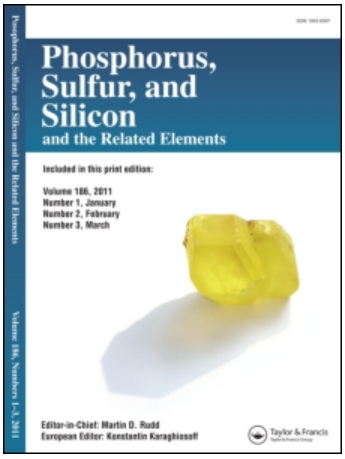

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Dobromir D. Enchev[a]
[a] Department of Organic Chemistry, Faculty of Chemistry, "Bishop Konstantin Preslavski" University, Bulgaria

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NEW PHOSPHORUS DERIVATIVES OF SALICYLIC ACID

DOBROMIR D. ENCHEV*

Department of Organic Chemistry, Faculty of Chemistry, "Bishop Konstantin Preslavski" University, 9700 Shoumen, Bulgaria

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The chemistry of phosphorus derivatives of salicylic acid has been revived and the synthesis of alkadienephosphonate derivatives of salicylic acid is reported.

Keywords: salicylic acid; allenephosphonates; alkadienephosphonate derivatives

INTRODUCTION

The acyl derivatives of salicylic acid are well known with their applications as medicines. The analgetic properties of acetylsalicylic acid are well known[1].

On the other hand the wide scope of application of the organophosphorus compounds as physiological active substances are also well documented[2].

In general the combination of the fragments of both salicylic and organo-phosphorus derivatives in one molecule would be of particular interest from the point of view of the possibilities of synthesis of biologically active compounds.

The chemistry of the phosphorylated derivatives of salicylic acid was summarized in 1992 by Russian autors[3]. There are a number of synthesized phosphorylated derivatives of salicylic acid but there are no publications concerning the synthesis of allenephosphonate derivatives of salicylic acid.

* Correspondence Author.

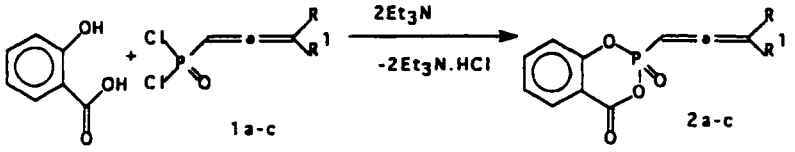
The salicylic acid has two functional groups capable for interaction with phosphorus in its tri-[4], tetra-[5], or pentacoordinated[6] state. As a result there are reported a number of methods for the preparation of phosphorus derivatives of salicylic acid.

RESULTS AND DISCUSSION

Having in mind the well known high reactivity of the dichlorides of 1,2-alkadienephosphonic acids in the substitution reactions[7–16], we tried very successfully to synthesize the salicylic derivatives of 1,2-alkadienephosphonic acids.

The reaction take place in benzene by heating to 50°C.

The reaction follows the scheme:



	R	R^1
a	Me	Me
b	Me	Et
c	$-(CH_2)_2-$	

The synthesized compounds are isolated by distillation. After the distillation the compounds ***2a-c*** crystallized.

The structure of the compounds ***2a-c*** are confirmed by their spectral data as well as by the elemental analysis data.

In the IR spectra of the starting dichlorides of the 1,2-alkadienephosphonic acids besides the very characteristic bands for the allenic system and the phosphoryl group at 1980 – 1990 cm^{-1} and 1280 – 1285 cm^{-1} respectively, there are no bands in the area of 1000 – 900 cm^{-1}. At the same time in the IR spectra of the salicylic acid there are characteristic bands for the hydroxyl group at 3210 – 3220 cm^{-1} and for the carbonyl group at 1660 cm- [1]. It is very well known that the carbonyl group in the salicylic acid dimer appears at 1663 cm^{-1}, while the same band in the sali-

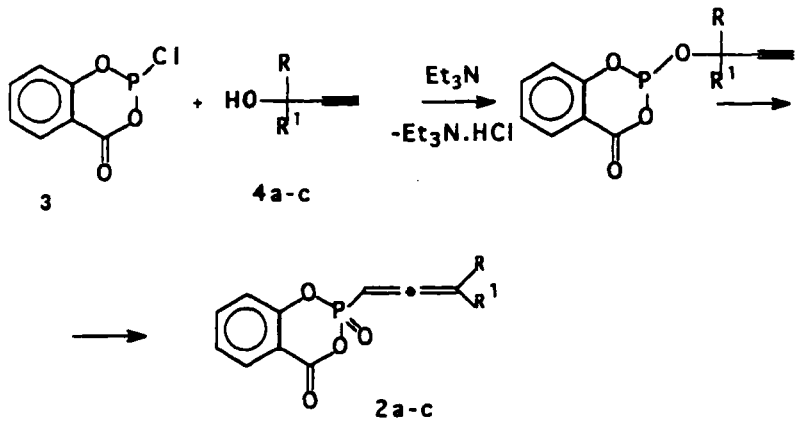
cylic acid monomer appears at 1720 cm-1. On the other hand the band for the carbonyl group in the IR spectra of the salicylic acid methyl ester appears in the area of 1770 cm^{-1}.

The above discussed IR spectral data support our assumption for the successful synthesis of the title compounds.

The IR spectra of the compounds ***2a-c*** exhibit bands at 1980 cm^{-1} and 1280 cm^{-1} for the allenic system and the phosphoryl group, respectively, and bands at 1790 cm^{-1} for the carbonyl group as well as two bands at 1020 and 930 cm^{-1} for the C-O-P bonds. The very characteristic shift of the bands for the carbonyl group, which is easily explained by the fact that the carboxylic group in the salicylic acid is involved in the formation of dimer structures on the basis of hydrogen bonds, which is impossible in the case of compounds ***2a-c***.

The ^{1}H nmr spectral data confirm the suggested structure of the compounds ***2a-c***. The ^{31}P spectra of these compounds are in accordance to those for phosphorylated allenic derivatives, namely the signals appear in the area of 16 – 18 ppm.

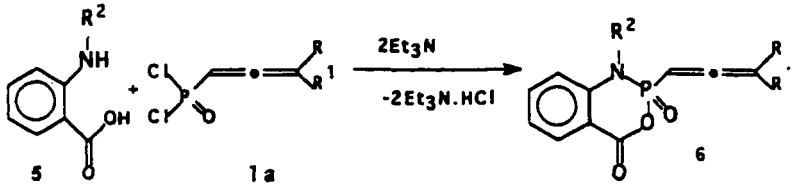
To confirm the synthesis of allenephosphonate derivatives of salicylic acid, we synthesized salicylchlorophosphite **3**, using the procedure described earlier[4], and tried to synthesize the title compounds by the reaction of **3** with α-acetylenic alcoholes. The reaction follows the scheme:

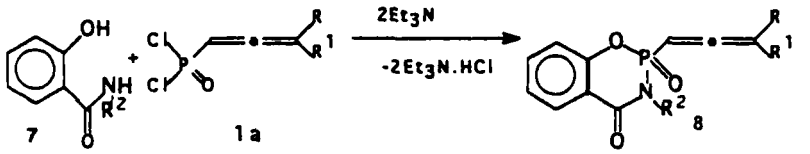


We also synthesized the allenephosphonate derivatives of the ethylamide of salicylic acid and of the 2-ethylamino benzene carboxylic acid. Both

reactions are carried out in the same condition, described for the allenephosphonate derivatives of salicylic acid preparation.

The following schemes ilustrate the reactions:





The spectral and elemental analysis data confirm the structure of the allenephosphonate derivatives of the ethylamide of the salicylic acid and of the 2-ethylamino benzene carboxylic acid as well.

The described synthesis of alkadienephosphonate derivatives of the salicylic acid and of their derivatives is a new, fruitful synthetic way for the preparation of phosphorus-containing derivatives of this acid, which eventually could be an interesting object for further investigations.

The work is in prgress to study the chemical behavior of the title compounds.

EXPERIMENTAL

1. Starting materials

Phosphorus trichloride, acetylenic alcoholes, triethylamine and salicylic acid are commercial by available from Fluka.

All the reagents are purified using standart procedures.

2. Analytical methods

IR spectra were registered on an IR 72 Karl Zeiss Jena spectrophotometer.

1H-nmr spectra were registered on a Tesla BS(80 MHz) at normal temperature as $CDCl_3$ solution with TMS as an internal standard.

3. Synthesis of 2-(1,2-alkadienyl)-2,4 dioxo-benzo-[b]-1,3,2-dioxaphosphorines 2a-c. I

General procedure

To a solution of salicylic acid in dry benzene at 45–50°C and stirring a mixture of an equimolar amount of the corresponding dichloride of 1,2-alkadienephosphonic acid and two equivalents of triethylamine were added dropwise. The reaction mixture was stirred an additional hour at the same conditions and let stand over night. Then the precipitate was filtered off, the solvent was evaporated and the residue was distilled.

2a, ^1H NMR 5.02d(1H, $^2J_{HP}$ 7.0 Hz), 1.68d(6H), 7.7 m; $C_{12}H_{11}O_4P$; Calcd. P(%) 12.3, Found P(%) 12.00; b.p. °C 125–127; Yield (%) 72; IR (cm^{-1}) $1280_{\nu(P=O)}$, $1980_{\nu(C=C=C)}$, $1790_{\nu(C=O)}$, 1020, $930_{\nu(P-O-C)}$

2b, ^1H NMR 5.04d(1H, $^2J_{HP}$ 6.8 Hz), 1.67d(6H), 7.8 m; $C_{13}H_{13}O_4P$; Calcd. P(%) 11.7, Found P(%) 11.58; b.p. °C 129–131; Yield (%) 75; IR (cm^{-1}) $1285_{\nu(P=O)}$, $1976_{\nu(C=C=C)}$, $1785_{\nu(C=O)}$, 1010, $920_{\nu(P-O-C)}$

2c, ^1H NMR 5.04d(1H, $^2J_{HP}$ 6.9 Hz), 1.68d(6H), 7.8 m; $C_{15}H_{15}O_4P$; Calcd. P(%) 10.6, Found P(%) 10.45; b.p. °C 136–138; Yield (%) 76; IR (cm^{-1}) $1280_{\nu(P=O)}$, $1978_{\nu(C=C=C)}$, $1790_{\nu(C=O)}$, 1030, $920_{\nu(P-O-C)}$

4. Synthesis of 2-(1,2-alkadienyl)-2,4 dioxo-benzo-[b]-1,3,2-dioxaphosphorines 2a-c. II

General procedure

To a solution of 2-chloro-4-oxo-benzo-[b]-1,3,2-dioxaphosphorine **3** in dry diethyl ether at −5°C a solution of an equimolar amount of pyridine was added. After 15min stiring at the same conditions a solution of an equimolar amount of the corresponding α-acetylenic alcohol dissolved in the same solvent was added. After an additional hour of stirring the reaction mixture was warmed up to room temperature, the precipitate was filtered off, the solvent was removed and the residue was distilled.

5. Synthesis of 2-(3-methyl-1,2-butadienyl)-2,8-dioxo-benzo [c]-1,3,2-oxazaphosphorine 6 and of 2-(3-methyl-1,2-butadienyl)-2,4-dioxo-benzo-[b]-1,3,2-oxazaphosphorine 8

General procedure

To a solution of 0.2mol (3.3g) of salicylic acid ethylamide or of 0.2mol (3.3g) 2-ethyl-amino benzene carboxylic acid in 300 ml of dry benzene a solution of 0.4mol (56 ml) of triethylamine and 0.2mol (36.9g) of the dichloride of 3-methyl-1,2-butadienephosphonic acid were added dropwise at 45–50°C. The reaction mixture was stirred an additional hour at the same conditions and was warmed to room temperature. After removing of the precipitate and solvent, the residue was distilled.

6, ^{1}H NMR 5.04d(1H, $^2J_{HP}$ 6.8 Hz), 1.67d(6H), 7.8 m; $C_{14}H_{16}O_3NP$; Calcd. P(%) 10.8, N (%) 5.0; Found P(%) 10.75, N(%) 4.9; b.p. °C 141–143; Yield (%) 72; IR (cm^{-1}) $1260_{\nu(P=O)}$, $1989_{\nu(C=C=C)}$, $1785_{\nu(C=O)}$, 1020, $930_{\nu(P\text{-}O\text{-}C)}$

8, ^{1}H NMR 5.02d(1H, $^2J_{HP}$ 6.7 Hz), 1.68d(6H), 7.6 m; $C_{14}H_{15}O_3NP$; Calcd. P(%) 10.8, N(%) 5.0; Found P(%) 10.75, N(%) 4.9; b.p. °C 142–144; Yield (%) 72; IR (cm^{-1}) $1285_{\nu(P=O)}$, $1980_{\nu(C=C=C)}$, $1785_{\nu(C=O)}$, 1030, $920_{\nu(P\text{-}O\text{-}C)}$

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