 m × 0.01 mm + 1 m guard column. Temperature programming, 1.4 °C/2 min/20 °C/1 min/1.4 °C/55 min. Bp; *m*/*z* 140; Scan (90). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.43 (s, 1H), 5.51 (s, 1H), 5.95–5.98 (dd, 1H, H$_{\beta\text{-thienyl}}$, $^4J_{HH}$ 1.11 Hz, $^3J_{HH}$ 7.71 Hz), 6.23–6.27 (dd, 1H, H$_{\alpha\text{-thienyl}}$, $^4J_{HH}$ 2.22 Hz, $^3J_{HH}$ 4.95 Hz), 7.17–7.60 (m, 14H, 2H$_{Ph}$ + 4H$_{thienyl}$). ^{13}C NMR (125 MHz, CDCl$_3$) see Figure 2. Found (%): C, 52.31; H, 2.78; N, 4.42; S, 40.60. Calc. for $C_{28}H_{18}N_2S_6$ (638.94) (%): C, 52.64; H, 2.84; N, 4.38; S, 40.14.

X-ray structure determination. Crystals of **3a** were obtained as yellow plates from CHCl$_3$ or CHCl$_3$–hexane. Data were collected at 297 K on a Siemens P3 diffractometer with graphite monochromated MoKα radiation using variable speed $\theta/2\theta$ scans out to 55° in 2θ. The structure was solved by direct methods and the difference Fourier technique and refined by full-matrix least squares on F^2. Hydrogen atom positions were either located directly or calculated and allowed to ride on their respective atoms. The CHCl$_3$ solvent of crystallization is disordered with Cl(3) having a much larger displacement parameter than Cl(1) or Cl(2), Cl(3) is best modeled occupations three positions, the occupancies set at 0.3, 0.3 or 0.4 for Cl(3), Cl(3a) or Cl(3b), respectively. The refinement converged to R_1 = 5.31 and wR_2 = 13.70 for 5962 reflections with $I > 2\sigma(I)$ and 415 variable parameters. A final difference Fourier map showed maximum residual electron density of 0.724 eÅ^{-3}.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 174439. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2006.

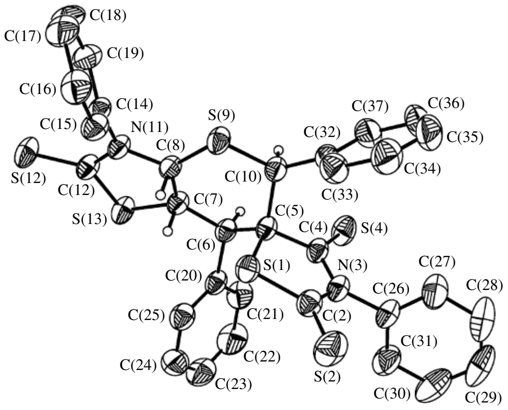
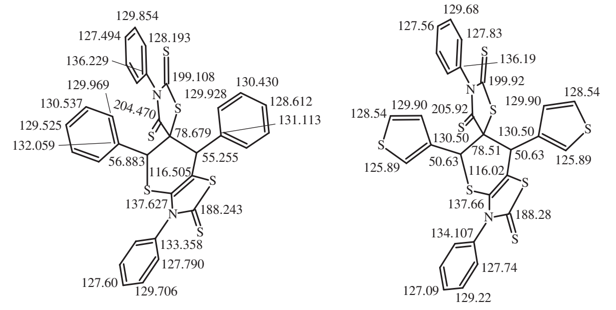


Figure 1 X-ray structure of the thermal ellipsoid plot of 3,3′,5′,7′-tetraphenylspiro(2,4-dithioxo-1,3-thiazolidine-5,6′-perhydrothiopyrano[2,3-*d*]-1′,3′-thiazolidine)-2′-thione **3a** with the labeling scheme. The thiopyrano ring is puckered with C(5) (–0.494 Å) and C(10) (0.385 Å) out of the plane generated by C(6)–C(7)–C(8)–S(9) (0.005 Å deviation from planarity).

Table 1 Values of *m*/*z* and abundance (%) of **A**, **B**, **C**, **D** and **E** fragments.

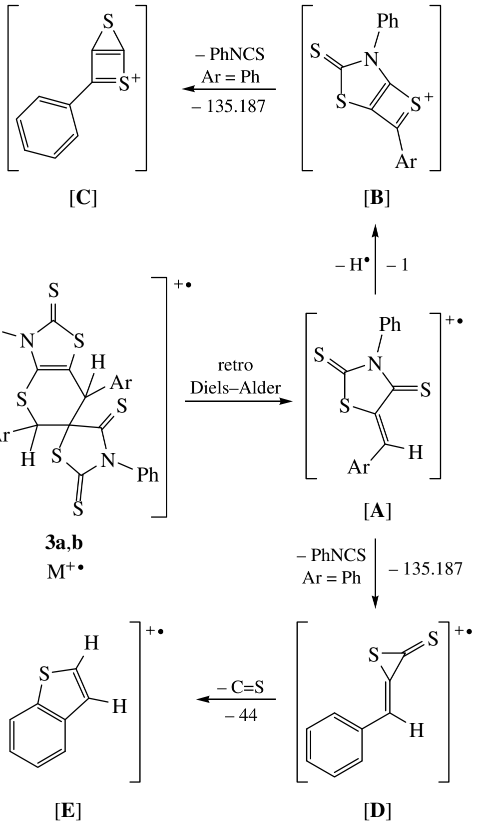
Compounds	Fragmentation, *m*/*z* (% abundance)				
	[**A**]	[**B**]	[**C**]	[**D**]	[**E**]
3a	313 (28.3)	312 (19.3)	177 (28.5)	178 (10.6)	134 (68)
3b	319 (30.5)	318 (20.3)	183 (10.5)	184 (10.5)	140 (100)



3a **3b**

Figure 2 ^{13}C NMR (125 MHz, $CDCl_3$) data for compounds **3a** and **3b**.

The crystal and molecular structures of 3,3′,5′,7′-tetraphenylspiro(2,4-dithioxo-1,3-thiazolidine-5,6′-perhydrothiopyrano[2,3-*d*]-1′,3′-thiazolidine)-2′-thione **3a** crystallizes as a $CHCl_3$ solvate from the slow evaporation of either $CHCl_3$ or $CHCl_3$–hexane solutions (Figure 1). A slight fold of 3.1° is observed along the C(7)–C(8) bond of the thiazolidine moiety. The spiro thiazolidine ring attaches to the thiazolidine ring at C(5) and is approaching the expected perpendicular configuration (dihedral angle of 72.7°). The spiro thiazolidine ring puckering and dihedral angle in 1,8-diphenylindolo[2,3-*b*]-1,4,5,6-tetrahydrothiane-3-spiro-(3′-indoline-2′-thione) are 0.7° and 79.5°, respectively.[24] The relative stereochemistry about C(6) and C(10) has been established by crystallography to be (*S*) and the configuration about the C(7)–C(8) double bond is *cis*, the C=S [range 1.623(3)–1.663(3) Å] and C–S [range 1.729(3)–1.828(3) Å] bond distances are generally consistent with 1,8-diphenylindolo[2,3-*b*]-1,4,5,6-tetrahydrothiane-3-spiro(3′-indoline-2′-thione) (C=S, 1.658 Å; C–S, 1.731 or 1.817 Å),[25] 3*H*-**3a**, 4-dihydro-3-isopropoxycarbonyl-**3a**, 7-dimethylthieno[3′,2′]-5,6-thiopyrano[4,3-*c*]isoxazole (C=S, 1.705–1.821 Å),[26] 2-diethylamino-5,6-bis(*tert*-butylsulfonylimino)-2-methyl-1-thiacyclohex-2-ene (C=S, 1.781–1.808 Å),[27] 6-amino-3,5-dicyano-3,4-dihydro-2,4-bis(3-methoxyphenyl)-3*H*-thiapyrano-3-carbothioamide (1.734, 1.818 Å),[28] 3-(3-phenyl-1,3-thiazoline-2-thio-5-ylcarbonyl)-5-(*N*,*N*-dimethylamino)-2,1-benzisothiazole (C=S, 1.659 Å; C–S, 1.721–1.752 Å).[29] The extended packing of this molecule is such that π-overlap is maximised between the substituted phenyl rings, two types of intermolecular interactions are observed consistent with published data.[30] Namely, C–H···Cl [C(6)–H(6)···C(11), 3.840(3) Å, 161°] and C–H···S [C(25)–H(25)···S(12), 3.802(4) Å, 170°; C(38)–H(38)···S(12), 3.513(4) Å, 170°].



Scheme 4 Pathways of the fragmentation of compounds **3a**,**b**.

Compounds **3a**,**b** show promising antifungal activity. The biological activity of compounds **3a**,**b** and other derivatives, as well as the effect of substituents at the 3-position of the thiazolidine ring on the ratio of thiono dimer **3a**,**b** to 2,4-dithio derivative **2a**,**b**, will be published elsewhere.

References

1 A.-S. S. Hamad Elgazwy, *Tetrahedron*, 2003, **59**, 7445.
2 A.-S. S. Hamad Elgazwy and M. E. Azab, *Bollettino Chimico Farmaceutico*, 2001, **140**, 233.
3 A.-S. S. Hamad Elgazwy and M. E. Azab, *Phosphorus Sulfur Silicon Relat. Elem.*, 2001, **173**, 105.
4 T. Sasaki, *Chem. Pharm. Bull.*, 1954, **2**, 104.
5 (*a*) P. Koschucharoff, *Pharmazie*, 1960, **15**, 492; (*b*) P. Koschucharoff and T. Harisanova, *Pharmazie*, 1962, **17**, 134.
6 K. Yoneda, A. Ota and Y. Kawashima, *Chem. Pharm. Bull. (Tokyo)*, 1993, **41**, 876.
7 F. C. Brown, *Chem. Rev.*, 1961, **61**, 463.
8 S. P. Singh, S. S. Pamer, K. Raman and V. I. Stenberg, *Chem. Rev.*, 1981, **81**, 175.
9 R. K. Razdan, R. J. Bruni, A. C. Mehta, K. K. Weinhardt and Z. B. Papanastassiou, *J. Med. Chem.*, 1978, **21**, 643.
10 E. Elsanger, *Prog. Drug Res.*, 1974, **18**, 99.
11 M. L. Barreca, A. Chimmirri, L. De Luca, P. Monforte, M. Zappala, J. Balzarini, E. De Clercq, C. Pannecouque and M. Witvrouw, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1793.
12 N. A. Kassab, S. O. Abdallah and H. A. Ead, *Z. Naturforsch.*, 1975, **30B**, 441.
13 S. O. Abdallah, H. A. Hammouda and F. A. Ali, *J. Heterocycl. Chem.*, 1985, **22**, 497.
14 S. O. Abdallah, H. A. Hammouda and F. A. Ali, *Pharmazie*, 1986, **41**, 101.
15 M. Zhang and R. Y. Zhang, *Gaodeng Xuexiao Huaxue Xuehas*, 1989, **10**, 1095.
16 H. A, Ead and O. Abdelhamid, *Phosphorus Sulfur Silicon Relat. Elem.*, 1990, **54**, 9.
17 H. A. Ead, N. H. Metwalli and N. M. Morsi, *Arch. Pharmacol. Res.*, 1990, **13**, 5.
18 H. A. Ead, N. A. Kasab, H. Koppel, W.-D. Bloedorn and K.-D. Shleinitz, *J. Prakt. Chem.*, 1980, **322**, 155.
19 H. A. Ead, S. O. Abdallah, N. A. Kassab and N. A. Metwalli, *Sulfur Lett.*, 1989, **9**, 23.

20 H. A. Ead, *Phosphorus Sulfur Silicon Relat. Elem.*, 1990, **48**, 235.

21 A. Mackie and A. I. Misra, *J. Chem. Soc.*, 1954, 3919.

22 T. Nishio and M. Ori, *Heterocycles*, 2000, **52**, 111.

23 S. Katamani, H. Ohmura, H. Tanaka and S. Motoki, *Chem. Lett.*, 1982, 793.

24 J. S. A. Brunskill, De. Asish and D. F. Ewing, *J. Chem. Soc.*, 1978, 629.

25 A. M. Thompson, M. Boyd and W. A. Denny, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1835.

26 M. M. Krayushkin, L. G. Vorontsova, M. G. Kurella, E. Yu. Zvezdina and M. A. Kalik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1995, 302 (*Russ. Chem. Bull.*, 1995, **44**, 293).

27 G. L'abbe, L. Huybrechts, S. Toppel, J. P. Declercq, G. Germain and M. Van Meerssche, *Bull. Soc. Chim. Belg.*, 1978, **87**, 893.

28 J. S. A. Brunskill, A. De, D. F. Ewing and A. J. Welch, *Acta Crystallogr., Sect. C*, 1984, **40**, 493.

29 E. Aqad, A. Ellern and V. Khodorkovsky, *Tetrahedron Lett.*, 1998, **39**, 3311.

30 R. Taylor and O. Kennard, *J. Am. Chem. Soc.*, 1982, **104**, 5063.

31 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

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