Reactions of sodium *N*-benzylideneglycinate with dialkyl chlorophosphites: formation of 1,4-bis[α-(dialkoxyphosphoryl)benzyl]piperazine-2,5-diones

Mudaris N. Dimukhametov, Marina A. Abaskalova, Elena Yu. Davydova, Evgenia V. Bayandina, Alexey B. Dobrynin, Igor A. Litvinov and Vladimir A. Alfonsov*

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 8432 75 5322; e-mail: alfonsov@iopc.knc.ru

DOI: 10.1070/MC2004v014n01ABEH001867

The reactions of sodium *N*-benzylideneglycinate with dialkyl chlorophosphites gave 1,4-bis[α-(dialkoxyphosphoryl)benzyl]-piperazine-2,5-diones, novel phosphorylated derivatives of α-aminocarboxylic acids.

The derivatives of α-aminoalkylphosphonic acids are of interest because these compounds exhibit biological activities and can act as enzyme inhibitors.[1,2] The stereoselectivity of reactions used for their synthesis is of special importance.[2,3] We found previously[4–7] that 1,2-iminoalcohols react with dialkyl chlorophosphites to give cyclic derivatives of α-aminoalkylphosphonic acids, *viz*., 1,4,2-oxazaphosphorines. The reaction occurs by the intramolecular cyclisation of intermediates containing the trivalent three-coordinate phosphorus atom. A distinctive feature of the reaction is that the formation of the new intracyclic fragment (P–C*RR′–N) occurs stereospecifically.[6–7] Considering the formal structural similarity between α-iminocarboxylic acids and 1,2-iminoalcohols, namely, the same number of carbon atoms between the hydroxy and imino groups, we assumed that these compounds would also be capable of closing the 1,4,2-oxazaphosphorine ring in reactions with dialkyl chlorophosphites.

To check this assumption, we studied model reactions of sodium *N*-benzylideneglycinate **1** with dialkyl chlorophosphites. We obtained sodium *N*-benzylideneglycinate **1** using the reaction of glycine with benzaldehyde in a solution of an alkali in a water–alcohol mixture. Note that no information on reactions between α-iminoacids and P^{III} derivatives was hitherto available. It was unexpectedly found that compound **1** reacts with dialkyl chlorophosphites under very mild conditions to give 1,4-bis[α-(dialkoxyphosphoryl)benzyl]piperazine-2,5-diones **3a–c** (as a mixture of diastereomeric *d*,*l*- and *meso*-forms) as final reaction products.† Products **3a**,**b** were isolated by column chromatography. Moreover, both forms (*d*,*l* and *meso*, in the case of **3b**) or one form (*d*,*l*, in the case of **3a**) were obtained as individual compounds. One of the stereoisomers of compound **3b** can be crystallised; this allowed us to use X-ray diffraction analysis to determine its molecular structure and the relative configurations of the chiral centres.‡ It was found that this compound is the *meso*-form of 1,4-bis[α-(diisopropoxyphosphoryl)benzyl]-piperazine-2,5-dione with opposite configurations of the C(1) and C(1′) carbon atoms (Figure 1).

The configurations of the other stereoisomeric forms of compounds **3a**,**b** were determined by comparing their ^{1}H NMR spectra with those of compound **3b** (*meso*). The position of the HCP proton doublet served as the determining criterion for assigning each stereoisomer to a specific form. For *meso*-form **3b**, the signal of these protons is observed upfield in comparison with the signal of the corresponding protons for the *d*,*l*-form.

Pure compound **3c** was not isolated because of its instability. However, by carrying out the reaction of compound **1** with the ethylenechlorophosphite with the simultaneous monitoring of the reaction mixture in time by means of ^{31}P NMR spectroscopy, we detected the formation of intermediate phosphite **2c** with a trivalent three-coordinate phosphorus atom (δ_P 127.8 ppm) at the beginning of the reaction. The fact that this intermediate product is detectable probably results from the decreased nucleophilicity of the trivalent phosphorus atom incorporated in a five-membered ring in comparison with acyclic analogues. The reaction mixture formed from the starting reagents also displays signals in the region δ_P 40–42 ppm, which probably correspond to **3c** stereoisomers, whose intensity increases in time with a simultaneous decrease in the signal from compound **2c** at δ 127.8 ppm. The signals of product **3c** in the ^{31}P NMR spectrum are shifted downfield in comparison with those of products

† *General procedure for the synthesis of compounds* **3a**,**b**. An equimolar amount of an appropriate dialkyl chlorophosphite in $CHCl_3$ (5 ml) was added with stirring to a suspension of 6.8 mmol of compound **1** in 20 ml of anhydrous $CHCl_3$ in dry argon at room temperature. After one day, the precipitate was filtered off; the residue obtained after removal of the solvent from the filtrate was separated by column chromatography on Chemapol (L 100/160 mesh) in the acetonitrile–toluene system (1:4). The yields of products from the column were monitored by TLC on Silufol UV 254 plates. The overall yields of products **3a** and **3b** determined by summing up their amounts in different eluate fractions were 52 and 58%, respectively.

3a (*meso*): colourless thick liquid, n_D^{20} 1.5375. ^{1}H NMR [Bruker MSL-400, 250 MHz, $(CD_3)_2CO$, TMS] δ: 1.11 (t, 6H, 2Me, $^3J_{HP}$ 7 Hz), 1.15 (t, 6H, 2Me′, $^3J_{HP}$ 7 Hz), 3.98 (d, 2H, 2HCNCP, $^2J_{HH}$ 17 Hz), 4.52 (d, 2H, 2H′CNCP, $^2J_{HH}$ 17 Hz), 3.94–4.22 (m, 8H, 4H_2CO), 6.10 (d, 2H, 2HCP, $^2J_{HP}$ 22 Hz), 7.38–7.62 (m, 10H, 2Ph). ^{31}P NMR [Bruker CXP-300, 36.48 MHz, $(CD_3)_2CO$, 85% H_3PO_4] δ: 19.6. IR (ν/cm^{-1}): 1024 (P–O–C), 1221 (P=O), 1662 (C=O). Found (%) N, 5.32; P, 11.26. Calc. for $C_{26}H_{36}N_2O_8P_2$ (%): N, 4.94; P, 10.95.

3a (*d*,*l*): [from a mixture with compound **3a** (*meso*), 1:1]. ^{1}H NMR [$(CD_3)_2CO$] δ: 1.31 (t, 6H, 2Me, $^3J_{HP}$ 7 Hz), 1.33 (t, 6H, 2Me′, $^3J_{HP}$ 7 Hz), 3.93–4.22 (m, 10H, 4CH_2O + 2HCNCP), 4.58 (d, 2H, 2H′CNCP, $^2J_{HH}$ 17 Hz), 6.17 (d, 2H, 2HCP, $^2J_{HP}$ 23 Hz), 7.40–7.65 (m, 10H, 2Ph). ^{31}P NMR [$(CD_3)_2CO$] δ: 19.4.

3b (*meso*): colourless crystals, mp 141–142 °C. ^{1}H NMR ($CDCl_3$) δ: 0.95–1.24 (4d, 24H, 8Me, $^3J_{HP}$ 6.5 Hz), 3.92 [d, 2H, 2HCNC(O), $^2J_{HH}$ 17 Hz], 4.50 [d, 2H, 2H′CNC(O), $^2J_{HH}$ 17 Hz], 4.61 (m, 2H, 2HCOP), 4.69 (m, 2H, 2H′COP), 6.15 (d, 2H, 2HCP, $^2J_{HP}$ 23 Hz), 7.32–7.59 (m, 10H, 2Ph). ^{31}P NMR ($CDCl_3$) δ: 17.2. IR (ν/cm^{-1}): 988–1010 (P–O–C), 1233 (P=O), 1659 (C=O). Found (%) N, 4.32; P, 10.35. Calc. for $C_{30}H_{44}N_2O_8P_2$ (%): N, 4.50; P, 9.97.

3b (*d*,*l*): colourless thick liquid, n_D^{20} 1.5160. ^{1}H NMR [$(CD_3)_2CO$] δ: 1.03–1.37 (4d, 24H, 8Me, $^3J_{HP}$ 6.5 Hz), 3.84 [d, 2H, 2HCNC(O), $^2J_{HH}$ 16 Hz], 4.65 [d, 2H, 2H′CNC(O), $^2J_{HH}$ 16 Hz], 4.64 (m, 2H, 2HCOP), 4.80 (m, 2H, 2H′COP), 6.12 (d, 2H, 2HCP, $^2J_{HP}$ 23 Hz), 7.39–7.59 (m, 10H, 2Ph). ^{31}P NMR [$(CD_3)_2CO$] δ: 17.2. IR (ν/cm^{-1}): 988–1010 (P–O–C), 1240 (P=O), 1675 (C=O). Found (%) N, 4.43; P, 9.65.

‡ *X-ray diffraction analysis of compound* **3b**. The crystal of **3b**, $C_{30}H_{44}N_2O_8P_2$, is triclinic, space group $P\bar{1}$. At 20 °C, a = 6.268(2), b = 9.130(3), c = 14.351(4) Å, α = 88.62(2), β = 84.75(2), γ = 85.20(2)°, V = 814.9(4) Å^3, Z = 1 (molecule in a special position), M = 622.44, d_{calc} = 1.27 g cm^{-3}, μ(Mo) = 1.76 cm^{-1}, F(000) = 332. The intensities of 2639 reflections were measured on an Enraf-Nonius CAD-4 diffractometer at 20 °C (MoKα radiation, $\omega/2\theta$ scanning, $2\theta_{max}$ = 53°); of these, 1722 reflections with $I \geq 3\sigma$ were observed. The structure was solved by the direct method using the SIR software[10] within the MolEN software package.[11] The structure was refined by a full-matrix least-squares method in an anisotropic approximation. All hydrogen atoms were located by a difference synthesis, and the contributions to the structural amplitudes were taken into account in final least-squares iterations with fixed positions and isotropic temperature parameters. The final divergence factors were R = 0.048, R_w = 0.061 based on 1662 reflections with $F^2 \geq 3\sigma$.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 230983. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

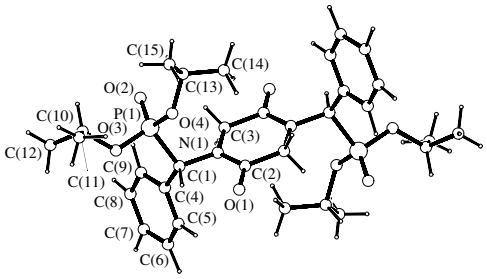
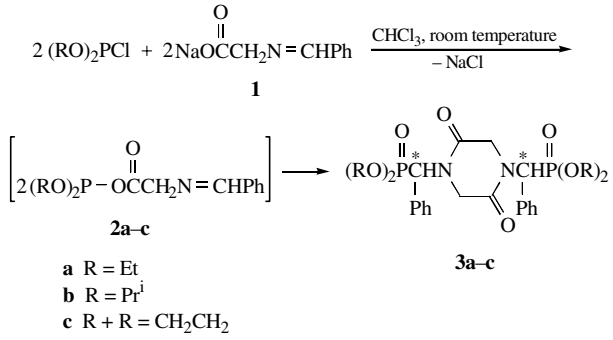


Figure 1 Molecular geometry of **3b** in a crystal. Selected bond lengths (Å): P(1)–O(2) 1.464(3), P(1)–O(3) 1.565(3), P(1)–O(4) 1.565(3), P(1)–C(1) 1.825(4), O(1)–C(2) 1.236(4), O(3)–C(10) 1.457(5), O(4)–C(13) 1.481(5), N(1)–C(1) 1.470(4), N(1)–C(2) 1.340(4), N(1)–C(3) 1.468(5), C(1)–C(4) 1.530(5), C(2)–C(3′) 1.492(5); selected bond angles (°): O(2)–P(1)–O(3) 115.2(2), O(2)–P(1)–O(4) 113.7(1), O(2)–P(1)–C(1) 118.1(2), O(3)–P(1)–O(4) 105.7(2), O(3)–P(1)–C(1) 99.7(2), O(4)–P(1)–C(1) 102.6(1), P(1)–O(3)–C(10) 121.1(2), P(1)–O(4)–C(13) 124.1(2), C(1)–N(1)–C(2) 118.4(3), C(1)–N(1)–C(3) 117.8(3), C(2)–N(1)–C(3) 123.6(3), P(1)–C(1)–N(1) 109.4(2), P(1)–C(1)–C(4) 116.3(2), N(1)–C(1)–C(4) 111.5(3), O(1)–C(2)–N(1) 122.6(3), O(1)–C(2)–C(3′) 117.8(3), N(1)–C(2)–C(3′) 119.6(3), N(1)–C(3)–C(2′) 116.3(3).

3a,**b** owing to the cyclic structure of the phosphorus-containing fragment in **3c**, whereas the incorporation of a phosphorus atom in a five-membered ring results in a downfield shift by 20–30 ppm.[8] Prolonged exposure of the reaction mixture or attempts at its chromatographic separation resulted in the decomposition of product **3c**, which manifests itself as the disappearance of signals around δ 40 ppm and the appearance of a group of signals around δ 15–20 ppm. Most likely, these changes in the spectra occur due to the decomposition of the five-membered ring.

Based on the data obtained, the most probable pathway for the formation of piperazine-2,5-diones **3a–c** from compound **1** and dialkyl chlorophosphites appears to include initial nucleophilic substitution of chlorine at the P^{III} atom under the action of iminocarboxylate **1** to give *O*,*O*-dialkyl-*O*-[(*N*-benzylidene)-glycinoyl]phosphites **2a–c**, which are then converted to final piperazinediones **3a–c** through a series of rearrangements and dimerisation (Scheme 1).



Scheme 1

Dimerisation into piperazine-2,5-diones is typical of α-amino-carboxylic acid derivatives.[9]

This work was supported by the Russian Foundation for Basic Research (grant no. 03-03-33082), the Research and Development Foundation of the Tatarstan Academy of Sciences (grant no. 07-7.2-129/2002) and the Russian Academy of Sciences.

References

1 P. Kafarski and B. Lejczak, *Phosphorus Sulfur Silicon Relat. Elem.*, 1991, **63**, 193.
2 *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, eds. V. P. Kukhar and H. R. Hudsonm, John Wiley & Sons, New York, 2000.
3 O. I. Kolodiazhnyi, *Tetrahedron Asimmetry*, 1998, 1279.
4 M. N. Dimukhametov, E. V. Bayandina, E. Yu. Davydova, A. B. Dobrynin, A. T. Gubaidullin, I. A. Litvinov and V. A. Alfonsov, *Mendeleev Commun*., 2001, 196.
5 M. N. Dimukhametov, E. V. Bayandina, E. Yu. Davydova, T. A. Zyablikova, A. B. Dobrynin, I. A. Litvinov and V. A. Alfonsov, *Izv. Akad. Nauk, Ser. Khim*., 2001, 2357 (*Russ. Chem. Bull., Int. Ed*., 2001, **50**, 2468).
6 M. N. Dimukhametov, E. Yu. Davydova, E. V. Bayandina, A. B. Dobrynin, I. A. Litvinov and V. A. Alfonsov, *Mendeleev Commun*., 2001, 222.
7 M. N. Dimukhametov, E. V. Bayandina, E. Yu. Davydova, I. A. Litvinov, A. T. Gubaidullin, A. B. Dobrynin, T. A. Zyablikova and V. A. Alfonsov, *Heteroatom Chem.*, 2003, **14**, 56.
8 *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*, eds. L. D. Quin and J. G. Verkade, John Wiley & Sons, New York, 1994.
9 S. Rajappa and M. V. Natekar, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Academic Press, San Diego, 1993, vol. 57, pp. 187–289.
10 A. Altomare, G. Cascarano, C. Giacovazzo and D. Viterbo, *Acta Crystallogr., Sect. A*, 1991, **46**, 744.
11 L. H. Straver and A. I. Schierbeek, *MolEN. Structure Determination System*. Nonius B.V., Delft, Netherlands, 1994, vols. 1 and 2.

Received: 25th November 2003; Com. 03/2193