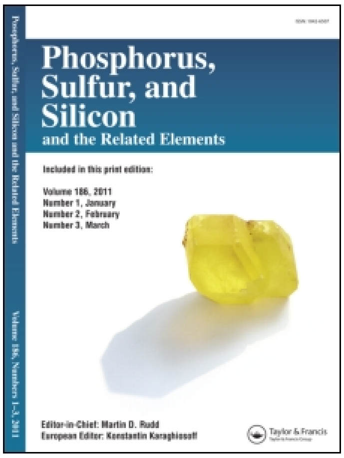


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

INVESTIGATION IN THE CHROMONE SERIES. PART XX. CHROMONE-3-PHOSPHONIC ACIDS AND ESTERS

Krzysztof Kostka[a]; Sławomir Pastuszko[a]; Marek Porada[a]
[a] Institute of Chemistry, Faculty of Pharmacy, University of Medicine, Łódź, Poland

To cite this Article Kostka, Krzysztof , Pastuszko, Sławomir and Porada, Marek(1992) 'INVESTIGATION IN THE CHROMONE SERIES. PART XX. CHROMONE-3-PHOSPHONIC ACIDS AND ESTERS', Phosphorus, Sulfur, and Silicon and the Related Elements, 71: 1, 67 — 74

To link to this Article: DOI: 10.1080/10426509208034497

URL: http://dx.doi.org/10.1080/10426509208034497

Phosphorus, Sulfur, and Silicon, 1992, Vol. 71, pp. 67–74
Reprints available directly from the publisher
Photocopying permitted by license only

INVESTIGATION IN THE CHROMONE SERIES. PART XX.† CHROMONE-3-PHOSPHONIC ACIDS AND ESTERS

KRZYSZTOF KOSTKA, SŁAWOMIR PASTUSZKO and MAREK PORADA
Institute of Chemistry, Faculty of Pharmacy, University of Medicine, Muszyńskiego 1, 90-151 Łódź, Poland

(Received May 19, 1992; in final form June 3, 1992)

In the Arbuzov and Perkow reactions of 2-bromo-2′-acyloxyacetophenone with trimethyl phosphite the derivatives in position 2 of 3-phosphonochromone acids and esters and 1-2′-acyloxyphenylvinylphosphates were obtained.

Key words: Substituted chromone 3-phosphonic acids and 1-2′-acyloxyphenyl-vinylphosphates, synthesis of.

4H-1-benzopyran-4-on (chromone) and its derivatives have for years been of interest because of their varied biological activity and low toxicity. The gathering of oxygen atoms in chromone molecule gives great complex-forming abilities. So far, chromone derivatives with oxygen, nitrogen, and halogen substituents have been obtained. The following esters and acids—chromone phosphoric derivatives—have been described: chromone-2- and 3-methanephosphonic[1] and chromone-2- and 3-α-hydroxymethanephosphonic.[2] Chromone derivatives containing phosphorus atom directly connected with the γ-pyrone ring have not been described.

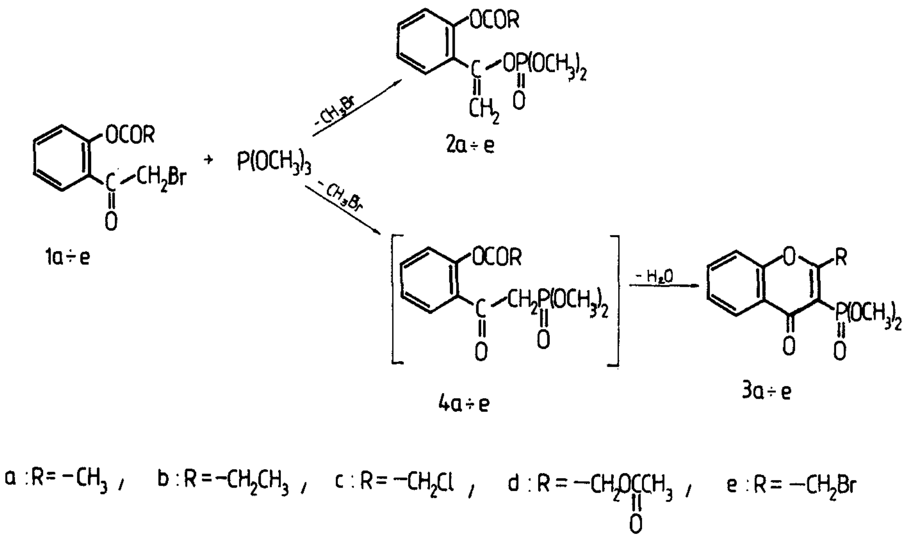
While trying to find convenient methods of synthesis of chromonephosphonic compounds we have discovered an interesting course of reactions of acyl derivatives of 2-bromo-2′-hydroxyacetophenone with trimethyl phosphite.

As a result of the reaction of 2-bromo-2′-acetoxyacetophenone (**1a**) with trimethyl phosphite two products were obtained and identified as dimethyl-1-2′-acetoxyphenylvinylphosphate (**2a**)—product of the Perkow reaction—and as 2-methylchromone-3-dimethylphosphonate (**3a**) (Scheme I). No Arbuzov reaction product was obtained (**4a**). The application of other acyl derivatives of 2-bromo-2′-hydroxyacetophenone (R = C_2H_5; CH_2Cl; CH_2OCOCH_3; CH_2Br) in the reaction with trimethyl phosphite resulted in the formation of analogous products. In each case 1-2′-acyloxyphenylvinyldimethylphosphate was obtained as well as a phosphonic derivative of chromone in which the phosphorus is bound to the C-3 carbon of benzo-γ-pyrone. Performing the reactions at higher temperature causes a better yield of the chromone derivatives but also leads to the decomposition of the products of the Perkow reaction.

The analysis of the reaction abilities of type **1** compounds with trimethyl phosphite points to the fact that apart from the Perkow rearrangement products **2**, products of simple condensation of the Arbuzov type **4** can be obtained. The formation of chromone derivatives **3** can be explained with the appearance of intermediate

---

†Part XIX, K. Kostka and R. Modranka, Phosphorus, Sulfur and Silicon (in press).

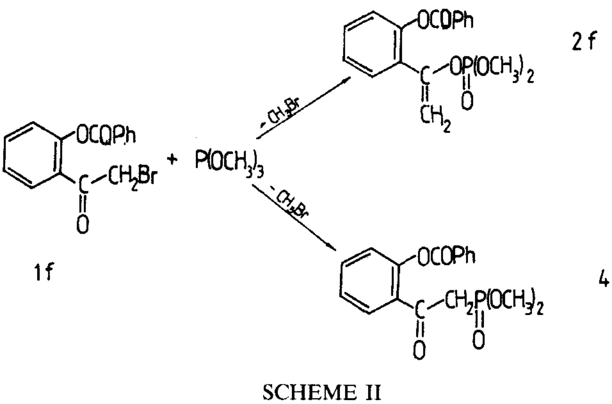


a: $R = -CH_3$, b: $R = -CH_2CH_3$, c: $R = -CH_2Cl$, d: $R = -CH_2OC(=O)CH_3$, e: $R = -CH_2Br$

SCHEME I

products of type **4** which under the reaction conditions are unstable and change immediately.

The application of benzoic acid ester of 2-bromo-2′-hydroxyacetophenone has confirmed our assumption. Apart from the Perkow reaction product **2f**, 2-dimethylphosphono-2′-benzoyloxyacetophenone (**4f**) has been obtained with good yield as the Arbuzov reaction product, according to Scheme II.

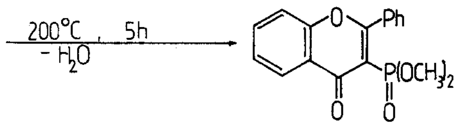


SCHEME II

Compound **4f** is stable and converts into a chromone derivative only at higher temperature (ca 200°C, 5h) (Scheme III).

The separation of compound **4f** and its thermically converted one into 3-dimethylphosphonoflavone (**3f**) points to the identical reaction course in the synthesis **3a–e**. It is highly probable that the very fast conversion of Arbuzov reaction products **4a–e** into chromone derivatives is caused by the presence of hydrogen in position α of the phenolic ester group.

4f



3f

SCHEME III

Dimethyl chromone phosphonates (**3a–f**) underwent decomposition to phosphonic acids (**5a–f**) by means of 40% hydrogen bromide in anhydrous acetic acid.[3] 2-Chloromethylchromone-3-dimethylphosphonate gives during hydrolysis with 40% hydrogen bromide in acetic acid a mixture of two acids: 2-chloromethyl- and 2-bromomethylchromone-3-phosphonic acids. The substitution of chlorine by bromine was also observed in the investigations of other compounds.[4]

The method of transitional silylation with bromotrimethylsilane followed by hydrolysis of the silyl derivatives[5] was used with no effect. In this case also the mixture of 2-bromo- and 2-chloromethylchromone-3-phosphonic acids was obtained. The ^{1}H NMR spectrum of this mixture contains the signal of the bromomethyl group at $\delta = 2.34$ ppm, and a signal of the chloromethyl group at $\delta = 2.44$ ppm. The relative intensity of these groups in the spectrum, and thus also the acids in the mixture, depends on the duration of deestrification.

Derivatives **1a–f** were obtained as a result of the bromination of acyl derivatives of 2′-hydroxyacetophenone.[6] The structure of the compounds was determined by chemical methods (elemental analysis) and spectroscopy (^{1}H, ^{31}P NMR, IR, MS).

Compounds **2a–f** are in the majority thick oils decomposing at the attempts of distillation at reduced pressure, quickly darkening at room temperature.

Compounds **2a–f** give in ^{1}H NMR a typical multiplet (a double doublet of doublets—visible as a doublet of triplets) of vinyl protones which as a result of their similarity to the benzene ring are not equivalent chemically. Precise measurements with high resolution (200 MHz) apparatus have shown that the coupling between vinyl protons is: $^2J_{H_EH_Z} = 2.32$ Hz, while the coupling hydrogen–phosphorus is different for each hydrogen and is: $^4J_{PH_E} = 2.37$ Hz and $^4J_{PH_Z} = 2.53$ Hz.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR was performed by means of Varian EM-360 (60 MHz), Bruker AC 200F (200 MHz), ^{31}P NMR with FT Joel FX60 (24.3 MHz) with H_3PO_4 as internal standard. IR was performed with a Pye-Unicam 200G spectrometer in KBr or film, mass spectrometry was performed with LKB-2091 Mass Spectrometer (70 eV). For chromatographic columns Silica gel 70-230 mesh (Merck) was used. TLC was performed with DC-Alufolien Kieselgel 60 F_{254} (Merck).

2-Substituted-3-dimethylphosphonochromone (**3a–e**) *and 1-2′-acyloxyphenylvinyldimethylphosphate* (**2a–e**). Into 0.01 mol of a corresponding 2-bromo-2′-acyloxyacetophenone (**1a–e**) dissolved in 10 ml xylene, 1.50 g (0.012 mol) of trimethyl phosphite were added dropwise at the boiling temperature of the solvent. After 10 minutes of heating the excess phosphite and xylene were distilled off. The obtained brownish oily liquid was separated on a chromatographic column by means of a solvent system (chloroform : acetone = 9:1). Their composition was determined by means of thin layer chromatography. After evaporation of the solvents the residue was crystallized from diethyl ether with a 2% addition of methanol. Oily substances were dried in a desiccator over P_2O_5 (Tables I and II).

TABLE I

Chromone-3-phosphonic esters and acids

Comp. No.	Summary formula (Molecular mass)	m.p. °C Yield %	Analyses % Cald / Found C	H	P	IR (cm^{-1})	^{31}P-NMR (ppm)	^{1}H-NMR */ (ppm)	MS $\frac{m}{z}$ (%)
3a	$C_{12}H_{13}O_5P$ (268.21)	91÷92 45	53.74 53.98	4.89 5.09	11.55 11.32	1640(C=O) 1240(P=O) 1065(COC) 1030(POC)	16.8	**/2.89(d,3H,CH_3, $^4J_{PH}$=1.7 Hz); 3.87(d,6H,2CH_3, $^3J_{PH}$=11.7 Hz); 7.33÷7.46 (m,2H_{ar}); 7.65÷7.74(m,1H_{ar}); 8.13÷8.19(m,1H_{ar})	268(M^+,100); 253(22); 223(13); 174(34); 173(30); 160(65); 158(11); 144(27); 121(21); 120(32); 92(19).
3b	$C_{13}H_{15}O_5P$ (282.23)	38.5÷40 41	55.32 55.41	5.36 5.41	10.97 10.82	1630(C=O) 1240(P=O) 1080(COC) 1045(POC)	17.3	1.40(t,3H,CH_3); 3.32(dq,2H, CH_2, $^4J_{PH}$=2 Hz); 3.87(d,6H, 2CH_3, $^3J_{PH}$=11 Hz); 7.17÷8.20 (m,4H_{ar})	282(M^+,100); 281(96); 253(72); 251(11); 250(15); 249(24); 235(25); 220(15); 187(15); 174(27); 173(32); 162(13); 161(14); 129(13); 121(32); 120(11); 115(15); 109(14); 93(11); 92(46).
3c	$C_{12}H_{12}ClO_5P$ (302.65)	90÷91 18	47.62 47.86	4.00 3.83	10.23 10.24	1635(C=O) 1245(P=O) 1080(COC) 1050(POC)	14.8	3.87(d,6H,2CH_3, $^3J_{PH}$=11 Hz); 5.20(d,2H,CH_2, $^4J_{PH}$=2 Hz); 7.20÷8.20(m,4H_{ar})	304(36); 303(19); 302(M^+, 100); 267(20); 253(76); 236(13); 160(13); 121(22); 109(16); 92(28).
3d	$C_{14}H_{15}O_7P$ (326.24)	106÷108 45	51.54 51.59	4.63 4.77	9.49 9.46	1720(C=O) 1626(C=O) 1240(P=O) 1075(COC) 1045(POC)	15.3	2.20(s,3H,CH_3); 3.87(d,6H, 2CH_3, $^3J_{PH}$=11 Hz); 5.63(d, 2H,CH_2, $^4J_{PH}$=2 Hz); 7.20÷ 8.23(m,4H_{ar})	326(M^+, 5.3); 284(16); 283(53); 266(91); 252(100) 251(24); 223(13); 109(12); 92(11).
3e	$C_{12}H_{12}BrO_5P$ (347.10)	80÷81 22	41.50 41.45	3.46 3.49	8.92 8.72	1640(C=O) 1245(P=O) 1085(COC) 1045(POC)	15.0	3.84(d,6H,2CH_3, $^3J_{PH}$=11 Hz); 5.10(d,2H,CH_2, $^4J_{PH}$=2 Hz); 7.20÷8.23(m,4H_{ar})	348(26); 347(M^+,4.3); 346(26); 268(14); **267(100)** 253(20); 237(10); 235(30); 209(17); 207(12); 205(13); 121(16); 102(11); 92(29).

3f	$C_{17}H_{15}O_5P$ (330.28)	142÷143 45	61.82 61.91	4.58 4.57	9.38 9.23	1630(C=O) 1250(P=O) 1050(COC, POC,broad peak)	15.6	3.65(d,6H,2CH$_3$, $^3J_{PH}$= 11 Hz) 7.20÷8.30(m,9H$_{ar}$)	330(M$^+$,44); 329(17); 315(39); 283(13); 236(21); 235(100); 234(28); 165(12); 120(35); 102(11); 92(37).
5a	$C_{10}H_9O_5P$ (240.15)	245(R) 79	50.01 49.78	3.78 3.83	12.90 12.73	2300÷3000 (OH) 1640(C=O) 1245(P=O) 1040(COC)		2.82(d,3H,CH$_3$, $^4J_{PH}$= 2 Hz); 7.28÷8.02(m,4H$_{ar}$); 9.97(s, 2H,2OH)	
5b	$C_{11}H_{11}O_5P$ (254.18)	230(R) 78	51.98 51.89	4.36 4.41	12.18 11.89	2300÷3000 (OH) 1640(C=O) 1245(P=O) 1030(COC)		1.27(t,3H,CH$_3$); 3.23(q,2H, CH$_2$); 7.27÷8.07(m,4H$_{ar}$); 9.37(s,2H,2OH)	
5d	$C_{12}H_{11}O_7P$ (298.19)	195(R) 65	48.34 48.03	3.72 3.79	10.39 10.37	2300÷3000 (OH) 1745(C=O) 1615(C=O) 1230(P=O) 1030(COC)		2.17(s,3H,CH$_3$); 5.60(d,2H, CH$_2$, $^4J_{PH}$=2 Hz); 7.20÷8.13 (m,4H$_{ar}$); 9.97(s,2H,2OH)	
5e	$C_{10}H_8BrO_5P$ (319.05)	201(R) 73	37.45 37.70	2.53 2.63	9.71 9.46	2300÷3000 (OH) 1610(C=O) 1225(P=O) 1020(COC)		5.34(s,2H,CH$_2$); 7.27÷8.14 (m,4H$_{ar}$); 10.00(s,2H,2OH)	
5f	$C_{15}H_{11}O_5P$ (302.22)	246(R) 84	59.61 59.49	3.67 3.68	10.25 10.16	2300÷3000 (OH) 1610(C=O) 1225(P=O) 1020(COC)		7.30÷8.20(m,9H$_{ar}$); 10.63 (s,2H,2OH)	

*/ For the esters in $CDCl_3$ and for the acids in DMSO-d_6.

**/ The spectrum was recorded by means of a spectrophotometer Bruker AC 200F (200 MHz).

TABLE II

1-2′-Acyloxyphenylvinyldimethylphosphates

Comp. No.	Summary formula (Molecular mass)	m.p. °C Yield %	Analyses % Cald / Found		IR (cm^{-1})	^{31}P-NMR*/ (ppm)	^{1}H-NMR*/ (ppm)	MS $\frac{m}{z}$ (%)
			C	H				
2a	$C_{12}H_{15}O_6P$ (286.23)	oil 24	50.36 50.26	5.28 5.38	1685(C=O) 1250(P=O) 1160(COC) 1025(POC) 985(POC)	-3.9	2.30(s,3H,CH_3); 3.85(d,6H, 2CH_3, $^3J_{PH}$=11 Hz); 5.03(t, 1H,CH_2); 5.30(t,1H,CH_E); 6.90÷7.60(m,4H_{ar})	287(4.3); 286(M^+,0.6); 245(11); 244(99); 229(14); 161(8.1); 132(6.2); 127(99); 119(17); 118(100); 109(59); 95(6.0); 91(19); 90(49).
2b	$C_{13}H_{17}O_6P$ (300.25)	oil 34	52.00 51.57	5.71 5.96	1680(C=O) 1245(P=O) 1165(COC) 1025(POC) 985(POC)	-3.8	1.23(t,3H,CH_3); 2.57(q,2H, CH_2); 3.70(d,6H,2CH_3, $^3J_{PH}$= 11 Hz); 5.03(t,1H,CH_Z); 5.30(t,1H,CH_E); 6.83÷7.60 (m,4H_{ar})	301(0.7); 300(M^+,0.6); 245(3.3) 244(34); 243(2.1); 132(3.7); 127(100); 119(3.9); 118(32); 109(13); 91(5.0); 90(11).
2c	$C_{12}H_{14}ClO_6P$ (320.67)	oil 11	49.95 49.51	4.40 4.83	1690(C=O) 1240(P=O) 1160(COC) 1020(POC) 980(POC)	-3.8	3.70(d,6H,2CH_3, $^3J_{PH}$=11 Hz) 4.33(s,2H,CH_2); 4.97(t,1H, CH_Z); 5.20(t,1H,CH_E); 6.90÷ 7.50(m,4H_{ar})	322(0.7); 321(0.6); 320(M^+,1.8) 245(3.5); 244(33); 229(6.5); 136(26); 127(100); 121(67); 118(34); 109(15); 96(23); 95(9.4); 93(9.6); 92(5.1); 91(6.6) 90(14).
2d	$C_{14}H_{17}O_8P$ (344.26)	oil 28	48.85 48.38	4.98 5.37	1720(C=O) 1690(C=O) 1230(P=O) 1175(COC) 1145(COC) 1025(POC) 995(POC)	-3.8	2.17(s,3H,CH_3); 3.75(d,6H, 2CH_3, $^3J_{PH}$=11 Hz); 4.83(s, 2H,CH_2); 5.03(t,1H,CH_Z); 5.30(t,1H,CH_E); 6.90÷7.60 (m,4H_{ar})	345(3.3); 344(M^+,1.7); 343(4.2) 245(14); 244(99); 243(16); 229(18); 176(5.9); 132(6.7); 127(99); 121(8.8); 119(9.8); 118(95); 110(8.9); 109(52); 101(30); 95(6.7); 94(6.6); 93(6.1); 91(9.6); 90(22).

2e	$C_{12}H_{14}BrO_6P$ (365.12)	oil 18	39.48 39.50	3.86 3.98	1685(C=O) 1235(P=O) 1160(COC) 1020(POC) 985(POC)	-3.9	3.73(d,6H,2CH_3, $^3J_{PH}$=11 Hz) 4.10(s,2H,CH_2); 5.07(t,1H, CH_Z); 5.30(t,1H,CH_E);6.87÷ 7.60(m,4H_{ar})	367(0.8); 366(0.8); 365(M^+,0.8) 364(0.7); 285(4.2); 245(9.5); 244(100); 229(14); 132(5.3); 127(99); 123(12); 121(14); 119(9.4); 118(93); 109(62); 95(16); 93(16); 91(11); 90(40).
2f	$C_{17}H_{17}O_6P$ (348.29)	61÷62 38	58.63 58.40	4.92 4.81	1660(C=O) 1240(P=O) 1165(COC) 1030(POC) 985(POC)	-4.0	3.60(d,6H,2CH_3, $^3J_{PH}$=11 Hz) 5.07(t,1H,CH_Z); 5.27(t,1H, CH_E); 6.90÷8.20(m,9H_{ar}):	349(0.9); 348(M^+,4.6); 347(0.5) 320(1.1); 243(1.2); 229(1.1); 223(1.8); 222(5.3); 194(1.1); 127(1.1); 109(4.4); 106(7.7); 105(100); 90(1.6).

*/ in $CDCl_3$

2-Dimethylphosphono-2'-benzoyloxyacetophenone (**4f**) *and 1-2'-benzoyloxyphenylvinyldimethylphosphate* (**2f**). Into 3.20 g (0.01 mol) of 2-bromo-2'-benzoyloxyacetophenone melted in a flask, 1.50 g (0.012 mol) of trimethyl phosphite were added dropwise at 110–120°C. After about 30 minutes of heating the excess of phosphite was distilled off. The obtained yellow oil was separated on a chromatographic column with a solvent system (chloroform : acetone = 5 : 1). 2.55 g of compound **2f** (Table II) and 3.70 g of compound **4f** were obtained:
Yield = 55%; thick, light yellow oil.

$C_{17}H_{17}O_6P$	calc.:	C 58.63	H 4.92	P 8.89
(348.29)	found:	C 58.47	H 5.10	P 8.81

IR (film): (cm^{-1}) = 3060, 3000, 2950, 2850 (CH); 1740, 1685 (C=O); 1270 (P=O); 1065 (C—O—C); 1040 (P—O—C).
^{31}P NMR ($CDCl_3$): $\delta = 22.1$.
^1H NMR ($CDCl_3$) 60 MHz: $\delta = 3.55$ (d, 2H, CH_2, $^2J_{PH} = 22$ Hz); 3.65 (d, 6H, 2CH_3, $^3J_{PH} = 11$ Hz); 7.10–8.25 (m, 9H_{ar}).
MS m/z (%) = 348 = $M^{+}\cdot$(4.4), 121 (6.1), 110 (16), 109 (11), 106 (5.7), 105 (100), 95 (5.5).

2-Phenyl-3-dimethylphosphonochromone (**3f**). 2.10 g (6 mmol) of 2-dimethylphosphono-2'-benzoyloxyacetophenone (**4f**) were heated in an oil bath at 190–200°C for 5 hours. The obtained thick brownish oil was separated on a chromatographic column with a solvent system (chloroform : acetone = 9 : 1). The raw product was crystallized with a small addition of methanol (Table I).

2-Substituted-chromone-3-phosphonic acids (**5a, b, d, e, f**). *A general method of deestrification by HBr in CH_3COOH (anhydr.).* Into 0.01 mol of the corresponding ester **3a, b, d, e, f**, a stoichiometric amount of 40% hydrogen bromide in anhydrous acetic acid was added. The sediment of a respective ester dissolved. After 24 hours at room temperature the formed crystals were filtered off and crystallized from methanol (Table I).

REFERENCES

1. G. Mouysset, J. Bellan, M. Payard and J. Tisne-Versailles, *Farmaco, Ed. Sci.*, **42,** 805 (1987).
2. K. Kostka and R. Modranka, *Phosphorus, Sulfur and Silicon*, **57,** 279 (1991).
3. C. Wasilewski, A. Sobczak and J. Szewczyk, *Rocz. Chem. Ann. Soc. Chim. Polonorun*, **50,** 1795 (1976).
4. H. K. Fiedorowa, L. G. Ananiewa and N. G. Fieszczenko, *Zh. Obshch. Khim.*, **50,** 2620 (1980).
5. C. E. McKenna, *Tetrahedron Lett.*, 155 (1977).
6. A. Hercouet, M. Le Corre and Y. Le Floc'h, *Synthesis*, **7,** 597 (1982).