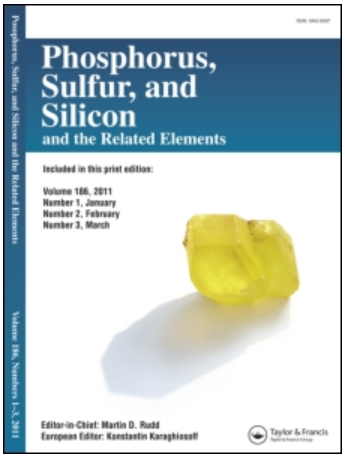

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Synthesis of Phosphonodithioate, Oxathiaphosphinin, Oxathiaphosphole, and Dithiaphosphole Derivatives from the Reaction of Lawesson's Reagent with Phenolic Mannich Bases and Oxime Derivatives

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Synthesis of Phosphonodithioate, Oxathiaphosphinin, Oxathiaphosphole, and Dithiaphosphole Derivatives from the Reaction of Lawesson's Reagent with Phenolic Mannich Bases and Oxime Derivatives

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*The reaction of Lawesson's reagent **1a**, with niclosamide **2** proceeded by thionation and formation of carbothioamide **3** and the zwitterionic oxathiaphosphinin **4a**. LR reacted with 8-hydroxyquinoline (**5**), 2-methylquinoline-4-ol (**7**), and β-naphthol (**9**) to give the phosphonodithioates **6**, **8**, or **10**. The reaction of LR with the Mannich bases **11** and **14** afforded the oxathiaphosphinins **13** and **15**, whereas the phosphonodithioates **17** and **19** were isolated in the case of Mannich bases **16** and **18**. LR reacted with phthalimide Mannich base **20** to give the dithione **21** and N-methylphthalimide (**22**). Reaction of ketone monoxime **23** with LR resulted in the formation of the oxathiaphosphole **24** and the dithiaphosphole **25**, whereas the monoxime **26** afforded the thioxoethanone thioxime **27**. Ketone dioximes **28** and **34** afforded the phosphonodithioates **29** and **36**, respectively, when they were allowed to react with LR, whereas the dioxime **30** gave compounds **32** and **33**. Moreover, the molluscicidal potency of the newly synthesized compounds against Biomphalaria glabrata snails was studied, too.*

Keywords Dithiaphosphole; Lawesson's reagent; oxaphosphole; oxathiaphosphinins; phosphonodithioates

INTRODUCTION

Lawesson's reagent 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide (**1a**) has been shown to be a good starting material for the construction of cyclic systems containing phosphorus and sulfur.[1–3] This reagent is used also in thionation of carbonyl-containing compounds.[4–6] Lawesson's reagent 1a exists in equilibrium with the

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monomeric form **1b**, which can be incorporated with the substrate.[7] The development in the application of this powerful reagent provide an overview about novel reactions and uses of Lawesson's reagent in the synthesis of new organophosphorus and sulfur compounds that are of potential interest in industrial[8] and pharmacological purposes.[9]

As an ongoing program devoted to produce new bioactive heterocyclic phosphorus substances,[3,10] it was of interest to investigate the reaction of niclosamide **2**, 8-hydroxyquinoline (**5**), 2-methylquinoline-4-ol (**7**), and β-naphthol (**9**) with Lawesson's reagent **1b** and compare the reactivity of these phenolic compounds with the phenolic Mannich bases **11**, **14**, **16**, **18**, and **20** toward LR **1b**. The reaction of ketone oxime derivatives **23**, **26**, **28**, **30**, and **34** with the same reagent **1b** has been studied. Moreover, the biological evaluation of the synthesized compounds as molluscicidal against *Biomphalaria glabrata* snails has been performed.

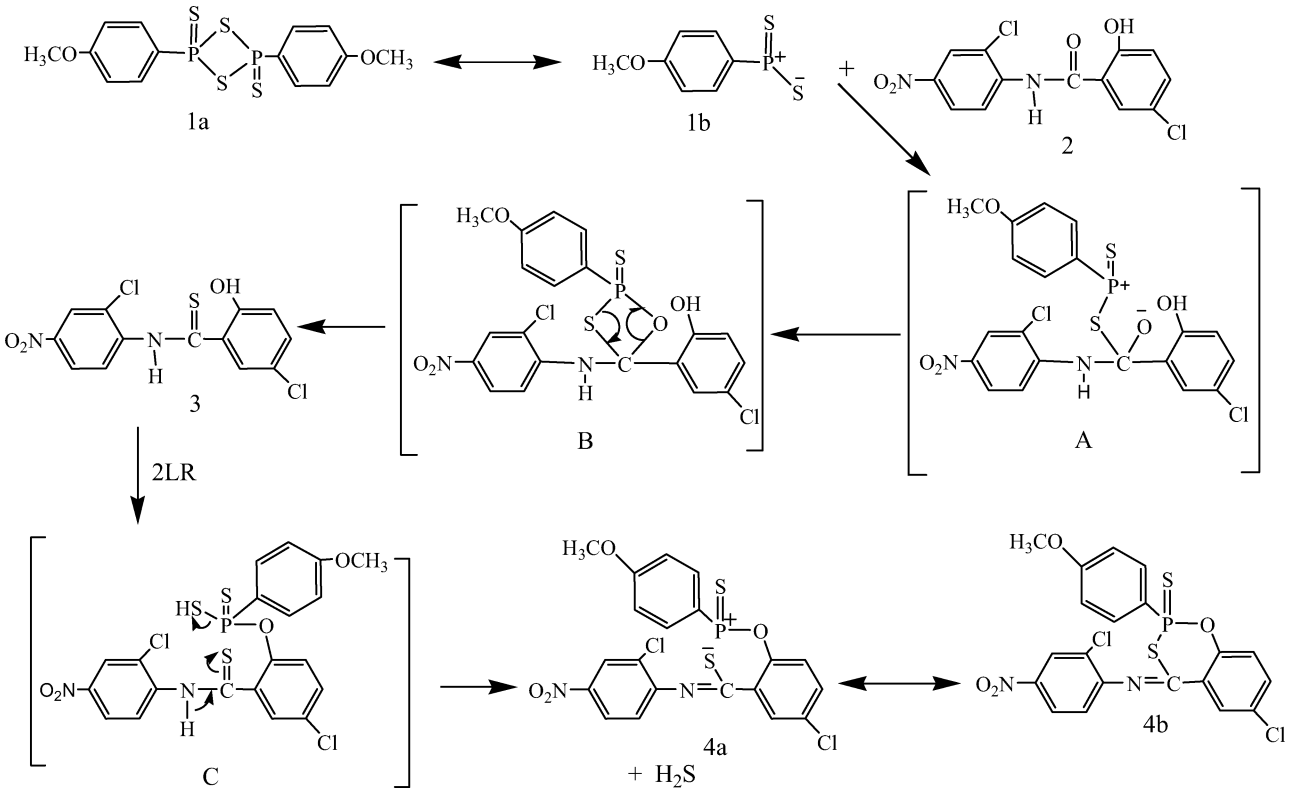
RESULTS AND DISCUSSION

Niclosamide [5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide] (**2**) is the active ingredient of bayluscide, which has been used as a molluscicide of great significance in the last decade.[11] It was also introduced as an official drug in many pharmacopoeas.[12] Moreover, the synthesis of carbothioamides is of great interest due to their applications in syntheses, medicine, and agar chemistry.[13] Therefore, the aim of the present investigation has been extended to synthesize carbothioamide **3**, from the reaction of niclosamide **2** and Lawesson's reagent **1b**. When the bifunctional niclosamide **2** was reacted with one mol equivalent of LR **1b** in boiling dry acetonitrile for one day, [5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzene carbothioamide] (**3**) was only isolated in fairly good yield. The structure of the carbothioamide **3** was elucidated from elemental microanalysis and spectroscopic data. The IR spectrum of **3** showed absorption bands at υ 3447 (OH), 3098 (NH), 1613 (C=C, aromatics) and disclosed the absence of (C=O, amide) and presence of C=S absorption band at 1168 cm^{-1}. In the ^1H NMR spectrum of **3**, signals were observed at δ 10.87 (s, 1H, OH), 9.04 (s, 1H, NH) (exchangeable with D_2O), and 6.7–8.3 (m, 6H, aromatics). Its ^{13}C NMR spectrum showed signals at δ 194.62 (C=S), 157.83 (C-N) ppm, and in the MS of 3 m/e = 341 (M^-), when the reaction was repeated using one mol equivalent of niclosamide **2** and two mol equivalents of LR **1b**, the carbothioamide **3** was isolated together with 2-chloro-N-(6-chloro-2-(4-methoxyphenyl)-2-sulfanylene-4*H*-benzo [*e*][1,3,2]oxathiaphosphinin-4-ylidene)-4-nitrobenzene amine (**4**). The elemental microanalysis, IR,

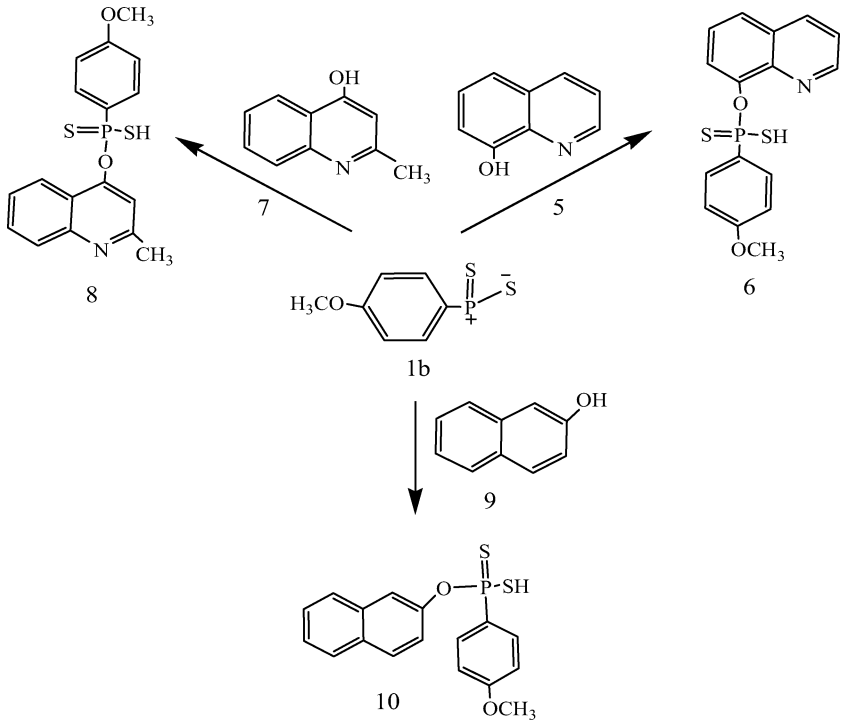
^{1}H, ^{31}P NMR, and MS data agreed with structure **4**. The IR spectrum showed absorption bands at 2921 (OCH_3) and 1594 (C=N), 1525 (C=C, aromatics), 1348–1284 (C-O-C), and 628 cm^{-1} (P=S). It revealed the absence of (C=O, amide), NH, and OH groups. In the ^{1}H NMR spectrum of **4**, signals were observed at δ 3.8 (s, 3H, OCH_3) and 6.8–8.6 (m, 10H, aromatics). A signal at δ 14.02 ppm was observed in the ^{31}P NMR, which fits with the zwitterionic oxathiaphosphinin **4a** rather than **4b**,[14] and in the mass spectrum, the M^+ was found at m/e = 511. It is believed that LR reacted firstly with niclosamide **2** as thionating agent to form the thioxo derivative **3**. The last compound **3** reacted with another molecule of LR by addition to give the intermediate phosphonodithioic acid A, which cyclized with expulsion of hydrogen sulfide to give the dipolar oxathiaphosphinin **4a** (Scheme 1).

It has been found that 8-hydroxyquinoline (**5**) was used in controlling photodegradation of the neem-based pesticide azardirachtin-A.[15] Its derivatives are used in several pharmacological purposes as antimalarial drugs,[16] and their copper complexes are useful as chemotherapeutic agents.[17,18] Moreover, their antiretroviral activity in HIV-infected cells was tested.[19] Therefore, when 8-hydroxyquinoline (**5**) was allowed to react with LR **1b** under the reflux temperature in acetonitrile for 10 h, the corresponding (4-methoxyphenyl)phosphonodithioic acid-*O*-quinolin-8-yl ester (**6**) was obtained. The IR spectrum of **6** confirms the proposed structure. It revealed the absence of OH group and presence of SH band at υ 2373, 2954 (OCH_3),[20] 1595 (C=C, aromatics), 1385–1289 (C-O-C),[20] and 692 cm^{-1} (P=S).[21] Its ^{1}H NMR spectrum showed signals at δ 3.7 (s, 3H, OCH_3), 6.2 (s, 1H, SH, exchangeable with D_2O), and 6.9–8.9 (m, 10H, aromatics). The ^{31}P NMR shift recorded for **6** was at δ 14.1 ppm and the mass spectrum of 6 showed an ion peak at m/e 348 (M^+) (Scheme 2).

In addition, the reactions of 2-methylquinoline-4-ol (**7**), and/or β-naphthol (**9**) with LR **1b** were studied. These reactions were performed under the same experimental conditions to give the (4-methoxyphenyl)phosphonodithioic acid *O*-(2-methylquinolin-4-yl) ester (**8**) and *O*-naphthalen-6-yl *S*-hydrogen 4-methoxyphenylphosphonodithioate (**10**), respectively. Compounds **6** and **8** were equally obtained, irrespective of whether one or two mol equivalents of Lawesson's reagent **1b** was used. It could be demonstrated that the formation of phosphonodithioates **6**, **8**, and **10** from the reaction of Lawesson's reagent **1b** and the phenolic compounds **5**, **7**, and **9** occurred by the nucleophilic attack of the oxygen center of the phenolic compounds **5**, **7**, and **9** to the electron-deficient center in the monomeric species of LR 1b, followed by migration of the proton to the electron-rich center of the molecules (Scheme 2).



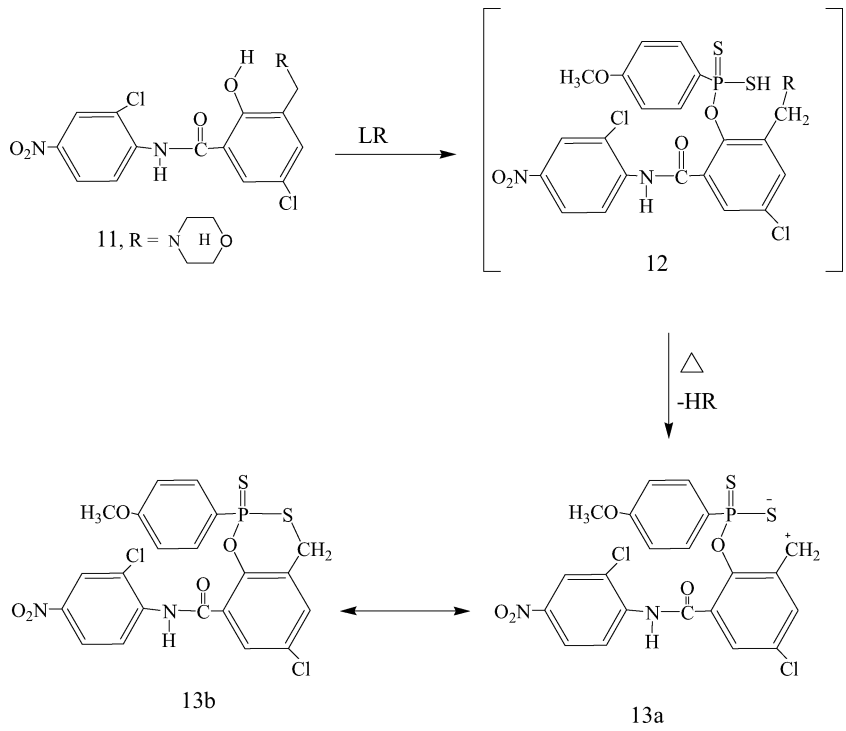
SCHEME 1



SCHEME 2

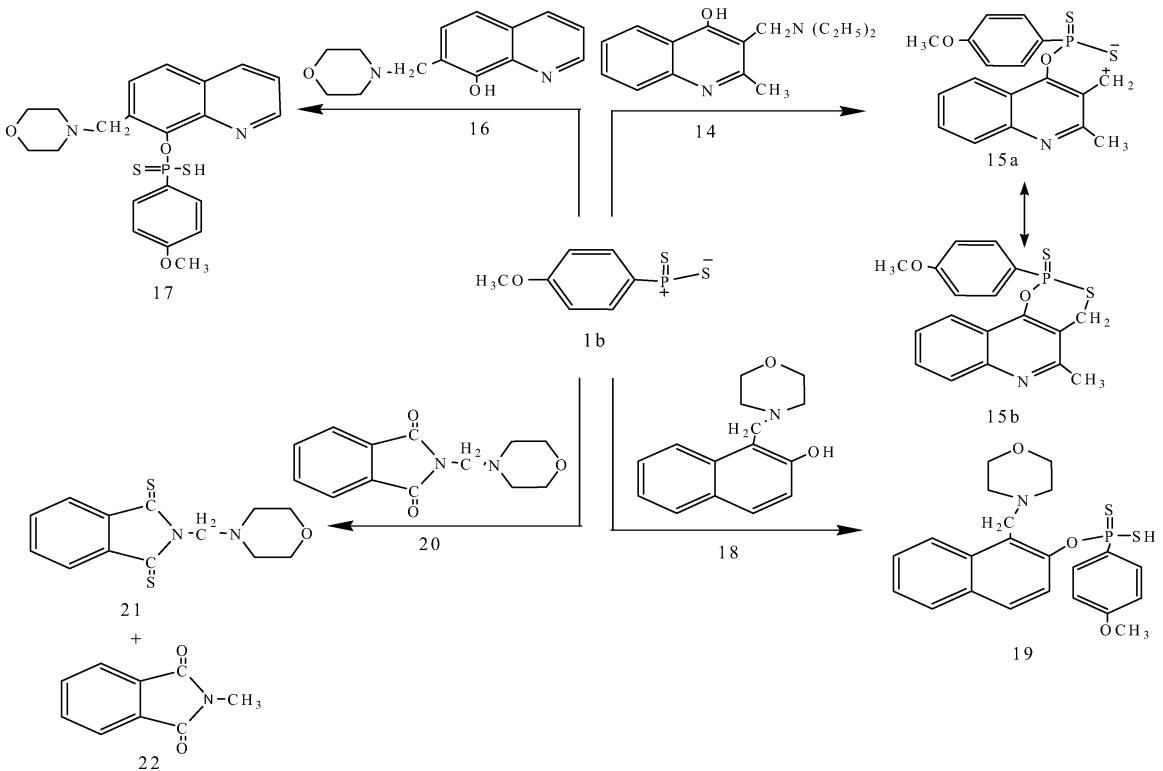
It was of interest to prepare phenolic Mannich bases of niclosamide **11** (Scheme 3), 2-methylquinoline-4-ol **14**, 8-hydroxyquinoline **16**, *β*-naphthol **18**, and phthalimide **20** (Scheme 4), and react them with Lawesson's reagent **1b** to synthesize new organic compounds containing phosphorus and sulfur of biological[19] and industrial interest.[15] When the reaction of LR was preformed using the Mannich bases of niclosamide **11** and 2-methylquinoline-4-ol **14**, the corresponding new heterocyclic oxa-thiaphosphinins **13** and **15** were obtained, whereas in the case of the Mannich bases 8-hydroxyquinoline **16** and *β*-naphthol **18** only the (4-methoxyphenyl)phosphonodithioic acid *O*-(7-morpholin-4-yl methylqui-nolin-8-yl) ester (**17**) and *O*-1-(morpholinomethyl)naphthalene-2-yl-*S*-hydrogen-4-methoxyphenylphosphonodithioate (**19**) were isolated.

On the other hand, the phthalimide Mannich base **20** afforded the isoindolinedithione **21** along with N-methyl phthalimide (**22**). The corresponding 6-chloro-2-(methoxyphenyl)-2-thioxo-4*H*-2λ^5benzo-[*e*][1,3,2] oxathi-aphosphinin-8-carboxylic acid (2-chloro-4-nitrophenyl)



SCHEME 3

amide (**13**) was presumably obtained by electrophilic attack of LR **1b** on the phenolic OH group to form the intermediate **12** followed by the expulsion of the amine moiety to give **13**. This finding also exclude the elimination of the amine group from the Mannich base **11** to form the quinone-methylene that could react with LR to form the oxathiaphosphinine **13**. The IR spectrum of **13** showed no OH absorption band, which was exhibited by Mannich base **11** at 3422 cm^{-1}. Absorption bands were shown in compound **13** at υ 3296 (NH), 2941 (OCH_3), 2675 (CH_2), 1648 (C=O amide), 1391–1261 (C-O-C), and 615 cm^{-1} (P=S). Its ^1H NMR spectrum showed signals at δ 3.1 (s, 1H, NH, exchangeable with D_2O), 3.8 (s, 3H, OCH_3), 4.2 (d, 2H, CH_2 due to coupling with P atom), and 6.9–8.9 (m, 10H, aromat). Presence of the C=O amide, OCH_3, CH_2 groups in compound **13** were also attested by signals at δ 168.4, 55.22, and 22.75 ppm in its ^{13}C NMR spectrum. The ^{31}P NMR shift recorded for compound **13** was δ 14.3 ppm,[14] which supported the zwitterionic adduct **13a** rather than the cyclic structure **13b**. In the MS of **13** the M^+ was found at m/e 541. Compound **13** was



SCHEME 4

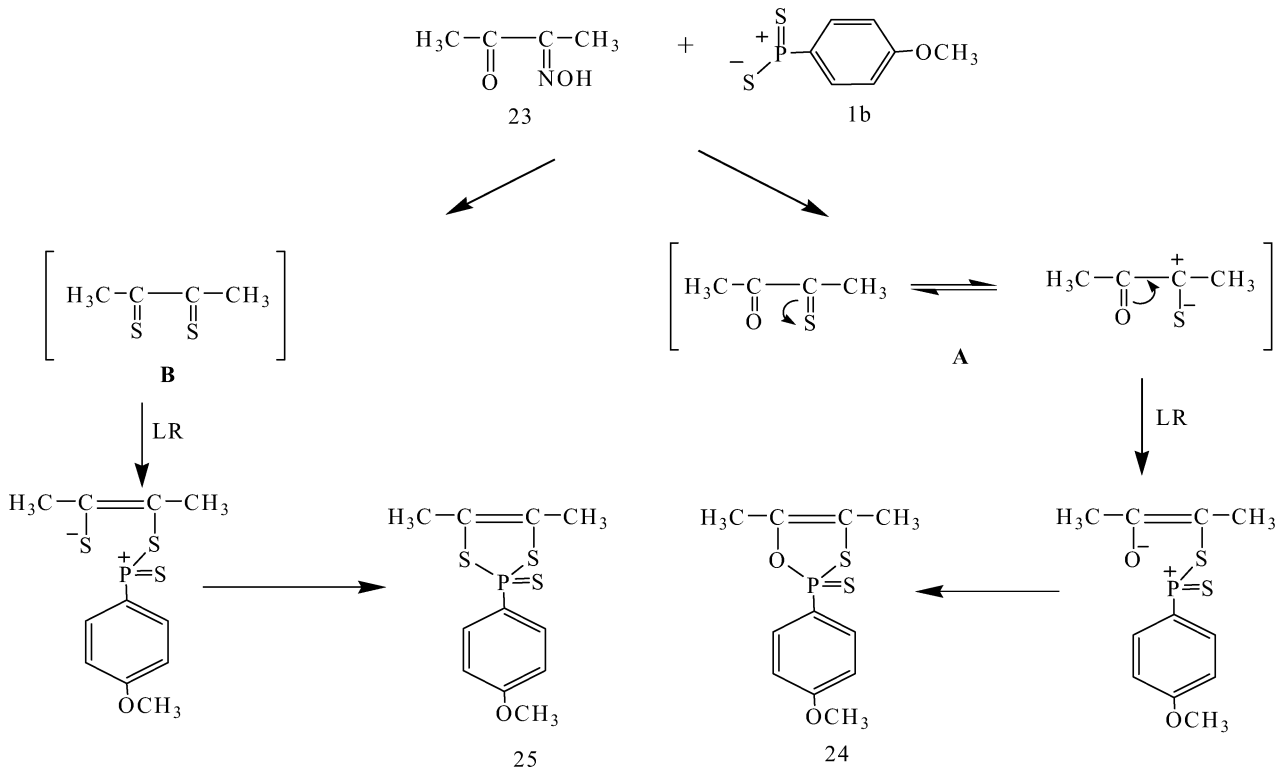
equally obtained irrespective of whether one or two mol equivalents of LR **1** were allowed to react with the Mannich base **11**. This means that no reaction was observed between LR and the amide groups of **11** (Scheme 3). Moreover, 2-(4-methoxyphenyl)-5-methyl-2-sulfanylene-4*H*-[1,3,2]-oxathiaphosphinino[5,b-c]quinoline (**15**) was obtained from the reaction of the Mannich base **14** with LR **1b**. On the other hand, when Mannich bases of 8-hydroxyquinoline **16** and β-naphthol **18** were treated with one mol equivalent of Lawesson's reagent **1** under similar conditions, the corresponding (4-methoxyphenyl)phosphonodithioic acid *O*-(7-morpholin-4-yl methylquinolin-8-yl) ester (**17**) and *O*-1-(morpholi-nomethyl)naphthalene-2-yl-*S*-hydrogen-4-methoxyphenylphosphonodithioate (**19**) were isolated, respectively. The structure of compound **17** was elucidated from elemental analysis, IR, ^{1}H, ^{31}P NMR, and MS data, which agreed with structure **17**. In this case, the addition occurred through nucleophilic attack of the phenolic OH group on the phosphorus atom of LR followed by migration of a proton to the sulfur anion to give the stable compound **17**. Its IR spectrum showed no OH absorption band, which is exhibited in the starting Mannich base **16** at 3428 cm^{-1}, and the presence of absorption bands at ν 2370 (SH), 2879 (OCH_3), 2571 (CH_2), 1546 (C=C, aromatics), 1339–1257 (C-O-C), and 629 cm^{-1} (P=S). In the ^{1}H NMR spectrum of **17**, signals were observed at δ 2.5 (t, 4H, $2CH_2$ morpholin), 3.0 (t, 4H, $2CH_2$ morpholin), 3.7 (s, 3H, OCH_3), 4.2 (s, 2H, CH_2), 5.3 (s, 1H, SH exchangeable with D_2O), and 6.9–8.8 (m, 9H, aromatics). A signal at δ 14.07 was observed in the ^{31}P NMR of the phosphonodithioate **17** and in its MS spectrum the M^+ was found m/e 447. In the same manner, when compound **18** was treated with LR the phosphonothioate **19** was obtained (Scheme 4).

We have also found that when the Mannich base of phthalimide **20** reacted with Lawesson's reagent **1** in molar ratio 1:1 in dry benzene for 15 h, the corresponding 2-(morpholinomethyl)isoindoline-1,3-dithione (**21**) and 2-methylisoindoline-1,3-dione (**22**) were obtained. It could be concluded that LR affects thionation of phthalimide Mannich base **20** to give the dithione derivative **21** and/or split the amine moiety of **20** with the formation of the N-methyl derivative **22**. The IR spectrum of **21** revealed the presence of absorption bands at ν 2623 (CH_2), 1119 (C=S) cm^{-1} and absence of the two C=O groups that were exhibited by the Mannich base **20** at 1626 cm^{-1}. Its ^{1}H NMR spectrum showed signals at δ 2.4 (t, 4H, $2CH_2$ morpholin), 3.0 (t, 4H. $2CH_2$ morpholin), 3.6 (s, 2H, CH_2), and 7.3–7.8 (m, 4H, aromatics) ppm. Furthermore, signals at δ 198.91, 22.83 ppm were observed in the ^{13}C NMR spectrum of **21** that are attributed to the two C=S, and CH_2 groups. In its MS the

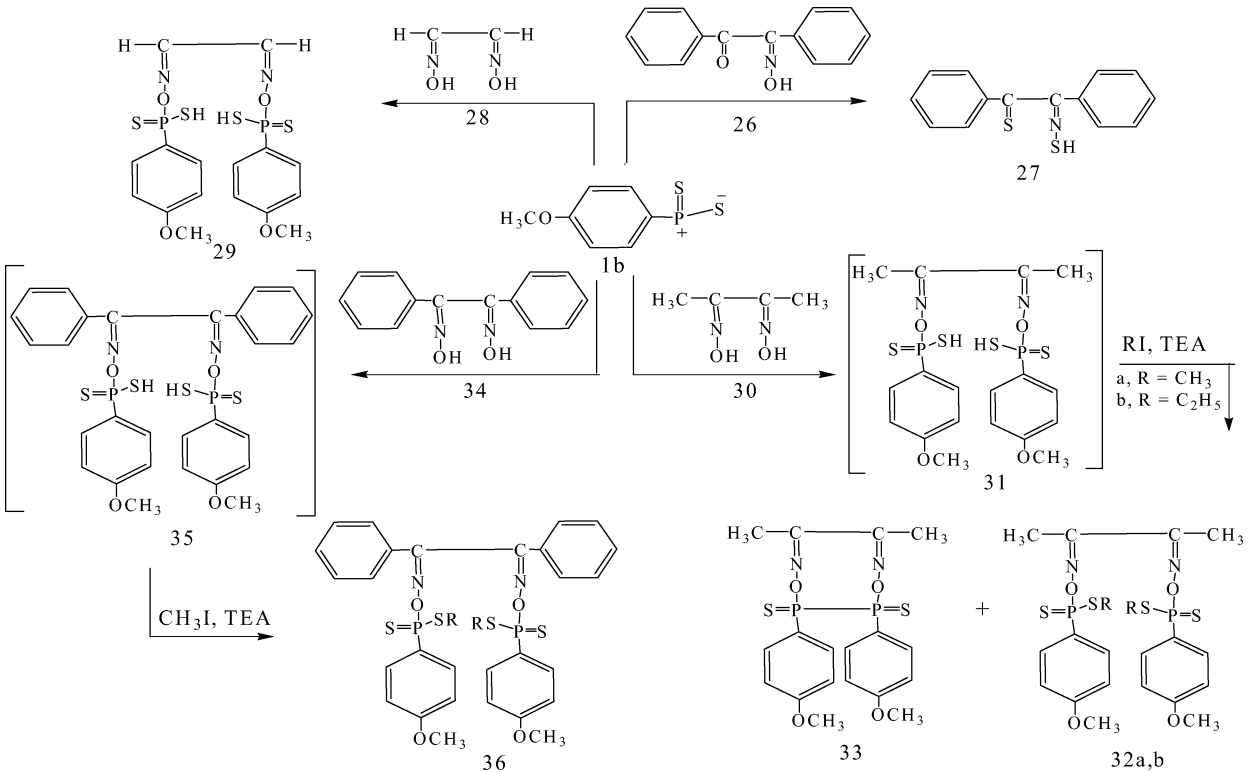
(M^+) was found at m/e 279. Moreover, the IR spectrum of **22** revealed the presence of absorption band of C=O group at υ 1665 cm^{-1}. In its ^1H NMR spectrum the CH_3 group appeared at δ 1.6 ppm as a singlet and 7.2–7.9 multiple 4H aromatics. The ^{13}C NMR spectrum of **22** showed signals at δ 169.14 (C=O) and 39.87 (CH_3) ppm. In the mass spectrum M^+ was found at m/e 162 (Scheme 4).

The work also focused on the reaction of LR **1b** with ketone monoximes **23** and **26** or dioximes **28**, **30**, and **34** derivatives. When butane-2,3-dione oxime (**23**) was treated with equimolar amounts of Lawesson's reagent **1b** in dry toluene under reflux for 15 min, 2-(4-methoxyphenyl)-4,5-dimethyl-1,3,2-oxathiaphosphole-2-sulfide (**24**) was obtained in a good yield, together with 2-(4-methoxyphenyl)-4,5-dimethyl-1,3,2-dithiaphosphole-2-sulfide (**25**) in a moderate yield. Reaction of the ketone monoxime **23** with LR 1b resulted in thionation of the N-OH group[22] and formation of the intermediate **A**, which reacted with LR **1b** to give the corresponding oxathiaphosphole **24**. In addition, thionation of both the carbonyl and oxime groups of the ketone monoxime **23** resulted in the formation of the intermediate **B**, which reacted with LR to form the dithiaphosphole **25** (Scheme 5). The IR spectrum of **24** revealed the absence of =N-OH and C=O bands that appeared in the starting material **23** at υ 3384 and 1670 cm^{-1} and showed bands at υ 2837 (OCH_3), 1594 (C=C), 1300–1264 (C-O-C), 1128 (P-O-C), and 669 cm^{-1} (P=S). The ^1H NMR spectrum of **24** exhibited signals at δ 1.5 (s, 6H, $2CH_3$), 3.8 (s, 3H, OCH_3), and 7.0–8.3 (m, 4H, aromatics) ppm whereas its ^{13}C NMR spectrum revealed the absence of C=O and C=N-OH groups and the presence of C-P, C-O, OCH_3, and CH_3 at δ 164.25, 128.23, 55.56, and 23.12 ppm, respectively. The ^{31}P NMR shifts for **24** were at δ 73.88 ppm. In the MS of **24** m/e = 273 (M^+). The structure of the dithiaphosphole **25** was elucidated from spectroscopic data (Table I).

When 1,2-diphenylethane-1,2-dione oxime (**26**) was reacted with Lawesson's reagent **1b** in dry boiling toluene for 5 h, the corresponding 1,2-diphenyl-2-thioxoethanonethioxime (**27**) was only obtained in a good yield. The elemental microanalysis, IR, ^1H, ^{13}C NMR, and MS data agreed with structure **27**. The IR spectrum showed no absorption bands of =N-OH, and C=O groups and revealed the presence of absorption bands at υ 2370 (SH), 1624 (C=N), and 1276 cm^{-1} (C=S). In the ^1H NMR spectrum of **27**, signals at δ 2.89 (s, 1H, SH exchangeable with D_2O) and 7.2–7.8 (m, 10H, aromatics) ppm were shown. The presence of C=S and C=N groups in **27** was also attested to by signals at δ 202.91 and 139.83 ppm in its ^{13}C NMR spectrum and in the MS of **27** m/e = 258 (M^+). Compound **27** was equally obtained irrespective of whether one or two mol equivalents of LR **1b** was used (Scheme 6).



SCHEME 5



SCHEME 6

TABLE I Spectroscopic Data (IR, NMR, and MS) for Compounds 8, 10, 15, 19, and 25

Compound no.	IR: ν /cm^{-1}	NMR: δ /ppm		MS
		^{1}H NMR	^{31}PNMR	
8	2935 (OCH_3, CH_3), 2354 (SH), 1648 (C═C, aromatics), 1362–1300 (C-O-C), and 677 (P═S)	2.4 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 5.7 (s, H, SH exchangeable with D_2O), and 6.8–8.6 (m, 9H, aromatics)	14.01	362
10	2835 (CH_3), 2373 (SH), 1626 (C═C, aromatics), 1304–1263 (C-O-C), and 665 (P═S)	3.77 (s, 3H, OCH_3), and 6.9–7.6 (m, 11H, aromatics, and SH)	14.02	348
15	2940 (CH_3), 2676 (CH_2), 1393–1260(C-O-C), 1478 (P-C-aryl), and 612 (P═S)	2.1 (s, 3H, CH_3), 3.3 (s, 2H, CH_2), 3.7 (s, 3H, OCH_3), and 6.8–7.6 (m, 8H, aromatics)	14.42	373
19	2962 (OCH_3), 2600 (CH_2), 2311 (SH), 1628 (C═C, aromatics), 1309–1289 (C-O-C), and 672 (P═S)	2.4 (t, 4H, $2CH_2$ morpholin), 3.1 (t, 4H, $2CH_2$ morpholin), 3.5 (s, 1H, SH, exchangeable with D_2O), 3.7 (s, 3H, OCH_3) , 4.0 (s, 2H, CH_2), and 6.8–8.0 (m, 10H, aromatics)	13.95	446
25	2833 (OCH_3), 1589 (C═C), 1313–1254 (C-O-C) and 687 (P═S)	1.6 (s, 6H, $2CH_3$), 3.8 (s, 3H, OCH_3), and 7.9–8.1 (m, 4H, aromatics)	84.13	288

In addition, the reaction of ethanediol dioxime (**28**) with Lawesson's reagent **1b** was performed in boiling dimethylformamide and the corresponding compound **29** was isolated as a sole product. Structural assignment for **29** was supported by the elemental microanalysis, MS, IR, ^{1}H, and ^{31}P NMR spectroscopic data. The IR spectrum of compound **29** showed strong absorption bands at υ 2833 OCH_3, 2320 SH, 1624 C═N, 1345–1225 (C-O-C), and 625 cm^{-1} (P═S). The ^{1}H NMR shifts of **29** were 2.49 (s, 2H, 2CH), 3.56 (s, 6H, $2OCH_3$), 5.07 (br, 2H, 2SH, exchangeable with D_2O), and 6.88–7.59 (m, 8H, aromatics). The ^{31}P NMR spectrum showed signal at δ 13.24 ppm and in the mass spectrum m/e 493 (M^+) (Scheme 6).

Moreover, when butane-2,3-dione dioxime (**30**) was allowed to react with Lawesson's reagent **1b** in molar ratio in dry toluene at reflux temperature for 15 min, compound **31** along with **33** was obtained. Compound **31** was not isolated; however, upon in situ alkylated with methyl iodide and/or ethyl iodide, compounds **32a**, **b** were isolated.

The products **32a**, **b** and **33** were identified by elemental analyses and spectroscopic data. The ^{1}H NMR spectrum of **32a** showed the singlet at δ 2.1 due to the two CH_3, the two SCH_3 protons appeared as doublet at 2.5 ppm (due to the presence of P atom), a singlet at 3.8 ppm is due to the two OCH_3 protons, and a multiple at δ 6.9–7.9 aromatics protons. The IR spectrum of **32a** confirmed the proposed structure, showing no absorption for the two =NOH groups. The OCH_3, C=N, and P=S groups appeared at υ 2800, 1560, and 692 cm^{-1}, respectively, in its IR spectrum, whereas its ^{13}C NMR spectrum revealed the presence of the signals at δ 159.5 (C=N-O), 55.4 (OCH_3), 32 (CH_3), and 14.9 (SCH_3). The ^{31}P NMR shifts recorded for **32a** at δ 105.15–106.12 ppm is in conformity for similar structures,[22] and its MS m/e = 547 (M^-). In case of alkylation with ethyl iodide, **32b** was isolated under the same experimental conditions. The structure of **32b** was based on its elemental microanalysis, IR, ^{1}H, ^{31}P NMR, as well as its mass spectrum. The IR spectrum of **32b** exhibited the presence of 2927 (CH_3), 2867 (OCH_3), 1591 (C=N), and 600 cm^{-1} (P=S), and the absence of =N-OH groups. Its ^{1}H NMR spectrum showed the presence of signals at δ 1.3 (t, 6H, 2S-CH_2-$\underline{CH_3}$), 2.2 (s, 6H, $2CH_3$), 3.2 (q, 4H, 2S-$\underline{CH_2}$-CH_3), 3.8 (s, 6H, $2OCH_3$), and 6.9–7.9 (m, 8H, aromatics) ppm. The ^{31}P NMR spectrum showed peaks at δ 104.91–104.96, which is in accordance with earlier findings of such structures,[22] and the mass of **32b** m/e = 577 (M^+). In addition, the structure of the second product, namely, 7,8-dihydro-7,8-bis-(methoxyphenyl)-3,4-dimethyl-7,8-disulfanylene-1,6,2,5,7,8-dioxadiazadiphosphocine (**33**), was supported by the elemental analysis, IR, ^{1}H, ^{31}P NMR, and MS spectroscopic data. The IR spectrum is characterized by the absence of =NOH groups and the presence of absorption bands at υ 2925 (OCH_3), 1653 (C=N), 1297, 1364 (C-O-C), and 602 cm^{-1} (P=S). The ^{1}H NMR spectrum of **33** revealed the presence of signals at δ 2.1 (s, 6H, $2CH_3$), 3.8 (s, 6H, $2OCH_3$), and 7.1–7.9 (m, 8H, aromatics). The ^{31}P NMR shifts recorded for **33** at δ 104.54 ppm. The MS supported the structure of compound **33** and showed the molecular ion peak at m/e = 454 (Scheme 6).

When 1,2-diphenylethane-1,2-dione dioxime (**34**) was reacted with LR **1b** in dry toluene under reflux for 15 min, compound **35** was obtained. Compound **35** was not isolated, and subjected to alkylation in situ with methyl iodide, compound **36** was isolated. The IR spectrum of **36** showed no =N-OH groups and the presence of absorption bands at 2926 (OCH_3), 1592 (C=N), 1267–1179 (C-O-C), and 697 cm^{-1} (P=S). In its ^{1}H NMR spectrum signals were at δ 2.8 (d, 6H, $2SCH_3$ due to presence of P atom), 3.7 (s, 6H, $2OCH_3$) and 6.8–8.1 (m, 18H, aromatics) ppm. The ^{31}P NMR shift recorded for **36** at δ 104.5 ppm, which is

in accordance with similar structures,[22] and its mass spectrum showed m/e 672. Formation of the phosphonodithioic acid derivatives **29**, **32a**, **b**, and **36** occurred *via* addition of the dioximes **28**, **30**, and **34** to LR. In the case of the reaction of the dioxime **30** and LR, part of compound **31** lost H_2S and S to give the dioxadiazadiphosphocine **33**.

CONCLUSION

The reaction of LR **1b** with different functional compounds such as phenolics, Mannich bases, ketone monoximes, and/or ketone dioximes represents an interesting approach to the construction of new bioactive compounds containing phosphorus and sulfur. The heterocyclic oxathiaphosphinines **4**, **13**, **15**, and **24** were obtained from the reaction of niclosamide **2**, niclosamide Mannich base **11**, 2-methylquinoline4-ol (**14**), and the ketone monoxime **23**, respectively. Moreover, the phosphonothiaoates **6**, **8**, **10**, **17**, **19**, **21**, **32**, and **36** were isolated from the reaction of LR 1b with the phenolic compounds **5**, **7**, **9**, Mannich bases **16**, **18**, and the ketone dioximes **28**, **30**, **34**, respectively. We noticed also that the behavior of LR toward the ketone monoximes is different from that of the ketone dioximes. In the case of the monoximes, thionation reactions occured, whereas the ketone dioxime afforded the formation of the phosphonothioates. This process can be considered as a simple route for the formation of the above-mentioned new compounds, which are difficult to obtain by other conventional methods.

BIOLOGICAL EVALUATION OF THE TESTED COMPOUNDS

Schistosomiasis is estimated to affect 200 million people around the world, causing high levels of morbidity and mortality in 74 countries in tropical and subtropical areas. Egypt was one of the most highly endemic areas in the world, with infection rates exceeding 80% in some localities in the Nile Valley.[23] As intermediate hosts, molluscs play a major role in the transmission of schistosomes, because they are the sites of an intense multiplication of the parasites. The use of molluscicides has always been considered to be a major supportive procedure in integrated schistosomiasis control.[11] Among synthetic compounds, niclosamide (the active ingredient of bayluscide) is still the molluscicide of choice, being highly active at different stages of the snail life cycle and also effective on the schistosome larvae. Niclosamide is not toxic to humans, domestic animals, and crops.[24] Therefore, the present work aims to examine the efficacy of the newly prepared compounds containing sulfur or containing phosphorus and sulfur derivatives as

molluscicides for controlling such snails in the laboratory, hoping to find a suitable one for eradicating the disease through its intermediate host.

Materials

- Snails: *Biomphalaria glabrata snails* used in this study were obtained from colonies of the Schistosome Biological Supply Program (SBSP), Theodor Bilharz Research Institute, Giza, Egypt. The original stock of snail species were obtained from London University and maintained for many years in the laboratory (SBSP). A group of laboratory-produced snails of the same size (4–6 mm in diameter) were used for testing the molluscicidal potency of the tested compounds and were maintained in the laboratory in glass aerated aquaria, containing dechlorinated tap water, nostoc algae, and lettuce leaves. The temperature was kept at 25°C +1.
- Chemicals: The tested molluscicides, namely, carbothioamide **3**, oxathiaphosphinines **4**, **13**, and **15**, phosphonodithioates **6**, **8**, **10**, **17**, **19**, **29**, **32**, and **36**, isoindolinedithione **21**, N-methylphthalimide **22**, oxathiaphosphole **24**, dithiaphosphole **25**, thioxoethanonthioxime **27**, and dioxadiazadiphosphocine **33**, were prepared as mentioned in the text.

The molluscicidal potency of the newly synthesized compounds against *Biomphalaria glabrata* snails, which the intermediate host of *Schistosoma mansoni* was studied, and compared them with niclosamide. The results showed that all newly tested compounds have low or no molluscicidal potency against *B. glabrata* snails; however, two compounds (**3** and **33**) showed highly molluscicidal activity against the snails. Moreover, thionated niclosamide **3** determined 100% mortality of *B. glabrata* at 0.1 ppm immediately, whereas compound **33** showed 100% mortality of the snails at 1.2 ppm compared to niclosamide, which killed 100% of *B. glabrata* snails at 1.5 ppm after 2 h exposure.[11]

Therefore, further studies on the effect of these two newly niclosamide derivatives **3** and oxime derivative **33** as promising molluscicides are needed to ensure their safety on aquatic biota on larger scale and their selective activity on target snails.

EXPERIMENTAL

All melting points were measured on a Gallenkamp electrothermal melting point apparatus and were uncorrected. The infrared spectra

were recorded in KBr pellets on a Pye unicam SP 3300 and FTIR 8101PC Shimadzu Infrared Spectrometers. NMR spectra were obtained in deuterated $CDCl_3$ or DMSO on a Varian MERCURY (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometer using TMS as an internal reference. ^{31}P NMR spectra were run on the same spectrometer using H_3PO_4 (85%) as external reference. Mass spectra were recorded on a Shimadzu GC-MS QP 1000 Ex Spectrometer at (E I, 70 ev). Elemental analyses were carried out at the Microanalytical Center of the National Research Center, El-Tahrir Street, Dokki, Cairo. Their results were in agreement with the calculated values.

The reported yields are of pure isolated materials obtained by column chromatography using silica gel 60 (Merck).

Physical and spectroscopic data are shown in Tables I and II.

TABLE II Physical Data of Compounds 3, 4a, 6, 8, 10, 13, 15, 17, 19, 21, 22, 24, 25, 27, 29, 32a, 32b, 33, and 36

Compound no.	mp (°C)	Solvent of crystallization	Yield (%)	Formula	Mol. wt./g mol^{-1}
3	132	Pet. ether/ethyl acetate	80	$C_{13}H_8Cl_2N_2O_3S$	342
4a	208	Pet. ether/ethyl acetate	25	$C_{20}H_{13}Cl_2N_2O_4PS_2$	510
6	199	Pet. ether/acetone	75	$C_{16}H_{14}NO_2PS_2$	347
8	210	Benzene	75	$C_{17}H_{16}NO_2PS_2$	361
10	200	Benzene/pet. ether	35	$C_{17}H_{15}O_2PS_2$	346
13	185	Ethanol	85	$C_{21}H_{15}Cl_2N_2O_5PS_2$	540
15	115	Benzene	40	$C_{18}H_{16}NO_2PS_2$	373
17	212	Ethanol	85	$C_{21}H_{23}N_2O_3PS_2$	446
19	149	Chloroform/pet. ether	55	$C_{22}H_{24}NO_3PS_2$	445
21	175	n-Hexane/ethyl acetate	75	$C_{13}H_{14}N_2OS_2$	278
22	231	n-Hexane/ethyl acetate	85	$C_9H_7NO_2$	161
24	160	Benzene	80	$C_{11}H_{13}O_2PS_2$	272
25	51	Benzene	35	$C_{11}H_{13}OPS_3$	288
27	112–114	Cyclohexane	65	$C_{14}H_{11}NS_2$	257
29	295	Ethanol	85	$C_{16}H_{18}N_2O_4P_2S_4$	492
32a	123	n-Hexane/acetone	75	$C_{20}H_{26}N_2O_4P_2S_4$	548
32b	100	n-Hexane/acetone	75	$C_{22}H_{30}N_2O_4P_2S_4$	576
33	152–154	n-Hexane/acetone	25	$C_{18}H_{20}N_2O_4P_2S_2$	454
36	Oily	n-Hexane/ethyl acetate	40	$C_{30}H_{30}N_2O_4P_2S_4$	672

Reaction of Lawesson's Reagent (1) with Phenolic Compounds 2, 5, 7, and 9: Synthesis of Carbothioamide 3, Oxathiaphosphinin 4, and Phosphonodithioic Acids 6, 8, and 10

A solution of Lawesson's reagent **1**[25] (0.001 mol) in 20 mL of dry anhydrous acetonitrile was added under reflux and stirring to the solution of phenolic compounds **2**, **5**, **7**, and **9** (0.001 mol) in 30 mL of acetonitrile, respectively. The reaction mixture was refluxed for one day in case of **2** and for 5–10 h in case of **5**, **7**, and **9**, until no more of the starting materials could be detected (TLC). Acetonitrile was distilled off under reduced pressure and the remaining residue was crystallized from the specified solvents to give the carbothioamide **3** and phosphonodithioic acids **6**, **8**, and **10**, respectively. When the reaction of niclosamide **2** was repeated using one mol equivalent of **2** and two mol equivalents of LR, the same product of carbothioamide **3** was isolated together with oxathiaphosphinin **4**.

Reaction of Lawesson's Reagent 1b with Phenolic Mannich Bases 11, 14, 16, and 18: Synthesis of Oxathiaphosphinins 13 and 15 or Phosphonodithioic Acids 17 and 19

A mixture of Lawesson's reagent **1** (0.001 mol) and phenolic Mannich bases **11**, **14**, **16**, and **18** (0.001 mol) was refluxed with stirring in anhydrous acetonitrile 50 mL for 72 h in case of **11** and for 5–8 h when compounds **14**, **16**, and **18** were used, until no more of the starting materials could be detected (TLC). The solvent was distilled off under reduced pressure and the remaining residue was crystallized from the specified solvent to give oxathiaphosphinins **13** and **15** or phosphonodithioic acids **17** and **19**, respectively. When the reaction of LR **1** and niclosamide Mannich base **11** was repeated by using 2 mol of LR and 1 mol of compound **11** the same product of oxathiaphosphinin **13** was isolated, too.

Reaction of Lawesson's Reagent 1 with Phthalimide Mannich Base 20: Synthesis of 2-(Morpholinomethyl)isoindoline-1,3-dithione (21) and 2-Methylisoindoline-1,3-dione (22)

A solution of LR **1** (0.001 mol) in 30 mL dry benzene was refluxed with the solution of phthalimide Mannich base **20** (0.001 mol) until no more of the starting materials could be detected (TLC). Benzene was distilled off under reduced pressure and the remaining residue was

chromatographed on silica gel using n-hexane/ethyl acetate as eluent (90:10, v/v) to give compounds **21** and **22**.

Reaction of Lawesson's Reagent 1 with Ketone Monoxime Compounds 23 and 26: Synthesis of Oxathiaphosphole 24 and Dithiaphosphole 25 or Thioxoethanonethioxime 27

To a solution of Lawesson's reagent **1** (0.001 mol) in 20 mL of dry toluene was added a solution of ketone monoxime **23** or **26**[26] (0.001 mol) in 30 mL toluene. The reaction mixture was refluxed for 15 min in case of **23** and for 5 h in case of **26**. After the solvent have been distilled off, the residue was chromatographed on silica gel using n-hexane/ethyl acetate as eluent to give the oxathiaphosphole **24** and dithiaphosphole **25** or thioxoethanonethio oxime **27**, respectively.

Reaction of Lawesson's Reagent (1) with Ethanediol Dioxime (28)

To a solution of Lawesson's reagent **1** (0.001 mol) in 15 mL of dimethylformamide was added a solution of the dioxime compound **28** (0.001 mol) in 15 mL dimethylformamide, and the reaction mixture was refluxed for 2 h. The solvent was distilled off under reduced pressure, and the residue was purified on silica gel by column with pet. ether/ethyl acetate (30:70, v/v) as eluent and recrystallized from ethyl alcohol.

Compound **29** was synthesized as white crystals.

Reaction of Lawesson's Reagent 1 with Butane-2,3-dione Dioxime (30)

A mixture of Lawesson's reagent **1** (0.001 mol) and the dioxime **30** (0.001 mol) was boiled under reflux in dry toluene for 15 min until no more of the starting materials could be detected (TLC). The solution was cooled in an ice bath and methyl iodide or ethyl iodide (0.001 mol) and triethyl amine (0.0012 mol) was added drop-wise. Toluene was distilled off under reduced pressure and the remaining residue was chromatographed on silica gel using n-hexane/acetone as eluent, and compounds **32a** and **32b** along with **33** were separated.

Reaction of Lawesson's Reagent 1 with 1,2-Diphenylethane-1,2-dione Dioxime (34)

A mixture of Lawesson's reagent **1** (0.001 mol) and the dioxime **34** (0.001 mol) was boiled under reflux in dry toluene for 15 min until no more of the starting materials could be detected (TLC). The solution

was cooled in an ice bath and methyl iodide (0.001 mol) was added dropwise followed by triethyl amine (0.0012 mol). Toluene was distilled off under reduced pressure and the residue was chromatographed on silica gel using pet. ether/ethyl acetate (20:80, v/v) as eluent and compound **36** was separated as an oily compound.

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