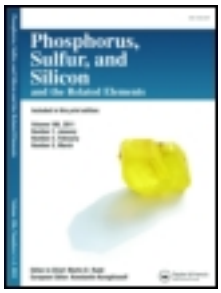


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Studies With 2-Benzothiazolylacetonitrile: Synthesis of New 2-Thienylbenzothiazoles and N-Thienyl maleimide Derivatives

Yehya Mahmoud Elkholy [a]

[a] Chemistry Department, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt

Version of record first published: 27 Oct 2010.

To cite this article: Yehya Mahmoud Elkholy (2002): Studies With 2-Benzothiazolylacetonitrile: Synthesis of New 2-Thienylbenzothiazoles and N-Thienyl maleimide Derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, 177:1, 115-122

To link to this article: http://dx.doi.org/10.1080/10426500210233

Phosphorus, Sulfur and Silicon, 2002, 177:115–122

1042-6507/02 $12.00 + .00

STUDIES WITH 2-BENZOTHIAZOLYLACETONITRILE: SYNTHESIS OF NEW 2-THIENYLBENZOTHIAZOLES AND N-THIENYL MALEIMIDE DERIVATIVES

Yehya Mahmmoud Elkholy
Chemistry Department, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt

(Received April 19 2001.)

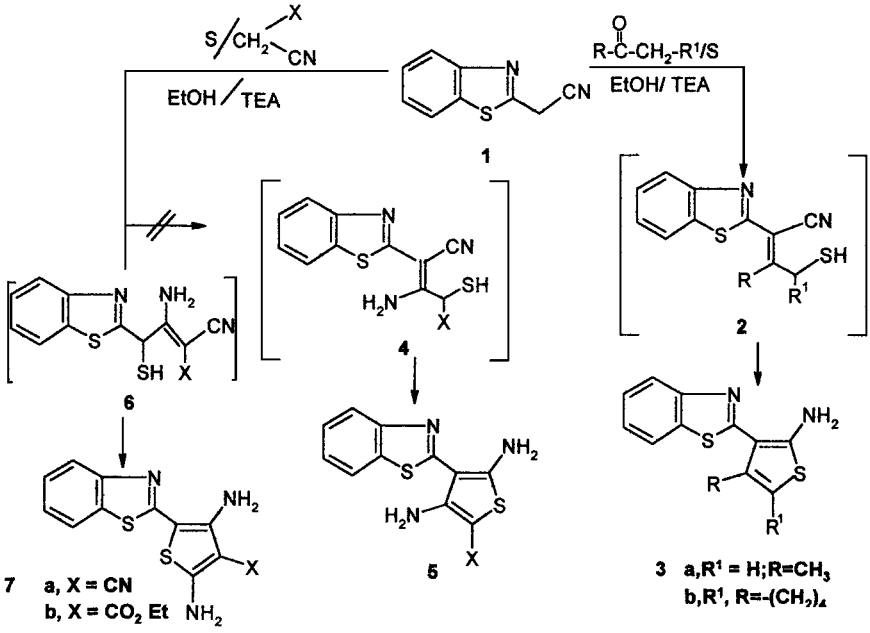
*The synthesis of new 2-thienylbenzothiazoles and N-thienyl maleimide derivatives utilizing 2-benzothiazolyl acetonitrile **1** as starting component.*

Keywords: 2-benzothiazolylacetonitrile; maleic anhydride; thiophene

Azolyl acetonitriles are readily obtainable compounds that have been extensively utilized as intermediates in heterocyclic synthesis[1–3] which are of potential biological activity.[4,5] Thiazole and its derivatives are long known for their antibacterial[6] activity and their use as hypoglycemic,[7] fungicidal[8] and herbicidal[9] agents. In conjunction with our previous work[10,11] we report here the results of our further work exploring the synthetic potential of 2-benzothiazolylacetonitrile **1**. Thus, it has been found that **1** reacts with acetone in the presence of sulfur and triethylamine in boiling ethanol solution to yield a product that is assigned the structure **3a** based on analytical and spectral data. The IR spectrum of this product revealed the absence of the CN signal and the appearance of the NH_2 signal as required by structure **3**. The formation of **3** is assumed to proceed via the nonisolated intermediate mercapto derivative **2** that cyclizes and then aromatized readily under the reaction condition to give **3**. Similarly, compound **1** reacts with cyclohexanone to yield the thienyl benzothiazole derivative **3b**. Furthermore, a mixture of malononitrile and sulfur reacted with compound **1** to yield either **5a** or **7a**. The formation of **7a** is assumed to proceed via addition of CH_2 group of the malononitrile to the CN

Address correspondence to Yehya Mahmmoud Elkholy, Chemistry Department, Faculty of Science, Helwan University, Ain-Helwan, Cairo, Egypt. E-mail: Y_elkholy@yahoo.com

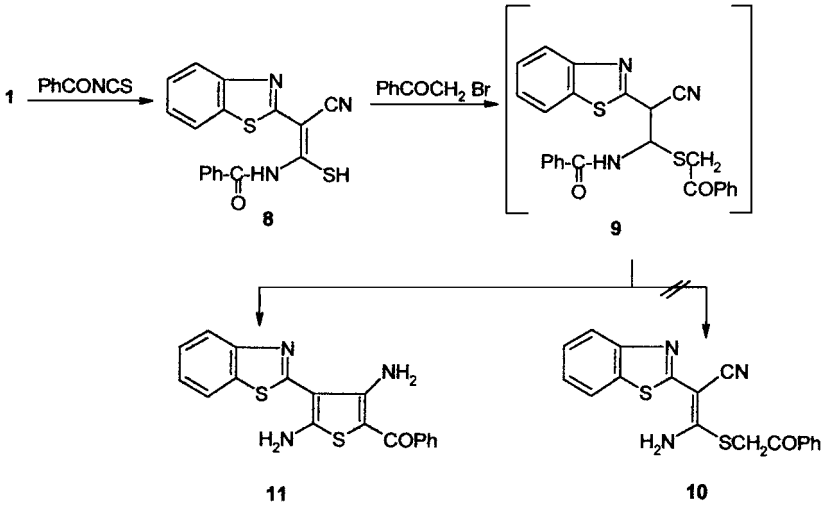
function in **1** followed by reaction with sulfur to yield **6a** which was cyclized into **7a**. Alternatively CH_2 of **1** may added to the CN function of malononitrile and then reacted with sulfur to give the intermediate **4**, which was cyclized to **5**. Structure **7a** is preferred over possible **5a** based on the IR spectrum which showed a CN signal at 2250 cm^{-1}. Alternative **5a** is expected to show a CN signal at a lower frequency.[12] Similar to malononitrile, ethyl cyanoacetate yields **7b** (cf. Scheme 1).



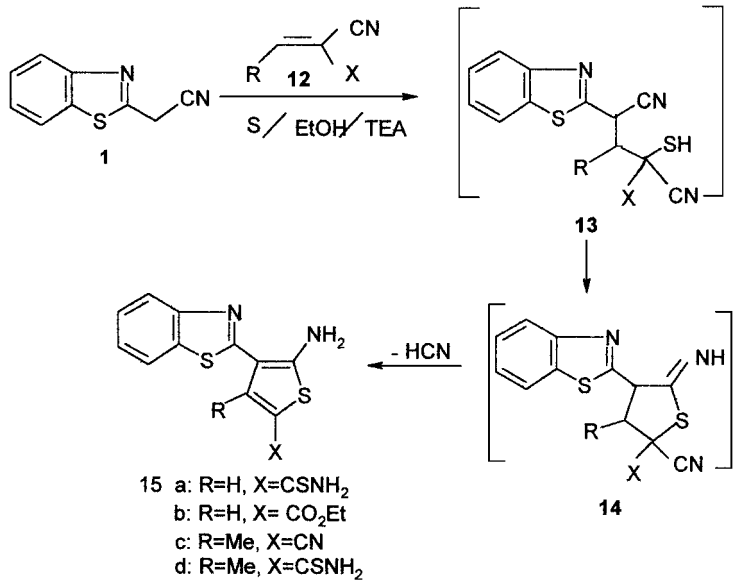
SCHEME 1

In other trials to prepare thienylbenzothiazole derivative with diamino substituent as a good dyestuff, compound **1** reacted with benzoylisothiocyanate to yield a 1:1 adduct which may be formulated as **8**. Structure **8** was established for the reaction product based on ^1H NMR which revealed the absence of the CH_2 function and the presence of NH as well as SH function. Compound **8** reacted with phenacyl bromide to yield a product which was formulated as **10** rather than isomeric **11**.[13] Compound **11** was established based on the IR spectrum, which showed signals for two NH_2 groups and disappearance of cyano group. Compound **11** is believed to be formed via the nonisolated intermediate **9**, which undergoes cyclization under the reaction condition to give the final isolated product. (cf. Scheme 2).

Furthermore, compound **1** reacts with methyldine derivative **12** and sulfur in the presence of ethanolic triethylamine to give



SCHEME 2

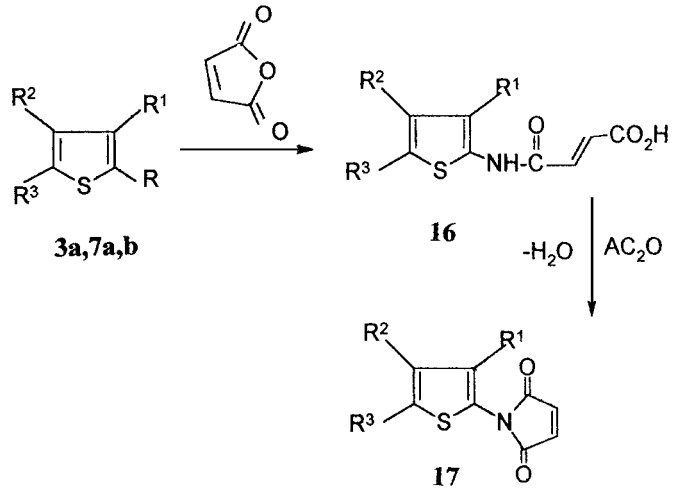


SCHEME 3

theinyl derivatives **15a–d** through the nonisolated intermediate **13** and **14**.

Compounds **3a**, **7a**, and **7b** reacted with maleic anhydride to give the thienylamidomaleic acid derivatives **16a–c**, which readily cyclized

to give N-thienylmaleimide derivatives **17a–c** via elimination of H_2O when heated in acetic anhydride (cf. Scheme 4).



17 a: R=NH_2, R^1=2-benzothiazolyl, R^2=Me, R^3=H
b: R=NH_2, R^1=CN, R^2=NH_2, R^3=2-benzothiazolyl
c: R=NH_2, R^1=CO_2Et, R^2=NH_2, R^3=2-benzothiazolyl

SCHEME 4

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were obtained on a Shimadzu 408 spectrophotometer. The ^1H NMR were measured in DMSO[d_6] on a Varian EM-390 MHz spectrometer using TMS as internal reference and chemical shifts are expressed as δ ppm. Analytical data were obtained from the Analytical Data Unit at Cairo University, Egypt.

General Procedure for the Synthesis of 2-Thienylbenzothiazole Derivatives (3a,b and 7a,b)

A solution of **1** (0.01 mol) in ethanol (30 ml) was treated with the appropriate amount of active methylene reagents (0.01 mol) and sulfur (0.01 mol) with catalytic amount of triethylamine (2 ml). The reaction mixture was heated under reflux for 5 h. The solvent was removed under reduced pressure and the residue was triturated with water and neutralized with conc. HCl. The solid product so formed was collected by filtration and recrystallized from DMF.

2-[3-(2-amino-4-methyl)thienyl]benzothiazole (3a)

Compound **3a** was obtained as yellow crystals (65%) from DMF; m.p. 127°C; IR: 3400–3100 (br. NH_2), 2990 (CH_3), 1600 (C=N) cm^{-1}. ^1H NMR: δ 2.2 (s, 3H, CH_3), 6.9–8.2 (m, 7H, aromatic and NH_2) ppm. Anal. requires for $C_{12}H_{10}N_2S_2$ (246.34): C, 58.5; H, 4.08, N, 11.37; S, 26.01. Found: C, 58.8; H, 4.1; N, 11.5; S, 26.2.

2-[3-(2-aminocyclohexa[b]thienyl)]benzothiazole (3b)

Compound **3b** was obtained as yellow crystals (68%) from DMF; m.p. 142°C; IR: 3400–3150 (br. NH_2), 1620(C=N) cm^{-1}. ^1H NMR: δ 2.6 (t, 4H, $2CH_2$); 3.6 (m, 4H, $2CH_2$); 6.9–8.3 (m, 6H, aromatic and NH_2). Anal. requires for $C_{15}H_{14}N_2S_2$ (286.40): C 62.90: H, 4.92, N, 9.78; S, 22.39. Found: C, 63.0; H, 4.4; N, 9.91; S, 22.7.

2-[2-(3,5-diamino-4-cyanothienyl]benzothiazole (7a)

Compound **7a** was obtained as yellow crystals (60%) from DMF; m.p. 146°C; IR: 3400–3150 (br. NH_2), 2250 (CN), 1620 (C=N) cm^{-1}. ^1H NMR: δ 7.2–7.9 (m, 8H, aromatic and NH_2 protons). Anal. requires for $C_{12}H_8N_4S_2$ (272.34): 52.92; H, 2.95; N, 20.57; S, 23.54. Found: C 53.2; H, 3.3; N, 20.8; S, 23.8.

2-[2-(3,5-diamino-4-ethoxycarbonyl)]benzothiazole (7b)

Compound **7b** was obtained as yellow crystals (70%) from DMF; m.p. 162°C; IR: 3450–3150 (br. NH_2), 1700–1680 (CO) cm^{-1}-^1H NMR: δ 1.3 (t, 3H, CH_3); 4.2(q, 2H, CH_2); 7.1–7.5 (m, 8H, aromatic and NH_2 protons). Anal. requires for $C_{14}H_{13}N_3O_2S_2$ (319.3) C, 52.66; H, 4.07; N, 13.16; S, 20.06. Found: C 52.9; H, 4.1; N, 13.5; S, 20.3.

Reaction of Compound 1 with Benzoylisothiocyonate

A solution of benzoylisothiocyonate (0.01 mol) in acetone (30 ml) was treated with compound **1** (0.01 mol). The reaction mixture was heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue was triturated with water. The solid product formed was collected by filtration and recrystallized from ethanol.

2-benzamido-1-benzothiazolyl-1-cyano-2-mercaptoethene (8)

Compound **8** was obtained as brown crystals (65%) from ethanol; m.p. 175°C; IR: 3150 (NH); 2200 (CN), 1680 (C=O); 1600 (C=N) cm^{-1}-^1H NMR: δ 7.3–8.3 (m, 10H, aromatic and NH protons); 10.6 (s, 1H, SH) Anal. requires for $C_{17}H_{11}N_3OS_2$ (337.39) C, 60.51; H, 3.28; N, 12.45; S, 19.0. Found: C, 60.8; H, 3.5; N, 12.7; S, 19.4.

Synthesis of Diaminothiophene Derivative (11)

A solution of compound **8** (0.01 mol) in dioxane (40 ml) was treated with phenacyl bromide (0.01 mol) and triethylamine (2 ml). The reaction mixture was heated under reflux for 4 h. The solvent was then evaporated under reduced pressure and the residue was triturated with water. The solid product formed was collected by filtration and recrystallized from DMF.

2-[3-(2,4-Diamino-5-benzoyl)thienyl]benzothiazole (11)

Compound **11** was obtained as yellow crystals (58%) from DMF; m.p. 210°C; IR: 3300 (br. $2NH_2$); 1680 (CO), 1600 (C=N) cm^{-1}-^{1}H NMR: δ 7.3–7.9 (m, 9H, aromatic protons); 8.2 (br, 4H, $2NH_2$). Anal. requires for $C_{18}H_{13}N_3OS_2$ (351.4): C, 61.52; H, 3.72; N, 11.95; S, 18.2 Found: C, 61.8; H, 3.5; N, 11.6; S, 17.9.

General Procedure for the Synthesis of Thienyl Derivatives (15a–d)

A solution of the appropriate methyldine derivatives **12a–d** (0.01 mol) [prepared in situ from the reaction of the corresponding aldehyde and active methylene in ethanol in the presence of a catalytic amount of triethylamine] and sulfur element (0.01 mol) were added to compound **1** (0.01 mol). The reaction mixture was heated under reflux for 4 h. The solid product so formed was collected by filtration and recrystallized from DMF.

2-[3-(2-amino-5-thiamido)thienyl]benzothiazole (15a)

Compound **15a** was obtained as brown crystals (67%) from DMF; m.p. 276°C; IR: 3400–3100 (NH_2)cm^{-1}-^{1}H NMR: δ 5.4 (br, 2H, NH_2); 7.1–8.3 ppm (m, 7H, aromatic, thiophene-H and NH_2 protons). Anal. requires for $C_{12}H_9N_3S_3$ (291.38): C 49.46; H, 3.10; N, 14.41; S, 33.02. Found: C, 49.6; H, 3.2; N, 14.8; S, 33.4.

2-[3-(2-amino-5-ethoxycarbonyl)thienyl]benzothiazole (15b)

Compound **15b** was obtained as brown crystals (71%) from DMF; m.p. 291°C; IR: 3350 (NH_2), 1700 (ester CO cm^{-1}-^{1}H NMR: δ 1.3 (t, 3H, CH_3); 4.2 (q, 2H, CH_2); 7.1–8.2 (m, 7H, aromatic, thiophene-H and NH_2 protons). Anal. requires for $C_{14}H_{12}N_2O_2S_2$ (304.34): C, 55.25; H, 3.96, N, 9.20; S, 21.06. Found: C, 55.6; H, 3.6; N, 9.5; S, 21.3.

2-[3-(2-amino-5-cyano-4-methyl)thienyl]benzothiazole (15c)

Compound **15c** was obtained as yellow crystals (68%) from DMF; m.p. 298°C; IR: 3200–3100 (NH_2), 2210 (CN) cm^{-1}-^{1}H NMR: δ 1.7 (s, 3H, CH_3); 7.1–8.2 (m, 6H, aromatic and NH_2 protons). Anal. requires for $C_{13}H_9N_3S_2$ (271.33): C 57.54; H, 3.33; N, 15.48; S, 23.63. Found: C, 57.6; H, 3.6; N, 15.8; S, 23.7.

2-[3-(2-amino-4-methyl-5-thiamido)thienyl]benzothiazole (15d)

Compound **15d** was obtained as yellow crystals (65%) from DMF; m.p. 283°C; IR: 3400–3100 (NH_2) cm^{-1}-^{1}H NMR: δ 1.7 (s, 3H, CH_3), 4.2 (br., 2H, NH_2), 7.1–8.2 (m, 6H, aromatic and NH_2). Anal. requires for $C_{13}H_{11}N_3S_3$ (305.4): C, 51.12; H, 3.62; N, 13.75; S, 31.49. Found: C, 51.4; H, 3.8; N, 13.9; S, 31.6.

Reaction of 3a, 7a, and 7b with Maleic Anhydride

A solution of compounds **3a**, **7a**, and **7b** (0.01 mol) in DMF (40 ml) was treated with maleic anhydride (0.01 mol) and the reaction mixture was heated under reflux for 5 h. The solvent was then evaporated in vacuo and the residue was treated with ice and water; the solid product formed on standing was collected by filtration and recrystallized from DMF.

Compound **16a** was obtained as yellow crystals (61%) from DMF; m.p. 243°C; IR: 3380–3350 (NH, OH), 1730, 1670 (2CO) cm^{-1}.^{1}H NMR: δ 5.4, 5.6 (2d, 2H, 2CH), 1.7 (s, 3H, CH_3), 7.1–8.2 (m, 4H, aromatic protons) 10.12 (s, 1H, OH), 13.2 (br, 1H, NH). Anal. requires for $C_{16}H_{12}N_2O_3S_2$ (344.35): C, 55.80; H, 3.50; N, 8.13; S, 18.62. Found: C, 55.6; H, 3.6; N, 8.4; S, 18.7.

Compound **16b** was obtained as yellow crystals (68%) from DMF; m.p. 233°C; IR: 3400–3350 (OH, NH), 2210 (CN), 1740, 1665 (CO) cm^{-1}.^{1}H NMR: δ 5.4, 5.6 (2d, 2H, 2CH), 7.1–8.1 (m, 6H, aromatic-protons and NH_2); 10.10 (s, 1H, OH); 13.10 (br, 1H, NH). Anal. requires for $C_{16}H_{10}N_4O_3S_2$ (370.35): C, 51.88; H, 2.71; N, 15.12; S, 17.31. Found: C, 51.4; H, 2.6; N, 15.6; S, 17.7.

Compound **16c** was obtained as yellow crystals (68%) from DMF; m.p. 213°C; IR: 3400–3100 (OH, NH), 1740–1670 (CO), 1735 (CO) cm^{-1}. ^{1}H NMR: δ 1.3 (t, 3H, CH_3); 4.2 (q, 2H, CH_2); 8.2 (br, 4H, $2NH_2$), 7.1–7.6 (m, 4H, aromatic protons), 10.0 (s, 1H, OH); 13.10 (br, 1H, NH). Anal. requires for $C_{18}H_{15}N_3O_5S_2$ (417.37): C, 51.79; H, 3.61; N, 10.06; S, 15.36. Found: C, 51.6; H, 3.4; N, 10.4; S, 15.4.

Synthesis of N-thienylmaleimide Derivatives (17a–c)

A solution of **16a–c** (0.01 mol) in acetic anhydride (30 ml) was heated under reflux for 2 h. The reaction mixture was treated with ice and water; the solid product formed on standing was collected by filtration and recrystallized from absolute ethanol.

Compound **17a** was obtained as yellow crystals (50%) from EtOH; m.p. 280°C; IR: 1680 (CO) cm^{-1}. ^1H NMR: δ 1.7 (s, 3H, CH_3), 6.4, 6.8 (2d, 2H, 2CH), 7.1–8.2 (m, 4H, aromatic protons). Anal. requires for $C_{16}H_{10}N_2O_2S_2$ (326.35): C, 58.88; H, 3.08; N, 8.58; S, 19.64. Found: C, 58.6; H, 3.2; N, 8.4; S, 19.7.

Compound **17b** was obtained as yellow crystals (48%) from EtOH; m.p. 250°C; IR: 3400–3100 (NH_2), 2210 (CN), 1680 (CO) cm^{-1}. ^1H NMR: δ 6.4, 6.8 (2d, 2H, 2CH), 7.1–8.1 (m, 6H, aromatic-protons, and NH_2). Anal. requires for $C_{16}H_8N_4O_2S_2$ (352.35): C, 54.53; H, 2.28; N, 15.89; S, 18.19. Found: C, 54.4; H, 2.6; N, 15.6; S, 18.4.

Compound **17c** was obtained as yellow crystals (45%) from EtOH; m.p. 220°C; IR: 3400–3100 (NH_2), 1675 (CO), 1735 (CO) cm^{-1}. ^1H NMR: δ 1.3 (t, 3H, CH_3); 4.2 (q, 2H, CH_2); 7.1–8.1 (m, 6H, aromatic protons, and NH_2). Anal. requires for $C_{18}H_{13}N_3O_4S_2$ (399.37): C, 54.13; H, 3.27; N, 10.51; S, 16.05. Found: C, 54.4; H, 3.4; N, 10.4; S, 16.4

REFERENCES

[1] K. U. Sadek, A. E. Mourad, A. Elhafeez, and M. H. Elnagdi, *Synthesis*, 739 (1983).
[2] J. L. Soto, C. Seoane, P. Zamsrans, and F. J. Cwadrado, *Synthesis*, 529 (1981).
[3] K. Saito, S. Kampe, and Y. Nanano, *Synthesis*, 210 (1983).
[4] A. Andreani, A. Locatelli, A. Leoni, M. Rambaldi, R. Morigi, R. Bossa, M. Chiericozzi, A. Fraccari, and I. Galatulas, *Eur. J. Med. Chem.*, **32 (11),** 919 (1997).
[5] K. Yousuke, N. Shigetaka, T. Tetsuo, S. Kazuo, M. Yoshimi, I. Hirohumi, and T. Hisashil, *Bioorg. Med. Chem. Lett.*, **8,** 1307 (1998).
[6] V. K. Chadha, H. S. Chaudharv, and H. K. Piyari, *Indian. J. Chem.*, **7,** 769 (1969).
[7] D. E. Kuhla, U. S. Pat. 3860718, CA **82,** 140133 (1975).
[8] K. C. Joshi, V. N. Pathak, and P. Arya, *Agric. Biol. Chem.*, **41,** 543 (1977).
[9] J. J. D'Amico, U. S. Patent 3225059, CA, **64,** 8193 (1966).
[10] G. E. H. Elgemeie, H. Z. Shams, Y. M. Elkholy, and N. S. Abbas, *Phosph., Sulfur, Silicon and Related Elements*, **165,** 265 (2000).
[11] Y. M. Elkholy, F. A. Abou-Shanb, and A. W. Erian, *Phosph., Sulfur, Silicon, and Related Element*, **167,** 151 (2000).
[12] L. S. Bellamy, *The Infrared Spectra of Complex Organic Molecules* (Wiley, New York, 1958), 2nd ed.
[13] M. H. Elnagdi, K. U. Sadek, M. A. El-Magraby, M. A. Selim, A. K. Khalafalla, and M. A. Rasalan, *Phosph., Sulfur, Silicon, and Related Elements*, **105,** 51 (1995).