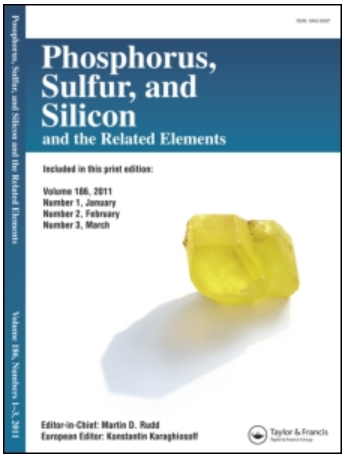

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4-DERIVATIVES COUMARIN-3-PHOSPHONIC ACIDS AND ESTERS

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In the Arbuzov reactions of 2'-bromoacetoxyphenone with trimethyl phosphite the derivatives in position 4 of 3-phosphonocoumarinic acids and esters were obtained.

Keywords: 4-substituted coumarin-3-phosphonic acids; synthesis of

In the course of a comprehensive study on the reactions of phenone bromoesters and bromoacetophenone esters with phosphites it has been demonstrated that, depending on the bromoderivative used, 3-phosphonic chromone derivatives[1] substituted in position 2, or 3-phosphonic coumarin derivatives substituted in position 4 are formed.

3-Phosphonic coumarin derivatives without the substituent in position 4 have been known for many years. Robinson and Addison were the first to report the synthesis of such a compound in 1966[2]. Coumarin-3-phosphonic acid was then obtained as a result of hydrolysis of the mixture of products yielded by the reaction of salicylic aldehyde with triethyl phosphonoacetate.

In 1985 Singh and Rogers[3] and independently in 1987 Chen Chin et al.[4] published the synthesis of a series of derivatives (substituted in the benzene ring) of diethyl ester of coumarin-3-phosphonic acid. The authors performed a condensation of an appropriate salicylic aldehyde derivative with triethyl phosphonoacetate in a pyridine medium, in the presence of titanium tetrachloride used as a catalyst.

Bouyssou and Chenault[5] obtained a series of 3-diethylphosphonocoumarinic and 3-oxodiphenylphosphinocoumarinic compounds using for the

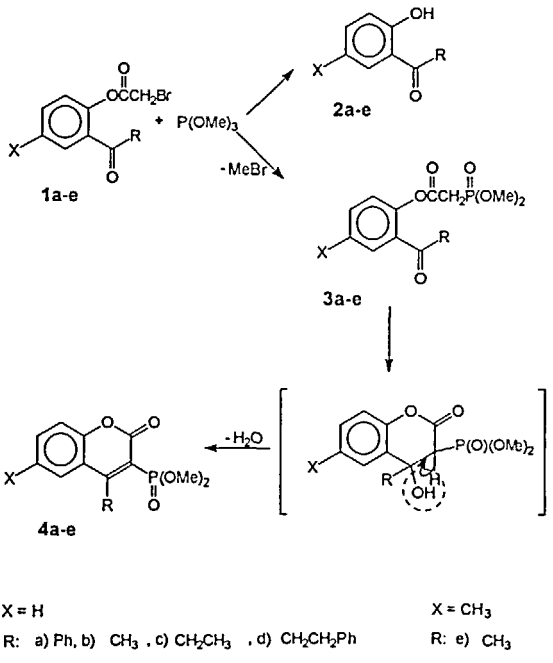
reaction appropriate derivatives of acetoxysalicylic aldehyde and ethyl ester of phosphinoacetic acid or trimethyl ester of phosphonoacetic acid. Detailed comparative studies on the reactions of salicylic aldehydes with phosphonoacetates were carried out by Bojilova et al.[6] In 1991 Bestmann and Lehnen[7]obtained 3-diethylphosphonocoumarins as a result of hydrolysis of imine, the product of reaction of N-phenyl-bis(diethylphosphono)-ketenoimine and sodium salt of salicylic aldehyde.

Phosphonic derivatives of coumarin in which phosphorus is not directly bonded with the α-pyrone group[8,9].

On analysing the mechanism of the synthesis of 3-phosphonic chromone derivatives[1] it was observed that the intramolecular condensation of the Arbuzov reaction product, 2′-acyloxy-2-(dimethylphosphono) acetophenone, to an appropriate chromone derivative occurs with the participation of the carbonyl group. The oxygen atom from the carbonyl group is eventually eliminated together with two hydrogens of the methylenophosphonic group as a water molecule.

The transpose of the electrophilic centre in a 2′-hydroxyphenone derivative by moving the bromine atom from the methylketone to the methylester group seems interesting. By analogy to the obtained phosphonic chromone derivatives, producing appropriate coumarin derivatives (depending on the phenone type) was expected.

In the reaction of 2′-bromoacetoxybenzophenone (**1a**) and trimethyl phosphite the mixture of compounds was obtained, from which two compounds were isolated and identified by means of column chromatography. The first of them with highest R_f =0.75, was identified as 2′-hydroxybenzophenone (**2a**). The second one, (R_f=0.40),crystalline, demonstrated a characteristic signal in ^{31}P-NMR spectrum with a chemical shift δ=13.9 ppm, whereas the ^{1}H-NMR spectrum consisted of two groups of signals. A multiplet of nine protons was observed within the range of chemical shifts δ=7.01–7.62 ppm, as well as a doublet originating from six methoxyl protons associated with phosphorus, whose chemical shift was δ=3.56 ppm and coupling $^{3}J_{PH}$=11.4 Hz. In the IR spectrum there were characteristic absorption bands at 1710 cm^{-1} (C=0) and 1250 cm^{-1}(P=0). Spectroscopic properties and results of elemental analysis as well as the presence of m/z=330 molecular peak of 100% intensity in the MS spectrum enabled us to state that the obtained compound was 4-phenyl-3-dimethylphosphonocoumarin (**4a**) (Scheme 1).



SCHEME 1

In the post-reaction mixture no product of Perkov reaction was detected. This fact confirms the general principle that α-halogenoesters do not form the product of Perkov transformation[10–12].

In order to confirm the general character of the observed reaction, the reactions of trimethyl phosphite with other 2′-bromoacetoxyphenones were investigated. The following bromoderivatives, obtained as a result of generally known reaction of bromoacetyl bromide with sodium salts of appropriate phenones, were used for the reactions:

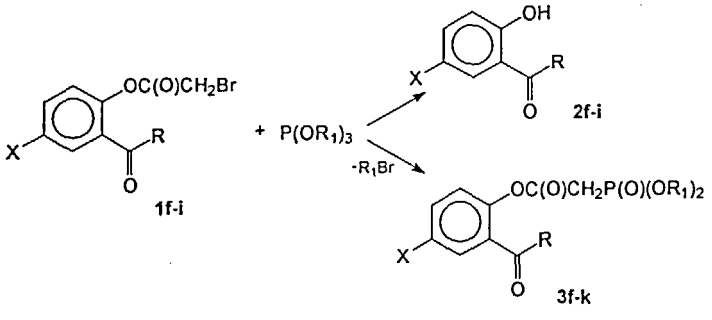
- 2′-bromoacetoxyacetophenone (**1b**)
- 2′-bromoacetoxypropiophenone (**1c**)
- 2′-bromoacetoxy-3-phenylpropiophenone (**1d**)
- 2′-bromoacetoxy-5-methylacetophenone (**1e**)

As a result of the performed reactions, two products were obtained from each. The first of them, with higher R_f, did not contain phosphorus in their

structures, and their ^{1}H-NMR spectra and physical properties corresponded with respective 2′-hydroxyphenones (**2b-e**). The compounds of the second group were identified as 3-dimethylphosphonocoumarins substituted in position 4 (**4b-e**) (Scheme 1).

Using the above described procedure of separation of the post-reaction mixture (column chromatography) it was impossible to isolate the intermediate products (**3a-e**). It was found that these compounds were present in the post-reaction mixture (TLC, ^{31}P-NMR). In the course of chromatographic separation on silicagel they undergo a quantitative change into coumarin derivatives. Extraction of the post-reaction mixture with petroleum ether led to the isolation of homogeneous compounds **3b** and **3c**, which in the presence of silicagel or aluminium oxide underwent changes into coumarin derivatives **4b** and **4c**.

By analogy to the reactions of phenone derivatives, the reactions of methyl-2′-bromoacetoxybenzoate (**1f**) and amides of 2′-bromoacetoxybenzoic acid (**1g-i**) with trialkyl phosphites were investigated. The isolated compounds were either methyl-2′-dimethylphosphonoacetoxybenzoate (**3f**) and methyl ester of salicylic acid (**2f**), or amide of 2′-dimethylphosphonoacetoxybenzoic acid (**3g-k**) and amide of salicylic acid (**2g-i**). (Scheme 2).

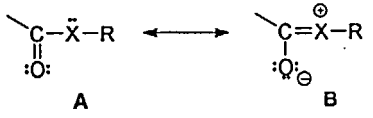


1f R = OCH_3, X = H
1g R = $N(CH_2)_4$, X = H
1h R = NHPh, X = H
1i R = NHPh, X = Cl

3f R = OCH_3, X = H, R_1 = Me
3g R = $N(CH_2)_4$, X = H, R_1 = Me
3h R = NHPh, X = H, R_1 = Me
3i R = NHPh, X = Cl, R_1 = Me
3j R = NHPh, X = H, R_1 = Et
3k R = NHPh, X = Cl, R_1 = Et

SCHEME 2

Compounds **3** were subjected to attempts of cyclization under various conditions (high temperature, presence of alkaline compounds NaH, Na_2CO_3 or acid ones: HBr in anhydr. acetic acid). In none of the above mentioned cases phosphonic coumarin derivatives were obtained. In the HBr/CH_3COOH medium only the formation of respective phosphonic acids was observed. The lack of reaction leading to formation of coumarin derivatives may be explained by the possibility of two mesomeric structures **A** and **B**, in which the carbonyl carbon atom of the amide or ester group is enriched with electrons which makes it unable to form a bond with the emerging carboanion of the acetyl group

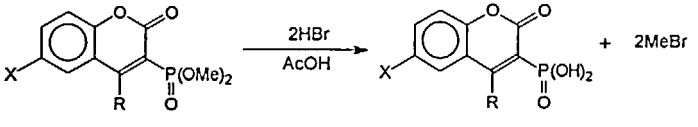


A **B**

X = O, NH

R = CH_3, Ph, CH_2Ph

The methyl esters of the respective coumarin-3-phosphonic acids (**4a-e**) obtained for the first time were subjected to non-hydrolytic transformation to acids according to the general method of obtaining phosphonic acids from their esters[13], using HBr in anhydr. acetic acid. Respective coumarin-3-phosphonic acids were obtained with a good yield (**5 a-e**) (Scheme 3)



4a-e **5a-e**

X = H

R: a) Ph, b) CH_3, c) CH_2CH_3, d) CH_2CH_2Ph

X = CH_3

R: e) CH_3

SCHEME 3

After crystallization from methanol, colourless products with high melting points, exceeding 220°C, were obtained. In their ^{1}H-NMR spectra there were signals associated with respective substituents at C-4 carbon of coumarin, broad signals coming from two exchangeable protons (O-H), located next to phosphorus within the δ=7.2–10.0 ppm range of chemical shifts, and a multiplet of aromatic protons within the δ=7.2–8.45 range. In the IR spectra characteristic absorption bands are present within the ranges: 1650–1680 cm^{-1} (C=O), 1185–1200 cm^{-1}(P=O). Elemental analysis fully confirmed the percentage composition of the compounds.

EXPERIMENTAL

Melting points were determined in Electrothermal 1A9100 apparatus and were not corrected. The IR spectra were obtained using a Pye-Unicam 200 G spectrophotometer in the discs with KBr. The ^{1}H-NMR spectra were obtained on a Varian EM-360 spectrophotometer (60MHz). The ^{31}P-NMR spectra were obtained by means of a Brucker AC 200 F spectrophotometer (81 MHz) with H_3PO_4 as an internal standard. The MS spectra were obtained with an LKB 2091 spectrophotometer (70 eV ionization energy).

4-Substituted 3-dimethylphosphonocoumarins (4a-e)

General method

Into 0.005 mol of a respective 2′-bromoacetophenone (**1a-e**), heated to 110°C (oil bath) and stirred, 0.70 cm^3 (0.006 mol) of trimethyl phosphite was added in drops. Following the addition of phosphite, the post-reaction mass was heated for 30 min and excess phosphite was distilled off. A yellow,thick oil

A) was separated on a chromatographic column (150g of Kieselgel $60F_{254}$ gel, 0.063–0.200 mm, MERCK) in a chloroform:acetone system (5 :1). The composition of fractions was controlled by means of TLC. The obtained precipitates of 3-dimethylphosphonocoumarins (**4 a-e**) were crystallized from ethyl eter or ethyl ether:methanol mixture (20:1). Melting points, spectroscopic data, results of elemental analysis and yields of the obtained 3-dimethylphosphonic coumarin derivatives (**4a-e**) have been presented in Table I;

TABLE I Substituted coumarin 3-dimethylphosphonoesters

Comp. No.	Sum. form. (Mol. mass)	M.p. (°C) Yield (%)	Analyses % Cald / Found C	H	P	IR ν(cm^{-1})	^{31}P NMR[1] δ(ppm)	^{1}H NMR[1] δ (ppm)	MS m/z(%)
4a	$C_{17}H_{15}O_5P$ (330.28)	128 - 130 28	61.82 61.87	4.58 4.60	9.38 9.52	1025–1065 (POC, COC) 1250 (P=O) 1710 (C=O)	13.9	7.01 – 7.62(m, 9H, aromat), 3.56(d, 6H, $^{3}J_{PH}$=11.4Hz, $POCH_3$)	331(19), 330(M+*, 100), 329(36), 299(23), 298(27), 297(18), 285(43), 270(27), 236(16), 235(75), 234(24), 221(23), 220(24), 207(35), 194(33), 165(49), 164(20), 163(21), 93(50)
4b	$C_{12}H_{13}O_5P$ (268.21)	111 – 112 38	53.74 53.60	4.89 4.90	11.55 11.41	1030–1090 (POC, COC) 1260 (P=O) 1700 (C=O	16.0	7.00 – 7.80(m, 4H, aromat.), 3.80(d, 6H, $^{3}J_{PH}$=12Hz, $POCH_3$), 2.83(d, 3H, $^{4}J_{PH}$=2.5Hz, CH_3).	268(M+*, 69), 253(26), 237(16), 236(67), 193(15), 174(27), 173(100), 160(23), 147(14), 145(35), 132(17), 131(54), 115(14), 109(17), 103(31), 102(37), 93(13),
4c	$C_{13}H_{15}O_5P$ (282.23)	106 – 108 24	55.32 55.59	5.36 5.52	10.97 10.70	1025–1085 (POC, COC) 1240 (P=O) 1700 (C=O	15.7	7.30 – 7.90(m, 4H, aromat.), 3.90(d, 6H, $^{3}J_{PH}$=12Hz, $POCH_3$), 3.53(dq, 2H, $^{4}J_{PH}$=2.5Hz CH_2), 1.37(t, 3H, CH_3).	-
4d	$C_{19}H_{19}O_5P$ (358.33)	141 – 142 29	63.68 63.36	5.30 5.48	8.64 8.43	1020–1065 (POC, COC) 1240 (P=O) 1710 (C=O	15.7	7.10 – 8.20(m,9H, aromat.), 3.60 – 4.20(m, 8H, $POCH_3$+ CH_2), 3.00(m, 2H, CH_2).	-
4e	$C_{13}H_{15}O_5P$ (282.23)	88.5 – 90 36	55.32 55.23	5.36 5.43	10.97 10.82	1030–1090 (POC, COC) 1260 (P=O) 1700 (C=O	16.7	7.23 – 7.60(m, 3H, aromat.) 3.90(d, 6H, $^{3}J_{PH}$=12Hz, $POCH_3$), 2.97(d, $^{4}J_{PH}$=2.5Hz, CH_3), 2.46 (s, 3H, CH_3),	282(M+*, 6.6), 250(18), 249(100), 172(7.8), 134(48), 100(15), 78(12).

[1]-in $CDCl_3$

B) was subjected to multiple extractions with petroleum ether to eliminate 2′-hydroxyphenone. The solidified crude phosphonoacetoxyphenone (**3b**) was recrystallized from ethyl ether. In this way was obtained

2′-(dimethylphosphonoacetoxy)acetophenone (3b)

A colourless, macrocrystalline compound, m.p. 56–58°C, yield 74%. Elemental analysis for the $C_{12}H_{15}O_6P$ formula (286.22)
calc. C 50,35% H 5,28% P 10,82%
found C 50,31% H 5,52% P 11,58%
^{1}H-NMR ($CDCl_3$) δ(ppm) 2.57 (s, 3H, CH_3CO), 3.30 (d, 2H, CH_2P, $^2J_{HP}$=21Hz), 3.87 (d, 6H, CH_3O,^{3} J_{HP}=11Hz), 7.12–7.87 (m, 4H, aromat.)
^{31}P-NMR ($CDCl_3$) δ(ppm) 22.1
IR (KBr) ν(cm^{-1}) 1245 (P=O), 1690, 1755 (C=O)

2′-(dimethylphosphonoacetoxy)propiophenone (3c)

A light-yellow oil, yield 68%.
Elemental analysis for the $C_{13}H_{17}O_6P$ formula
calc. C 52,00% H 5,71% P 10,32%
found C 51,06% H 5,74% P 9,34%
^{1}H-NMR ($CDCl_3$) δ(ppm) 1.17 (t, 3H, CH_3CH_2, $^3J_{HH}$=7Hz), 2.93 (q, 2H, CH_3CH_2), 3.30 (d, 2H, CH_2P, $^2J_{HP}$=21Hz), 3,87 (d, 6H, CH_3O, $^3J_{HP}$=11Hz), 7.12–7.84 (m, 4H, aromat.) ^{31}P-NMR ($CDCl_3$) δ(ppm) 22.2
IR (KBr) ν(cm^{-1}) 1270 (P=O), 1690, 1760 (C=O)

4-Substituted coumarin-3-phosphonic acids (5a-e)

General method

The reaction was conducted at room temperature. To 0.005 mol of a respective ester **4 a-e** 1.70 cm^3 (0.012 mol) of 40% HBr in anhydr. acetic acid was added. After ca 10 min a clear, light-yellow, thick oil was formed, from which a precipitate crystallized. After ca 20 h a colourless precipitate was filtered off which was then crystallized from methanol or ethanol. Melting points, spectroscopic data, results of elemental analysis and yields of the obtained coumarin-3-phosphonic acids (**5a-e**) have been presented in Table II.

TABLE II Substituted coumarin phosphonic acids

Comp. No	*Sum. form. (Mol. mass.)*	*M. p. (°C) Yield (%)*	*Analyses % Cald/Found*			*IR ν(cm^{-1})*	*^{1}H-NMR$^{1)}$ δ(ppm)*
			C	*H*	*P*		
5a	$C_{15}H_{11}O_5P$ (302.22)	266+267 79	59.61 59.67	3.67 3.52	10.25 10.08	1185(P=O) 1650(C=O)	9.45(s, 2H, OH), 7.10+8.30(m, 9H, aromat.).
5b	$C_{10}H_9O_5P$ (240.15)	244+245 92	50.01 49.83	3.78 3.76	12.90 12.81	1195(P=O) 1675(C=O)	7.40+8.00(m, 4H, aromat.), 7.20(s, 2H, OH), 2.86(d, 3H, $^{4}J_{PH}$=2.5Hz, CH_3).
5c	$C_{11}H_{11}O_5P$ (254.18)	229+230 93	51.98 51.93	4.36 4.32	12.18 12.10	1200(P=O) 1680(C=O)	10.00(s, 2H, OH), 7.20+8.30(m, 4H, aromat.), 3.45(m, 2H, CH_2), 1.13(t, 3H, CH_3).
5d	$C_{17}H_{15}O_5P$ (330.27)	225+226 94	61.82 61.59	4.55 4.27	9.38 9.25	1190(P=O) 1655(C=O)	9.73(s, 2H, OH), 7.10+8.33(m, 9H, aromat.), 3.73(m, 2H, CH_2), 2.90(m, 2H, CH_2).
5e	$C_{11}H_{11}O_5P$ (254.18)	248+249 91	51.98 51.82	4.36 4.25	12.18 12.06	1190(P=O) 1660(C=O)	9.62(s, 2H, OH), 7.25+7.70(m, 3H, aromat.), 2.96(d, 2H, $^{4}J_{PH}$=2.6Hz, CH_3), 2.44(t, 3H, CH_3).

$^{1)}$-in DMSO-d_6

TABLE III Ester (3f) and amides (3g-k) of 2'-dialkylphosphonoacetoxybezioc acid

Comp. No	*Sum. Form. (Mol mass)*	*M.p. (°C) Yield (%)*	*Analyses % Calc/Found*			*IR ν(cm^{-1})*	*^{31}P NMR$^{1)}$ δ (ppm)*	*^{1}H NMR$^{1)}$ δ(ppm)*
			C	*H*	*P*			
3f	$C_{12}H_{15}O_7P$ (302,23)	75–76 57	47,65 47,81	4,97 5,08	10,25 10,18		22,20	3,31(d, 2H, CH_2P, $^2J_{PH}$= 21 Hz); 3,87(d, 6H, $2POCH_3$); 3,87(s, 3H, OCH_3).
3g	$C_{15}H_{20}NO_6P$ (341,29)	- 48	52,79 52,10	5,91 6,03	9,07 9,19	1260(P=O) 1670, 1720(C=O)	21,91	1,86–1,93(m, 4H, CH_2-pyrrolidyl, 3,19(d, 2H, CH_2, $^2J_{PH}$=18,0 Hz); 3,31–3,52(m, 4H, CH_2-pyrrolidyl), 3,64(d, 6H, CH_3,$^3J_{PH}$=8,0 Hz); 7,13–7,42(m, 4H, aromat.).
3h	$C_{17}H_{18}NO_6P$ (363,29)	135 – 137 50	56,20 56,30	4,99 5,01	8,52 8,76	1240(P=O) 1670, 1760(C=O) 3212(NH)	24,85	3,18(d, 2H-CH_2-, $^2J_{PH}$=21,4 Hz); 3,73(d, 6H, -CH_3, $^3J_{PH}$=11,3 Hz); 7,12–7,85(m, 9H, aromat.); 8,29(s, 1H, NH).
3i	$C_{17}H_{17}NO_6PCl$ (397,79)	136–138 45	51,33 51,46	4,31 4,51	7.79 8,01	1230(P=O) 1610, 1630(C=O)	24,86	3,06(d, 2H, CH_2, $^2J_{PH}$=21,6 Hz); 3,69(d, 6H, -CH_3, $^3J_{PH}$=11,27 Hz); 7,08–7,98(m, 8H, aromat.); 10,45(s, 1H, NH)
3j	$C_{19}H_{22}NO_6P$ (391,35)	104 – 105 45	58,30 58,26	5,67 5,42	7,91 –	1235(P=O) 1680, 1760(C=O) 3200(NH)	18,99	1,36(t, 6H, -CH_3); 3,15(d, 2H, CH2, $^2J_{PH}$=21,4 Hz); 4,11(dq, 4H, CH_2-CH_3): 7,03–7,87(m, 9H, aromat.); 8,47(s, 1H, 1NH).
3k	$C_{19}H_{21}NO_6PCl$ (425,84)	226- 227 48	53,59 53,74	4,97 5,04	7,27 7,41	1280(P=O) 1640, 1750(C=O) 2340–3160, 3288(NH)	19,85	1,23(t, 6H, CH_3): 3,34(d, 2H, -CH_2-, $^2J_{PH}$=21,4 Hz), 4,06(dq, 4H, -CH_2); 7,21–7,74(m, 8H, aromat.); 10,36(s, 1H, NH).

[1)] in $CDCl_3$

Ester (3f) and amides (3g-k) of 2′-dialkylphosphonoacetoxybenzoic acid

To 0.01 mol of 2′-bromoacetoxy derivative of benzoic acid (**1f-i**) heated to 100°C, 0.012 mol of trialkyl phosphite was added in drops during the period of 15 min. A strong exothermic effect of the reaction was observed. After ca 30 min of heating, excess phosphite was distilled off. From the cooled thick, light-yellow liquid, a precipitate was obtained after ca 30 min, which was then recrystallized from ethyl ether or from ether-methanol mixture. Melting points, yields, results of elemental analysis and spectroscopic data have been presented in Table III

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