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Convenient Synthesis of Phosphonate Derivatives of 4-Chloro-2*H*-chromenes

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2,4-Dichloro-2*H*-chromene-3-carboxylates are formed in good yield in the condensation of the appropriate precursors with $SOCl_2$. These derivatives readily react with trialkyl phosphites to produce 2-phosphonate derivatives of 4-chloro-2*H*-chromene-3-carboxylates.

Key words: chromones, chromenes, chlorination, phosphonylation

Benzopyrans are an important group of naturally occurring compounds [1]. Chromones and chromenes show various astonishing biological properties such as antibacterial and antiviral [2], anti-inflammatory [3], anti-allergic [4]. On the other hand, phosphonate derivatives also demonstrate many biological activities. For example phosphonoformate has pronounced antiviral properties [5]. Previous work has shown that phosphonic derivatives of benzopyrans exhibit antitumor activity. For example dimethyl 1-(chromone-2-yl)-1-(dimethoxyphosphoryl)methanephosphoric acid ester showed antineoplastic activity *in vitro* against Sarcoma L1210 in mice [6].

The pointed out biological significance of benzopyran derivatives and of phosphonates promoted continuation of our previous work on phosphonate system [6] and to prepare novel phosphonate derivatives of chromenes, compounds which combine benzopyran ring with phosphonate residue.

The chlorination of the cyclic ketones like pyran, xanthone and their thioheterocyclic analogues with thionyl chloride and/or oxalyl chloride has been reported in the formation of dichlorderivatives [7]. There are in fact many reports on chlorination reaction of substituted chromones [8], isoflavones [9], and substituted flavones [10]. As far as examples of product resulting from the chlorination reaction of methyl 4-oxo-4*H*-chromene-2-carboxylate [11] and 4-oxo-4*H*-chromene-2-carboxylic acid [12] are concerned, only geminal dichloroderivatives are known. Reaction of oxalyl chloride with chromone and 3-deuterochromone appear not to have been studied in great detail [13]. The identification of the products of halogenation reactions was made on the basis of their ^{1}H NMR spectra only; the ^{13}C NMR spectroscopic method

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has not been applied [13]. On the basis of these spectra authors incorrectly suggested the products of the halogenation reaction exhibit the geminal 4,4-dichloroderivatives forms only.

The products of chlorination of chromones readily react with nucleophiles. The most reactive electrophilic centres of pyran ring are C2 and C4 atoms. Attack of oxygen nucleophiles (alcohols, water) [14] and carbon nucleophiles (carbanions) [15] takes place at C2 and C4, while nitrogen nucleophiles (amines [11] and hydroxylamine [16]) attack exclusively at the carbon atom C4, yielding Schiff's bases or oximes respectively.

RESULTS AND DISCUSSION

The principal objective of the work reported here has been to investigate the chlorination reaction of benzopyran derivatives and the synthesis of 2-dialkoxyphosphoryl-2*H*-chromene derivatives (Figure 1).

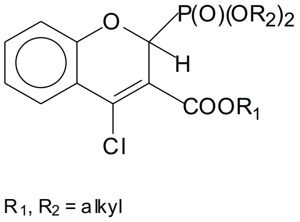
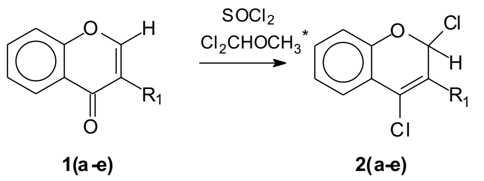


Figure 1. Structure of alkyl 4-chloro-2*H*-chromene-2-dialkoxyphosphoryl-3-carboxylate derivatives **3**.

Modification of the benzopyran system involving the introduction of Cl atoms in place of the hydrogen atoms have led to the preparation of a series of dichlorosubstituted of 2*H*-chromene that have interesting properties both in terms of their aromatic character and their ability to react with nucleophiles *e.g.*, phosphites.

Chromone **1a** [17] and several esters of 4-oxo-4*H*-chromene-3-carboxylic acid **1b–e** were synthesized and further chlorinated to form the corresponding dichlorderivatives **2a–e**. Dichloroderivatives of 2*H*-chromenes **2a–e** have been synthesized (Scheme 1) in the reaction of compounds **1b–e** with thionyl chloride or 1,1-dichlorodimethyl ether for **1a**.

Chromone **1a** reacts with 1,1-dichlorodimethyl ether (see Experimental) to produce **2a**. The ^{1}H NMR spectrum of **2a** is consistent with the reported ^{1}H NMR spectrum [13]. Treatment of 4-oxo-4*H*-chromene-3-carboxylic acid esters **1b–e** with thionyl chloride produced **2b–e** (Scheme 1). The ^{13}C NMR spectra of **2a–e** exhibit the resonances at *ca* 90 ppm (see Experimental section) which are consistent with the tetrahedral geometry of the C2 carbon atom in chlorotetrahydropyrans [18,19] rather than trigonal geometry. A chemical shift of *ca* 130 ppm, typical for sp^{2} hybridisation, has been detected for the C2 atom in the ^{13}C NMR spectra of 2*H*-pyrans [19].

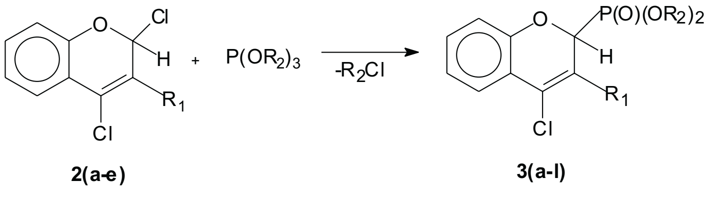


a [20]:R_1=H, **b**[21]:R_1=COOMe, **c**[22]:R_1=COOEt
d:R_1=COOPr, **e**:R_1=$COOCH_2CH_2Cl$
*- for compound **1a**

Scheme 1. Synthetic route to 2,4-dichloro-2*H*-chromene derivatives **2a–e**.

Dichloroderivatives **2a–e** are very unstable and reactive: *e.g.*, they vigorously react with water and alcohols producing chromone **1a** [23] or appropriate esters **1b–e** respectively. The formed compounds chromone **1a**, methyl 4-oxo-4*H*-chromene-3-carboxylate **1b** [24], ethyl ester **1c** [22], propyl ester **1d**, 2-chloroethyl ester **1e** has been fully characterized with ^{1}H NMR and IR spectroscopic data as well on the basis of the results of microanalyses and melting points values.

The dichloroderivatives **2a–e** readily react with trialkyl phosphites yielding monophosphonate compounds **3a–l** (Scheme 2), easily identified on the basis of their ^{1}H and ^{13}C NMR spectra. The compounds **3a–l** are derivatives of esters of (4-chloro-2-dialkoxyphosphoryl)2*H*-chromene-3-carboxylic acid resulting from nucleophilic attack of phosphites on carbon C2 of the pyrane ring, followed by Arbuzov type reaction dealkylating of the intermediate with chloride anion. The C2 carbon atom of **3a–l** produces resonance at δ = ~70–80 ppm which is consistent with a tetrahedral geometry of C2 carbon atom in tetrahydropyrans [18,19]. The coupling constant J_{CP} ~160 Hz confirms the presence of C–P bond. The presence of resonances at δ = ~ 5.50–6.00 ppm for CH2 in ^{1}H NMR spectra suggests the equatorial position of this proton [25]. The ^{31}P NMR spectra recorded for the reaction mixture did not contain resonances indicating formation of any other phosphonic derivatives, *e.g.* resulting from an attack of phosphites on the carbon atom C4 of the pyrane ring.



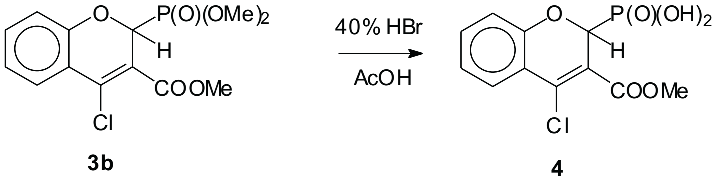
a:R_1=H, R_2=Me; **b**:R_1=COOMe, R_2=Me; **c**:R_1=COOMe, R_2=Et; **d**:R_1=COOMe, R_2=iPr;
e:R_1=COOMe, R_2=CH_2CH_2Cl; **f**:R_1=COOMe, R_2=Bu; **g**:R_1=COOEt, R_2=Me;
h:R_1=COOEt, R_2=Et; **i**:R_1=COOEt, R_2=CH_2CH_2Cl; **j**:R_1=COOPr, R_2=Me
k:R_1=COOPr, R_2=Et; **l**:R_1=$COOCH_2CH_2Cl$, R_2=$COOCH_2CH_2Cl$

Scheme 2. Synthetic route to 4-chloro-2*H*-chromene-2-phosphonate derivatives **3a–l**.

Crystal and molecular structures of dimethyl (4-chloro-2*H*-chromen-2-yl)phosphonate **3a** and ethyl 4-chloro-2-(dimethoxyphosphoryl)2*H*-chromene-3-carboxylate **3b** were determined in an X-ray diffraction study [26].

The results of the present study enable the formulation of a general route of the phosphonylation reaction of 2,4-dichloroderivatives of 2*H*-chromenes (Scheme 2).

Methyl 4-chloro-2-(dimethoxyphosphoryl)-2*H*-chromene-3-carboxylate **3b** in reaction with hydrobromic acid gave only phosphonic acid **4**, even excess of HBr did not remove methyl group from carboxylic moiety (Scheme 3).



Scheme 3. Dealkylation of compound **3b** to acid **4**.

In conclusion the presented data have proven that the chlorination of chromone **1a** and 4-oxo-4*H*-chromene-3-carboxylate **1b–e** led to the formation 2,4-dichloroderivatives type **2**. It has to be pointed out that our findings are not in disagreement with numerous studies [7] that have reported a formation of geminal dichlorderivatives upon chlorination reactions of benzopyrane derivatives. The dichloroderivatives vigorously react with phosphorus nucleophiles to yield 2-dialkoxyphosphoryl-2*H*-chromene derivatives.

This is of interest in view of the biological significance of chromones in general and the antitumor activity of platinum(II) complexes of benzopyrans [27].

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on an ATI MATTSON Infinity Series spectrometer. EI and HRMS (EI) (70 eV) mass spectra were run on a FINNIGAN MAT 95 mass spectrometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury (300 MHz) spectrometer in $CDCl_3$ and chemical shifts were reported in ppm downfield relative to TMS (internal standard) and 80% phosphorus acid (external standard) in phosphorus spectra. Microanalyses were made on a Perkin Elmer 2400 CHNS apparatus.

General procedure for the synthesis of esters of 4-oxo-4*H*-chromene-3-carboxylic acid 1 (d–e). 4-Oxo-4*H*-chromene-3-carbonyl chloride [22] (4.17 g, 20 mmol) was dissolved in dry benzene (20 ml). The appropriate alcohol (20 mmol) in dry benzene (10 ml) was added dropwise with stirring. After the exothermal reaction had been over, the solution was refluxed for an additional 0.5 h. The reaction mixture was left at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was recrystallized from appropriate solvent.

Propyl 4-oxo-4*H*-chromene-3-carboxylate (1d). Colourless crystals, m.p. 63–65°C, (diethyl ether), (65%); IR (KBr): 1743, 1643 cm^{-1}; ^1H NMR (*δ*): 8.67 (1H, s, C*H*$_2$), 8.30–7.30 (4$H_{arom.}$ m), 4.30 (2H, t, C*H*$_2$$CH_2CH_3$, *J* = 6.1 Hz), 1.77–1.81 (2H, m, CH_2C*H*$_2$$CH_3$), 1.04 (3H, t, CH_2CH_2C*H*$_3$, *J* = 7.6 Hz). Anal. Calcd. for $C_{13}H_{12}O_4$ (232.23): C, 67.2; H, 5.1. Found: C, 67.4; H, 5.5.

2-Chloroethyl 4-oxo-4*H*-chromene-3-carboxylate (1e). Colourless crystals, m.p. 87–89°C (acetone); (85%); IR (KBr): 1743, 1650 cm^{-1}; ^1H NMR (*δ*): 8.73 (1H, s, C*H*$_2$), 7.45–8.30 (4$H_{arom.}$ m), 4.58 (2H, t, OC*H*$_2$$CH_2Cl$, *J* = 5.2 Hz), 3.83 (2H, t, OCH_2C*H*$_2$Cl, *J* = 5.2 Hz). Anal. Calcd. for $C_{12}H_9ClO_4$ (252.65): C, 57.0; H, 3.5. Found: C, 57.5; H, 3.9.

General procedure for the synthesis of dichloroderivatives 2 (a–e). **2,4-Dichloro-2*H*-chromene (2a)** [20]. Colourless crystals, bp. 110–115°C/2 hPa, m.p. 115–118°C; IR (nujol): 1600, 1575, 1210, 1170 cm^{-1}; ^1H NMR (*δ*): 6.89–7.71 (4H $_{arom.}$ m), 7.12 (1H, d, C*H*$_2$, $J_{2,3}$ = 4.5 Hz); 6.22 (1H, d, C*H*$_3$, $J_{3,2}$ = 4.5Hz); ^{13}C NMR (*δ*): 149.38 (C8a), 131.84 (C4), 131.54 (C7), 124.75 (C5), 123.78 (C6), 119.52 (C4a), 119.22 (C3), 117.28 (C8), 89.88 (C2); EIMS m/z (%): 165 (100), 146 (12), 102 (10), 101 (10), 75 (6); MS EI HR: Calcd. for $C_9H_6ClO(M\text{-}Cl)^+$: 165.01030. Found: 165.01072.

Chlorination of 4-oxo-4*H*-chromene-3-carboxylic acid esters 1(b–e). $SOCl_2$ (30 ml), DMF (1–3 drops as catalyst) was added to the appropriate ester **1b–e** and the mixture was refluxed for 8 h. The unreacted $SOCl_2$ was removed at room temperature under reduced pressure. The residue was dissolved in petroleum ether, filtered, and evaporated to dryness. The crude product (solid or oil) which was of sufficient purity to be used as a reagent for further synthesis without purification.

Methyl 2,4-dichloro-2*H*-chromene-3-carboxylate (2b). Colourless crystals, m.p. 184–186°C (benzene), (90%), IR (nujol): 1725, 1605, 1570, 1480, 760 cm^{-1}. ^1H NMR (*δ*): 7.00–7.94 (4H $_{arom.}$ m), 6.80 (1H, s, C*H*$_2$), 3.55 (3H, s, C*H*$_3$); ^{13}C NMR (*δ*): 162.82 (*C*OOMe), 151.70 (C8a), 139.76 (C4), 132.36 (C7), 127.06 (C5), 122.66 (C6), 120.12 (C4a), 117.61 (C8 or C3), 116.60 (C3 or C8), 90.63 (C2), 51.89 (COO*C*H_3), EIMS m/z (%): 223 (100), 211 (16), 209 (41), 164 (9), 129 (6), 101 (8); MS EI HR: Calcd. for $C_{11}H_8ClO_3(M\text{-}Cl)^+$: 223.01620. Found: 223.01660.

Ethyl 2,4-dichloro-2*H*-chromene-3-carboxylate (2c). Colourless oil, IR (neat): 1727, 1605, 1571, 1479 cm^{-1}, ^1H NMR (*δ*): 7.13–7.92 (4$H_{arom.}$ m), 7.51 (1H, s, C*H*$_2$), 4.37 (2H, q, C*H*$_2$$CH_3$, *J* = 7.1 Hz), 1.41 (3H, t, CH_2C*H*$_3$, *J* = 7.1 Hz); ^{13}C NMR (*δ*): 161.73 (*C*$OOCH_2CH_3$), 150.29 (C8a), 138.88 (C4), 133.52 (C7), 127.09 (C5), 124.26 (C6), 120.73 (C4a), 118.80 (C8 or C3), 117.81 (C3 or C8), 89.08 (C2), 62.08 (COO*C*H_2CH_3), 14.41 ($COOCH_2$*C*H_3), EIMS m/z (%): 237 (100), 211 (14), 209 (44), 174 (13), 173 (37), 164 (11), 146 (40), 121 (20), 120 (59), 101 (8); MS EI HR: Calcd. for $C_{12}H_{10}ClO_3(M\text{-}Cl)^+$: 237.03185. Found: 237.03290.

Propyl 2,4-dichloro-2*H*-chromene-3-carboxylate (2d). Colourless oil, IR (nujol): 1728, 1606, 1572, 1479, 1457 cm^{-1}; ^1H NMR (*δ*): 7.13–7.92 (4$H_{arom.}$ m), 7.51 (1H, s, C*H*$_2$), 4.30 (2H, t, C*H*$_2$$CH_2CH_3$, *J* = 6.7 Hz), 1.83–1.76 (2H, m, CH_2C*H*$_2$$CH_3$, *J* = 6.7 Hz), 1.04 (3H, t, CH_2CH_2C*H*$_3$, *J* = 6.7 Hz), ^{13}C NMR (*δ*): 161.83 (*C*$OOCH_2CH_2CH_3$), 150.29 (C8a), 138.85 (C4), 133.50 (C7), 127.07 (C5), 124.24 (C6), 120.43 (C4a), 118.22 (C8 or C3), 117.80 (C3 or C8), 89.03 (C2), 67.70 (COO*C*$H_2CH_2CH_3$), 22.16, 10.80, EIMS (m/z): 251 (100), 211 (20), 210 (7), 209 (61), 173 (14), 166 (5), 164 (15), 121 (9), 101 (10), 72 (12); MS EI HR: Calcd. for $C_{13}H_{12}ClO_3(M\text{-}Cl)^+$: 251.04759. Found: 251.04760.

2-Chloroethyl 2,4-dichloro-2*H*-chromene-3-carboxylate (2e). Colourless oil, IR (neat): 1731, 1605, 1570, 1479, 1456 cm^{-1}; ^1H NMR (*δ*): 7.14–7.92 (4H $_{arom.}$ m), 7.51 (1H, s, C*H*$_2$), 4.57 (2H, t, OC*H*$_2$$CH_2Cl$, *J* = 5.1 Hz), 3.81 (2H, t, OCH_2C*H*$_2$Cl, *J* = 5.1 Hz); ^{13}C NMR (*δ*): 161.31 (*C*$OOCH_2CH_2CH_3$), 150.40 (C8a), 135.33 (C4), 133.86 (C7), 127.22 (C5), 124.32 (C6), 120.33 (C4a), 119.61 (C8 or C3), 117.89 (C3 or C8), 88.78 (C2), 65.26 (O*C*H_2CH_2Cl), 41.44 (OCH_2*C*H_2Cl), EIMS (m/z): 271 (100), 217 (15), 209 (21), 173 (56), 146 (7), 121 (12); MS EI HR: Calcd. for $C_{12}H_9Cl_2O_3(M\text{-}Cl)^+$: 270.99288. Found: 270.99210.

General procedure for synthesis of phosphonic derivatives of 4-chloro-2*H*-chromene 3(a–l): Dichloroderivative **2a–e** (20 mmol) was dissolved in dry benzene (20 ml) and then cooled in the refrigerator (10°C). To the cold solution the appropriate trialkyl phosphite (20 mmol) in dry benzene (5 ml) was added dropwise. The reaction mixture was left at room temperature for 24 h, then evaporated to dryness and kept at 4°C. Crude compounds **3a–c** were crystallized or oily products purified with column chromatography (silica gel; ethyl acetate).

Dimethyl (4-chloro-2*H*-chromen-3-yl)phosphonate (3a). Light yellow crystals, m.p. 55–56°C (diethyl ether), 90%; IR (KBr): 1220 (PO), 1030 (POC) cm^{-1}; ^{1}H NMR (δ): 6.78–7.46 ($4H_{arom.}$ m,), 5.93 (1H, dd, H_2, $J_{2,3} = 4.7$ Hz, $J = 2.7$ Hz), 5.33 (1H, dd, H_3, $J_{3,2} = 4.7$ Hz, $J = 9.9$ Hz), 3.76, 3.77 (6H, 2d, $J = 10.8$ Hz, $2CH_3$); ^{13}C NMR (δ): 53.26, 53.90 (2d, $J_{CP} = 11.3$ Hz, $P(OCH_3)_2$), 72.8 (d, $J = 167.1$ Hz, C2), 115.6 (C3), 115.71 (C8), 119.7 (C4a), 122.1 (C6), 124.7 (C5), 129.4 (d, $J = 14.1$ Hz, C4), 131.2 (C7), 153.2 (d, $J = 5.6$ Hz, C8a); ^{31}P NMR (δ): 17.30. Anal. Calcd. for $C_{11}H_{12}ClO_4P$ (274.64): C, 50.8; H, 2.1. Found: C, 50.9; H, 2.2.

Methyl 4-chloro-2-(dimethoxyphosphoryl)-2*H*-chromene-3-carboxylate (3b). Light yellow crystals, m.p. 105–107°C (benzene), 92%; IR (KBr): 1730, 1475, 1270, 1040 cm^{-1}; ^{1}H NMR (δ): 6.71–7.92 ($4H_{arom.}$ m), 5.92 (1H, d, $J = 12.0$ Hz, $H2$), 3.88 (3H, s, $COOCH_3$), 3.61, 3.69 (6H, 2d, $J = 11.9$ Hz, $P(OCH_3)_2$); ^{13}C NMR (δ): 52.41 ($COOCH_3$), 53.26, 53.90 (2d, $J = 11.3$ Hz, $P(OCH_3)_2$), 69.21 (d, $J = 161.5$ Hz, C2), 116.01 (C3), 116.91 (C8), 120.72 (C4a), 122.51 (C6), 127.06 (C5), 133.11 (C7), 136.36 (d, $J = 9.4$ Hz, C4), 154.24 (C8a), 163.05 (d, $J = 3.7$ Hz, $COOCH_3$), ^{31}P NMR (δ): 18.75. Anal. Calcd for $C_{13}H_{14}ClO_6P$ (332.67): C, 47.1; H, 4.2. Found: C, 47.0; H, 4.1.

Methyl 4-chloro-2-(diethoxyphosphoryl)-2*H*-chromene-3-carboxylate (3c). Light yellow crystals, m.p. 74–76°C (diethyl ether), 69%; IR (KBr): 1700, 1440, 1259, 1016 cm^{-1}; ^{1}H NMR (δ): 6.90–7.66 ($4H_{arom.}$ m), 5.84 (1H, d, $J = 12.0$ Hz, $H2$), 4.06–3.98 (4H, CH_2, m), 3.98 (3H, $COOCH_3$, s), 1.09–1.19 (6H, m, $P(OCH_2CH_3)_2$); ^{13}C NMR (δ): 16.44, 16.53 (2d, J=3,15 Hz, $P(OCH_2CH_3)_2$), 52.58 ($COOCH_3$), 63.12, 63.25 (2d, $J = 11.3$ Hz, $P(OCH_2CH_3)_2$), 72.77 (d, $J = 162.61$ Hz, C2), 116.08 (C3), 117.19 (C8), 120.98 (C4a), 122.43 (C6), 127.03 (C5), 133.00 (C7), 136.25 (d, $J = 7.73$ Hz, C4,), 154.34 (C8a), ^{31}P NMR (δ): 16.39. Anal. Calcd. for $C_{15}H_{18}ClO_6P$ (360.73): C, 49.1; H, 4.9. Found: C, 49.0; H, 4.8.

Methyl 4-chloro-2-(diisopropylphosphoryl)-2*H*-chromene-3-carboxylate (3d). Light yellow crystals, m.p. 110–112°C (ethyl acetate), 71%; IR (KBr): 1731, 1252, 1009 cm^{-1}; ^{1}H NMR (δ): 6.78–7.69 ($4H_{arom.}$ m), 5.80 (1H, d, $J = 12.0$ Hz, $H2$), 4.58–4.73 (2H, m, $CH(CH_3)_2$), 3.88 (3H, s, $COOCH_3$), 1.13, 1.15 (12H, 2d, J= 6.1 Hz, $CH(CH_3)_2$), ^{31}P NMR (δ): 13.90; EIMS m/z (%): 388 (2), 225 (31), 224 (11), 223 (100), 172 (3). Anal. Calcd. for $C_{17}H_{12}ClO_6P$ (388.78): C, 52.2; H, 5.7. Found: C, 52.4; H, 5.9.

Methyl 4-chloro-2-[bis(2-chloroethoxy)phosphoryl]-2*H*-chromene-3-carboxylate (3e). Light yellow crystals, m.p. 77–79°C (acetone), 61%; IR (KBr): 1703, 1274, 1033 cm^{-1}; ^{1}H NMR (δ): 6.95–7.63 ($4H_{arom.}$ m), 5.94 (1H, d, $J = 12.0$ Hz, $H2$), 4.29–3.91 (4H, m, OCH_2CH_2Cl), 3.88 (3H, s, $COOCH_3$), 3.55–3.44 (4H, m, OCH_2CH_2Cl); ^{13}C NMR (δ): 42.68, 42.75 (2d, $J = 6.0$ Hz, $POCH_2CH_2Cl$), 52.81 ($COOCH_3$), 66.23, 66,35 (2d, $J = 11.3$ Hz, $POCH_2CH_2Cl$,), 72.53 (d, $J = 162.6$ Hz, C2,), 116.10 (C3), 116.39 (C8), 120.93 (C4a), 122.79 (C6), 127.30 (C5), 133.30 (C7), 137.15 (d, $J = 8.0$ Hz, C4,), 154.10 (C8a), 163.28 (d, $J = 3.2$ Hz, $COOCH_3$), ^{31}P NMR (δ): 17.56; EIMS m/z (%): 225 (32), 223 (100), 164 (3). Anal. Calcd. for $C_{15}H_{16}Cl_3O_6P$ (429.62): C, 41.9; H, 3.8. Found: C, 42.1; H, 3.9.

Methyl 2-(dibutoxyphosphoryl)-4-chloro-2*H*-chromene-3-carboxylate (3f). Light yellow crystals, m.p. 74–76°C, (acetone), 69%; IR (KBr): 1727, 1606, 1265, 1023 cm^{-1}; ^{1}H NMR (δ): 6.90–7.67 ($4H_{arom.}$ m), 5.85 (1H, d, $J = 12.7$ Hz, $H2$), 3.76–4.11 (4H, m, $P(OCH_2CH_2CH_2CH_3)_2$), 3.85 (3H, s, $COOCH_3$), 1.18–1.51(8H, m, $POCH_2CH_2CH_2CH_3)_2$), 0.83–0.96 (6H, m, $POCH_2CH_2CH_2CH_3$); ^{13}C NMR (δ): 13.84, 13.86, 18.83, 18.85, 32.66, 32.68, 52.61 ($COOCH_3$), 66.86, 66.92 (2d, $J = 12.0$ Hz, $POCH_2CH_2CH_2CH_3$), 72.85 (d, C2, $J = 162.6$ Hz), 116.14 (C3), 117.27 (C8), 121.10 (C4a), 122.41 (C6), 127.11 (C5), 133.00 (C7), 136.20 (C4), 154.47 (C8a), 163.57 $COOCH_3$; ^{31}P NMR (δ): 16.63; EIMS m/z (%): 416 (1), 223 (100), 209 (3), 173 (2), 164 (2). Anal. Calcd. for $C_{19}H_{26}ClO_6P$ (416.8): C, 54.7; H, 6.3. Found: C, 54.9; H, 6.6.

Ethyl 4-chloro-2-(dimethoxyphosphoryl)-2*H*-chromene-3-carboxylate (3g). Light yellow crystals, m.p. 47–50°C (diethyl ether), 68%; IR (KBr): 1720, 1605, 1477, 1267, 1040 cm^{-1}; ^{1}H NMR (δ): 6.84–7.61 ($4H_{arom.}$ m), 5.81 (1H, d, $J = 12.1$ Hz, $H2$), 4.26 (2H, q, $J = 7.1$ Hz, $COOCH_2CH_3$), 3.47, 3.57 (6H, 2d, $J = 10.5$ Hz, $P(OCH_3)_2$), 1.28 (3H, t, $J = 7.1$ Hz, $COOCH_2CH_3$); ^{13}C NMR (δ): 14.38 ($COOCH_2CH_3$), 53.39, 53.59 (2d, $J = 14.8$ Hz, $P(OCH_3)_2$), 61.82 ($COOCH_2CH_3$), 72.50 (d, $J = 161.5$ Hz, C2), 116.01 (C3), 117.12 (C8), 120.87 (C4a), 122.50 (C6), 127.04 (C5), 132.15 (C7), 136.15 (d, $J = 8.0$ Hz, C4), 154.12 (C8a), 162.84 (d, $J = 3.2$ Hz, $COOCH_2CH_3$); ^{31}P NMR (δ): 18.63; EIMS (m/z): 346 (3), 239 (28), 237 (100), 211 (8), 209 (27), 165 (3), 164 (4), 129 (3), 101 (5). Anal. Calcd. for $C_{14}H_{16}ClO_6P$ (346.70): C, 48.5; H, 4.7. Found: C, 48.8; H, 4.9.

Ethyl 4-chloro-2-(diethoxyphosphoryl)-2*H*-chromene-3-carboxylate (3h). Colourless oil, 62%; IR (neat): 1726, 1606, 1478, 1264, 1028 cm^{-1}; ^{1}H NMR (δ): 6.83–7.59 ($4\mathrm{H}_{\mathrm{arom.}}$ m), 5.77 (1H, d, J = 12.3 Hz, H2), 4.26 (2H, q, J = 7.1 Hz, $\mathrm{COOC}H_2\mathrm{CH_3}$), 3.73–4.03 (4H, m, $\mathrm{P(OC}H_2\mathrm{CH_3)_2}$, 1.29 (3H, t, J = 7.1 Hz, $\mathrm{COOCH_2C}H_3$), 1.02–1.12 (6H, m, $\mathrm{P(OCH_2C}H_3)_2$); ^{13}C NMR (δ): 14.43 ($\mathrm{COOCH_2}C\mathrm{H_3}$), 16.45, 16.52 (2d, J = 3.15 Hz, $\mathrm{P(OCH_2}C\mathrm{H_3)_2}$), 61.81 ($\mathrm{COO}C\mathrm{H_2CH_3}$), 63.07, 63.17 (2d, J = 9.5 Hz, $\mathrm{P(O}C\mathrm{H_2CH_3)_2}$), 61.82 ($\mathrm{COO}C\mathrm{H_2CH_3}$), 72.79 (d, J = 162.6 Hz, C2), 116.05 (C3), 117.51 (C8), 121.10 (C4a), 122.38 (C6), 126.99 (C5), 132.87 (C7), 135.85 (d, J = 7.7 Hz, C4,), 154.34 (C8a), 163.06 (d, J = 3.2 Hz, $C\mathrm{OOCH_2CH_3}$), ^{31}P NMR (δ): 16.55; EIMS m/z (%): 374 (2), 239 (30), 238 (12), 237 (100), 211 (7), 209 (21), 165 (3), 164 (4), 129 (2), 101 (4). Anal. Calcd. for $\mathrm{C_{16}H_{20}ClO_6P}$ (374.75): C, 51.3; H, 5.4. Found: C, 51.6; H, 5.4.

Ethyl 4-chloro-2-[bis(2-chloroethoxy)phosphoryl]-2*H*-chromene-3-carboxylate (3i). Light yellow oil, 45%; IR (neat): 1723, 1251, 1082 cm^{-1}; ^{1}H NMR (δ): 6.90–7.74 ($4\mathrm{H}_{\mathrm{arom.}}$ m), 5.96 (1H, d, J = 12.0 Hz, H2), 4.31 (4H, dd, $\mathrm{P(OC}H_2\mathrm{CH_2Cl)_2}$, J = 5.6 Hz, J = 5.6 Hz), 3.88 (2H, t, J = 5.6 Hz, J = 7.1 Hz, $\mathrm{COOC}H_2\mathrm{CH_3}$), 3.44 (4H, dd, J = 5.6 Hz, J = 5.6 Hz, $\mathrm{P(OCH_2C}H_2\mathrm{Cl)_2}$, 1.37 (3H, t, J = 7.1 Hz, $\mathrm{COOC}H_3$); ^{13}C NMR (δ): 14.37 ($\mathrm{COOCH_2}C\mathrm{H_3}$), 42.52, 42.64 (2d, J = 6.0 Hz, $\mathrm{POCH_2}C\mathrm{H_2Cl}$), 62.00 ($\mathrm{COO}C\mathrm{H_2CH_3}$), 66.23, 66.35 (2d, J = 16.8 Hz, $\mathrm{PO}C\mathrm{H_2CH_2Cl}$,), 72.60 (d, J = 162.6 Hz, C2,), 116.02 (C3), 116.67 (C8), 120.96 (C4a), 122.69 (C6), 127.16 (C5), 133.12 (C7), 136.63 (d, J = 8.0 Hz, C4), 154.02 (C8a), 162.75 (d, J = 3.2 Hz, $C\mathrm{OOCH_2CH_3}$); ^{31}P NMR (δ): 17.20; EIMS m/z (%): 239 (29), 237 (100), 211 (5), 209 (17), 165 (2), 164 (3). Anal. Calcd. for $\mathrm{C_{16}H_{18}Cl_3O_6P}$ (443.64): C, 43.3; H, 4.1. Found: C, 43.5; H, 4.1.

Propyl 4-chloro-2-(dimethoxyphosphoryl)-2*H*-chromene-3-carboxylate (3j). Light yellow oil, 56%; IR (neat): 1726, 1605, 1267, 1034 cm^{-1}; ^{1}H NMR (δ): 6.93–7.70 ($4\mathrm{H}_{\mathrm{arom.}}$ m), 5.89 (1H, d, J = 12.1 Hz, H2), 4.21–4.29 (2H, m, $\mathrm{COOC}H_2\mathrm{CH_2CH_3}$), 3.56, 3.68 (6H, 2d, J = 10.7 Hz, $\mathrm{P(OC}H_3)_2$), 1.71–1.80 (2H, m, $\mathrm{COOCH_2C}H_2\mathrm{CH_3}$); 1.02 (3H, t, J = 7.7 Hz, $\mathrm{COOCH_2CH_2C}H_3$); ^{13}C NMR (δ): 10.75 ($\mathrm{COOCH_2CH_2}C\mathrm{H_3}$), 22.14 ($\mathrm{COOCH_2}C\mathrm{H_2CH_3}$), 53.55, 53.56 (2d, J = 16.8 Hz, ($\mathrm{P(O}C\mathrm{H_3)_2}$), 67.49 ($\mathrm{COO}C\mathrm{H_2CH_2CH_3}$), 72.56 (d, J = 162.1 Hz, C2), 116.04 (C3), 117.19 (C8), 120.95 (C4a), 122.52 (C6), 127.06 (C5), 132.99 (C7), 137.12 (d, J = 8.0 Hz, C4), 154.16 (C8a), 163.03 (d, J = 3.2 Hz, $C\mathrm{OOCH_3}$); ^{31}P NMR (δ): 16.55. Anal. Calcd. for $\mathrm{C_{15}H_{18}ClO_6P}$ (360.73): C, 49.9; H, 4.9. Found: C, 50.2; H, 5.2.

Propyl 4-chloro-2-(diethoxyphosphoryl)-2*H*-chromene-3-carboxylate (3k). Light yellow oil, 51%; IR (neat): 1727, 1605, 1264, 1026 cm^{-1}; ^{1}H NMR (δ): 6.96–7.62 ($4\mathrm{H}_{\mathrm{arom.}}$ m), 5.85 (1H, d, J = 12.5 Hz, H2), 4.19–4.29 (2H, m, $\mathrm{COOC}H_2\mathrm{CH_2CH_3}$), 3.79–4.11 (4H, m, $\mathrm{P(OC}H_2\mathrm{CH_3)_2}$), 1.73–1.83 (2H, m, $\mathrm{COOCH_2C}H_2\mathrm{CH_3}$), 1.10–1.26 (6H, m, $\mathrm{P(OCH_2C}H_3)_2$), 1.04 (3H, t, J = 7.3 Hz, $\mathrm{COOCH_2CH_2C}H_3$); ^{13}C NMR (δ): 10.73 ($\mathrm{COOCH_2CH_2}C\mathrm{H_3}$), 16.35, 16.42 (2d, J = 2.40 Hz, $\mathrm{P(OCH_2}C\mathrm{H_3)_2}$), 22.07 ($\mathrm{COOCH_2}C\mathrm{H_2CH_3}$), 63.08, 63.12, (2d, J = 12.0 Hz, $\mathrm{P(O}C\mathrm{H_2CH_3)_2}$), 67.38 ($\mathrm{COO}C\mathrm{H_2CH_2CH_3}$), 72.74 (d, J = 162.6 Hz, C2), 115.97 (C3), 117.47 (C8), 120.99 (C4a), 122.29 (C6), 126.88 (C5), 132.79 (C7), 135.70 (d, J = 7.7 Hz, C4), 154.27 (C8a), 163.09 (d, J = 3.21Hz, $C\mathrm{OOCH_2CH_2CH_3}$); ^{31}P NMR (δ): 19.33. Anal. Calcd. for $\mathrm{C_{17}H_{22}ClO_6P}$ (388.78): C, 52.6; H, 5.6. Found: C, 52.4; H, 5.8.

2-Chloroethyl 4-chloro-2-[bis(2-chloroethoxy)phosphoryl]-2*H*-chromene-3-carboxylate (3l). Light yellow crystals, m.p. 69–70°C (acetone), 51%; IR (KBr): 1739, 1210, 1026 cm^{-1}; ^{1}H NMR (δ): 6.90–7.75 (m, $4\mathrm{H}_{\mathrm{arom.}}$), 5.97 (1H, d, J = 12.0 Hz, H2), 4.48–4.59 (6H, m, $\mathrm{COOC}H_2\mathrm{CH_2Cl}$, $\mathrm{P(OC}H_2\mathrm{CH_2Cl)_2}$), 3.72–3.78 (6H, m, $\mathrm{COOCH_2C}H_2\mathrm{Cl}$, $\mathrm{P(OCH_2C}H_2\mathrm{Cl)_2}$); ^{31}P NMR ($\delta$): 17.10. Anal. Calcd. for $\mathrm{C_{16}H_{17}Cl_4O_6P}$ (478.09): C, 40.2; H, 3.6. Found: C, 40.4; H, 3.8.

Methyl 4-chloro-2-dihydroxyphosphoroxy-2*H*-chromene-3-carboxylate (4). Ester **3b** 3.32 g (0.01 mole) was dissolved in 20 ml of acetic acid and 5 ml of 40% HBr in acetic acid was added at room temperature. After 24 hours acetic acid was removed under reduced pressure and oily residue recrystallized twice from acetic acid. Obtained 1.12 g of compound **4** (37%). Colourless crystals, m.p. 198–201℃. IR (KBr): 3200–2750, 1678, 1620, 1608, 1476, 1294 cm^{-1}; ^{1}H NMR (DMSO-d_6) (δ): 10.50 (2H, s, $\mathrm{P(O}H)_2$), 6.84–7.59 (m, $4\mathrm{H}_{\mathrm{arom.}}$), 5.54 (1H, d, J = 13.2 Hz, H2), 3.76 (3H, s, $\mathrm{C}H_3$); ^{31}P NMR (DMSO-d_6) (δ): 14.96. Anal. Calcd. for $\mathrm{C_{16}H_{10}ClO_6P}$ (304.67): C, 43.4; H, 3.3. Found: C, 43.6; H, 3.2.

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REFERENCES

1. Ellis G.P., "Chromenes, chromanones and chromones", John Wiley & Sons. NY 1977 p. 1.
2. Burnham W.S., Sidwell R.W., Tolman R.L. and Stont M.G., *J. Med. Chem.,* **15**, 1075 (1972).
3. (a) Schneidewind E.M., Büge A., Kala M., Metzner J. and Zschumke A., *Pharmazie*, **34**, 103 (1979); (b) Metzner J., Bekemeier H., Paintz, M. and Schneidewind E.M., *Pharmazie*, **34**, 97 (1979).
4. Pfister J.R., Wyman W.E., Schuler M.E. and Roszkowski A.P., *J. Med. Chem.*, **23**, 335 (1980).
5. Zhang Y., Schols D. and De Clercq D., *Antiviral Res*., **43**, 23 (1999).
6. Kostka K., Modranka R., Szadowska A., Graczyk J. and Orszulak D., *Eur. J. Pharm. Sci*., **2,** 143 (1994).
7. (a) Schönberg A., Schütz O. and Nickel S., *Ber. dtsch. Chem. Ges.,* **61**, 1375 (1928); (b) Schönberg A. and Nickel S., *Ber. dtsch. Chem. Ges.,* **67**, 1795 (1934); (c) Schönberg A. and Asker W., *J. Chem. Soc.,* 272 (1942); 604 (1946); (d) Schönberg A. and v.Ardenne R., *Chem. Ber.,* **101**, 346 (1968); (e) Schönberg A. and Frese E., *Chem. Ber.,* **101**, 694 (1968); (f) Föhlisch B. and Krockenberger D., *Chem. Ber.*, **101**, 3990 (1968).
8. Merchant J.R., Bhat A.R. and Rege D.V., *Tetrahedron Lett.*, **20**, 2061 (1972).
9. Merchant J.R. and Martynes G., *J. Heterocyclic Chem.,* **17**, 1331 (1980).
10. Merchant J.R. and Rege D.V., *Tetrahedron,* **27**, 4837 (1971).
11. Zagorevskii V.A., Tsvetkova I.D. and Orlova E.K., *Zh. Obsch. Khim*., **34**, 1911 (1964).
12. Zagorevskii V.A. and Zykov D.A., *Zh. Obsch. Khim.*, **30**, 3100 (1960); *ibid*, **30**, 1378 (1960).
13. Föhlisch B., *Chem. Ber.,* **104**, 350 (1971).
14. Zagorevskii V.A., Zykov D.A. and Orlova E.K., *Zh. Obsch. Khim*., **31**, 568 (1961).
15. Zagorevskii V.A., Tsvetkova I.D., Orlova E.K. and Portnova S.L., *Khim. Geterotsikl. Soedin.*, **3**, 422 (1969).
16. Mesheriakova L.M., Tsikalova T.S., Orlova E.K., Burov Y.V., Speranskaya N.P. and Zagorevskii V.A., *Khim. Farm. Zh.,* **3**, 37 (1976).
17. Kostka K., *Roczn. Chem.,* **41**, 71 (1967).
18. Booth H., Khedhair K.A. and Readshaw S.A., *Tetrahedron*, **43**, 4699 (1987).
19. Eliel E., Manoharan M. and Pietrusiewicz K.M., *Org. Magn. Reson.*, **21**, 94 (1983).
20. Zagorevskii V.A., Orlova E.K. and Tsvetkova I.D., *Khim. Geterotsikl. Soedin.,* **8**, 1028 (1970).
21. Nohara A., Kuriki H., Saijo T., Sugihara H., Kanno M. and Sanno Y., *J. Med. Chem.,* **20**, 141 (1977).
22. Klutchko S., Comen H.P., Shavel Jr. J. and von Strandtman J., *J. Heterocyclic Chem.,* **11**, 183 (1972).
23. (a) Schönberg A. and Sina A., *J. Am. Chem. Soc.,* **72**, 3396 (1950); (b) Bressel U., Katrizky A.R. and Lea J.R., *J. Chem. Soc. (B)*, 11 (1971).
24. Cremins P.J., Saengchantara S.T. and Wallace T.W., *Tetrahedron*, **43**, 3075 (1987).
25. Pouget C., Fagnere C., Basly J.P., Leveque H. and Chulia A.J., *Tetrahedron*, **56**, 6047 (2000).
26. Olszak T.A., Grabowski M., Stępień A., Modranka R. and Kostka K., *Acta Cryst.* **C53**, 1514 (1997).
27. Ochocki J. and Zyner E., (2003) Patent PL Nr P. 185585.