Unexpected tetrahydrophosphepine oxides by the ring enlargement of tetrahydrophosphinine oxides

György Keglevich,*[a] Hoang Thi Thai Thanh,[a] Áron Szöllősy,[b] Kálmán Újszászy[c] and László Tőke[d]

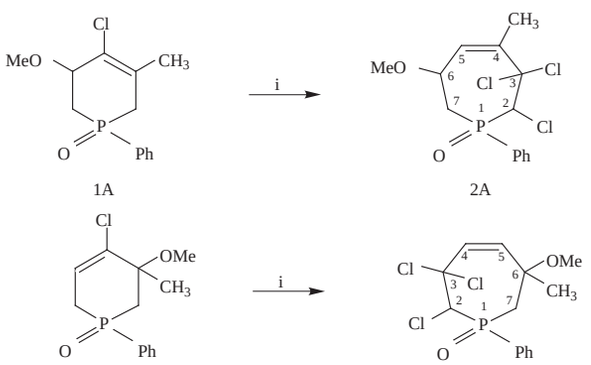
[a] *Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary*
[b] *Department of General and Analytical Chemistry, Technical University of Budapest, 1521 Budapest, Hungary*
[c] *Department of General and Inorganic Chemistry, Eötvös University, 1518 Budapest, Hungary*
[d] *Research Group of the Hungarian Academy of Sciences at the Department of Organic Chemical Technology, Technical University of Budapest, 1521 Budapest, Hungary*

Received (in Cambridge) 10th July 1998, Accepted 7th September 1998

Reaction of the regioisomers (A and B) of tetrahydrophosphinine oxide 1 with NaOH–H_2O–$CHCl_3$ under PTC conditions affords tetrahydrophosphepine oxides 2A and 2B through an unexpected path involving isomerisation of 1 and cyclopropanation *via* Michael addition of CCl_3^-.

Phosphepine derivatives constitute an important category of P-heterocycles.[1] The ring enlargement of phosphinine derivatives by dichlorocarbene is a useful method for construction of the seven-membered ring.[2] The ring expansion of 1,2-dihydrophosphinine oxides gives phosphepine oxides,[3] while that of 1,2,3,6-tetrahydrophosphinine oxides leads to 2,7-dihydrophosphepine oxides.[4]

We wished to apply the ring enlargement to a tetrahydrophosphinine oxide with a methoxy substituent in position 3 (**1**),



Scheme 1 i, 50% aq. NaOH, TEBAC, $CHCl_3$, 26–65 °C.

which is readily available *via* 3-methyl-1-phenyl-2,5-dihydro-1*H*-phosphole 1-oxide.[5] Its regioisomers **1A** and **1B**, both consisting of stereoisomers,[5] were reacted with 50% aqueous sodium hydroxide–chloroform under phase transfer conditions. Flash chromatography of the concentrated organic phase furnished a four-component mixture with δ_P 38.2 (47%), 37.7 (28%), 37.2 (16%) and 36.1 (9%). These isomers were, however, neither the expected adducts with dichlorocarbene, nor the related dihydrophosphepine oxides. ^{13}C and ^1H NMR spectra of a refined sample with δ_P 38.2 (55%) and 37.7 (45%) obtained in 22% yield suggested 2,3,6,7-tetrahydrophosphepine structures **2A** and **2B** (Scheme 1). The species with δ_P 37.2 and 36.1 are, presumably, additional diastereomers of products **2A** and **2B**, respectively. It is assumed that the four isomers of tetrahydrophosphinine **1** are converted to distinct isomers of **2**. As only four of the theoretically possible eight isomers could be detected by ^{31}P NMR spectroscopy (there are three stereogenic centers in both **2A** and **2B**), it can be assumed that isomers of the product **2** are formed in a selective manner.

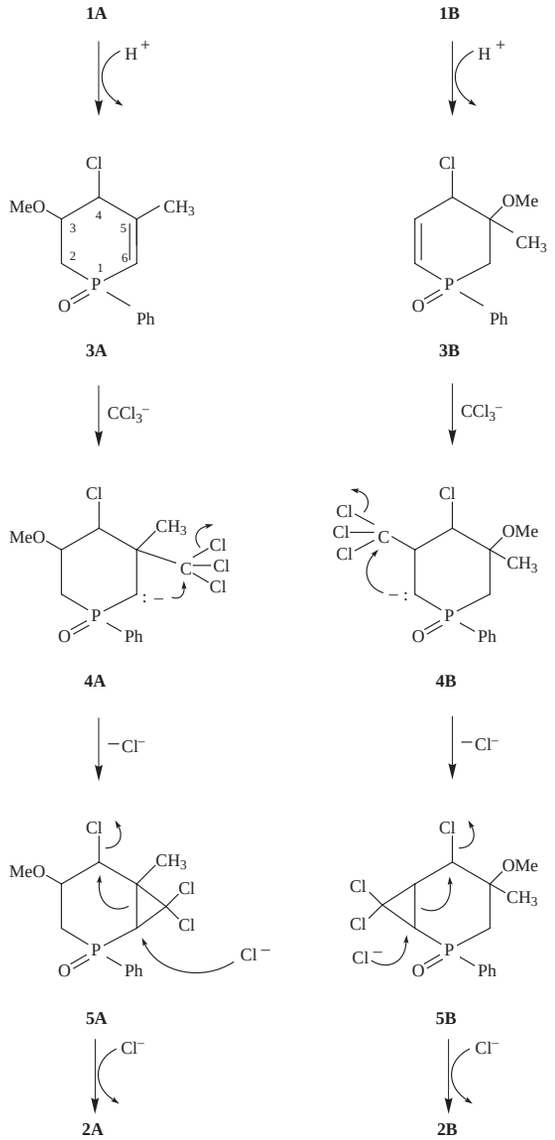
Skeletal carbon atoms of the isomers of tetrahydrophosphepines **2A** and **2B** were well-established in the ^{13}C NMR spectrum (Table 1). The CH_2 and the CHCl signals at δ_C 30/36 and 56/59, respectively, were split by $^1J_{PC}$ of 63–66 Hz, while the CCl_2 unit could be seen at δ_C 74/79. In the isomer of **2A**, the methoxy group was attached to a CH moiety, while in the isomer of **2B** it was attached to a quaternary carbon atom. The isomer of **2B** revealed two olefinic protons, while that of **2A** a single one. The carbon atom bearing the methoxy group appeared at δ_C 84 for **2A** and at δ_C 81 for **2B**. From among the ^1H NMR data, the shift of the C^4–H and C^5–H for **2B** at δ_H 6.03 and 6.41 coupled by 2.6 Hz, as well as the singlet of C^5–H for **2A** at δ_H 5.66, are worthy of mention. The C*H*–OMe of **2A** appeared at δ_H 4.55 (dd, J_1 = 11.4 Hz, J_2 = 6.6 Hz). The structures of tetrahydrophosphepine oxides **2A** and **2B** were also confirmed by two-dimensional correlation diagrams, such as an HMQC spectrum. Due to the thermal instability of the tetrahydrophosphepine **2**, EI and CI mass spectroscopy were not useful in confirming the molecular weight. Thermal examination by DSC showed that product **2** decomposed above 96 °C.

According to our explanation, the key step for the formation

Table 1 ^{13}C NMR data for the isolated isomers of tetrahydrophosphepine oxides **2A** and **2B** ($CDCl_3$)

	δ (J_{PC} in Hz)							
	C^2	C^3	C^4	C^5	C^6	C^7	Me	MeO
2A[a]	55.6	74.3	150.8	127.1	83.8	29.6	14.1	59.1
	(64.1)	—	(16.9)	(5.2)	(7.3)	(66.2)	—	—
2B[b]	59.2	79.1	142.6[c]	135.6[c]	80.5	35.8	22.3	51.9
	(63.0)	—	(16.2)	(6.0)	(5.8)	(65.3)	—	—

[a] Signals for the phenyl group of **2A**, $C^{2'}$: 128.8 (11.9),[d] $C^{3'}$: 130.8 (9.6),[d] $C^{4'}$: 132.5. [b] Signals for the phenyl group of **2B**, $C^{2'}$: 128.8 (11.9),[e] $C^{3'}$: 131.0 (8.9),[e] $C^{4'}$: 132.5. [c,d,e] May be reversed.



Scheme 2

of tetrahydrophosphepines **2A** and **2B** may be the base-catalysed isomerisation of 1,2,3,6-tetrahydrophosphinine oxides **1A** and **1B** to 1,2,3,4-tetrahydro derivatives **3A** and **3B** (Scheme 2). As a close analogy, the 2,5-dihydro-1*H*-phosphole 1-oxides can readily isomerise to the 2,3-dihydro derivatives.[6,7] The next step may involve Michael-type addition of a trichloromethyl anion at the end of the double bond of **3A** and **3B** followed by cyclopropanation. This protocol for the formation of the dihalogenocyclopropane ring is quite common with suitable double bonds.[8–11] Direct cyclopropanation of the –CH=CH–P(O)Ph moiety by an electrophilic dichlorocarbene unit can be excluded on the basis of our earlier experiences.[12]

The intermediacy of species **3** in the above mechanism seems to be supported, as tetrahydrophosphinine **1** could be isomerised to compound **3** in a separate experiment. Treatment of the chlorofom solution of starting materials **1A** and **1B** with 50% aqueous sodium hydroxide at 25 °C led to a mixture containing 40% of unreacted **1A** and **1B** according to GC-MS. The remaining 60% represented four isomers of a product with the same molecular weight ($M^+ = 270$). The new species were assumed to be the isomers (**A** and **B**)† of 1,2,3,4-tetrahydrophosphinine **3**. The major isomer of **3** (δ_P 13.3) was separated by repeated column chromatography in a purity of 91%. The ^{13}C NMR spectral parameters suggested that this was an isomer of **3A**. Beside the ^{13}C NMR chemical shifts and couplings, the upfield δ_P of 13.3 detected for **3A** also adds evidence for the double bond being in conjugation with the phosphoryl group.

Reaction of the isomerised tetrahydrophosphinine **3A** with the trichloromethyl anion led selectively to an isomer of tetrahydrophosphepine **2A** (δ_P 38.3).

It can be concluded that the ability of tetrahydrophosphinine **1** to isomerise in aqueous sodium hydroxide is responsible for the unexpected outcome of the above reaction. Further investigations on the mechanism are in progress. We wish to explore if the reaction is of general value and to study the reaction of 1,2,3,4-*tetrahydrophosphinines* **3** with other nucleophiles. The reaction may have potential for extension to other kinds of heterocycles.

Experimental

Ring enlargement of the isomers (A and B) of tetrahydrophosphinine oxide 1

A solution of NaOH (15.0 g, 0.375 mol) in water (15 cm^3) was added dropwise to a mixture of isomeric tetrahydrophosphinine oxides (**1A** and **1B**)[5] (1.0 g, 3.7 mmol) and triethylbenzylammonium chloride (TEBAC) (0.28 g, 1.23 mmol) in alcohol-free $CHCl_3$ (40 cm^3). The contents of the flask were stirred at the boiling point for 3 h. The mixture was filtered and the organic phase made up to its original volume with $CHCl_3$. This treatment with aqueous NaOH was repeated two times, as above. The crude product obtained after drying (Na_2SO_4) and evaporating the solvent was purified by repeated column chromatography (silica gel, 3% MeOH in $CHCl_3$) to give **2** (0.29 g, 22%) as a mixture of isomer **A** (55%, δ_P 38.2) and isomer **B** (45%, δ_P 37.7).

Isomerisation of tetrahydrophophinine oxide 1

A mixture of isomeric tetrahydrophosphinine oxides (**1A** and **1B**)[5] (0.35 g, 1.30 mmol), $CHCl_3$ (18 cm^3) and NaOH (3.5 g, 87.5 mmol) in water (3.5 cm^3) was stirred at room temperature for 22 h. The pH was adjusted to 7 using dilute hydrochloric acid, the mixture filtered and the organic phase separated and concentrated. According to GC-MS, the crude product consisted of 40% of the isomers of **1** (*m*/*z* 270) and 60% of the four isomers of **3** (*m*/*z* 270). Repeated column chromatography (as above) afforded an isomer of **3A** in a purity of 91% (0.08 g, 21%). ^{31}P NMR ($CDCl_3$) δ 13.3; ^{13}C NMR ($CDCl_3$) δ 25.1 ($^3J_{PC}$ = 14.5, C^5–*C*H_3), 26.4 ($^1J_{PC}$ = 69.2, C^2), 56.2 ($^3J_{PC}$ = 12.8, C^4), 57.5 (CH_3O), 77.7 ($^2J_{PC}$ = 7.1, C^3), 120.6 ($^1J_{PC}$ = 94.5, C^6), 151.5 (C^5); GC-MS, *m*/*z* (rel. int.) 270 (M^+, 2), 205 (100), 177 (60), 77 (46).

Acknowledgements

We thank Professor Martin G. Banwell (Australian National University at Canberra) for his useful comments. OTKA support of this research is gratefully acknowledged (Grant No: T 014917).

Notes and references

† Theoretically, both regioisomers (**3A** and **3B**) may consist of four diastereomers due to the three chiral centers. Only four isomers could be detected.

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Communication 8/05403G