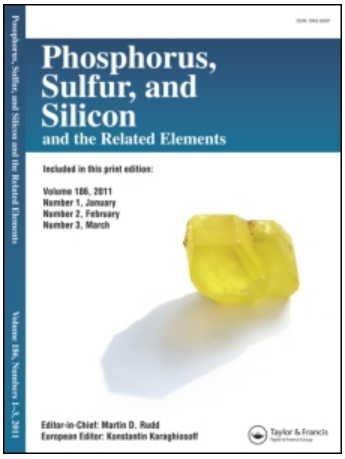

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SYNTHESIS OF SOME DIETHYLPHOSPHONO SUBSTITUTED 2,5-DIHYDROFURAN, 2H-1-BENZOPYRANS AND 3H-NAPHTO[2,1-b]PYRAN

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SYNTHESIS OF SOME DIETHYLPHOSPHONO SUBSTITUTED 2,5-DIHYDROFURAN, 2H-1-BENZOPYRANS AND 3H-NAPHTO[2,1-b]PYRAN

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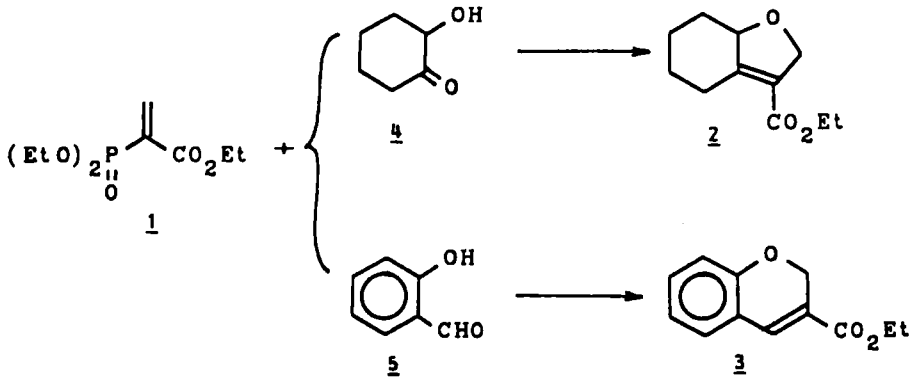
The preparation of α,β unsaturated monophosphonate heterocycles is reported. 9-diethylphosphono-7-oxabicyclo[4.3.0]non-1(9)-ene, some 3-diethylphosphono-2H-1-benzopyrans and 2-diethylphosphono-3H-naphtol[2,1-b]pyran have been prepared from tetraethyl ethylidene gem-bisphosphonate and 2-hydrocyclohexanone, substituted salicylaldehydes or 2-hydroxy-1-naphthaldehyde respectively.

Key words: gem-bisphosphonate, tetraethyl ethylidene gem-bisphosphonate, diethylphosphono 2,5-dihydrofuran, diethylphosphono 2H-1-benzopyran, diethylphosphono 3H-naphto[2,1-b]pyran, synthesis of related compounds.

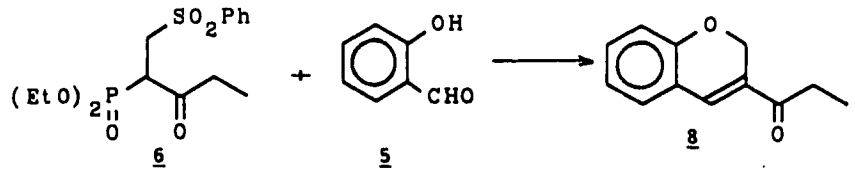
INTRODUCTION

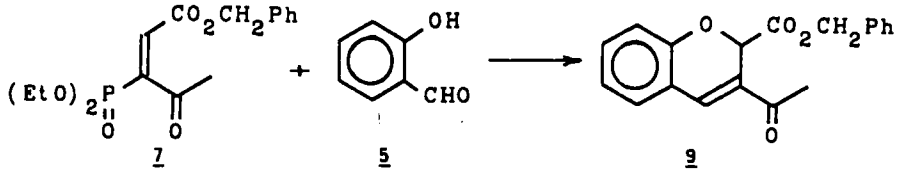
Previous communications have shown that vinyltriphenylphosphonium salts[1–4] or other phosphonium salts[5] are of great interest in preparative organic chemistry of unsaturated heterocycles.

Recently, Heathcock has improved this reaction of vinylphosphonates[6] by the synthesis of heterocyclic molecules containing carbon-carbon double bonds, using an intramolecular Horner-Emmons reaction.[7–10] Thus, ethyl 2-diethylphosphonoacrylate **1** leads to 9-ethoxycarbonyl-7-oxabicyclo[4.3.0]non-1(9)-ene **2** and 3-ethoxycarbonyl-2H-1-benzopyran **3** when reacted with 2-hydroxycyclohexanone **4** and salicylaldehyde **5** respectively.

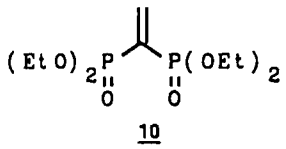


Ketonic benzopyrans, resembling **8** and **9**, have been prepared in our laboratory[11] by reacting salicylaldehyde **5** with a sulfone-masked vinylphosphonate such as **6**, or a β-cetophosphonate ester such as **7**, respectively.





Our intention was to prepare new unsaturated heterocyclic monophosphonates, and so we attempted to improve the reaction starting from tetraethyl ethylidene gem-bisphosphonate **10**.[12]



RESULTS AND DISCUSSION

However, this approach would seem to be doomed to failure, as Hutchinson and Thornton reported in 1988 the impossibility of Michael condensation of oxygen nucleophiles with compound **10**.[13] In consequence, our work began with a preliminary ^{31}P NMR study. This was based upon the previous observations by Degenhardt and Burdsall[14] concerning tetraethyl 2-methoxyethylidene gem-bisphosphonate **11**, when they described the synthesis of compound **10**. We finished the study by the ensuing preparation of some gem-bisphosphonate ethers.

The various conditions of condensation are summarized in Table I. Crude yields are given after extraction ($H_2O/CHCl_3$) from the neutralised reaction media, followed by evaporation of the dried organic layer.

These results lead us to the following three principal conclusions:

—addition of primary and secondary alcohols, or phenyl alcohols, with tetraethyl ethylidene gem-bisphosphonate occurs within a few minutes. Therefore the singlet corresponding to tetraethyl ethylidene gem-bisphosphonate **10** (towards 12 ppm ($CDCl_3$)) disappears very rapidly, leading to the appearance of a new peak, corresponding to the gem-bisphosphonate ether formed. Chemical shifts vary between 21.1 and 21.4 ppm ($CDCl_3$) depending on the alcohol used.

—no addition occurs with *tert*-butanol.

—the stability of the isolated tetraethyl 2-alkoxy and tetraethyl 2-phenoxyethylidene gem-bisphosphonates is quite variable. Tetraethyl 2-phenoxyethylidene gem-bisphosphonates (10% weight solution in $CDCl_3$) appear to be very stable, since we did not observe retro-Michael reactions with these compounds. On the other hand, tetraethyl 2-alkoxyethylidene gem-bisphosphonates have, under the same

TABLE I

Alcohol + tetraethyl ethylidene gem-bisphosphonate $\xrightarrow[\text{Solvent}]{\text{Base}}$ tetraethyl gem-bisphosphonate ether

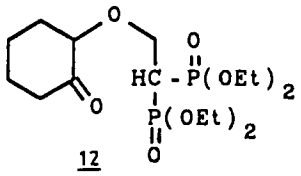
Alcohol	Solvent	Base	Yield (%)
methanol	methanol	MeO-+Na	91
ethanol	ethanol	EtO-+Na	78
cyclohexanol	*tert*-butanol	tBuO-+K	53
2-hydroxycyclohexanone	*tert*-butanol	tBuO-+K	18 (a)
phenol	ethanol	EtO-+Na	95
salicylaldehyde	ethanol	EtO-+Na	57 (b)

(a) Non isolated ("in situ" yield).
(b) After chromatographic purification (solvent: ethyl acetate).

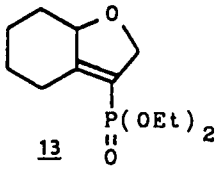
conditions, a decreasing stability from methoxy to cyclohexyloxy, due to the increasing inductive effect of the hydroxylated carbon. This could also explain why addition does not occur with *tert*-butanol; however the steric effect is equally plausible.

These various observations led us to determine the most appropriate experimental procedure for the preparation of α,β unsaturated monophosphonate heterocycles.

Since the starting gem-bisphosphonate ether **12** is difficult to obtain we attempted to carry out a "one pot" synthesis of 9-(diethylphosphono)-7-oxabicyclo[4.3.0]non-1(9)-ene **13**. With this objective in mind, we took inspiration from an experimental procedure described by Heathcock for monophosphonates.[6]



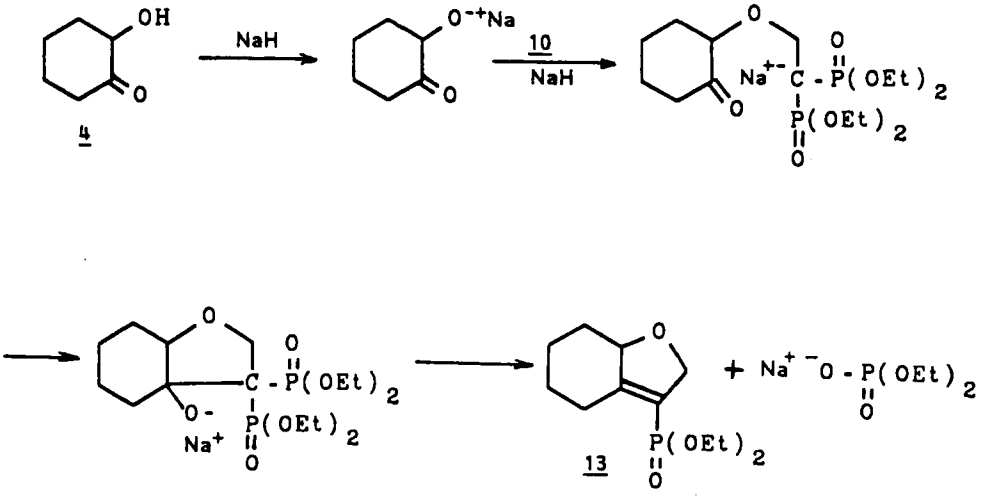
12



13

The sodium salt of 2-hydroxycyclohexanone **4** is prepared by the reaction of sodium hydride with compound **4** in an aprotic solvent. Ensuing addition of tetraethyl ethylidene gem-bisphosphonate **10** led directly, with excess of base in the reaction media and after refluxing, to the cyclisation leading to the expected heterocycle **13** and diethylphosphate.

The probable equation for the procedure is depicted in Scheme I.

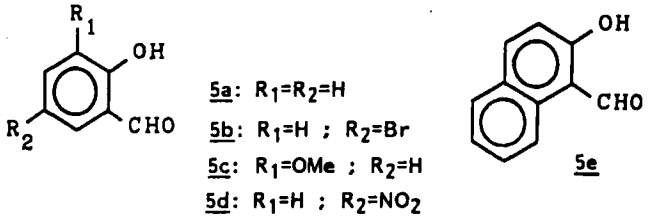


Scheme I

Two solvents, with different polarities,[15] have been tested to form the heterocycle **13**: THF, recommended by Heathcock, is a polar solvent, and toluene, a slightly polar solvent. Haelters[16] has effectively shown that utilisation of non-polar (or slightly polar) solvents contributes to intramolecular Horner-Emmons cyclisations.

When toluene is used, compound **13** is isolated, after the usual treatment, with a yield of 85%. On the other hand when THF is used, the residue must be subjected to chromatography on a silica gel column, and eluted with ethyl acetate-hexane (9:1, v/v) (yield: 69%).

The principle of synthesis of 3-diethylphosphono-2H-1-benzopyrans or 2-diethylphosphono-3H-naphto[2,1-b]pyran is globally similar to our previous description, and the equation from Scheme I can be generalized for the synthesis of these compounds. We used salicylaldehyde **5a** and some of its derivatives **5b–e** to perform the synthesis.



5a: $R_1=R_2=H$
5b: $R_1=H$; $R_2=Br$
5c: $R_1=OMe$; $R_2=H$
5d: $R_1=H$; $R_2=NO_2$

5e

Various 3-diethylphosphono-2H-1-benzopyrans **14a–c** and 2-diethylphosphono-3H-naphto[2,1-b]pyran **14e** have been obtained. However attempted preparation of compound **14d** utilizing this procedure was unsuccessful. The different cyclisation results are summarized in Table II.

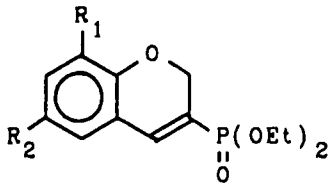
The results of Table II, which indicates yields obtained (after chromatography), confirm the previous observations described by Haelters.[16]

The ^{1}H-NMR spectra of the synthesized compounds **14a–c** and **14e** show patterns which are characteristic for this type of structure. In particular, the protons of the pyran ring system exhibit an A_2MX system (where X represent the hetero atom

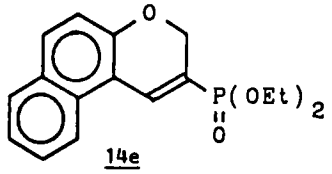
TABLE II

Yields and boiling points of the compounds **13** and **14a–e**

Product No.	Molecular Formula (a)	bp (°C) / mbar	Yield (%) in	
			THF	Toluene
13	$C_{12}H_{21}O_4P$	126-128 / 0.008	69	85
14a	$C_{13}H_{17}O_4P$	138-140 / 0.01	75	82
14b	$C_{13}H_{16}BrO_4P$	158 / 0.01	65	78
14c	$C_{14}H_{19}O_5P$	165 / 0.01	40	60
14e	$C_{17}H_{19}O_5P$	(b)	11	14



14a-c



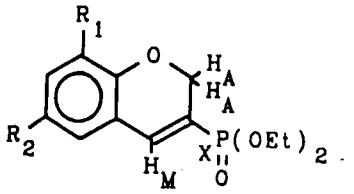
14e

(a) Satisfactory microanalyses obtained: C ± 0.36; H ± 0.19.
(b) This compound is sensitive towards heat and decomposition occurred before boiling point.

TABLE III

Chemical shifts and coupling constants of the A_2MX system of the compounds **14a–e**

Product	A	M	J_{AM}	J_{AX}	J_{MX}
14a	4.81	7.21	1.5	6.0	15.4
14b	4.83	7.15	1.5	5.9	19.4
14c	4.87	7.27	1.4	6.2	19.2
14e	4.89	7.98	1.2	6.9	18.7



phosphorus ^{31}P), whose splitting characteristics are summarized in Table III (chemical shifts: ppm; coupling constants J: Hertz).

CONCLUSION

Our work has shown that it is possible to obtain gem-bisphosphonate ethers through addition of various oxygen nucleophiles to tetraethyl ethylidene gem-bisphosphonate. However, the stability of these compounds is variable according to the electronic environment of the oxygen. Generally, this stability is good enough to perform intramolecular Horner-Emmons reactions with some carbonylated compounds leading to α,β unsaturated monophosphonate heterocycles.

EXPERIMENTAL

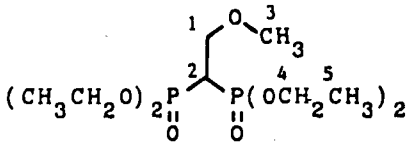
The primary chemicals used are commercial products (Aldrich or Janssen). The solvents were distilled both for the reactions and for chromatography. Tetrahydrofuran was dried on a molecular sieve (4 Å). The purity of products and the reaction progress was monitored on CCM plates ($60F_{254}$ Merck) and liquid chromatography was carried out on a silica gel column (Merck 60, 70–230 mesh).

^{31}P NMR spectra were recorded on a JEOL JNM-FX 100 FT spectrometer; the chemical shifts are reported in ppm to phosphoric acid as reference (85% H_3PO_4 in heavy water). ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC 300 spectrometer; the chemical shifts are reported in ppm using TMS (tetramethylsilane) in organic solvent ($CDCl_3$) as reference. Coupling constants J are reported in Hertz.

Tetraethyl ethylidene gem-bisphosphonate **10**. This compound was synthetised using the technique described by us.[17,18] An alternative method developed by Degenhardt[13] may also be used.

Typical alcohol addition procedure. Tetraethyl ethylidene gem-bisphosphonate (1 g, 3.3 mmol) is added to a solution of sodium methoxylate (0.18 g, 3.3 mmol) in methanol (10 mL). The reaction mixture is stirred for 45 minutes at room temperature. The mixture is neutralised by an aqueous solution saturated with ammonium chloride (5 mL), then the methanol is evaporated under reduced pressure. The residue is extracted using chloroform (3 × 10 mL); after drying the organic layer ($MgSO_4$), the solvent is evaporated in a rotating evaporator under reduced pressure (10^{-2} mbar). Crude yield: 1.0 g (91%).

Spectral Data

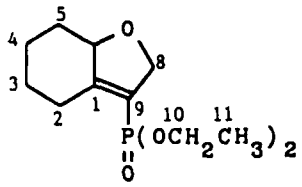


^{1}H NMR 1.32 (t, 12H); 2.74 (tt, J_{PH} = 23.7, 1H); 3.33 (s, 3H); 3.84 (td, J_{PH} = 16.2, 2H); 4.15 (qt, 8H)
^{13}C NMR 16.0 (C_5); 38.4 (C_2, t, J_{CP} = 132.4); 49.1 (C_3); 62.2 (C_4); 66.5 (C_1)
^{31}P NMR 21.2

9-(diethylphosphono)-7-oxabicyclo [4.3.0]non-1(9)-ene **13**. A suspension of sodium hydride (0.288 g, 12 mmol) in toluene (30 mL) is stored under nitrogen. 2-Hydroxycyclohexanone (adipoin) (1.14 g, 10 mmol), freshly distilled (b.p. 88°C/13 mbar), is added dropwise and the reaction mixture is stirred for 2 h at room temperature. Tetraethyl ethylidene gem-bisphosphonate (3 g, 10 mmol) is then added and the reaction mixture is refluxed for 2 h. The mixture is neutralised by an aqueous solution saturated with ammonium chloride (5 mL), then the toluene evaporated under reduced pressure. The residue is extracted using chloroforme (3 × 25 mL); after drying the organic layer ($MgSO_4$), the solvent is evaporated in a rotating evaporator under reduced pressure (10^{-2} mbar), leading directly to the isolation of compound **13**. Yield: 2.15 g (85%).

When THF is used in this reaction, the organic layer must be chromatographed on silica gel, eluting with ethyl acetate/hexane (9:1, v/v). Yield: 1.7 g (69%).
bp = 126–128°C/8.10^{-3} mbar

Spectral Data



^{1}H NMR 1.27 (td, 6H); 1.42–1.67 (m, 2H); 1.71–2.06 (m, 4H); 2.10–2.28 (m, 2H); 3.21–3.32 (m, 1H); 4.03 (qt, 4H); 4.68 (m, 2H)
^{13}C NMR 15.9 (C_{11}); 22.4, 34.7 (C_2, C_4); 26.0 (C_3 & C_5); 60.9 (C_{10}); 75.7 (C_8, d; J_{CP} = 21.3); 86.5 (C_6, d, J_{CP} = 19.8); 126.1 (C_9, d, J_{CP} = 134.2); 157.7 (C_1, d, J_{CP} = 13.7)
^{31}P NMR 12.9

Typical procedure: preparation of 3-diethylphosphono-2H-1-benzopyrans **14a–c** *and 2-diethylphosphono-3H-naphto[2,1-b]pyran* **14e**. A suspension of sodium hydride (0.228 g, 12 mmol) in toluene (30 mL) is stored under nitrogen. Salicylaldehyde (1.22 g, 10 mmol) is added and the reaction mixture is stirred for 2 h at room temperature. Tetraethyl ethylidene gem-bisphosphonate (3 g, 10 mmol) is added,

TABLE IV

Spectral data of compounds **14** prepared

Product No.	^{1}H-NMR ($CDCl_3$/TMS)	^{13}C-NMR ($CDCl_3$)	^{31}P-NMR ($CDCl_3$)
14a	1.33(t,6H);4.23(false qt,4H);4.81(dd, J_{PH}=6.0,J_{HH}=1.5,2H);6.79-6.95 & 7.08-7.29(m,4H);7.21(dd,J_{PH}=15.4, J_{HH}=1.5,1H)	16.2(C_{10});61.9(C_9);64.2(C_2,d,J_{CP}=17.5); 115.9(C_8);120.4(C_3,dJ_{CP}=192.1);120.7(C_{4a}, d,J_{CP}=16.8);121.6,128.2,131.5(C_5,C_6,C_7); 136.9(C_4,d,J_{CP}=7.6);154.5(C_{8a})	15.1
14b	1.35(t,6H);4.13(false qt,4H);4.83(dd, J_{PH}=5.9,J_{HH}=1.5,2H);6.70-6.75 & 7.12-7.32(m,3H);7.15(dd,J_{PH}=19.4, J_{HH}=1.5,1H)	16.2(C_{10});62.1(C_9);64.6(C_2,d,J_{CP}=17.4); 113.6(C_6);117.8(C_8);122.3(C_3,d,J_{CP}=188.9); 122.5(C_{4a},d,J_{CP}=17.5);130.5,134.0(C_5,C_7) 135.4(C_4,d,J_{CP}=7.8);153.5(C_{8a})	14.3
14c	1.33(t,6H);3.86(s,3H);4.12(false qt, 4H);4.87(dd,J_{PH}=6.2,J_{HH}=1.4,2H); 6.73-6.79 & 6.84-6.91(m,3H);7.27(dd, J_{PH}19.2,J_{HH}=1.4,1H)	15.9(C_{11});55.6(C_9);61.7(C_{10});64.3(C_2,d, J_{CP}=17.6);113.9(C_6);119.0,121.1(C_5,C_7); 120.2(C_3,d,J_{CP}=189.0);121.2(C_{4a},d,J_{CP}=16.9) 136.8(C_4,d,J_{CP}=7.8);143.1,147.4(C_8,C_{8a})	14.9
14e	1.35(t,6H);4.19(false qt,4H);4.89(dd, J_{PH}=6.9,J_{HH}=1.2,2H);7.36-8.04(m,6H); 7.98(dd,J_{PH}=18.7,J_{HH}=1.2,1H)	15.9(C_{12});61.7(C_{11});64.9(C_3,d,J_{CP}=17.2); 113.9(C_{10b},d,J_{CP}=17.0);117.4(C_2,d,J_{CP}=191.5) 117.0,120.9,123.9,127.2,128.2,128.9,130.0, 132.1(C_5,C_6,C_{6a},C_7,C_8,C_9,C_{10},C_{10a});133.4 (C_1,d,J_{CP}=8.9);153.4(C_{4a})	15.6

then the reaction mixture is refluxed for 2 h. After water is added (10 mL), the toluene is evaporated in a rotating evaporator. The residue is diluted with a 0.25 M sodium hydroxide solution (20 mL), extracted using ether (3 × 30 mL) and washed with an aqueous solution saturated with sodium chloride (15 mL). The dried organic layer ($MgSO_4$) is evaporated under reduced pressure to give compound **14a**. Yield: 2.2 g (82%).

However, compounds **14a–c** and **14e** may be chromatographed on silica gel, and eluted with ethyl acetate/hexane (1:1, v/v).

Analytical and spectral data are summarized in Table IV.

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