Pergamon

Tetrahedron 55 (1999) 4815–4824

TETRAHEDRON

Reaction of Dimethyl 2-Methyl- and Dimethyl 2-phenyl-4-oxo-4*H*-chromen-3-yl-phosphonate with Amines[1]

Budzisz Elżbieta[2] and Pastuszko Sławomir[3]

Institute of Chemistry, Faculty of Pharmacy, Medical University of Łódź, 90-151 Łódź, Muszyńskiego 1, Poland

Received 27 November 1998; revised 19 January 1999; accepted 11 February 1999

Abstract: The reaction of dimethyl 2-methyl- and dimethyl 2-phenyl-4-oxo-4*H*-chromen-3-yl-phosphonate with various aliphatic and aromatic amines was investigated. A novel class of cyclic phosphonic analogues of chromone, **1** (2-methoxy-3-[1-(alkylamino)ethylidene or benzylidene]-2,3-dihydro-2,4-dioxo-2λ^5-benzo[e]--[1,2]oxaphosphinane), was obtained when primary amines were used as nucleophiles. An analogous reaction with aromatic or secondary amines led to the hydrolysis of one methyl ester group in the phosphonic acid residue.

Keywords: Phosphonic analogues of chromone, nucleophilic substitution of chromone

INTRODUCTION

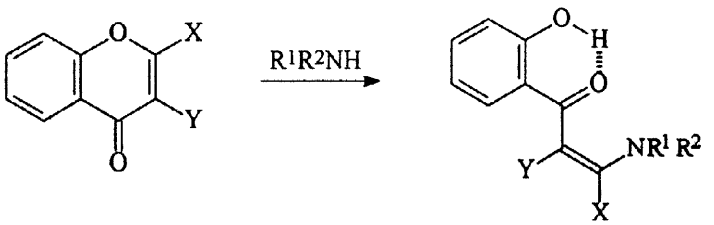
Chromone derivatives **2** are known for their interesting biological and chemical properties [1-8]. They serve as therapeutics in treatment of the blood circulatory system and in asthma diseases as well as in liver cell regeneration. The most investigated chemical property of chromones is their reaction with nitrogen nucleophiles [9-11]. In this process (Scheme 1) chromones are transformed efficiently into enamine-type compounds **3** exhibiting a typical lemon-yellow colour. The reaction is of analytical significance and thus it is applied in qualitative and quantitative assessment of primary and secondary aliphatic and aromatic amines [12-14].

[1] This paper is dedicated to the late Professor Krzysztof Kostka

[2] Corresponding author, Institute of Chemistry, Faculty of Pharmacy, Medical University of Łódź, 90-151 Łódź, Muszyńskiego 1, email: elora@ich.am.lodz.pl

[3] Present address: Polfa Tarchomin S.A. ul. Fleminga 2, 03-176 Warszawa , Poland

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00153-2



2 3

X, Y = alkyl (R), COOH, COOR, CN, CHO

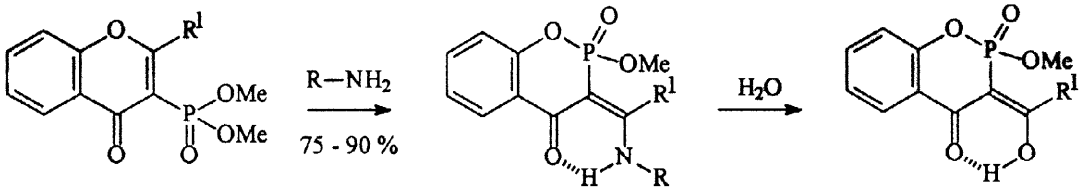
R^1, R^2 = H or alkyl

Scheme 1.

Since the discovery of compounds possessing a C-P bond in sea anemones, *Methridium sensile* [15,16], an examination of the biological and chemical properties of phosphonate derivatives became of interest to many laboratories [17-19]. Incorporation of a C-P bond into the chromone backbone offers a new class of compounds of potential biological importance. In our previous work we described the synthesis of dimethyl 2-methyl- and dimethyl 2-phenyl-4-oxo-4*H*-chromen-3-yl-phosphonates **4a** and **4b**, respectively [20]. Here, we present our study on the reaction of **4a** and **4b** with primary and secondary amines.

RESULTS

At first we investigated the reaction of dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate **4a** with ammonia and various primary amines (RNH_2, where R = methyl, ethyl, benzyl, 2-hydroxyethyl, isopropyl, morpholinyl, Scheme 2). The reaction was carried out at room temperature in anhydrous methanol. In each case a colourless crystalline compound showing a sharp melting temperature (Table 1) was obtained in high yield (75-90%) as a sole product. This was a rather unexpected result, since so far all the products of analogous reactions performed on the chromone system have yielded lemon-yellow crystalline enamines of general formula **3**. Analysis of ^1H and ^{31}P NMR spectra, as well as IR spectra and MS data, presented in Table 1, indicates that the compounds obtained are cyclic phosphonic analogues of chromone of a general structure **1** (2-methoxy-3--[1-(alkylamino)ethylidene]-2,3dihydro-2,4-dioxo-2λ^5-benzo[e][1,2]oxaphosphinane) are cyclic phosphonic analogues of chromone. This structure is confirmed by the chemical shift of phosphorus in the ^{31}P NMR spectra, where the value of the resonance signal at 21-22 ppm indicates the presence of a phosphorus atom built in the ring system. In the ^1H NMR spectra we can see only one methyl ester group bound to the phosphonic acid residue. A series of IR spectra performed in chloroform for derivatives **1** various concentrations (1 mM to 1000 mM) confirm the presence of a strong intramolecular hydrogen bond exhibiting a broad band at ν 3430 - 3450 cm^{-1}. From the negative result of the test reaction with $FeCl_3$ we excluded the presence of a free phenol group in the structure.



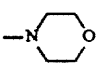
4a, b **1a-h** **5**

R^1= Me: **1a-g, 4a, 5**; R^1= Ph: **1h, 4b**

R= H: **1a**, CH_3: **1b, h**, CH_2CH_3: **1c**, CH_2Ph: **1d**, CH_2CH_2OH: **1e**, $CH(CH_3)_2$: **1f**.  : **1g**

Scheme 2

As expected, an analogous reaction of dimethyl 2-phenyl-4-oxo-4*H*-chromen-3-yl-phosphonate **4b** with methylamine gave a colourless crystalline product **1h** (2-methoxy-3-[1-(methylamine)benzylidene]-2,3-dihydro--2,4-dioxo-2λ^5-benzo[e][1,2]oxaphosphinane) in 82 % yield.

Compound	R	m.p.[°C]	^{31}P NMR[1] δ (ppm)	^{1}H NMR[2] P-OMe ($J_{P\text{-}Me}$ (Hz))	δ (ppm) N-H	δ (ppm) CH_3	MS[3] m/z	IR[4] (cm^{-1})
1a R^1=CH_3	H	170-172	21.8	3.75; (12.0)	12.20	2.55	253	3430
1b R^1=CH_3	CH_3	163-165	21.4	3.70; (12.0)	13.20	3.10	268	3370
1c R^1=CH_3	CH_2CH_3	134-135	21.8	3.70; (12.0)	13.30	2.60	281	3420
1d R^1=CH_3	CH_2Ph	130-132	21.7	3.77; (12.0)	13.90	2.60	343	3420
1e R^1=CH_3	CH_2CH_2OH	165-167	23.0	3.55; (11.0)	13.67	2.50	297	3320
1f R^1=CH_3	$CH(CH_3)_2$	92-94	21.6	3.70; (12.0)	13.40	2.57	295	3370
1g R^1=CH_3		144-146	20.6	3.80; (12.0)	14.15	2.75	334	3420
1h R^1=Ph	CH_3	169-170	19.5	3.3; (12.0)	13.50	-	328	3440

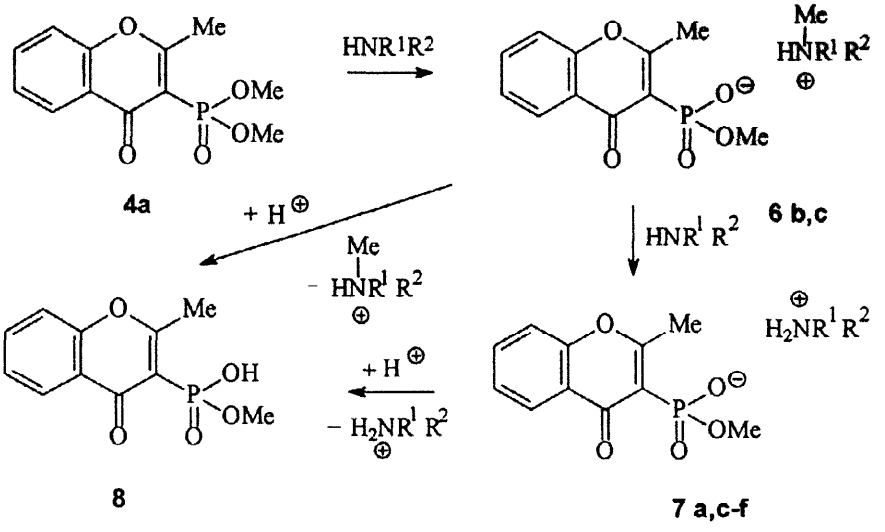
1. Spectra were done in $CDCl_3$. Phosphoric acid was used as an external standard. *2*. Spectra were recorded on Varian EM-360 in $CDCl_3$. TMS was used as internal standard. *3*. EI , 70 eV, *4*. Spectra were carried out in chloroform with the concentration of **1** from 1 to 1000 mM.

Table 1. Characteristics of cyclic phosphonic analogues of chromone **1**.

Compounds **1** are unstable in alkaline solutions. Derivatives **1a-g** were transformed easily into one common compound **5** (2-methoxy-3-[1-(hydroxy)ethylidene]-2,3-dihydro-2,4-dioxo-2λ^5-benzo[e][1,2]oxaphosphinane), of molecular weight 254. Spectral and elemental analysis of **5** confirms the stability of the cyclic phosphonic chromone backbone in aqueous conditions, however in the presence of water substitution of an alkylamino

group by a hydroxyl group at the ethylidene carbon 3' occurs. This structure provides the presence of a strong intramolecular hydrogen bond, as observed in the IR spectrum.

When aromatic (aniline or 2-aminopiridine) or secondary amines (dimethylamine, dipropylamine, piperidine and morpholine) were used as nucleophilic agents in the reaction with **4a**, colourless crystalline compounds with non-sharp melting temperatures, soluble in water, were obtained. According to the stoichiometry of the reagents we were able to isolate salts **6** or **7**, when equimolar or six-fold excess of amine over **4a**, respectively, was used (Scheme 3). The formation of methylated salts in the first step of the reaction was confirmed by the presence of N-Me protons in the ^{1}H NMR spectra of isolated salts **6**. Acidification of salts **6** or **7** with 5 % H_2SO_4 yielded phosphonic acid derivative **8** (Scheme 3).



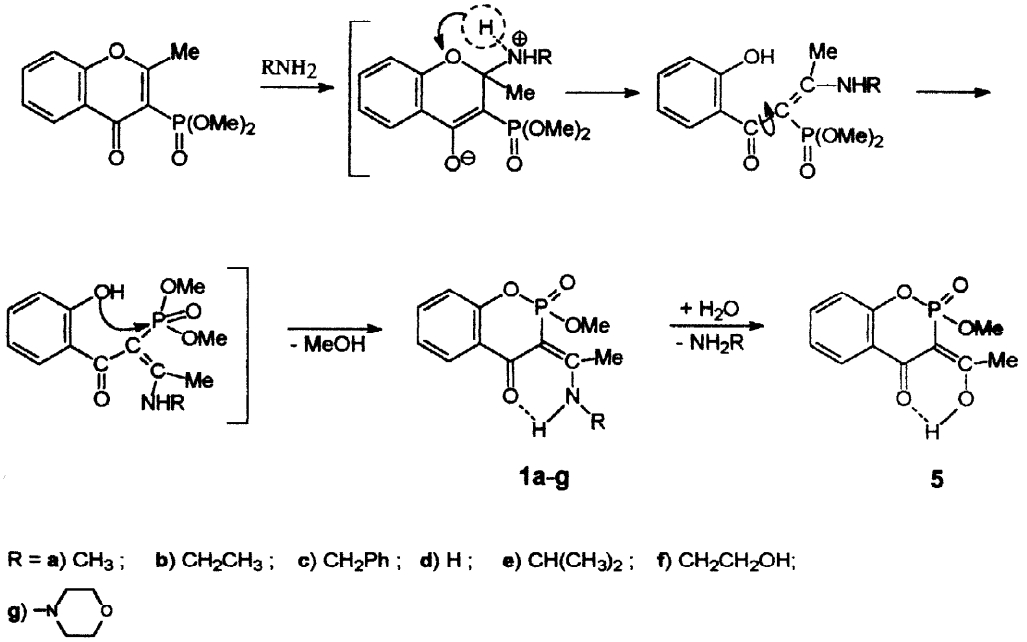
a: R^1=H, R^2=Ph, b: R^1=H, R^2=  , c: R^1= R^2=CH_3, d: R^1=R^2=$CH_2CH_2CH_3$, e: piperidine, f: morpholine

Scheme 3

DISCUSSION

As it is emphasised by many authors the carbon C-2 of the chromone is a target for the primary nucleophilic attack of the amine [21-26]. This reaction results in enamine-type compounds of general formula **3**. However, nucleophilic substitution of dimethyl 2-methyl- and dimethyl 2-phenyl-4-oxo-4*H*-chromen-3-yl-phosphonate **4a** and **4b** with primary amines leads to cyclic phosphonic analogues of chromone of general formula **1**. Thus, we propose the following reaction pathway for this reaction (Scheme 4): after nucleophilic attack of the amine on chromone carbon C-2, there is an opening of the benzo-γ-pyrone ring and subsequent conformational rearrangement followed by cyclization which is a result of nucleophillic substitution on the phosphorus atom by

the phenol group. Despite conducting the reaction at lower temperatures (-20°C) it was not possible to isolate any intermediate product.



R = a) CH_3 ; b) CH_2CH_3 ; c) CH_2Ph ; d) H ; e) $CH(CH_3)_2$; f) CH_2CH_2OH;

g)

Scheme 4

An analogous reaction of **4a** with less basic aromatic or secondary amines (pKa 7-9) does not lead to the opening of the benzo-γ-pyrone ring, instead amines react exclusively with the ester group of the phosphonic acid giving ammonium salts of methyl-4-oxo-4*H*-chromen-3-yl-phosphonate. Such transfer of a methyl ester group from phosphonic esters to amines has been exhaustibly described in many studies [27,28] and has been a subject of many patents [29-31].

Cyclic phosphonic analogues of chromone of general formula **1** are a new class of chromone derivatives. The only product of similar structure known up to now is 2*H*-3,4-dihydro-6,8-dihydroxy-3-methyl-2-dimethylo-amino-2,4-dioxo-1,2-benzoxaphosphorinane obtained by Hill *et al.* [32] in the reaction of β-ketophosphamido-1–(2',3',5'-trimethoxy-phenyl)-2-(bis-dimethylaminophosphono)-propanone with boron tribromide in dichloro--methane. Due to the lack of information of biological properties of such derivatives cyclic phosphonic analogues of chromone **1** as well **6** and **7** are the subject of intensive biological screening.

CONCLUSIONS

The reaction of dimethyl 2-methyl- and dimethyl 2-phenyl-4-oxo-4*H*-chromen-3-yl-phosphonate with various aliphatic and aromatic amines was investigated. When strong primary amines (pKa 3-5) were used as nucleophilic agents a novel class of cyclic phosphonic analogues of chromone of general formula **1**

(2-methoxy-3-[1-(alkylamino)ethylidene or benzylidene]-2,3-dihydro-2,4-dioxo-2λ^5-benzo[e][1,2]oxaphosphinane), was obtained. An analogous reaction performed with aromatic or secondary amines led to the hydrolysis of one methyl ester group in the phosphonic acid residue resulting in a phosphonic acid monoester. Biological and pharmacological investigations of the derivatives obtained are in progress.

ACKNOWLEDGEMENTS

Financial support from Medical University of Łódź is gratefully acknowledged. We gratefully acknowledge Dr Barbara Nawrot for the help in preparation of this manuscript.We thank Mrs. Agnieszka Siedlecka for her skilled experimental contributions.

EXPERIMENTAL SECTION

General. The melting points were determined using an Electrothermal 1A9100 apparatus and they are uncorrected. The IR spectra were recorded on a Pey-Unicam 200G Spectromether in KBr. The ^{1}H NMR spectra were registered at 60 MHz on a Varian EM-360 spectrophotomer. ^{31}P NMR spectra were recorded on a Brucker AC 200F spectrometer operating at 81 MHz. Positive chemical shift values are reported from compounds absorbing at lower fields than phosphoric acid. The MS data was obtained on a LKB 2091 spectrophotometer (70 eV ionization energy).

Dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate **4a** and dimethyl 2-phenyl-4-oxo-4*H*-chromen-3-yl--phosphonate **4b** were prepared according to the described procedure [20] .

I. *Synthesis of 2-methoxy-3-[1-(alkylamine)ethylidene]-2,3-dihydro-2,4-dioxo-2λ^5-benzo[e][1,2]oxaphosphinane* (**1a-h**).

To a mixture of dimethyl 2-methyl-4-oxo-*4H*-chromen-3-yl-phosphonate **4a** or dimethyl 2-phenyl-4-oxo-*4H*-chromen-3-yl-phosphonate **4b** (20 mmol) in methanol (0.5 mL), suitable amine (listed in Table 1, 20 mmol) in methanol (0.5 mL) was added. The mixture was left overnight at room temperature, and then cooled to -10°C. The solvent was removed *in vacuo* and crude product **1** was purified by crystallization. Colourless products **1** were obtained with 75-90 % yields. The properties of compounds **1** are listed in Table 1. **1a** [Found C, 52.4; H, 4.6; P, 12.3; N, 5.6. $C_{11}H_{12}NO_4P$ requires C, 52.18; H, 4.38; P, 12.23; N, 5.53 %], **1b**[Found: C, 53.8; H, 5.5; P, 11.3; N, 5.1. $C_{12}H_{14}NO_4P$ requires C, 53.94; H, 5.28; P, 11.59; N, 5.24 %], **1c**[Found: C, 55.4; H, 5.6; P, 11.0; N, 4.8 $C_{13}H_{16}NO_4P$ requires C, 55.52; H, 5.73; P, 11.01; N, 4.98 %], **1d**[Found: C, 63.0; H, 5.2; P, 9.0; N, 3.8. $C_{18}H_{18}NO_4P$ requires 62.97; H, 5.28; P, 9.02; N, 4..08 %], **1e**[Found: C, 52.6; H, 5.3; P, 10.5; N, 4.4. $C_{13}H_{16}NO_5P$ requires C, 52.53; H, 5.43; P, 10.42; N, 4.71 %], **1f**[Found: C, 56.8; H, 6.3; P, 10.3; N, 4.7. $C_{14}H_{18}NO_4P$ requires C, 56.95; H, 6.14; P, 10.49; N, 4.74 %], **1g**[Found: C, 53.0; H, 5.5; P, 9.2; N, 8.3.

$C_{15}H_{19}NO_5P$ **requires** C, 53.26; H, 5.66; P, 9.16; N, 8.28 %], **1h**[Found: C, 61.9; H, 4.9; P, 9.5; N, 4.4. $C_{17}H_{16}NO_4P$ **requires** C, 62.01; H, 4.90; P, 9.41; N, 4.25 %].

II. *Synthesis of 2-methoxy-3-[1-(hydroxy)ethylidene]-2,3-dihydro-2,4-dioxo-2λ⁵-benzo[e][1,2]oxa-phosphinane* (**5**)

To the aqueous solution of potassium carbonate (5 %, 30 mL), was added suitable compound **1** (0.75 mmol). The suspension was heated for 1 h at 85-90°C until clear yellow solution was obtained. The reaction mixture was cooled to 0° C and aqueous solution of sulphuric acid (10 %, 10 mL) was added in two parts. Precipitation started after few minutes. The crude solid was filtered off, dried, and crystallized with petrol-ether, to give 2-methoxy-3-[1-(hydroxy)ethylidene]-2,3-dihydro-2,4-dioxo-2λ⁵-benzo[e][1,2]oxa- phosphinane **5** (42 - 45 %) as a white solid, m.p. 95-97°C; [Found: C, 52.1; H, 4.6; P, 12.0. $C_{11}H_{11}O_5P$ (254.18) requires C, 51.98; H, 4.36; P, 12.19%]; ν_{max}(KBr) 1040(P-O -C), 1275 (P=O), 1400, 1545 (C=C), 2800-3400 (OH); δ_P ($CDCl_3$) 14.5; δ_H ($CDCl_3$) 18.10 (s, 1H, OH disap. in D_2O), 7.1-8.3 (m, 4H, aromat), 3.90(d, 3H, $^3J_{HH}$ =12 Hz, $POCH_3$), 2.60(s, 3H, CH_3); *m/z* 254 (M^+, 42.0), 240(8.6), 239(100), 212(7.1), 207(6.5), 170(25), 139(7.7), 134(44), 121(13), 119(5.8), 105(7.5), 92(7.0), 77(24), 75(5.1).

III. Reaction of dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate (**4a**) with secondary aliphatic amines and aromatic amine.

III.1. *Methylaminopyridinium methyl 2-methyl- 4-oxo-4H-chromen-3-yl-phosphonate* (**6b**)

To compound **4a** (0.27g, 1 mmol) in methanol (0.20 mL) was added 2-aminopyridine (0.1g, 1.07 mmol). The reaction mixture was refluxed for 2.5 h. The reaction progress was monitored by TLC. After substrate disappearance methanol (0.5 mL) and charcoal were added to the reaction mixture and it was refluxed for 10 min and then worked-up. After separation of charcoal the solvent was removed *in vacuo*. The crude product was purified by crystallization (acetone) to give the methylaminopyridinium methyl 2-methyl- 4-oxo-4*H*--chromen-3-yl-phosphonate **6b** (0.24g, 66%) as a white solid m.p.176-178 °C; [Found: C, 56.2; H, 4.9; N, 7.8; P, 8.9. $C_{17}H_{19}N_2O_5P$ (362.32) requires C, 56.35; H, 5.3; N, 7.73; P,8.55%]; ν_{max}(KBr) 1040 (P-O-C), 1230 (P=O), 1460, 1540 (C=C), 1625 (C=O); δ_P ($CDCl_3$) 11.7; δ_H ($CDCl_3$) 9.90 (s, 2H, NH broad disap. in D_2O), 6.50-8.30 (m, 8H, aromat.), 4.40 (s, 3H, N-CH_3), 3.60 (d, 3H, $^3J_{PH}$= 12 Hz, $POCH_3$), 2.90 (d, 3H, $^4J_{PH}$ = 2 Hz, CH_3).

III.2. *Trimethylammonium methyl 2-methyl-4-oxo-4H-chromen-3-yl-phosphonate* (**6c**)

To compound **4a** (0.54 g, 2 mmol) in methanol (0.5 mL) was added 0.095 M solution of dimethylamine (2 mmol) in methanol (0.21 mL). The reaction mixture was left at room temperature for 90 h. Then, the solvent

was evaporated under reduced pressure. The crude product was purified by crystallization (acetone / methanol, 4/1) to give trimethylammonium methyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate **6c** (0.21g, 34 %) as a white solid, m.p. 229-231°C; [Found: C, 57.2; H, 6.7; N, 4.8; P, 9.7. $C_{14}H_{20}NO_5P$ (313.28) requires C, 57.50; H, 6.44; N, 4.47; P, 9.87%]; ν_{max}(KBr) 1070 (P-O-C), 1215 (P=O), 1460, 1545 (C=C), 1615 (C=O), 2800-3550 (P-O$^-$, NH); δ_P (DMSO-d_6) 11.1; δ_H (D_2O) 7.10-8.15 (m, 4H, aromat.), 3.73 (d, 3H, $^3J_{PH}$ =12Hz, $POCH_3$), 3.35 (s, 9H, NCH_3), 2.90 (d, 3H, $^4J_{PH}$ = 2 Hz, CH_3).

III.3. *Anilinium methyl 2-methyl-4-oxo-4H-chromen-3-yl-posphonate* (**7a**)

Aniline (0.55 mL, 6 mmol) was added to compound **4a** (0.27g, 1 mmol). The mixture was left for 20 days at room temperature (TLC monitoring). Then, an excess of aniline was evaporated under reduced pressure. The yellow solid was crystallized (ethyl ether /methanol, 5/1) to give anilinium methyl 2-methyl-4-oxo-4*H*-chromen-3-yl-posphonate **7a** (0.19g, 55%) as a white solid, m.p. 102-104°C; [Found: C, 58.9; H, 5.0; N, 3.8; P, 8.7. $C_{17}H_{18}NO_5P$ (347.29) requires C 58.79; H, 5.22; N, 4.03; P, 8.92 %]; ν_{max}(KBr) 1040 (P-O-C), 1210 (P=O), 1470, 1540 (C=C), 1620 (C=O), 2400-3100(P-O$^-$), 3400, 3510(NH); δ_P (DMSO-d_6) 12.0; δ_H (DMSO-d_6) 6.60-8.30 (m, 9H, aromat.), 5.93 (s, 3H, NH, disap. in D_2O), 3.70 (d, 3H, $^3J_{PH}$ = 12 Hz, $POCH_3$), 2.93 (d, 3H, $^4J_{PH}$ =2 Hz CH_3).

III.4. *Dimethylammonium methyl 2-methyl-4-oxo-4H-chromen-3-yl-phosphonate* (**7c**)

The remaining solid after rection III.2 was recrystallized with a mixture of ethyl ether, acetone and methanol (15/15/1). The *title product* **7c** (0.31g, 52 %) as a white solid, was obtained; m.p. 67-68°C; [Found: C, 56.6; H, 6.3; N, 4.5; P 10.2. $C_{13}H_{18}NO_5P$ (299.25) requires C, 56.19; H, 6.06; N, 4.68; P, 10.35%]; ν_{max}(KBr) 1070 (P-O-C), 1210 (P=O), 1460, 1540(C=C), 1625 (C=O), 2700-3550 (P-O$^-$, NH); δ_P (DMSO-d_6) 11.0; δ_H ($CDCl_3$) 9.70 (s, 2H, broad, disap. in D_2O), 7.15-8.20 (m, 4H, aromat.), 3.55 (d, 3H, $^3J_{PH}$ =12 Hz, $POCH_3$), 2.85 (d, 3H, $^4J_{PH}$ = 2 Hz, CH_3), 2.75 (s, 6H, NCH_3).

III.5. *Dipropylammonium methyl 2-methyl-4-oxo-4H-chromen-3-yl-phosphonate* (**7d**)

To the compound **4a** (0.27g, 1 mmol) in methanol (0.5 mL) dipropylamine (6 mmol, 0.82 mL) was added. The reaction mixture was left at room temperature for 45 min. The solvent and excess of the amine were removed *in vacuo*. Then 5.0 mL of ethyl ether was added to the yellow oil and after cooling the obtained yellow solid was filtered off and was recrystallized with ethyl ether/acetone (1/1). The *title product* **7d** (0.23g, 65%) as a white solid was obtained; m.p. 84-87°C; [Found: C, 61.1; H, 7.2; N, 4.2; P, 8.4. $C_{17}H_{26}NO_5P$ (355.37) requires C, 60.83; H, 7.37; N, 3.94; P, 8.71 %]; ν_{max}(KBr) 1060(P-O-C), 1210 (P=O), 1460,1540 (C=C), 1620 (C=O), 2700-3550 (P-O$^-$, N-H); δ_P ($CDCl_3$) 10.5; δ_H ($CDCl_3$) 9.80 (s, 2H, NH broad, disap.in D_2O), 7.20-8.30 (m, 4H,

aromat.), 3.60 (d, 3H, $^3J_{PH}$=12 Hz, $POCH_3$), 3.00 (t, 4H, NCH_3), 2.90 (d, 3H, $^4J_{PH}$ = 2 Hz, CH_3), 1.80 (m, 4H, CH_2), 0.90 (t, 3H, CH_3).

III.6 *Piperidinium methyl 2-methyl-4-oxo-4H- chromen-3-yl-phosphonate* (**7e**)

To the compound **4a** (0.27g, 1 mmol) piperidine (0.59 mL, 6 mmol) was added. The reaction mixture was refluxed at 50°C for 30 min. The solvent and excess of amine were removed *in vacuo*.The obtained yellow solid was crystallized with diethyl ether / acetone (1/1) mixture and piperidinium methyl 2-methyl-4-oxo-4*H*--chromen-3-yl-phosphonate **7e** (0.24g, 71%) as a white solid was obtained; m.p.121-124 °C; [Found: C, 56.4; H, 6.2; N, 4.1; P, 8.9. $C_{16}H_{22}NO_5P$ (339. 33) requires C, 56.43; H, 6.54; N, 4.13; P, 9.13%]; ν_{max}(KBr) 1055 (P-O-C), 1201 (P=O), 1460, 1545 (C=C), 1645(C=O), 2700-3550 (P-O$^-$, NH); δ_P ($CDCl_3$) 8.90; δ_H ($CDCl_3$) 8.50 (s, 3H, NH, broad, disap. in D_2O), 7.20-8.30 (m, 4H, aromat.), 3.57 (d,3H, $^3J_{PH}$ = 12 Hz, $POCH_3$), 3.20 (t, 4H, NCH_2), 2.93 (d, 3H, $^4J_{PH}$ = 2 Hz, CH_3), 1.75 (m, 6H, CH_2).

III.7 *Morpholinium methyl 2-methyl-4-oxo-4H-chromen-3-yl-phosphonate* (**7f**)

To compound **4a** (0.27g, 1 mmol) morpholine (6 mmol, 0.52 mL) was added. The reaction mixture was left at room temperature for 50 hours (TLC monitoring). After cooling the brownish oil precipitation was obtained. The crude product was crystallized with ethyl ether/methanol (20/3) and morpholinium methyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate **7f** (0.25g ,73 %) as a white solid was obtained; m.p. 167-169°C; [Found: C, 53.0; H, 6.1; N, 4.3; P, 8.8. $C_{15}H_{20}NO_6P$ (341.30) requires C, 52.78; H, 5.91; N, 4.10; P, 9.07%]; δ_P ($CDCl_3$) 6.3; δ_H ($CDCl_3$) 10.15 s,2H, NH, broad, disap. in D_2O), 7.25-8.35 (m, 4H, aromat.), 4.05 (m, 4H, OCH_2), 3.57(d, 3H, $^3J_{PH}$ = 12 Hz, $POCH_3$), 3.40 (m, 4H, NCH_2), 2.90 (d, 3H, $^4J_{PH}$ = 2 Hz, CH_3).

IV. *Synthesis of methyl ester (2-methyl- 4-oxo-4H-chromen-3-yl)-phosphonic acid* (**8**)

To the solution of corresponding compounds **6** or **7** (1 mmol) in water (10.0 mL) 5% solution of H_2SO_4 (2 mL) was added dropwise. The mixture was stirred at room temperature for 30 min.. After cooling the reaction mixture was filltered off. The crude product **8** was recrystallized from the mixture of ethyl ether/ methanol (20/1) and methyl ester (2-methyl- 4-oxo-4*H*-chromen-3-yl)-phosphonic acid **8** (0.17g , 71%) as a white solid was obtained; m.p. 149-151°C; [Found: C, 51.9; H, 4.6; P, 11.8. $C_{11}H_{11}O_5P$ (254.18) requires C, 51.98; H, 4.36; P, 12.19%]; ν_{max}(KBr) 1050 (P-O-C), 1260 (P=O), 1465, 1545 (C=C), 1645 (C=O); δ_P ($CDCl_3$) 14.2; δ_H ($CDCl_3$) 10.70 (s, 1H, POH, disap. in D_2O), 7.35-8.40 (m, 4H, aromat.), 3.85 (d, 3H, $^3J_{PH}$ = 12 Hz $POCH_3$), 2.90 (d,3H, $^4J_{PH}$ = 2 Hz, CH_3); *m/z* 254 (M^+, 100), 239(18), 224(10), 223(15), 222(40), 174(16), 173 (18), 160(97), 121(44), 120(36), 93(11), 92(46), 77(77), 76(10).

References

[1] Gabor M., The pharmacology of benzopyrone derivatives and related compunds; Akademiai Kiado, Budapest 1988.
[2] Vejdelek Z., Treka V., et al. *Chem. Listy*, 1953, 47: 575-579.
[3] Schmutz J., Hirt R., Lauener H.; *Helv. Chim. Acta*, 1952, 35: 1168-1178.
[4] Schmutz J., Lauener H., Hirt R.; *Helv. Chim. Acta*, 1951, 34: 767-779.
[5] Barker G., Ellis G., *J. Med. Chem.*; 1973, 6: 87-89.
[6] Cairns H., Fitzmaurice C., et al; *J. Med. Chem.*, 1972, 15: 583-589 .
[7] Setnikar I., Rawasi M., Da Re P., *J. Pharm. Exp. Ther.* 1960, 130: 356.
[8] Nagai H., Osuga K., Koda A.; *Jap. J. Pharmacol.* 1975, 25: 763-772.
[9] Kostka K.: *Chem. Anal.*, 1969, 14: 1145-1160.
[10] Kostka K.: *Rocz. Chem.*, 1973, 47: 305-313.
[11] Kostka K.: *Rocz. Chem.*, 1973, 47: 841-852.
[12] Kostka K., Zyner E.: *Chem. Anal.* 1979, 24: 103-108.
[13] Kostka K., Zyner E.: *Chem. Anal.* 1980, 25: 61-68.
[14] Kostka K., Zyner E.: *Kontakte* (Dormstadt), (1983) 30-37.
[15] Kirkpatrick D. S., Bishop S. H., *Biochemistry*, 1973, 12(15): 2829-2840.
[16] Korn E. D., Dearborn D. G., Wright P. L., ; *J. Biol. Chem.;* 1974, 11:3335-3341.
[17] Orstein P. L., Schaus J. M., Chambers J. W., et. al. *J. Med. Chem.*, 1989, 32: 827-832.
[18] Hays S. J., Bigge Ch. F., et al.; *J. Med. Chem.*, 1980, 33: 2916-2924.
[19] Yudelevic W.J., Komarow E.W., Ionin B.J.; *Khim. Farm.* 1985, 19: 668-685
[20] Kostka K., Pastuszko S., Porada M.: *Phosphorus, Sulfur, Silicon;* 1992, 71: 67-74.
[21] Basiński W., Jerzmanowska Z.: *Rocz. Chem.*, 1971, 48: 2217-2224.
[22] Basiński W., Jerzmanowska Z.: *Rocz. Chem.*, 1976, 50: 1067-1073.
[23] Jerzmanowska Z., Kostka K.: *Rocz. Chem.* 1963, 37: 413-427.
[24] Jerzmanowska Z., Kostka K.: *Rocz. Chem.* 1963, 37: 429-436.
[25] Kostka K., Nawrot J.: *Pol. J. Chem.*, 1980, 54: 15-21.
[26] Basiński W., Jerzmanowska Z.: *Rocz. Chem.*, 1974, 48: 989-998.
[27] Gray M., Smith D.: *Tetrahedron Lett.* 1980, 21: 859-860.
[28] Troev K., Borisov G.: *Phosphorus, Sulfur, Silicon;* 1987, 29: 129-145.
[29] US Pat. 2815345 (1953);ICA. 1958, 52: 5485.
[30] US Pat. 2824113 (1953); CA. 1958, 52: 11110
[31] US Pat. 3253036 (1966); CA. 1966 , 65: 5397
[32] Hill R., Macaulay G., MacLachlan U.: *J. Chem. Soc. Perkin Trans.*, I, 1987: 2209-2215.