# Solvolysis of 1-oxo-2,8-diphenyl-2,5,8-triaza-1λ⁵-phosphabicyclo[3.3.0]octane: new rearrangement of an eight- to a five-membered phosphodiamidate system

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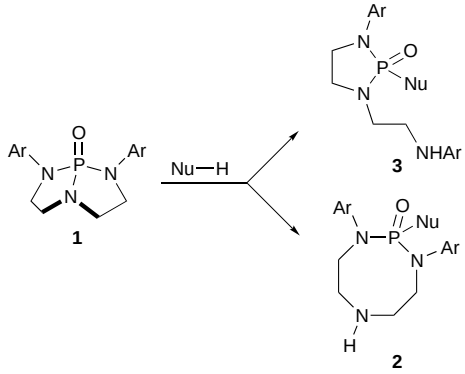
**The alcoholysis of the title compound with $RO^-$/ROH gives the 1,3,2-diazaphospholidine derivative *via* the cleavage of the P–N(2) bond, while under acidic catalysis the P–N(5) bond is broken leading to the eight-membered monocyclic product, which can isomerize *via* a new type of rearrangement to the former five-membered system.**

We have recently reported the preparation of the bicyclic phosphoric triamides **1** *via* the base-promoted cyclization of the corresponding 3-(2-chloroethyl)-2-oxo-1-aryl-2-arylamino-1,3,2-diazaphospholidines.[1] Nucleophilic cleavage of one of the P–N bonds in **1** can lead to another 1,3,2-diazaphospholidine derivative ['*exo*' departure of N(2)], or to a novel, eight-membered heterocyclic system **2** ['*endo*' departure of N(5)] (Scheme 1). We present here the results of the acid-catalyzed or base-promoted alcoholysis of **1a** (Ar = Ph). It was expected that under acidic conditions the regioselectivity governed by the first protonation site of the substrate[2] should involve the departure of the more basic N(5) atom. Our recent $^{15}$N NMR spectroscopic studies[3] indicated a high degree of 'p³' character, hence high basicity, of N(5) in **1**. Alcoholysis of **1a** carried out in an alcohol containing 1 equiv. of dry HCl led, as expected, to the exclusive cleavage of the P–N(5) bond, yielding the corresponding 1-oxo-1-alkoxy-2,8-diphenyl-2,5,8-triaza-1λ⁵-phosphacyclooctane **2a** (Ar = Ph; Nu = OMe) or **2b** (Ar = Ph; Nu = OEt).‡ Amido esters **2** are, however, rather unstable compounds and undergo further changes upon purification (*vide infra*); they could be converted into stable derivatives *via* acylation of the N(5) atom.§ Unambiguous evidence for the structure of the primary product of the solvolysis was obtained from the crystal structure of the *N*⁵-Bz derivative of **2b** (Fig. 1).¶ Structural parameters of the phosphodiamidate function in *N*⁵-Bz**2b** are similar to those reported for related structures, except for two points. First, we observe the short P···N(2) non-bonded distance of 3.242 Å, which should be even shorter in free, nonbenzoylated **2b**. Second, the two P–N bonds are non-equivalent: while one (1.651 Å) lies well within a typical bond distance for phosphoramidates,[4] the other (1.688 Å) indicates a significantly lower bond order.




**Scheme 1**

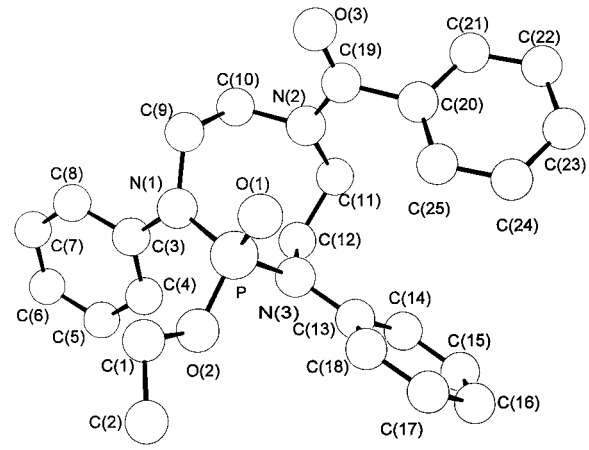



**Fig. 1** ORTEP plot of the structure of the *N*-benzoyl derivative of **2b**

When free cyclic diamido phosphates **2** were stored as neat substances, or as solutions in aprotic solvents, they underwent slow change yielding another phosphorus-containing product. Full conversion could be achieved by refluxing **2** in benzene or THF and, for **2b**, the product, after isolation and purification, was identified as the isomeric 3-[2-(phenylamino)ethyl]-2-oxo-2-ethoxy-1-phenyl-1,3,2λ⁵-diazaphospholidine **3b**.‖ The structure of this product was determined by X-ray diffraction (Fig. 2),** demonstrating unambigously the 8 → 5 ring contraction nature of the rearrangement. The only reported structure closely related to **3b** is that of Jones *et al.*,[5] the molecular parameters of both compounds correspond well to each other.

This new ring contraction **2b** → **3b** can be conveniently followed *via* $^{31}$P NMR spectroscopy ($\Delta\delta_P$ = 6.4 ppm). Reactions carried out in refluxing THF with variable initial concentrations of **2b** showed clearly the first order kinetics, with $k_1 = (4.1 \pm 0.1) \times 10^{-5}$ s$^{-1}$. The rearrangement can be explained in terms of intramolecular 1,5-nucleophilic attack of the amine nitrogen at the phosphoryl centre, followed by proton transfer and P–N bond cleavage (Scheme 2); this mechanism is also supported by the structural characteristics of *N*⁵-Bz**2a** discussed above. Similar transannular N–P interaction in an eight-membered heterocyclic system was postulated for the

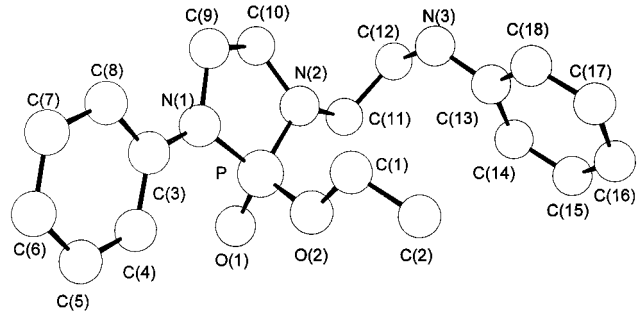
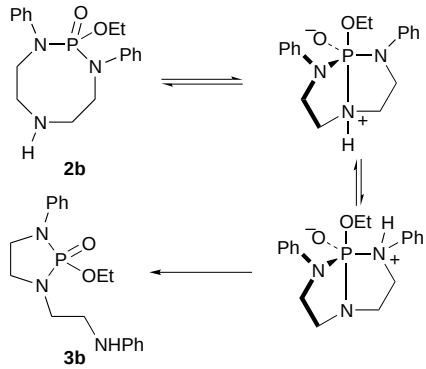



**Fig. 2** ORTEP plot of the structure of **3b**




**Scheme 2**

mechanism of the hydrolysis of medium-ring phosphate esters.[6] In that case, however, as well as in other cases of transannular interactions involving nitrogen and a carbonyl group,[7] the ring structure of the substrate remains intact, while for **2** we observe a change in the cyclic skeleton of the molecule. To the best of our knowledge, this is the first reported case of a rearrangement of this type.

Methanolysis of **1a** in $MeO^-$/MeOH led directly to the formation of **3a** (Ar = Ph; Nu = OMe) as a result of nucleophilic cleavage of the P–N(Ph) bond. In the absence of the activation of the N(5) atom in **1** *via* protonation, it is the leaving ability of the departing nitrogen (NPh) that determines the regioselectivity of the P–N bond cleavage. In the presence of an excess of $MeO^-$ ions, **3a** undergoes the opening of the second 1,3,2$\lambda^5$-diazaphospholidine ring, yielding dimethyl di(2-phenylaminoethyl)phosphoramidate **4a**.††

The **2** → **3** rearrangement reported here indicates greater thermodynamic stability of the latter heterocyclic system. The structure and conformational behaviour of **2**, as well as the mechanism of its rearrangement to **3**, is currently being studied in this laboratory.

## Notes and References

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‡ *Acid-catalysed alcoholysis* of **1a**: a solution of **1a** (0.50 g, 1.67 mmol) in anhydrous alcohol (15 ml) containing dry HCl (1.67 mmol) was kept at room temperature for 16 h, diluted with water (10 ml) and neutralised with aq. $Na_2CO_3$. The solution was extracted with $CHCl_3$ (3 × 10 ml), dried ($Na_2SO_4$) and evaporated under reduced pressure yielding **2** as a solid (**2a**) or a viscous oil (**2b**). Data for **2a** (0.55 g, 100%): mp 91.5–92.7 °C; $\delta_H$ (300 MHz, $CDCl_3$) 2.04 (1 H, br s), 2.87 (4 H, ddd, *J* 14.6, 6.7, 3.1), 3.50 (3 H, d, *J* 5.6), 3.60–3.85 (4 H, m), 7.08–7.50 (10 H, m); $\delta_C$ 47.4 (s), 51.8 (s), 53.2 (d, *J* 5.7 Hz), 123.5 (s), 124.1 (s), 129.2 (s), 143.3 (d, *J* 4.2); $\delta_P$ 13.6. For **2b** (0.58 g, 100%): oil; $\delta_H$ 0.99 (3 H, t, *J* 7.1), 2.06 (1 H, br s), 2.87 (4 H, ddd, *J* 14.6, 6.7, 3.1), 3.55–3.80 (4 H, m), 3.87 (2 H, dt, *J* 7.1), 7.08–7.50 (10 H, m); $\delta_C$ 15.6 (d, *J* 6.7), 47.3 (s), 51.5 (s), 62.9 (d, *J* 5.4), 123.4 (s), 123.9 (s), 129.1 (s), 143.2 (d, *J* 4.2); $\delta_P$ 12.1.

§ *Selected data* for $N^5$-Bz**2a**: (66%), mp 148.2–149.7 °C (from MeCN–hexane, 1 : 1); $\delta_P$ 12.0; Found: C, 66.22; H, 6.17; N, 9.50; $C_{24}H_{26}N_3O_3P$ requires: C, 66.19; H, 6.01; N, 9.64%. For $N^5$-Bz**2b**: (74%), mp 144.2–145.6 °C (from MeCN); $\delta_P$ 10.6; Found: C, 67.07; H, 6.29; N, 9.34. $C_{25}H_{28}N_3O_3P$ requires: C, 66.80; H, 6.27; N, 9.34%.

¶ *Crystal data* for $N^5$-Bz**2b**: $C_{25}H_{28}N_3O_3P$, *M* = 449.49, monoclinic, space group $P2_1/n$ (No. 14), *a* = 9.743(1), *b* = 12.443 (2), *c* = 19.334(2) Å, $\beta$ = 104.34(1)°, *U* = 2271(1) Å$^3$, *F*(000) = 952, $\lambda$(Mo-K$\alpha$) = 0.7107 Å, $\mu$(Mo-K$\alpha$) = 1.13 cm$^{-1}$, *T* = 295(1) K, *Z* = 4, $D_c$ = 1.30 g cm$^{-3}$. Data were collected on an Enraf Nonius CAD4 diffractometer in the range 3 ⩽ $\theta$ ⩽ 30° (7072 reflections). The structure was solved by direct methods (ref. 8) and refinement, based on *F*, was by full-matrix least-squares methods (ref. 9) to $R$ = 0.057, $R_w$ = 0.065 {weighting scheme [$\sigma^{-2}(F_o)$ + 0.000699 $F^2$]} for 293 parameters using 4047 unique reflections with $I > 3\sigma(I)$.

‖ *Rearrangement* of **2b** to **3b**: **2a** (0.345 g, 1 mmol) in dry benzene (15 ml) was heated under reflux for 18 h. After concentrating to *ca*. 1/4 volume, the solution was poured into dry $Et_2O$ (20 ml) with vigorous stirring. The precipitate (0.318 g, 92%) was filtered off and crystallized from MeCN. 1-Phenyl-2-ethoxy-2-oxo-3-[2-(phenylamino)ethyl]-1,2,3$\lambda^5$-diaza-phospholidine **3b**, mp 129.4–130.1 °C; $\delta_H$ 1.17 (3 H, t, *J* 7.1), 3.24–3.46 (6 H, m), 3.57–3.70 (2 H, m), 3.97 (2 H, dt, *J* 7.1), 6.60–7.30 (10 H, m); $\delta_C$ 16.2 (d, *J* 7.2), 41.6 (d, *J* 2.4), 43.1 (s), 43.3 (s), 44.4 (d, *J* 4.9), 63.6 (d, *J* 7.2), 112.5 (s), 115.9 (s), 122.9 (s), 129.2 (s), 129.3 (s), 141.3 (d, *J* 6.3), 148.0 (s); $\delta_P$ 18.5; Found: C, 62.18; H, 7.16; N, 12.08; $C_{18}H_{24}N_3O_2P$ requires: C, 62.59; H, 7.00; N, 12.16%.

** *Crystal data* for **3b**: $C_{18}H_{24}N_3O_2P$, *M* = 345.38, monoclinic, space group $P2_1/n$ (No. 14), *a* = 13.902(2), *b* = 6.046(5), *c* = 22.110(5) Å, $\beta$ = 94.59(3)°, *U* = 1852(1) Å$^3$, *F*(000) = 736, $\lambda$(Mo-K$\alpha$) = 0.7107 Å, $\mu$(Mo-K$\alpha$) = 1.24 cm$^{-1}$, *T* = 295(1) K, *Z* = 4, $D_c$ = 1.22 g cm$^{-3}$. Data were collected on an Enraf Nonius CAD4 diffractometer in the range 3 ⩽ $\theta$ ⩽ 30° (6077 reflections). The structure was solved by direct methods (ref. 8) and refinement, based on $F^2$, was by full-matrix least-squares methods (ref. 9) to $R$ = 0.063, $R_w$ = 0.040 {weighting scheme [$\sigma^2(f_o)$]} for 221 parameters using 2522 unique reflections with $I > 3\sigma(I)$. An intermolecular bond O(1)···H–N(3) of 2.042 Å is observed. Perspective drawings were prepared using ORTEP (ref. 10). CCDC 182/772.

†† *Base-promoted alcoholysis* of **1a**: a solution of **1a** (0.300 g, 1 mmol) and MeONa (3 mmol) in MeOH (20 ml) was kept at room temperature for 28 days (full conversion, as shown by $^{31}$P NMR spectroscopy), neutralised with methanolic HCl, filtered and evaporated under reduced pressure. The crude product (0.336 g, oil) consisted of two phosphorus-containing compounds ($\delta_P$ 19.9, 55%; $\delta_P$ 14.4, 45%) which were separated by column chromatography ($SiO_2$, $Et_2O$). *Selected data* for **3a**, oil; $\delta_H$ 3.39 (6 H, m), 3.61 (3 H, d, *J* 12.3), 3.63 (2 H, m), 4.42 (1 H, br s), 6.63 (2 H, d, *J* 7.6), 6.68 (1 H, t, *J* 7.5), 6.98 (1 H, t, *J* 7.3), 7.15 (4 H, m), 7.29 (2 H, t, *J* 7.9); $\delta_C$ 41.7 (s), 43.2 (d, *J* 7.7), 43.4 (d, *J* 6.5), 44.5 (s), 54.3 (d, *J* 7.8), 112.8 (s), 115.7 (s), 117.4 (s), 121.7 (s), 129.3 (s), 129.4 (s), 137.6 (d, *J* 5.2), 147.8 (s); $\delta_P$ 19.9; Found: C, 63.20; H, 7.48; N, 11.45. $C_{19}H_{26}N_3O_2P$ requires: C, 63.50; H, 7.29; N, 11.69%. For **4a**: oil; $\delta_H$ 3.28 (8 H, m), 3.69 (6 H, d, *J* 11.2), 6.56 (4 H, d, *J* 7.7), 6.68 (2 H, t, *J* 7.4), 7.15 (4 H, m); $\delta_C$ 41.5 (s), 45.8 (d, *J* 4.4), 53.5 (d, *J* 6.2), 112.7 (s), 117.9 (s), 129.3 (s), 147.8 (s); $\delta_P$ 14.2.


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