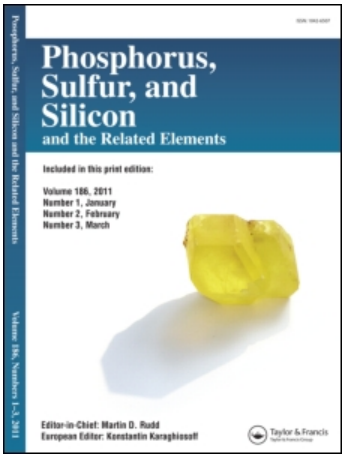

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF SOME DIETHYLPHOSPHONO SUBSTITUTED 3H-PYRROLIZINES

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To cite this Article Loussouarn, A. , Servant, G. , Guervenou, J. and Sturtz, G.(1996) 'SYNTHESIS OF SOME DIETHYLPHOSPHONO SUBSTITUTED 3H-PYRROLIZINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 113: 1, 275 — 285
To link to this Article: DOI: 10.1080/10426509608046399
URL: http://dx.doi.org/10.1080/10426509608046399

Phosphorus, Sulfur, and Silicon, 1996, Vol. 113, pp. 275–285
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SYNTHESIS OF SOME DIETHYLPHOSPHONO SUBSTITUTED 3H-PYRROLIZINES

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(Received January 25, 1996; in final form February 8, 1996)

The preparation of various alkyl substituted monophosphonate 3H-pyrrolizines via a tandem Michael □ Horner-Emmons reaction is reported. These products were prepared from tetraethyl ethylidene gem-bisphosphonate and corresponding 2-acylpyrroles.

Key words: Acylpyrrole, gem-bisphosphonate, tetraethyl ethylidene gem-bisphosphonate, Vilsmeier-Haack acylation, tandem Michael □ Horner-Emmons reaction, pyrrolizine.

INTRODUCTION

First described by Schweizer[1] in 1964, 3H-pyrrolizine structure **1** is reported to be an important synthetic intermediate in the chemistry of pyrrolizidines **2**. In fact, some pyrrolizidine derivatives prove to possess genuine therapeutic activities: antileukemic,[2] antiinflammatory[3] or analgesic.[3] Consequently, the preparation of diethylphosphono substituted 3H-pyrrolizines **3a** and/or **3b**, potential precursors of such pyrrolizidines structures, seemed to us of great interest.

In a recent paper,[4] we showed that a Michael[5] reaction starting from tetraethyl ethylidene gem-bisphosphonate **4**[6,7] can be joined to an intramolecular Horner-Emmons[8] ring closure, when the nucleophilic center is in the β- or γ-position to the carbonyl group. Previously, we described the preparation of some heterocycles: diethylphosphono substituted 2,5-dihydrofurans, 2H-1-benzopyrans and 3H-naphto [2,1-b]pyrans.

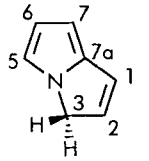
The purpose of the present work was to extend this study by using this tandem Michael □ Horner-Emmons reaction between tetraethyl ethylidene gem-bisphosphonate **4** and some 2-acylpyrroles **5**. Thus, a series of original annulated diethylphosphono-3H-pyrrolizines **3a** and/or **3b**, alkyl or aryl substituted, can be obtained.

With this objective in mind, we drew inspiration from experimental procedures described by Minami,[9,10] and also Flitsch,[11,12] who prepared 3H-pyrrolizines **6a** and/or **6b** from vinylphosphonates **7** and various 2-acylpyrroles.

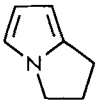
RESULTS AND DISCUSSION

Two intermediates have to be obtained before getting the new pyrrolizines **3a&b** tetraethyl ethylidene gem-bisphosphonate **4**, prepared in our laboratory,[6,7] and 2-acylpyrroles derivatives **5**.

†Computational part.



1



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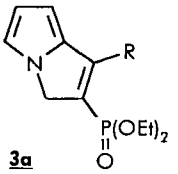
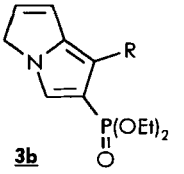


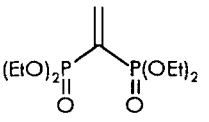
3a



3b

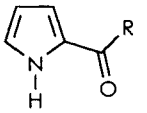
R = H, Me, Et, iPr, Hept,  , Ph

Fig. 1



4

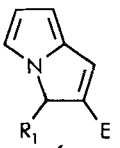
Fig. 2



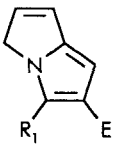
5

R = H, Me, Et, iPr, Hept, , Ph

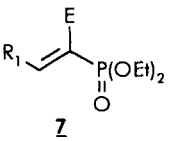
Fig. 3



6a



6b



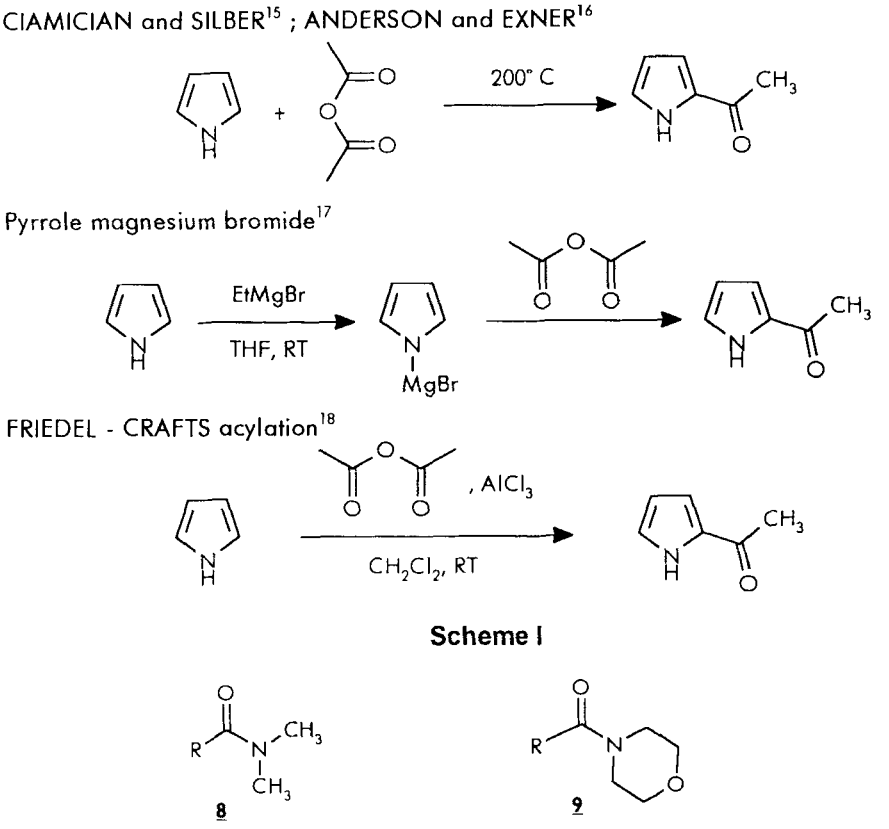
7

E = CO_2Et[10,11], CN[10], SO_2Ph[11], Ph[11]
R_1 = H[10,11], Ph[11]

Fig. 4

Preparation of 2-acylpyrroles 5

Several acylation ways of pyrrole leading to compounds 5 have been investigated: Vilsmeier-Haack reaction,[13,14] direct acylation with acetic anhydride,[15,16] acylation of pyrrylmagnesium bromide,[17] and Friedel-Crafts acylation in the presence of aluminium chloride.[18]



Scheme I

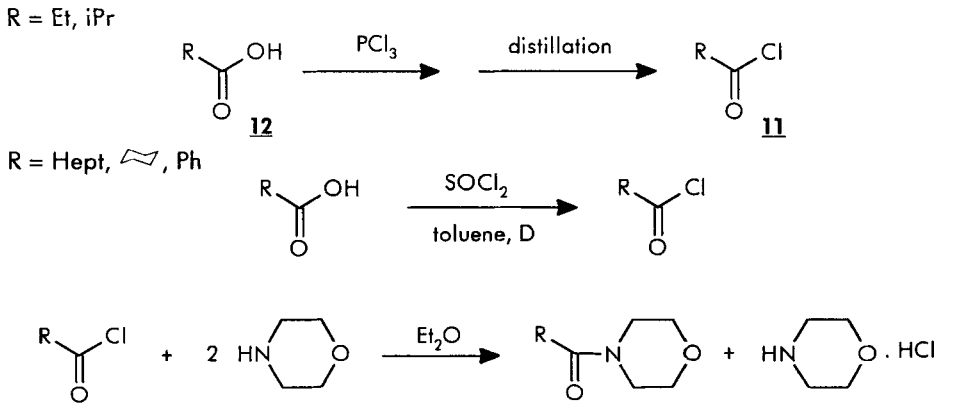
Fig. 5

The best synthesis way (selectivity and yield) seemed to be the one using the Vilsmeier-Haack process. In that case, acylation was carried out in 1,2-dichloroethane,[19] where a Vilsmeier complex between phosphorus oxychloride and an amide was formed. The different amides used were prepared in our laboratory, excepting dimethylformamide (DMF) and dimethylacetamide (DMA).

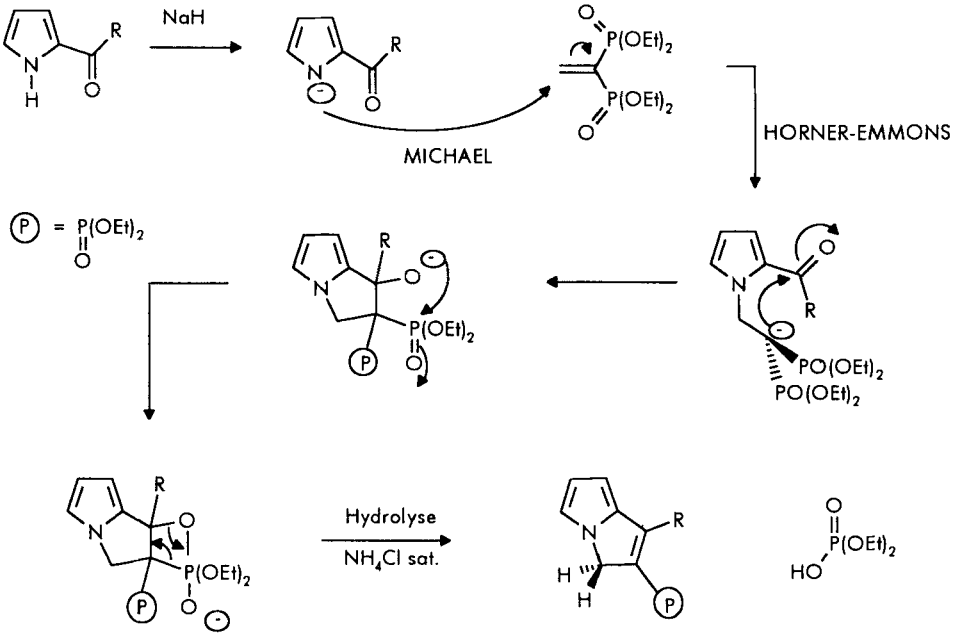
Preparation of Amides

Based on a literature review we have decided to choose two species of amides: N,N-dimethylamides **8** and morpholinamides[20] **9**. However, morpholinamides **9** appeared to give better yields when reacted in Vilsmeier-Haack acylation conditions.

Amides **9** were prepared by reacting morpholine **10** with acyl chlorides **11**, the latter being obtained from the corresponding acids **12**. Acyl chlorides **11** with low boiling points (<110°C) (R = Et, iPr) were obtained by treating acids with phosphorus trichloride, then distilled.[22] On the other hand, acyl chlorides **11** with high boiling points (180–200°C) (R = Hept, ⌇, Ph) were obtained by treating acids with thionyl chloride in refluxing toluene.[23] The common synthetic way to amides **9** consists in directly reacting acyl chlorides **11** with morpholine **10** in dry ethyl ether.



Scheme II



Scheme III

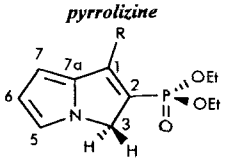
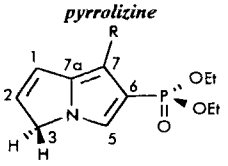
Preparation of Alkyl- and Aryldiethylphosphono-3H-pyrrolizines **3a** *and/or* **3b**

By the use of a tandem Michael □ Horner-Emmons reaction between 2-acylpyrroles **5** and tetraethyl ethylidene gem-bisphosphonate **4**, it is possible to realize a "one pot synthesis" leading to compounds **3a** and/or **3b**.

With this objective in mind, the pyrryl anion was obtained by treating 2-acylpyrrole **5** with sodium hydride. Ensuing addition of tetraethyl ethylidene gem-bisphosphonate **4** in the reaction mixture led to a Michael nucleophilic attack, which generate a gem-bisphosphonate carbanion *in situ*. The latter then reacts with the carbonyl group, leading to heterocycle **3** by an intramolecular Horner-Emmons ring closure. The corresponding mechanism is described in Scheme III, analogous to the mechanism described in Reference 4.

TABLE I

Heterocyclic compounds 3 from 4 and 5

R	*1-alkyl (ou aryl) -2-diethylphosphono-3H-pyrrolizine*  **3a**	*7- alkyl (ou aryl) -6-diethylphosphono-3H-pyrrolizine*  **3b**	Yield in THF	Yield in Toluene	Rf in Ethyl acetate
H		100%	41%	43%	0.13
methyl	49%	51%	76%	78%	0.50
ethyl	36%	64%	64%	71%	0.55
i-propyl	33%	67%	40%	75%	0.30
heptyl	52%	48%	48%	77%	0.32
cyclohexyl	22%	78%	40%	46%	0.59
phenyl		100%	24%	51%	0.25

Satisfactory microanalyses obtained :

R = H	$C_{11}H_{16}NO_3P$ (241.23)	calc.	: C 54.77 H 6.68
		found	: C 54.59 H 6.74
R = methyl	$C_{12}H_{18}NO_3P$ (255.25)	calc.	: C 56.47 H 7.11
		found	: C 56.71 H 7.23
R = heptyl	$C_{18}H_{30}NO_3P$ (339.41)	calc.	: C 63.70 H 8.91
		found	: C 63.44 H 8.99

Other compounds : C ± 0.37 ; H ± 0.19

Compounds 3 were oils, sensitive towards heat and decomposition occured before boiling point.

Reaction was carried out at room temperature and followed by ^{31}P NMR spectroscopy. Five hours of vigorous stirring appeared to be a minimum for full reaction, so our experiments were kept under stirring overnight.

In order to confirm our previous results,[4,23] all experiments were performed in two solvents: tetrahydrofuran, polar solvent, and toluene, slightly polar solvent. Again, better yields were obtained with toluene. Thus, we have established that non-polar or slightly polar solvents are of great interest in intramolecular ring closures.

A Horner-Emmons annulation logically leads to a 1-alkyl (or aryl) 2-diethylphosphonopyrrolizine **3a** form. However, an experiment starting from 2-formylpyrrole gave only the **3b** form. Following experiments with different R substituents showed that more often a mixture of the two isomers **3a** and **3b** was obtained, except in two cases (R = H, Ph) where only the **3b** form was obtained.

We may notice that Flitsch[11,12,24] has already observed the presence of two isomeric forms. The structure of compounds 3, and the coexistence of isomers **3a** and **3b**, were confirmed by DT and Off-Resonance ^{13}C NMR, and $^{1}H/^{1}H$ COSY correlation.

Here, the following steps can be noticed:

- the relative ratio of isomeric forms **3a** and **3b** does not depend on the solvent used (THF or toluene). In addition, stirring duration (1 night or 15 days) or temperature (RT or 50°C) have no effect on this ratio.
- all results, except R = Hept, show the preponderance of isomers **3b**. Thus, it seems

TABLE II

Heats of formation ΔF for compounds **3**

	1-alkyl (ou aryl) -2-diethylphosphono-3H-pyrrolizine **3a**	*7- alkyl (ou aryl) -6-diethylphosphono-3H-pyrrolizine* **3b**
R	ΔF (kcal)	ΔF (kcal)
phenyl	- 95.2	- 99.7
H	- 122.3	- 128.4
methyl	- 130.6	- 134.6
ethyl	- 136.1	- 139.7
i-propyl	- 138.9	- 142.3
heptyl	- 168.5	- 174.1
cyclohexyl	- 152.3	- 156.7

to prove that the **3a** form, outlet from the intramolecular ring closure, is converted into the **3b** form, under reacting conditions.

- ratio obviously depends on the nature of the R substituent. So, if we consider the inductive effect of R substituents, on the one hand we notice that the higher the +I inductive effect, the more the reaction is displaced towards the 7-alkyl-6-diethylphosphono-3H-pyrrolizine **3b**. On the other hand, substituents like phenyl (−I) or proton (nul effect) lead to the sole **3b** form.

Afterwards, our wish was to substitute for this "inductive effect" explanation, a geometrical explanation which integrates the ability of the molecule synthesized. MOPAC calculations[25,26] allowed us to reach, among other physical parameters, heats of formation ΔF for the different pyrrolizines prepared. The results obtained are summarized in Table II.

These results show that the lowest ΔF value always corresponds to the 7-alkyl-6-diethylphosphono-3H-pyrrolizine **3b**. Thus, these calculations confirm our previous observations which showed that **3b** might be the more stable form. It may be also noticed that ionization potentials (in the order of 8.7 to 8.9 eV), calculated for compounds **3a** and **3b**, are very close to the pyrrole one; the lowest value is again obtained for the **3b** forms.

At last, in spite of many tests, we were unsuccessful in the separation of pyrrolizines **3a** and **3b** by chromatography on silica gel column; also ternary eluents, as those described by Flitsch[11] did not work.

CONCLUSION

Our work shows that it is possible to obtain new alkyl- and aryl-diethylphosphono-3H-pyrolizines by using a tandem Michael □ Horner-Emmons "one pot" reaction. Synthesized pyrrolines are most frequently obtained as a mixture of two isomers, whose relative ratio depends on the R substituent inductive effect and also on thermodynamical parameters. Unfortunately, we failed to separate these two isomers.

EXPERIMENTAL

The primary chemicals used were commercial products (Aldrich or Janssen). The solvents were distilled both for the reactions and for chromatography. Tetrahydrofuran and toluene were dried on a molecular sieve (4 Å). The purity of products and the reaction progress were monitored on TLC plates ($60F_{254}$ Merck) and liquid chromatography was carried out on a silica gel column (Merck 60, 70-230 mesh). TLC revelation were carried out under a UV light (254 nm) or by reagents: iodine, DITTMER, DRAGENDORFF, ninhydrine. Melting points were determined on a KOFLER hot-stage apparatus.

^{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) with positive values being downfield. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 300 or Bruker DRX 400 spectrometers; the chemical shifts are reported in ppm using TMS (tetramethylsilane) in organic solvent ($CDCl_3$) as reference. Coupling constants J are reported in Hertz (Hz).

Different decoupling techniques were used: full decoupling ^{13}C NMR and ^{31}P NMR, off resonance with NOE ^{13}C NMR.

Tetraethyl Ethylidene Gem-bisphosphonate **4**

Prepared according to literature procedures.[6,7]

Spectral Data
^{1}H NMR δ: 1.20 (t, 12H); 4.10 (m, 8H); 6.85 (dd, 2H, J_{HP}^{trans} = 38.0, J_{HP}^{cis} = 34.0)
^{31}P NMR δ: 12.7

Synthesis of 2-acylpyrroles **5**: *Typical Procedures*

Compounds **5** were prepared from the corresponding amides; DMF (R = H) and DMA (R = Me) used were commercial products.

Way to Amides (R = Et, iPr, Hept,  *, Ph)*

- acylchlorides
  R = Et, iPr: prepared according to literature procedure[21] (yields about 80%).
  R = Hept, , Ph: prepared according to literature procedure[22] (yields about 70%).
- amides

200 mmol of acylchloride were poured into ether (30 mL) and then cooled under stirring to 15°C in a water-ice bath. The reaction mixture was kept at this temperature and morpholine (34.9 mL, 400 mmol) was added dropwise. The mixture was stirred for 4 hours, the temperature was allowed to reach room temperature. 100 mL of water were added, the mixture was extracted and the resultant aqueous layer was extracted three times with $CHCl_3$. The organic layers were combined and washed with molar aqueous HCl, then aqueous (5%) Na_2CO_3, before drying. The solvents were evaporated under reduced pressure to give the crude amide (yields about 65 to 70%).

Vilsmeier-Haack Procedure: Preparation of 2-acyl or 2-arylpyrroles

Prepared according to literature procedure.[19]

The chromatography of the residual oil over silica gel gave the pure 2-acyl(aryl)pyrrole.

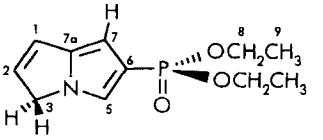
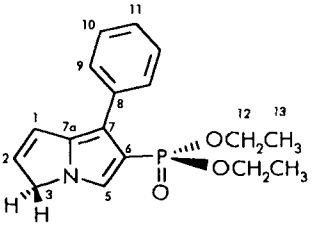
e.g. 2-formylpyrrole: eluent ethyl acetate/hexane (1/1)
44% yield
buff-coloured solid, mp = 45°C

Synthesis of Diethylphosphonopyrrolizines **3a&b**: *Typical Procedure*

5 mmol of acylpyrrole were added dropwise, under nitrogen, to a suspension of sodium hydride (5 mmol, 0.12 g) in toluene (or THF) (20 mL). The reaction mixture was stirred for 20 min at room temperature. Tetraethyl ethylidene gem-bisphosphonate (1.5 g, 5 mmol) was added, then the reaction mixture was allowed to stand with stirring for 15 hours at room temperature. The mixture was neutralised by an aqueous solution saturated with ammonium chloride (50 mL), then the toluene was evaporated under reduced pressure. The residual aqueous layer was extracted three times with $CHCl_3$. After drying ($MgSO_4$), the solvent was removed under reduced pressure. Chromatography of the residual oil over silica gel (ethyl acetate) yielded the pure pyrrolizine (yields are given in Table I and the spectral data are summarized in Table III).

TABLE III

Spectral data of synthetised 3H-pyrrolizines

6-diethylphosphono-3H-pyrrolizine	*7-benzyl-6-diethylphosphono-3H-pyrrolizine*
	
RMN ^{1}H	
1.29 (t, 6H) ; 4.07 (false qt, 4H) ; 4.45 (dddd, 2H) ; 6.11 (ddt, 1H) ; 6.26 (ddt, 1H) ; 6.56 (dtd, 1H) ; 7.39 (dddt, 1H)	1.13 (t, 6H) ; 4.02 (false qt, 4H) ; 4.53 (ddd, 2H) ; 6.32 (ddt, 1H) ; 6.70 (ddt, 1H) ; 7.24 (t, 1H), 7.36 (t, 2H) ; 7.54 (dddt, 1H) ; 7.58 (d, 2H)
RMN ^{13}C	
16.1 (C_9) ; 51.8 (C_3) ; 61.3 (C_8) ; 99.6 (C_7, $J_{C\text{-}P}$ = 12.7) ; 111.4 (C_6, $J_{C\text{-}P}$ = 213.5) ; 122.8 (C_2) ; 124.0 (C_5, $J_{C\text{-}P}$ = 23.7) 128.9 (C_1) ; 142.7 (C_{7a}, $J_{C\text{-}P}$ = 15.0)	16.0 (C_{13}) ; 52.2 (C_3) ; 61.4 (C_{12}) ; 109.9 (C_6, $J_{C\text{-}P}$ = 210.0) ; 116.2 (C_7, $J_{C\text{-}P}$ = 12.5) ; 122.9 (C_2) ; 126.0 (C_{11}) ; 126.9 (C_5, $J_{C\text{-}P}$ = 22.0) ; 128.0, 128.6 ($C_{9\text{-}10}$) ; 129.3 (C_1) ; 134.7 (C_8) 141.2 (C_{7a}, $J_{C\text{-}P}$ = 15.5)

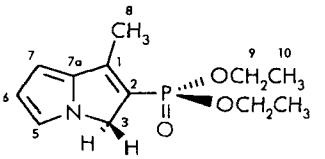
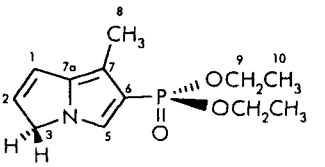
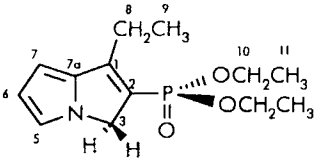
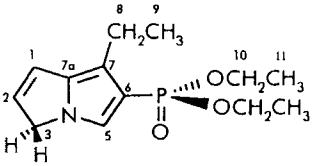
1-methyl-2-diethylphosphono-3H-pyrrolizine	*7-methyl-6-diethylphosphono-3H-pyrrolizine*
	
RMN ^{1}H	
1.31 (t, 6H) ; 2.36 (dt, 3H) ; 4.06 (false qt, 4H) ; 4.58 (dddd, 2H) ; 6.13 (dd, 1H) ; 6.32 (dtd, 1H) ; 6.99 (ddt, 1H)	1.33 (t, 6H) ; 2.19 (d, 3H) ; 4.09 (false qt, 4H) ; 4.43 (ddd, 2H) ; 6.16 (ddt, 1H) ; 6.55 (ddt, 1H) ; 7.38 (dddt, 1H)
RMN ^{13}C	
11.9 (C_8, $J_{C\text{-}P}$ = 3.0) ; 12.0 (C_{10}) ; 52.8 (C_3, $J_{C\text{-}P}$ = 20.6) ; 60.8 (C_9) ; 99.2 (C_6) ; 112.8 (C_7, $J_{C\text{-}P}$ = 2.3) ; 118.2 (C_2, $J_{C\text{-}P}$ = 207.5) ; 118.3 (C_5) ; 140.7 (C_{7a}, $J_{C\text{-}P}$ = 16.0) ; 146.5 (C_1, $J_{C\text{-}P}$ = 13.7)	10.1 (C_8) ; 12.0 (C_{10}) ; 51.7 (C_3) ; 61.3 (C_9) ; 109.4 (C_7, $J_{C\text{-}P}$ = 12.2) ; 110.4 (C_6, $J_{C\text{-}P}$ = 210.6) ; 121.7 (C_2) ; 124.9 (C_5, $J_{C\text{-}P}$ = 24.4) ; 126.8 (C_1) ; 142.3 (C_{7a}, $J_{C\text{-}P}$ = 21.4)

TABLE III (*Continued*)

1-ethyl-2-diethylphosphono-3H-pyrrolizine	*7-ethyl-6-diethylphosphono-3H-pyrrolizine*
	
RMN ^{1}H	
1.24 (t, 3H) ; 1.29 (t, 6H) ; 2.84 (dq, 2H) ; 4.11 (false qt, 4H) ; 4.57 (dddd, 2H) ; 6.15 (dd, 1H) ; 6.34 (ddt, 1H) ; 6.99 (ddt, 1H)	1.29 (t, 6H) ; 1.31 (t, 3H) ; 2.66 (q, 2H) ; 4.08 (false qt, 4H) ; 4.42 (ddd, 2H) ; 6.18 (ddt, 1H) ; 6.61 (ddt, 1H) ; 7.37 (dddt, 1H)
RMN ^{13}C	
13.7 (C_9, $J_{C\text{-}P}$ = 1.5) ; 16.4 (C_{11}) ; 20.5 (C_8, $J_{C\text{-}P}$ = 3.0) ; 53.2 (C_3, $J_{C\text{-}P}$ = 19.8) ; 61.3 (C_{10}) ; 100.1 (C_6) ; 113.1 (C_7, $J_{C\text{-}P}$ = 2.3) ; 117.9 (C_2, $J_{C\text{-}P}$ = 208.3) ; 118.3 (C_5) ; 140.3 (C_{7a}, $J_{C\text{-}P}$ = 16.8) ; 153.0 (C_1, $J_{C\text{-}P}$ = 13.4)	15.4 (C_9) ; 16.4 (C_{11}) ; 19.1 (C_8) ; 51.7 (C_3) ; 61.3 (C_{10}) ; 109.2 (C_6, $J_{C\text{-}P}$ = 210.6) ; 117.1 (C_7, $J_{C\text{-}P}$ = 13.0) 122.9 (C_2) ; 125.3 (C_5, $J_{C\text{-}P}$ = 23.7) ; 127.0 (C_1) ; 141.6 (C_{7a}, $J_{C\text{-}P}$ = 20.6)

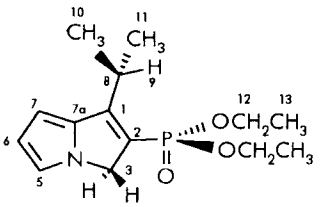
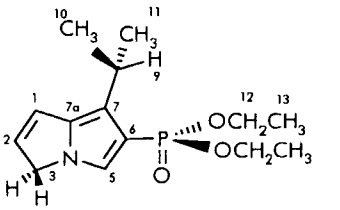
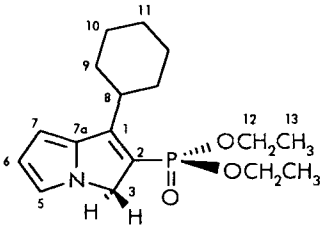
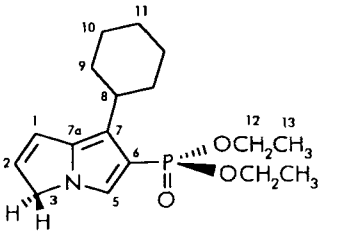
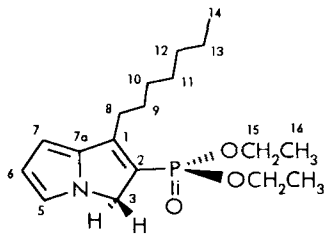
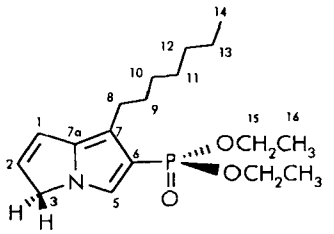
1-isopropyl-2-diethylphosphono-3H-pyrrolizine	*7-isopropyl-6-diethylphosphono-3H-pyrrolizine*
	
RMN ^{1}H	
1.20 (d, 6H) ; 1.25 (t, 6H) ; 3.65 (heptd, 1H) ; 4.07 (false qt, 4H) ; 4.57 (dddd, 2H) ; 6.17 (dd, 1H) ; 6.34 (ddt, 1H) ; 6.99 (ddt, 1H)	1.20 (d, 6H) ; 1.33 (t, 6H) ; 3.15 (heptd, 1H) ; 4.10 (false qt, 4H) ; 4.40 (dddd, 2H) ; 6.15 (ddt, 1H) ; 6.65 (ddt, 1H) ; 7.33 (dddt, 1H)
RMN ^{13}C	
16.1 (C_{11}) ; 26.0 (C_9) ; 27.3 (C_8, $J_{C\text{-}P}$ = 3.7) ; 52.9 (C_3, $J_{C\text{-}P}$ = 20.2) ; 61.1 (C_{10}) ; 101.6 (C_6) ; 113.9 (C_5) ; 117.0 (C_2, $J_{C\text{-}P}$ = 208.3) ; 139.2 (C_{7a}, $J_{C\text{-}P}$ = 16.5) ; 118.1 (C_7, $J_{C\text{-}P}$ = 2.1) ; 157.2 (C_1, $J_{C\text{-}P}$ = 14.7)	16.1 (C_{11}) ; 21.7 (C_9) ; 24.4 (C_8) ; 51.3 (C_3) ; 61.1 (C_{10}) ; 100.8 (C_6, $J_{C\text{-}P}$ = 239.5) ; 122.8 (C_7, $J_{C\text{-}P}$ = 13.8) ; 123.8 (C_2) ; 124.9 (C_5, $J_{C\text{-}P}$ = 23.0) ; 126.9 (C_1) ; 138.8 (C_{7a}, $J_{C\text{-}P}$ = 21.1)

TABLE III (*Continued*)

1-cyclohexyl-2-diethylphosphono-3H-pyrrolizine	*7-cyclohexyl-6-diethylphosphono-3H-pyrrolizine*
	
RMN ^{1}H	
1.33 (t, 6H) ; 1.93 (m, 10H) ; 3.49 (m, 1H) ; 4.05 (false qt, 4H) ; 4.57 (dddd, 2H) ; 6.14 (dd, 1H) ; 6.32 (ddt, 1H) ; 6.96 (ddt, 1H)	1.30 (t, 6H) ; 1.78 (m, 10H) ; 3.65 (m, 1H) ; 4.08 (false qt, 4H) ; 4.39 (dddd, 2H) ; 6.18 (ddt, 1H) ; 6.60 (ddt, 1H) ; 7.34 (dddt, 1H)
RMN ^{13}C	
16.3 (C_{13}) ; 25.7 (C_{11}) ; 26.9 (C_{10}) ; 31.7 (C_9, $J_{C\text{-}P}$ = 1.5) 37.6 (C_8, $J_{C\text{-}P}$ = 2.9) ; 52.8 (C_3, $J_{C\text{-}P}$ = 20.8) ; 61.7 (C_{12}) ; 101.8 (C_6) ; 112.9 (C_7, $J_{C\text{-}P}$ = 2.5) ; 117.0 (C_2, $J_{C\text{-}P}$ = 208.2) ; 118.1 (C_5) ; 139.1 (C_{7a}, $J_{C\text{-}P}$ = 16.4) ; 156.2 (C_1, $J_{C\text{-}P}$ = 14.0)	16.2 (C_{13}) ; 25.7 (C_{11}) ; 29.2 (C_{10}) ; 35.0 (C_9) ; 36.1 (C_8) ; 51.3 (C_3) ; 61.2 (C_{12}) ; 109.5 (C_6, $J_{C\text{-}P}$ = 210.3) ; 121.9 (C_7, $J_{C\text{-}P}$ = 13.6) ; 123.8 (C_2) ; 124.9 (C_5, $J_{C\text{-}P}$ = 23.5) ; 126.9 (C_1) ; 139.8 (C_{7a}, $J_{C\text{-}P}$ = 20.8)

1-heptyl-2-diethylphosphono-3H-pyrrolizine	*7-heptyl-6-diethylphosphono-3H-pyrrolizine*
	
RMN ^{1}H	
0.88 (t, 3H) ; 1.2-1.4 (m, 16H) ; 2.81 (dt, 2H) ; 4.13 (false qt, 4H) ; 4.58 (dddd, 2H) ; 6.12 (ddt, 1H) ; 6.33 (ddt, 1H) ; 6.99 (ddt, 1H)	0.88 (t, 3H) ; 1.2-1.4 (m, 16H) ; 2.60 (t, 2H) ; 4.10 (false qt, 4H) ; 4.42 (ddd, 2H) ; 6.18 (ddt, 1H) ; 6.58 (ddt, 1H) ; 7.37 (dddt, 1H)
RMN ^{13}C	
13.7 (C_{14}) ; 15.9 (C_{16}) ; 22.2,29.3,30.6,31.3 ($C_{10,11,12,13}$) 26.8 (C_8, $J_{C\text{-}P}$ = 2.8) ; 28.8 (C_9, $J_{C\text{-}P}$ = 1.7) ; 52.8 (C_3, $J_{C\text{-}P}$ = 20.5) ; 61.1 (C_{15}) ; 99.7 (C_6) ; 112.7 (C_7, $J_{C\text{-}P}$ = 2.4) ; 117.9 (C_2, $J_{C\text{-}P}$ = 208.2) ; 118.0 (C_5) ; 140.3 (C_{7a}, $J_{C\text{-}P}$ = 16.5) ; 151.4 (C_1, $J_{C\text{-}P}$ = 14.1)	13.7 (C_{14}) ; 15.9 (C_{16}) ; 22.3,28.8,29.1,31.5 ($C_{10,11,12,13}$) 25.4 (C_8) ; 28.7 (C_9) ; 51.4 (C_3) ; 60.8 (C_{15}) ; 110.0 (C_6, $J_{C\text{-}P}$ = 210.5) ; 115.1 (C_7, $J_{C\text{-}P}$ = 13.2) ; 122.4 (C_2) ; 126.3 (C_5, $J_{C\text{-}P}$ = 23.8) ; 126.9 (C_1) ; 141.5 (C_{7a}, $J_{C\text{-}P}$ = 21.1)

REFERENCES

1. E. E. Schweizer and K. K. Light, *J. Am. Chem. Soc.*, **86,** 2963 (1964).
2. W. K. Anderson and P. F. Corey, *J. Med. Chem.*, **20,** 812–8 (1977).
3. J. M. Muchowski and S. H. Unger, *J. Med. Chem.*, **28,** 1037–49 (1985).
4. J. Guervenou and G. Sturtz, *Phosphorus, Sulfur and Silicon*, **70,** 255–261 (1992).
5. A. Michael, *J. Prakt. Chem.*, **35,** 349–56 (1887).
6. (a) G. Sturtz, P. Voisin-Dacheux and G. Guillamot, *C. R. Acad. Sci. Paris*, **t.310,** Série II, 739–742 (1990); (b) G. Sturtz and P. Voisin-Dacheux, PCT Int. Appl. WO 88 06,158 (Cl.C07F9/65) 25 Aug. 1988, Fr. Appl. 87/2,449, 20 Feb. 1987 [CA 110-P193395].
7. C. R. Degenhardt and D. C. Burdsall, *J. Org. Chem.*, **51,** 3488 (1986).
8. (a) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83,** 1733–8 (1961); (b) W. S. Wadsworth and W. D. Emmons, *Org. Synth.*, **45,** 44 (1965); (c) G. Sturtz, G. Lavielle and H. Normant "Reactionen von α-phosphoryl-carbanionen," Chemiker Zeitung, p. 506, 1972; (d) W. S. Wadsworth and W. D. Emmons, *Org. React.*, **25,** 73–253 (1977).
9. T. Minami and J. Motoyoshiya, *Synthesis*, **4,** 333–412 (1992).
10. T. Minami, M. Suganuma and T. Agawa, *Chem. Lett.*, 258–8 (1978).
11. W. Flitsch and W. Lubish, *Chem. Ber.*, **117,** 1424–35 (1984).
12. W. Flitsch and R. Heidhues, *Chem. Ber.*, **101,** 3843–50 (1968).
13. A. Vilsmeier and A. Haack, *Chem. Ber.*, **60,** 119–22 (1927).
14. A. Hassner and C. Stumer, "Organic Synthesis Based on Named Reactions and Unnamed Reactions," p. 399, Pergamon, 1994.
15. G. L. Ciamician and P. Silber, *Chem. Ber.*, **18,** 1466 (1885).
16. A. G. Anderson and M. M. Exner, *J. Org. Chem.*, **42,** 3952–5 (1977).
17. (a) B. ODDO, *Ber.*, **43,** 1012–21 (1910); (b) G. P. Bean, *J. Heterocyclic Chem.*, **2,** 473–4 (1965).
18. (a) D. M. Ketcha, B. A. Lieurance, D. F. J. Homan and G. W. Gribble, *J. Org. Chem.*, **54,** 4350–6 (1989); (b) D. M. Ketcha and G. W. Gribble, *J. Org. Chem.*, **50,** 5451–7 (1985); (c) G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. III, part 1, pp. 92–3, Intersciences Publishers, 1964.
19. R. M. Silverstein, E. E. Ryskiewicz, C. Willard and R. C. Koehler, *J. Org. Chem.*, **20,** 668–72 (1955).
20. G. G. Kleinspehn and A. E. Briod, *J. Org. Chem.*, **26,** 1652–4 (1961).
21. A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., pp. 367–8, Longman, 1970.
22. J. S. Pizey, "Synthetic Reagents," Ellis Horwood Limited, Vol. I, pp. 333–7, John Wiley, New York, 1974.
23. J. P. Haelters, B. Corbel and G. Sturtz, *Phosphorus, Sulfur and Silicon*, **44,** 53–74 (1989).
24. W. Flitsch and G. Jones, "Advances in Heterocyclic Chemistry," Vol. 137, p. 47, Academic Press, Inc., 1984.
25. MOPAC 6.0 on SUN OS 413: Programme Exchange (QCPE), Dpt. of Chemistry, Indiana University—Bloomington, Indiana 47405.
26. AM1 method: M. Dewar, E. Zeobisch, E. Healy and J. Stewart, *J. Am. Chem. Soc.*, **107,** 3902–9 (1985).