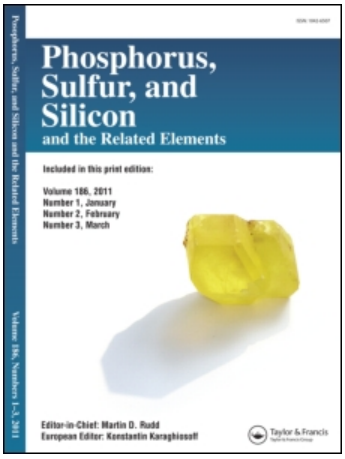

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DIETHYL 2,3-DIHYDRO-4H-1,3-BENZOXAZIN-4-ONE-2-PHOSPHONATE AND ITS REACTIONS

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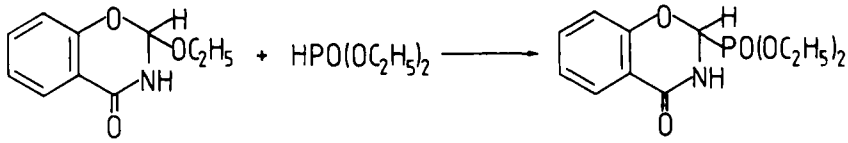
Diethyl 2,3-dihydro-4H-1,3-benzoxazin-4-one-2-phosphonate was obtained and its conversions with nucleophiles (lithium borohydride, diethyltrimethylsilyl phosphite, diphenylphosphine oxide, benzylamine and pyrrolidine) were studied. The attempts of its dehydrogenation were described.

Key words: 2,3-Dihydro-4H-1,3-benzoxazin-4-one-2-phosphonate; reaction with nucleophiles.

Organophosphoric derivatives of 1,3-benzoxazin-4-one have not been described so far. This work has been directed towards the synthesis and investigation of chemical properties of diethyl 2,3-dihydro-4H-1,3-benzoxazin-4-one-2-phosphonate (**1**). This compound has been synthesised by us in the reaction of 2-ethoxy-2,3-dihydro-4H-1,3-benzoxazin-4-one (**2**)[1] with diethyl phosphite according to Scheme 1.

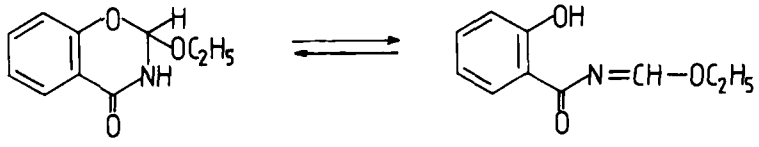


2 1

Scheme 1

This project is connected with our research program on synthesis of phosphoroorganic compounds exhibiting biological activity and chelating properties. Our interest in this class of compounds results from structural analogy to chromone and 3-azachromone—compounds which are biologically active and also to pharmacologically active derivatives of cyclophosphamide.[2]

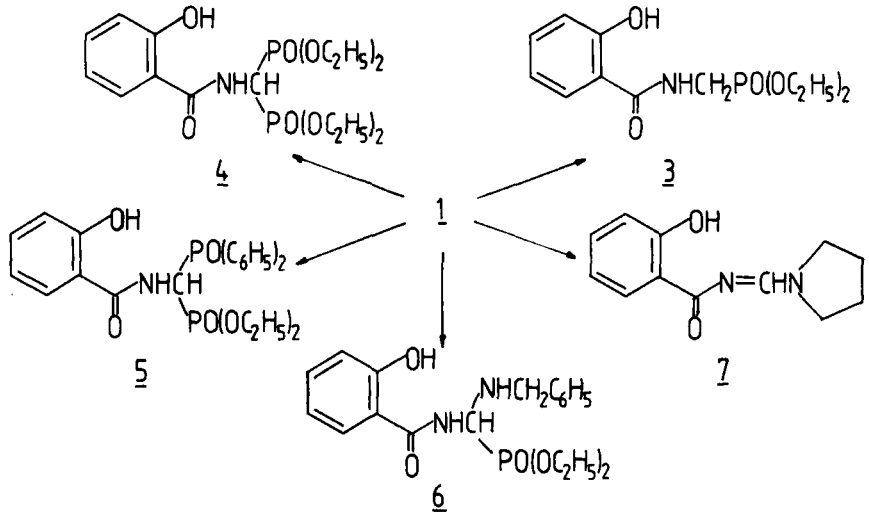
The structure of compound **1** was established on the basis of elemental analysis, MS, IR and NMR (^1H, ^{13}C, ^{31}P). These results confirm the bicyclic structure of **1**, as it was also suggested by Treppendahl and Jakobsen for compound **2**. Compounds **1** and **2** differ in test reaction with $FeCl_3$: whereas **2** forms instantly a dark-violet coloured complex with iron (III) compound **1** gives a negative result.



2a 2b

Scheme 2

Compound **1** reacts with several nucleophilic reagents. Thus, with lithium borohydride it forms diethyl N-salicyloylaminomethane-phosphonate (**3**). The reaction of **1** with diethyl trimethylsilyl phosphite leads to tetraethyl N-salicyloylaminomethane-bis-phosphonate (**4**) and in the reaction of **1** with diphenylphosphine oxide compound **5** is formed. In reaction of **1** with primary amine (benzylamine) compound **6** is obtained whereas secondary amine (pyrrolidine) caused elimination of diethyl phosphite with formation of formamidine **7**.

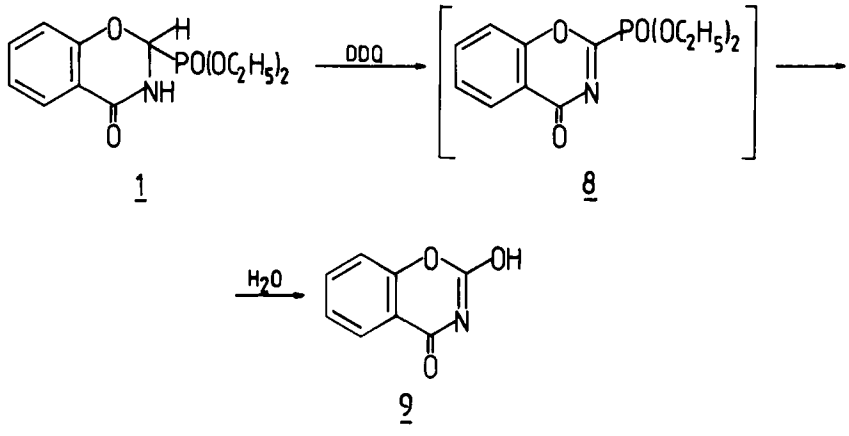


Scheme 3

These results of reactions of **1** with nucleophilic reagents suggested undoubtedly that the nucleophile attacks the C-2 carbon of azachromone system, which is also in accordance with the general mode of 1,4-benzopyrone (chromone) reactions with nucleophile agents.[3]

Compound **1** has also been found to be stable in a broad range of pH (2 to 12) of its aqueous-alcoholic solutions and also exhibits strong stability against dehydrogenation to 2-phosphono-3-azachromone (**8**). Thus, the attempts to dehydrogenate **1** using sulphur and also selenic dioxide as catalysts were unsuccessful at ambient temperature, and caused uncontrolled decomposition of **1** at higher temperatures. Attempts of controlled thermal decomposition of **1**, performed in derivatograph, up to 200°C, revealed no difference in the course of reaction carried out with and without catalyst (10% Pd/C)—in both cases no trace of the desired **8** was found. The thermogravimetric curves were identical. The thermal decomposition of **1** under reduced pressure (0.5 hPa) gave almost exclusively diethyl phosphite. The oxidation of **1** by means of trityl perchlorate leads quantitatively to diethyl triphenylmethanephosphonate evidently due to elimination of diethoxyphosphonyl anion instead of the desired elimination of hydride anion. The most interesting results have been obtained in dehydrogenation of **1** by means of DDQ. Thus, H_2DDQ was isolated almost quantitatively, from the reaction mixture, which contained also a new organophosphoric compound, homogeneous in ^{31}P-NMR ($\delta = -3.7$ ppm). The attempts for its

isolation led always to 2-hydroxyazachromone (**9**) due to elimination of phosphonyl moiety. Compound **9** has also been obtained in oxidation of **1** by means of H_2O_2, performed in alkaline solution. Also in this case 2-hydroxyazachromone (**9**) can only be formed, by conversion of intermediary 2-phosphono-3-azachromone (**8**) formed in the first stage of reaction.



1 8 9

Scheme 4

EXPERIMENTAL

All melting points are uncorrected. Solvent and commercial reagents were purified by conventional methods before use. IR spectra were taken on a Pye-Unicam 200G spectrometer, ^{1}H NMR spectra were recorded at 60 MHz using a Varian EM-360 spectrometer. ^{13}C NMR—at 25.2 MHz on a Tesla BS 567A and ^{31}P NMR—at 24.3 MHz on a FT Jeol FX-60 (external standard H_3PO_4). Mass spectra were measured on a LKB 2091 Mass Spectrometer (at 70 eV ionizing energy). Termogravimetric measurements were performed using a Derivatograph Q 1500 Hungarian Optical Works. TLC analysis were obtained on silica gel plates (Art. 5554 Merck).

Diethyl 2,3-dihydro-4H-1,3-benzoxazin-4-one-2-phosphonate (**1**). The mixture of 2-ethoxy-2,3-dihydro-4H-1,3-benzoxazin-4-one (**2**)[1] (7.0 g, 0.036 mole) and diethyl phosphite (40 ccm, 0.3 mole) was heated at 130°C (oil bath temp.) for 3 hrs. The excess of diethyl phosphite was evaporated under reduced pressure (14 hPa, 120°C of oil bath) to an oily residue, which solidified overnight. The crude **1** was triturated with ether, filtered and recrystallized from toluene (or benzene-cyclohexane mix.) giving 6.0 g of **1**, mp. 129–131°C, yield 58%.

$C_{12}H_{16}NO_5P$	calc.	C 50.53	H 5.65	N 4.91	P 10.86%
(285.2)	found	50.42	5.65	4.94	10.55

MS: m/z (%) = 285(M^+, 9.7), 148(M-OP/OEt/$_2$, 100), 121(45);
IR(KBr): ν(cm^{-1}) = 3200, 3100, 1680, 1615, 1250, 1020, 765;
^{1}H-NMR($CDCl_3$): δ(ppm) = 1.33(t, 6H, $\mathbf{CH_3}CH_2O$, $^3J_{HH}$ = 7 Hz), 4.20 (dq, 4H, $CH_3\mathbf{CH_2}O$, $^3J_{HH}$ = 7 Hz, $^3J_{HP}$ = 7 Hz), 5.63(d, 1H, CHP, $^2J_{HP}$ = 2 Hz), 6.80–8.10(m, 4H_{arom}), 8.00(1H, NH, broad);
^{13}C-NMR($CDCl_3$): δ(ppm) = 16.4; 64.0, 79.5(d, HCP, $^1J_{CP}$ = 186 Hz), 116.5, 118.2, 123.0, 128.0, 134.8, 157.2, 162.5;
^{31}P-NMR($CHCl_3$): δ(ppm) = 12.0.

Diethyl N-salicyloylaminomethanephosphonate (**3**). Into the solution of **1** (5.0 g, 1.75 mmole) in anhydrous THF (70 ccm) lithium borohydride (1.0 g, 45.5 mmole) was gradually added (foam formation). This suspension was stirred at room temperature for 10 hrs and the reaction was quenched with ethanol (96%). The solvents were evaporated under reduced pressure, the solid residue was dissolved in chloroform (80 ccm) and this solution was neutralized by means of saturated ammonium chloride aqueous solution. The phases were separated, the aqueous layer was additionally extracted

with chloroform (3 × 30 ccm) and combined organic extracts were dried with anh. sodium sulphate. Drying agent was filtered off, the filtrate was concentrated under reduced pressure (20 hPa and 0.1 hPa, 50°C of bath temp.) to an oily residue which solidified during 2 hrs. The crude **3** was recrystallized from diisopropyl ether giving 3.0 g of crystalline **3** mp. 70–71°C, yield 60%.

$C_{12}H_{18}NO_5P$	calc.	C 50.17	H 6.32	N 4.88	P 10.78%
(287.3)	found	50.19	6.30	5.03	10.56%

MS: m/z (%) = 287(M^+, 43), 121(100), 150(12);
IR(KBr): $\nu(cm^{-1})$ = 3250, 2980, 1640, 1590, 1210, 1020, 760;
^{1}H-NMR(CD_3COCD_3): δ(ppm) = 1.30(t, 6H, $\mathbf{CH_3}CH_2O$), 3.90(m, 2H, $NH\mathbf{CH_2}P$), 4.17(dq, 4H, $CH_3\mathbf{CH_2}O$), 6.67–8.03(m, $4H_{arom}$), 8.70(1H, NH, broad), 12.37(1H, OH, broad);
^{13}P-NMR(CH_3COCH_3): δ(ppm) = 22.1.

Tetraethyl N-salicyloylaminomethane-bis-phosphonate (**4**). To the suspension of **1** (4.0 g, 0.014 mole) in anhydrous toluene (30 ccm) was added through a septum cup (argon atmosphere) diethyltrimethylsilyl phosphite (3 ccm). The reaction mixture was refluxed for 7 hrs then quenched with water (0.5 ccm). The mixture was concentrated under reduced pressure (20 hPa and 0.2 hPa, 50°C) to an oily residue which solidified within several days. The crude **4** was recrystallized from benzene-cyclohexane solution giving 2.85 g of crystalline, pure **4** mp. 108–110°C, yield 48%.

$C_{16}H_{27}NO_8P_2$	calc.	C 45.39	H 6.43	N 3.31	P 14.63%
(423.3)	found	45.41	6.41	3.53	14.29%

MS: m/z (%) = 423(M^+, 11), 377(100), 121(81);
IR(KBr): $\nu(cm^{-1})$ = 3350, 3000, 1670, 1610, 1535, 1270, 1220, 1050, 770;
^{1}H-NMR($CDCl_3$): δ(ppm) = 1.23 and 1.35(2t, 12H, $\mathbf{CH_3}CH_2O$), 4.17(m, 8H, $CH_3\mathbf{CH_2}O$), 5.32(dt, 1H, $NH\mathbf{CH}P_2$, $^3J_{HH}$ = 10 Hz, $^2J_{HP}$ = 22 Hz), 6.67–7.93 (m, $4H_{arom}$), 8.27(d, 1H, NH, $^3J_{HH}$ = 10 Hz), 11.17(s, 1H, OH);
^{13}C-NMR($CDCl_3$): δ(ppm) = 16.3, 43.5(t, HCP_2, $^1J_{CP}$ = 148 Hz), 64.1, 115.2, 118.0, 119.4, 128.3, 134.3, 159.6, 167.6;
^{31}P-NMR($CHCl_3$): δ(ppm) = 15.5.

Diethyl N-salicyloyl-1-diphenylphosphinylaminomethanephosphonate (**5**). The mixture of **1** (0.56 g, 2 mmoles), diphenylphosphine oxide (0.40 g, 2 mmoles) and potassium t-butoxide (0.05 g, 0.5 mmole) was refluxed under an argon atmosphere for 8 hrs. After cooling the crystalls of **5** were filtered off and recrystallized from ethanol (96%); 0.15 g of pure **5** was obtained, mp. 217–220°C, yield 15%.

$C_{24}H_{27}NO_6P_2$	calc.	C 59.14	H 5.58	N 2.87	P 12.71%
(487.4)	found	58.74	5.35	2.93	12.74%

MS: m/z (%) = 487(M^+, 22), 469(100), 441(31), 202(30), 121(90);
IR(KBr): $\nu(cm^{-1})$ = 3290, 3000, 1650, 1540, 1260, 1025, 760, 730, 700;
^{1}H-NMR(CF_3COOH): δ(ppm) = 1.27(t, 6H, $\mathbf{CH_3}CH_2O$), 4.20(dq, 4H, $CH_3\mathbf{CH_2}O$), 6.23(m, 1H, PCHP), 6.80–8.35(m, $14H_{arom}$), 8.95(d, 1H, NH);
^{31}P-NMR(CF_3COOH): δ(ppm) = 41.3(d, $^2J_{PP}$ = 13 Hz) and 17.3(d).

Diethyl N^1-benzyl-N^2-salicyloyldiaminomethanephosphonate (**6**). The suspension of **1** (0.70 g, 2.5 mmole) in benzene (8 ccm) was treated with benzylamine (0.25 g, 2.5 mmole) and this mixture was stirred for 16 hrs (TLC control). After evaporation under reduced pressure (20 hPa, 40°C) the obtained solid residue was crystallized from ethanol (96%) giving 0.55 g of pure 6 mp. 102–103°C, yield 56%.

$C_{19}H_{25}N_2O_5P$	calc.	C 58.16	H 6.42	N 7.14	P 7.89%
(392.4)	found	58.13	6.80	6.99	7.94%

MS: m/z (%) = 285(M-$NHCH_2C_6H_5$,10), 255(M-$OP/OC_2H_5/_2$, 23), 121 (66), 91(100);
IR(KBr): $\nu(cm^{-1})$ = 3300, 2900, 1530, 1245, 1050, 755, 710;
^{1}H-NMR($CDCl_3$): δ(ppm) = 1.13 and 1.35(2t, 6H, $\mathbf{CH_3}CH_2O$), 2.67(s, 1H, $\mathbf{NH}CH_2C_6H_5$), 3.87(s, 2H, $N\mathbf{CH_2}C_6H_5$), 4.08(m, 4H, $CH_3\mathbf{CH_2}O$), 5.33(dd, 1H, $NH\mathbf{CH}$/NH/P, $^3J_{HH}$ = 9 Hz, $^2J_{HP}$ = 16 Hz), 6.67–7.92(m, $4H_{arom}$), 7.20(s, $5H_{arom}$), 8.67(d, 1H, $CO\mathbf{NH}CH$, $^3J_{HH}$ = 9 Hz), 12.30(S, 1H, OH);
^{31}P-NMR($CHCl_3$): δ(ppm) = 18.3.

N-salicyloylpyrrolidineformamidine (**7**). The suspension of **1** (1.40 g, 5 mmoles) in anh. ethanol

(8 ccm) was treated with pyrrolidine (0.37 g, 5 mmoles) and this mixture was stirred at room temperature for 16 hrs (TLC control). During this time yellow crystals precipitated from the solution. They were filtered off and the filtrate was concentrated to 3 ccm giving a second crop of crystals. The combined fractions of crude **7** were purified by recrystallization from ethanol (96%) giving 0.63 g of **7**, mp. 127–128.5°C, yield 58%.

$C_{12}H_{14}N_2O_2$	calc.	C 66.03	H 6.47	N 12.83%
(218.2)	found	66.36	6.52	12.81%

MS: m/z (%) = 218(M^+, 36), 148(M-NC_4H_8, 19), 121(28), 70(100); IR(KBr): $\nu(cm^{-1})$ = 2940, 1660, 1600, 1460, 1320, 775, 710;
^{1}H-NMR($CDCl_3$): δ(ppm) = 1.93(m, 4H), 3.57(m, 4H), 6.77, 7.27 and 8.00(m, $4H_{arom}$), 8.80(s, 1H, N=CH), 12.70(1H, OH, broad).

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