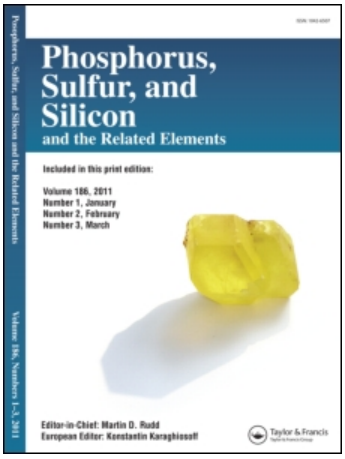


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THE SYNTHESIS OF CHROMONE-3-METHANEPHOSPHONIC ACID AND CHROMONE-2-METHANEPHOSPHONIC ACID

Krzysztof Kostka[a]; Roman Modranka[a]
[a] Institute of Chemistry, Faculty of Pharmacy, Medical School, Lodz, Muszynskiego, Poland

To cite this Article Kostka, Krzysztof and Modranka, Roman(1991) 'THE SYNTHESIS OF CHROMONE-3-METHANEPHOSPHONIC ACID AND CHROMONE-2-METHANEPHOSPHONIC ACID', Phosphorus, Sulfur, and Silicon and the Related Elements, 57: 3, 279 — 285
To link to this Article: DOI: 10.1080/10426509108038860
URL: http://dx.doi.org/10.1080/10426509108038860

Phosphorus, Sulfur, and Silicon, 1991, Vol. 57, pp. 279–285
Reprints available directly from the publisher
Photocopying permitted by license only

THE SYNTHESIS OF CHROMONE-3-METHANEPHOSPHONIC ACID AND CHROMONE-2-METHANEPHOSPHONIC ACID

KRZYSZTOF KOSTKA and ROMAN MODRANKA
Institute of Chemistry, Faculty of Pharmacy, Medical School, 90-151 Lodz, Muszynskiego 1, Poland

(Received April 24, 1990; in final form May 29, 1990)

Chromone-2- and chromone-3-hydroxymethanephosphonic- as well as chromone-2- and chromone-3-methanephosphonic acids and esters were synthesized.

Key words: Chromone-2- and -3-methanephosphonic acids; synthesis of.

4-oxo-4H-1-benzopyrone (chromone) derivatives,[1,2] as well as α-hydroxyalkanephosphonic and alkanephosphonic[3] esters, are substances which interest, because of their properties, both biologists and pharmacologists.

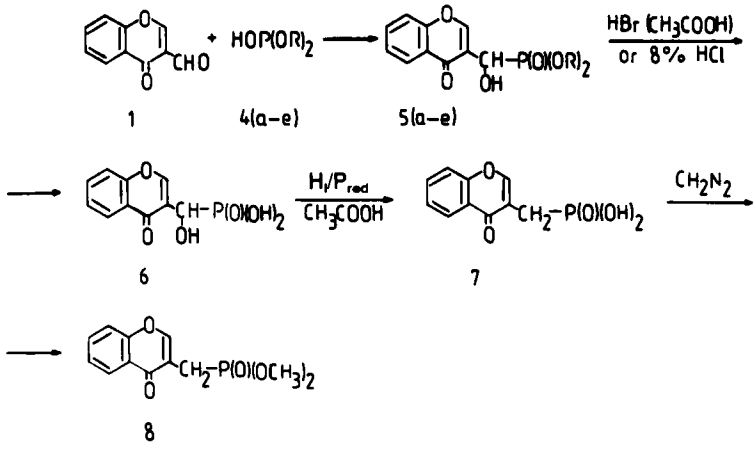
The aim of our study has been the synthesis of chromone derivatives containing α-hydroxyalkylphosphonic and alkylphosphonic substituents in positions (-2-) and (-3-). A convenient method of α-hydroxyalkanephosphonic ester synthesis is the addition of trialkyl phosphites[4] $P(OR)_3$ or dialkyl phosphites $HOP(OR)_2$ to aldehydes and ketones.[5] 3-Formylchromone **1** reacting with dialkyl phosphites **4(a–d)** and diphenyl phosphite **4e,** in the presence of catalytic amounts of appropriate trialkyl phosphites $P(OR)_3$ and triphenyl phosphite $P(OPh)_3$, forms the corresponding chromone-3-hydroxymethanephosphonic esters **5(a–e).** The reaction was conducted in the absence of solvents, at the temperature of 80–85°C.

Dialkyl esters **5(a–e)** hydrolyze readily in aqueous solutions of HCl and in acetic acid solutions of HBr, yielding chromone-3-hydroxymethanephosphonic acid **(6).** Acid **6** is then easily reduced, by means of hydrogen iodide,[6] to chromone-3-methanephosphonic acid **(7)** which, under the influence of diazomethane in methanol, forms the dimethyl ester of chromone-3-methanephosphonic acid **(8)** (Scheme 1).

2-Formylchromone **2,** in the presence of basic aluminium oxide,[7] reacts with dialkyl phosphites **4(a–b)** to form dialkyl esters of chromone-2-hydroxymethanphosphonic acid **9(a–b).** When hydrolyzed by means of HBr in acetic acid solution, these esters form chromone-2-hydroxymethanephosphonic acid **(10)** (Scheme 2). Acid **10** is not reduced to acid **(12)** by hydrogen iodide in acetic acid.

During reduction with hydrogen iodide in acetic acid, in the presence of red phosphorus (red P), at room temperature, only substrate **10** was detected after a few days, while under more drastic conditions (higher temperature, longer reaction time), thin-layer chromatography revealed the presence of some other products, but not of acid **12.** Reduction of esters **9a** and **9b** with hydrogen iodide in acetic acid, in the presence of red P, produced similar results.

The lack of reactivity to reducing agents of acid **10** and its esters **9a** and **9b** is probably due to the presence of a strong intramolecular hydrogen bond between



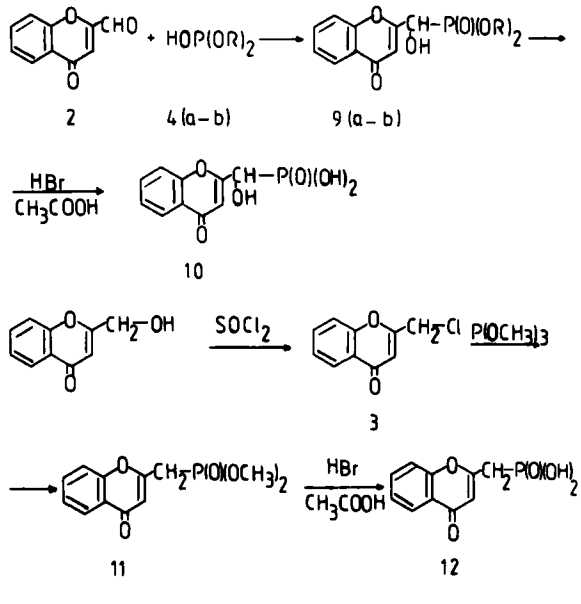
a: R=CH_3; b: R=C_2H_5; c: R=$CH(CH_3)_2$; d: R=C_4H_9(n); e: R=C_6H_5

SCHEME 1

the —OH group and the oxygen O-1 of 4-oxo-4H-1-benzopyrone, and to the electrophilic character of carbon C-2. Both these factors may preclude the formation of the carbo-cation in the acyclic carbon atom in the process of reduction with hydrogen iodide. IR absorption spectra performed in $CHCl_3$ confirm our hypothesis.

Ester **9b** shows a maximum absorption for the —OH group in the range of 3270 cm^{-1} (independent from concentration).

Ester **5b** however, has a maximum absorption in the range of 3340 cm^{-1} which



a: R=CH_3; b: R=C_2H_5

SCHEME 2

shifts slightly towards higher frequencies with decreasing concentrations. The appearance of a maximum absorption in the lower frequencies for the —OH group in compound **9b** indicates the formation of a stronger intramolecular hydrogen bond with the heterocyclic oxygen atom 0-1 of 4-oxo-4H-1-benzopyrone, than that between the —OH group and the oxygen atom[8] at the carbonyl carbon atom C-4 of compound **5b**. The dimethyl ester of chromone-2-methanephosphonic acid **11** was obtained by an Arbuzov reaction between 2-chlormethylchromone **3** and $P(OCH_3)_3$ which, when hydrolyzed by means of hydrogen bromide in acetic acid, forms chromone-2-methanephosphonic acid[12] **(12)** (Scheme 2).

The produced phosphonic esters **5(a–e), 8, 9(a–b),** are colourless (ester **11** though, is light yellow), crystalline substances, soluble in polar organic solvents (acetone, alcohols). The phosphonic acids **6, 7, 10, 12** are macrocrystalline, colourless, with high melting or breakdown temperatures, soluble in hot water and acetic acid.

EXPERIMENTAL

Melting temperatures were measured by means of a "Boethius" type apparatus, without correction. IR spectra were made using Pye-Unicam 200G Spectrometer, in KBr (tablets), ν_{max} in cm^{-1}.

^1H NMR spectra were recorded with a VARIAN EM-360 (60MHz) spectrometer, in DMSO-d_6, with TMS as internal standard, chemical shift in δ, ppm.

^{31}P NMR spectra were made using FT Jeol Fx-60 apparatus, frequency 24.3 MHz, in DMSO, with H_3PO_4 as external standard, chemical shift in δ, ppm.

2-Chlormethylchromone (3). 2.38 g (0.02 mole) of freshly distilled $SOCl_2$ was added dropwise to 1.76 g (0.01 mole) of 2-hydroxymethylchromone[9] in 70 ccm of anhydrous benzene. The mixture was stirred at room temperature for 6 hours. Benzene and excess $SOCl_2$ were distilled off under reduced pressure. Crude 2-chlormethylchromone **3** was crystallized from benzine (fraction with boiling temp. 80–90°C), producing 1.32 g (68%) of **3**, with mp. 118–120°C (Lit.[10]–127°C)-colourless needles.
Analysis

for $C_{10}H_7ClO_2$(194.6)	calculated:	C 61.7	H 3.6	Cl 18.2%
	obtained:	C 61.6	H 3.5	Cl 18.0%

^1H NMR: 4.8 (s, 2H, CH_2), 6.56 (s, C_3H), 7.25–8.14 (m, $4H_{arom.}$)

Dialkyl esters of chromone-3-hydroxymethanephosphonic acid 5(a–d) and diphenyl ester of chromone-3-hydroxymethanephosphonic acid (5e). General procedure (0.01 mole) of freshly distilled dialkyl phosphite **4(a–d)** or diphenyl phosphite **4e,** was added to 1.74 g (0.01 mole) of well-powdered 3-formylchromone[11] **1.** Then 1–2 drops of appropriate trialkyl phosphite $P(OR)_3$ or triphenyl phosphite $P(OPh)_3$ were added. The mixture was carefully stirred and heated in an oil bath at a temp. of 80–85°C, under a moisture-proof reflux condenser. After removing the oil bath, the mixture was left at room temperature for 24 hours. The post-reaction mixture (crystalline mass or oily residue) was crystallized twice.
5a, heating time 1.5 hours (80°C), crystallization: methanol,
2.64 g (93%), mp. 199–201°C.
5b, heating time 4 hours (85°C), crystallization: acetone,
2.24 g (72%), mp. 129–130°C.
5c, heating time 5 hours (85°C), crystallization: cyclohexane,
2.07 g (61%), mp. 135–137°C.
5d, heating time 5 hours (85°C), crystallization: diethyl ether,
2.58 g (70%), mp. 89–90°C.
5e, heating time 1.5 hours (80°C), crystallization: acetone,
3.43 g (84%), mp. 171–173°C.

TABLE I

Summary formula, molecular mass, analyses and spectral data of compou

Compound No.	Summary formula Molecular mass	Analyses % Calcd./Found C	H	P	^{31}P NMR	IR	
5a	$C_{12}H_{13}O_6P$ (284.2)	50.7 50.7	4.6 4.8	10.9 10.6	23.58	3183(OH) 1630(C=O), 1270(P=O)	3.65, 3.75(2 CH—OH OH)*/; 7. $^4J_{PH}$ = 4
5b	$C_{14}H_{17}O_6P$ (312.3)	53.9 53.6	5.5 5.7	9.9 9.8		3175(OH), 1638(C=O), 1268(P=O)	0.98–1.40(r 4H, 2CH $^2J_{PH}$ = 1 8.15(m, 4
5c	$C_{16}H_{21}O_6P$ (340.3)	56.5 56.0	6.2 6.6	9.1 9.1		3300(OH), 1630(C=O), 1208(P=O)	0.97–1.4(m CH_3/$_2$); 5 13Hz); 6. $4H_{arom.}$);
5d	$C_{18}H_{25}O_6P$ (368.4)	58.7 58.5	6.8 7.0	8.4 8.4		3210(OH), 1632(C=O), 1233(P=O)	0.82(m, 6H $2CH_2$/CH 5.14, 5.24 6.14–6.24 $4H_{arom.}$);
5e	$C_{22}H_{17}O_6P$ (408.3)	64.7 64.6	4.2 4.5	7.6 7.7		3235(OH), 1633(C=O), 1247(POPh)	5.55, 5.67(2 8.20(m, 1 $^4J_{PH}$ = 4
6	$C_{10}H_9O_6P$ (256.2)	46.9 46.7	3.5 3.7	12.1 11.6	18.22	3225(OH broad peak 2800(POH broad peak) 1615(C=O)	5.02(d, 1H, CH—OH $4H_{arom.}$);

7	$C_{10}H_9O_5P$ (240.2)	50.0 50.0	3.8 3.9	12.9 12.7	20.24	2820(POH broad peak) 1615(C=O), 1278(P=O)	2.87(d, 2H $4H_{arom.}$); 2H, P/O
8	$C_{12}H_{13}O_5P$ (268.2)	53.7 53.7	4.9 4.8	11.6 11.3	16.01	1585(C=O), 1252(P=O)	3.08(d, 2H 6H, 2CH C_2H, ^4J_P
9a	$C_{12}H_{13}O_6P$ (284.2)	50.7 50.6	4.6 4.8	10.9 10.8	19.54	3100(OH), 1655(C=O), 1235(P=O)	3.70, 3.88(CH—OI = 3Hz); $4H_{arom.}$)
9b	$C_{14}H_{17}O_6P$ (312.3)	53.9 53.9	5.6 5.4	9.9 9.8		3130(OH), 1647(C=O), 1205(P=O)	1.26(t, 6H $2CH_2$— = 16.5H 6.72, 6.8
10	$C_{10}H_9O_6P$ (256.2)	46.9 47.0	3.5 3.8	12.1 11.9	13.29	3180(OH broad peak), 2800(POH broad peak), 1608(C=O)	4.62(d, 1H C_3H, ^4J_P labile sit
11	$C_{12}H_{13}O_5P$ (268.2)	53.7 53.5	4.9 4.7	11.6 11.2	23.57	1660(C=O), 1275(P=O)	3.55(d, 2H 6H, 2CH 7.26–8.1
12	$C_{10}H_9O_5P$ (240.2)	50.0 49.8	3.8 3.8	12.9 12.6	15.11	2640, 2290(POH broad peaks), 1620(C=O), 1210(P=O)	3.15(d, 2H $^4J_{PH}$ = P/OH/$_2$

* Disappears after addition of D_2O to the sample.

Chromone-3-hydroxymethanephosphonic acid (6). Method A. 2.84 g (0.01 mole) of ester 5a was dissolved in 80 ccm of glacial acetic acid, and a stoichiometric amount of 40% HBr solution in acetic acid was added. The mixture was left at room temperature for 24 hours. Then the macrocrystalline precipitate was filtered, and the filtrate concentrated to 5 ccm and put into the refrigerator. The deposited precipitate was again filtered and rinsed with a small amount of glacial acetic acid. The combined precipitates were crystallized from acetic acid with addition of activated carbon, and dried in a vacuum desiccator, over P_2O_5. 2.3 g (90%) of **6** were obtained, mp. > 360°C (decomp.).

Method B. 2.84 g (0.01 mole) of ester 5a with 100 ccm of 8% HCl was refluxed for 10 hours. The solution was then condensed under reduced pressure to 10 ccm and left in the refrigerator. The deposited fine crystalline, fluffy precipitate was filtered and rinsed with a small amount of cold water, then dried in a vacuum desiccator over P_2O_5. After crystallization from glacial acetic acid 1.76 g (70%) of **6** were obtained, mp. > 360°C (decomp.).

Chromone-3-methanephosphonic acid (7). 2.56 g (0.01 mole) of acid **6,** 5 ccm of 57% H_I and 0.62 g (0.02 mole) of red P were added to 100 ccm of acetic acid and the mixture heated to 110–115°C for 6 hours. The hot reaction mixture was filtered, and the precipitate (red P) rinsed with 2 × 10 ccm of hot acetic acid. The brown filtrate was condensed to 15 ccm under reduced pressure, then decolorized by means of aqueous solution of Na_2SO_3 and put into the refrigerator. The deposited macrocrystalline precipitate was filtered and rinsed with a small amount of cold water. Crude acid **7** was dried in a vacuum desiccator over P_2O_5, and crystallized from glacial acetic acid; 2.1 g (70%) of **7** were obtained, mp. 238–240°C.

Dimethyl ester of chromone-3-methanephosphonic acid (8). 80 ccm of anhydrous methanol was added to 1.2 g (0.005 mole) of acid **7,** and while mixing an etheral solution of diazomethane was gradually added until the colour of the mixture became a stable light yellow. It was then left at room temperature for 12 hours. Methanol was distilled off under reduced pressure. After crystallization from acetone, 0.98 g (71%) of **8** were obtained, mp. 100.5–101.5°C.

Dialkyl esters of chromone-2-hydroxymethanephosphonic acid 9(a–b). General procedure (0.01 mole) of the appropriate freshly distilled dialkyl phosphite **4(a–b)** and 5.1 g (0.05 mole) of Al_2O_3 (Merck 90, act. I, basic, for column chromatography) were added to 1.74 g (0.01 mole) of well-powdered 2-formylchromone[9] **2.** After being carefully mixed, the reagents were adsorbed on Al_2O_3, and the mixture was left at room temperature for 72 hours. Aluminium oxide was then extracted with hot dichlormethane 3 × 50 ccm, and the solvent distilled off under reduced pressure.

9a, crystallization: acetone, 2.36 g (83%), mp. 161–163°C.

9b, crystallization: acetone, 1.59 g (51%), mp. 108–110°C.

Chromone-2-hydroxymethanephosphonic acid (10). 2.84 g (0.01 mole) of ester **9a** was dissolved in 70 ccm of glacial acetic acid, then a stoichiometric amount of 40% HBr solution in acetic acid was added. The mixture was left at room temperature for 24 hours, then acetic acid was distilled off under reduced pressure. Crude acid **10** was crystallized from acetic acid with the addition of activated carbon, and dried in a vacuum desiccator over P_2O_5. 2.18 g (85%) of **10** were obtained, mp. 225°C (decomp.).

Dimethyl ester of chromone-2-methanephosphonic acid (11). 1.24 g (0.01 mole) of freshly distilled trimethyl phosphite was added to 1.95 g (0.01 mole) of 2-chlormethylchromone **3,** then the mixture heated in an oil bath at 105–110°C. After 10 hours, 1.24 g (0.01 mole) of trimethyl phosphite was added, and heating continued for another 10 hours. The progress of the reaction was monitored by chromatography (silica gel plate, mobile phase – ethyl acetate + acetone 1:1). After $P(OCH_3)_3$ had been distilled off under reduced pressure (0.1–0.2 hPa, 50°C of oil bath), crude **11** was purified by column chromatography (Kieselgel 60, 0.2–0.5 mm; ethyl acetate + acetone 1:1). The solvents were evaporated under reduced pressure; a light yellow oil was obtained. It solidifies when placed in a refrigerator. After rinsing with anhydrous diethyl ether, 1.13 g (42%) of **11** were obtained, mp. 35–37°C.

Chromone-2-methanephosphonic acid (12). 1.34 g (0.005 mole) of ester **11** was dissolved in 30 ccm of glacial acetic acid. Acid **12** was obtained and purified following the same procedure as for acid **10.** 0.58 g (48%) of **12** were obtained, mp. 235°C (decomp.) Reference 12 –249°C.

This work was supported by the Polish Academy of Sciences within project 01.13.3.14.

REFERENCES

1. M. Payard, G. Mouysset, P. Tronche, P. Bastide and J. Bastide, *Eur. J. Med. Chem.-Chim. Ther.*, **20,** 117 (1985).
2. A. Nohara, H. Kuriki, T. Saijo, H. Sugihara, M. Kanno and Y. Sanno, *J. Med. Chem.*, **20,** 141 (1977).
3. K. Yoshino, T. Kohno, T. Uno, T. Morita and G. Tsukamoto, *J. Med. Chem.*, **29,** 820 (1986); L. M. Nguyen, E. Niesor and C. L. Bentzen, *ibid.*, **30,** 1426 (1987); G. K. Farrington, A. Kumar and F. C. Wedler, *ibid.*, **30,** 2062 (1987).
4. F. Ramirez, A. V. Patwardhan and S. R. Heller, *J. Am. Chem. Soc.*, **86,** 514 (1964).
5. W. S. Abramov, *Zh. Obshch. Khim.*, **22,** 647 (1952).
6. B. F. Gamaleya, A. E. Sorochinskii, A. M. Aleksandrov, A. F. Pavlenko and B. P. Kuzhar, *Zh. Obshch., Khim.*, **50,** 2619 (1980).
7. F. Texier-Boullet and A. Foucaed, *Synthesis*, 916 (1982).
8. A. I. Tolmachev, L. M. Shulezhko and A. A. Kisilenko, *Zh. Obshch. Khim.*, **35,** 1707 (1965).
9. M. Payard and J. Couquelet, *Synthesis*, 889 (1979).
10. H. A. Offe, *Chem. Ber.*, **71,** 1837 (1938).
11. A. Nohara, T. Umetani and Y. Sanno, *Tetrahedron*, **30,** 3553 (1974).
12. G. Mouysset, J. Bellan and M. Payard, *J. Tisne-Versailles, Farmaco, Ed. Sci.*, **42**(11), 805 (1987).