Ketones in the catalytic three-component "one-pot" Kabachnik—Fields synthesis of α-amino phosphonates

E. D. Matveeva, T. A. Podrugina, M. V. Prisyajnoy, and N. S. Zefirov*

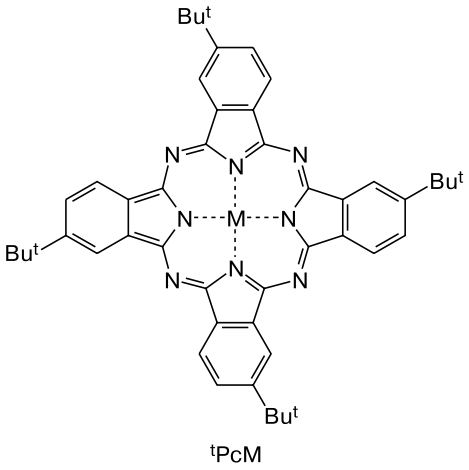
Department of Chemistry, M. V. Lomonosov Moscow State University, 1 Leninskie Gory, 119899 Moscow, Russian Federation. Fax: +7 (495) 939 02 90. E-mail: podrugina@mail.ru; matveeva@org.chem.msu.ru

Reactions of carbocyclic, heterocyclic, and steroidal ketones with benzylamine and diethyl phosphite in a catalytic three-component "one-pot" synthesis of α-amino phosphonates were studied. The activities of mono- and binuclear complexes of tetra(*tert*-butyl)phthalocyanines as catalysts for this process were compared.

Key words: α-amino phosphonates, Kabachnik—Fields reaction, phthalocyanines, ketones, amines, phosphites, organophosphorus compounds.

α-Amino phosphonic acids are phosphorus analogs of α-amino carboxylic acids ("bioisosterism"[1]). The biological activities of α-amino phosphonic acids, the occurrence of natural phosphonates, and proven reactions of phosphonates with various enzymes and receptors[2—6] motivate researchers to look for new routes to α-amino phosphonates,[7—11] many of which still remain not easily accessible. So far design of compounds of this chemotype presents a nontrivial problem, especially for sterically hindered compounds with complex carbocyclic fragments.

Previously,[12] we have proposed a new catalytic three-component "one-pot" version of the Kabachnik—Fields synthesis of α-amino phosphonates with metal tetra(*tert*-butyl)phthalocyanine complexes ^{t}PcM as catalysts.



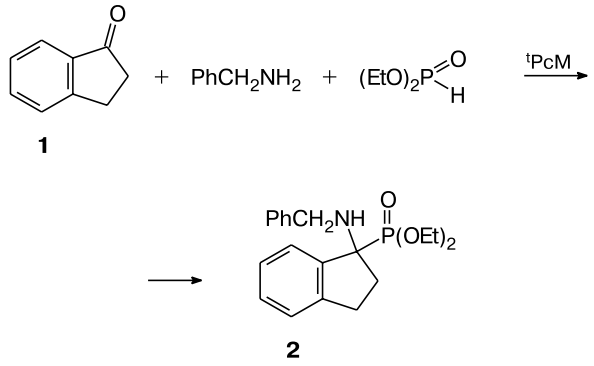
^{t}PcM

M = H_2, AlCl, CrCl, Co^{II}, Ni^{II}, Tb

The use of phthalocyanine catalysis has allowed this reaction to be extended to ketones, including sterically hindered ones.[12—15] Here we employed this method for the synthesis of earlier inaccessible α-amino phosphonates from various carbocyclic and heterocyclic ketones.

We carried out a model reaction of indan-1-one (**1**) with benzylamine and diethyl phosphite (Scheme 1) to compare the catalytic activities of tetra(*tert*-butyl)phthalocyanine ($^{t}PcH_2$) and some of its metal complexes under identical conditions.

Scheme 1



The dependence of the yield of α-amino phosphonate **2** on the catalyst nature is given in Table 1.

In reactions catalyzed by terbium diphthalocyanines, in which access to the metal ion is prevented by the phthalocyanine rings, the yield of amino phosphonate **2** was moderate and comparable with the yields attained with free $^{t}PcH_2$ (see Table 1). The yield of amino phosphonate **2** gradually increases when the central atom of the complex exhibit more pronounced metallic properties. The highest yield of the target product was obtained with ^{t}PcAlCl. In addition, we illustrated with amino phos-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1164—1169, July, 2006.

1066-5285/06/5507-1209

Table 1. Catalyst effect on the yield of α-amino phosphonate **2**

Tetra(*tert*-butyl)phthalocyanine complex	Yield of **2** (%)
^{t}PcAlCl	95
^{t}PcCrCl	85
^{t}PcCo^{II}	50
^{t}PcCo^{III}I	45
^{t}PcNi	45
^{t}PcH$_2$	30
(^{t}Pc)$_2$Tb (green or blue)	30
Without a catalyst	0

phonate **2** that ^{t}PcAlCl can be reused in a catalytic cycle without lowering the yield of the target product.

This catalytic three-component process was employed for the synthesis of α-amino phosphonates **2** and **15**—**24** from various mono- and dicarbonyl compounds **1** and **3**—**14**. A summary of these experiments is given in Table 2.

In many cases, this approach afforded amino phosphonates in high yields. However, the yields of the target products were lower for sterically hindered starting ketones. For instance, with camphor **8a**, the highest yield (30%) of the corresponding amino phosphonate **20** was reached only with a threefold excess of benzylamine and diethyl phosphite and microwave (MW) activation, which provided substantial reduction in the reaction time as well. In the absence of the catalyst, amino phosphonate **20** did not form even with MW activation.

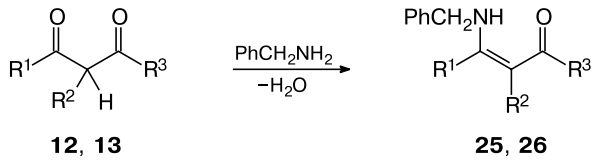
Catalytic reactions of β-dicarbonyl acetylacetone (**12**) and ethyl 2-oxocyclopentane-1-carboxylate (**13**) gave enamines **25**, **26** that did not react with diethyl phosphite (Scheme 2).[9]

Table 2. Yields of α-amino phosphonates in ^{t}PcAlCl-catalyzed reactions of different ketones with $PhCH_2NH_2$ and $(EtO)_2P(O)H$

Ketone	Reaction conditions			Product (yield (%))
	Solvent	τ/h	n^a	
Indan-1-one (**1**)	CH_2Cl_2	18	—	**2** (95)[b]
Fluorenone (**3**)	CH_2Cl_2	72	—	**15** (40)[c]
Anthrone (**4**)	CH_2Cl_2	72	—	**16** (20)
9,10-Anthraquinone (**5**)	CH_2Cl_2	72	2	**17** (75)
1,4-Benzoquinone (**6**)	CH_2Cl_2	24	3	**18** (50)
Cyclopropyl methyl ketone (**7**)	CH_2Cl_2	12	—	**19** (60)
Camphor (**8a**)	EtOH[d]	4	3	**20** (30)
(1*R*)-(+)-Camphor (**8b**)	$Pr^{i}OH$[e]	24·7	3	**20** (25)
N-Boc-Piperidone (**9**)	CH_2Cl_2	18	1.5	**21** (99)
Isatin (**10**)	CH_2Cl_2	48	2	**22** (90)
Pregnane (**11**)	CH_2Cl_2	24·7	2	**23** (40)
Acetylacetone (**12**)	CH_2Cl_2	48	2	—[f]
Ethyl 2-oxocyclopentane-1-carboxylate (**13**)	CH_2Cl_2	48	2	—[f]
Benzil (**14**)	CH_2Cl_2	48	2.5	**24** (30)

[a] With an excess of the reagents per mole of the ketone.
[b] The yield was 85% with the use of ^{t}PcCrCl.
[c] The yield was 5% with the use of ^{t}PcCrCl.
[d] MW activation.
[e] 80 °C.
[f] Under these reaction conditions, ketones **12** and **13** form the corresponding enamines.

Scheme 2



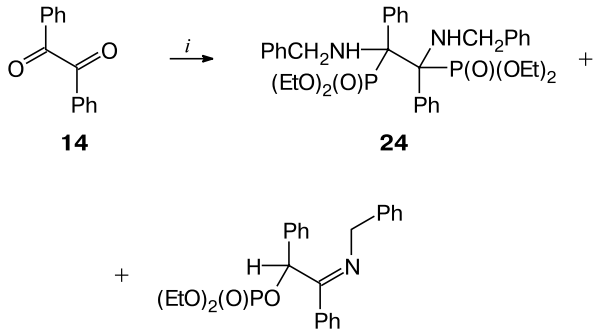
12, **13** **25**, **26**

$R^1 = R^3 = Me$, $R^2 = H$ (**12**, **25**);

$R^1+R^2 = (CH_2)_3$, $R^3 = OEt$ (**13**, **26**)

In contrast, α-diketone **14** reacted with two equivalents of benzylamine and diethyl phosphite to form the corresponding bis(α-amino phosphonate) **24** and 2-benzylimino-1,2-diphenylethyl diethyl phosphate (Scheme 3).

Scheme 3



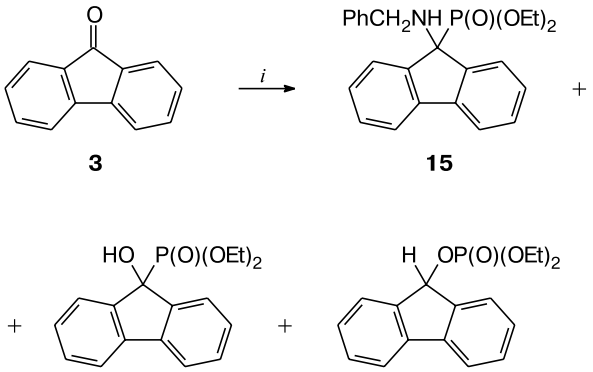
14 **24**

i. 2 $PhCH_2NH_2$, 2 $(EtO)_2P(O)H$, ^{t}PcAlCl.

Reactions with indan-1-one (**1**), fluorenone (**3**), and anthrone (**4**) gave, along with the target α-amino phosphonates **2**, **15**, and **16**, α-hydroxy phosphonates and phosphates as products of their rearrangement in low yields (5—15%) (Scheme 4).

The proposed method was used to obtain α-amino phosphonates from quinones. It was found that 9,10-anthraquinone (**5**) reacts with a double excess of benzylamine and diethyl phosphite to give bis(α-amino phosphonate) **17** in 75% yield. Under analogous conditions, 1,4-benzoquinone (**6**) produced the corresponding

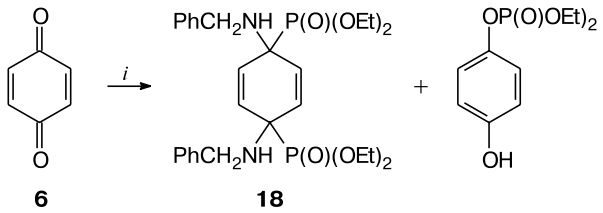
Scheme 4



i. $PhCH_2NH_2$, $(EtO)_2P(O)H$, ^{t}PcAlCl.

bis(α-amino phosphonate) **18** in ~30% yield. Its yield was increased to 50% by employing a triple excess of the reagents; in this case, diethyl 4-hydroxyphenyl phosphate formed as a by-product in 50% yield (Scheme 5).

Scheme 5



i. $PhCH_2NH_2$, $(EtO)_2P(O)H$, ^{t}PcAlCl.

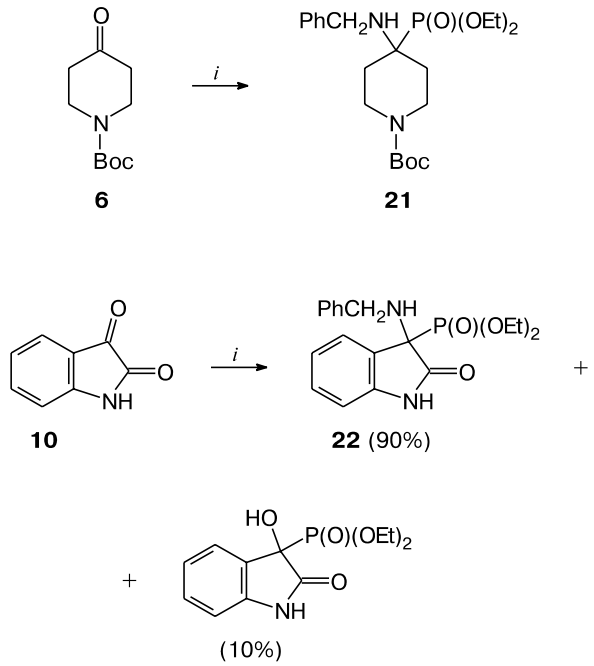
Under standard conditions, heterocyclic ketones such as *N*-Boc-piperidone (**9**) and isatin (**10**) gave the corresponding α-amino phosphonates **21** and **22** in high yields. Small amount of α-hydroxy phosphonate (diethyl 3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl phosphonate) was detected in the reaction with isatin (Scheme 6).

The title method allows access to amino phosphonates based on complex and polyfunctional ketones. For instance, the hormone pregnane **11** reacted with two equivalents of benzylamine and diethyl phosphite to give bis(α-amino phosphonate) **23** in 40% yield (Scheme 7).

Special experiments showed that these reactions do not follow the desired pathway in the absence of phthalocyanine catalysts. In addition, by-products (α-hydroxy phosphonates) in phthalocyanine-catalyzed reactions with benzylamine did not yield the corresponding α-amino phosphonates.

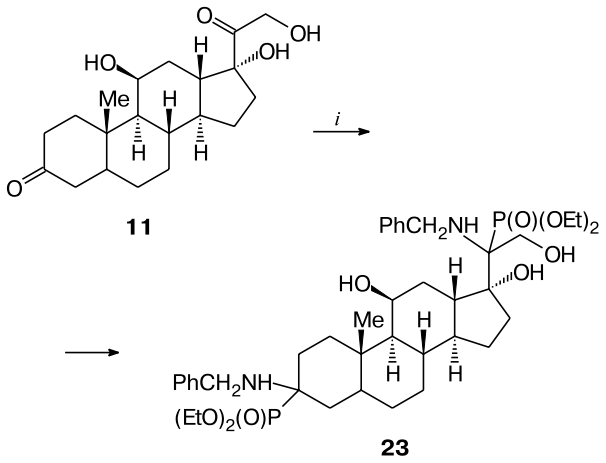
The structures of α-benzylamino phosphonates **2** and **15**—**24**, α-hydroxy phosphonates, and phosphates were confirmed by IR, NMR (^{1}H, ^{13}C, and ^{31}P), and mass spectra and elemental analysis data.

Scheme 6



i. $(EtO)_2P(O)H$, $PhCH_2NH_2$, ^{t}PcAlCl.

Scheme 7



i. 2 $PhCH_2NH_2$, 2 $(EtO)_2P(O)H$, ^{t}PcAlCl.

The ^{31}P NMR spectra of all the α-benzylamino phosphonates obtained show signals at δ 20.5—29.5 relating to the dialkyl phosphonate group.[16] Their IR spectra contain absorption bands at 1240—1250 (P=O), 3200—3400 (NH), and 1180 cm^{-1} (hydrogen-bonded P=O). It should be noted that the absorption intensities and frequencies of the P=O group and the associated group remained unchanged upon the dilution of solutions

of the amino phosphonates in CCl_4, which suggests intramolecular hydrogen bonding.

The ^1H NMR spectra of α-amino phosphonates show signals for chemically nonequivalent ethoxy groups. The signals for the methyl protons appear at δ 1.13 and 1.27 (both t, 1 : 1); the complex multiplets for the methylene protons of the ethoxy groups appear at δ 3.80—4.50. A broad singlet at δ 2.10—3.10 corresponds to the amino group. Signals for the diastereotopic methylene protons of the benzyl group appear as two doublets or AB system at δ 3.50—3.80 (^2J = 12.7—13.4 Hz).

The ^{13}C NMR spectra of α-amino phosphonates show signals at δ 55—60 ($^1J_{C,P}$ = 144—154 Hz) for the quaternary C atom at the P atom. Signals for the non-isochronous ethoxy groups appear as two, not always resolved doublets at δ 16 (CH_3, $^3J_{P,C}$ = 6.3—6.4 Hz) and two doublets at δ 62—63 (OCH_2, $^2J_{P,C}$ = 7—8 Hz). The signal for the CH_2Ph group appears as a not always resolved doublet at δ 50—51 (J = 12—18 Hz). The other signals in the ^1H and ^{13}C NMR spectra of α-amino phosphonates are consistent with the carbon framework structures of the starting ketones.

Experimental

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker Avance 400 instrument (400.13, 100.61, and 161.98 MHz, respectively) in $CDCl_3$ with Me_4Si (^1H and ^{13}C) and 85% H_3PO_4 (^{31}P) as the internal standards.

IR spectra were recorded on a UR-20 instrument in CCl_4.

Elemental analysis was carried out on a Vario-II CHN analyzer and by the Korshun—Klimova pyrolysis.

Mass spectra (MALDI) were recorded on an Autoflex II instrument (Bruker Daltonics) and an Agilent LC/MSD 1100 SL instrument with electrospray ionization at atmospheric pressure (AP-ESI) in the mode of positive ion detection (an ion trap as a mass analyzer). Recording conditions: temperature of the drying gas (nitrogen) 300 °C, flow rate 12 L min^{-1}, power supply voltage 5000 V, capillary outlet voltage 150 V, methanol as a solvent.

The course of the reactions was monitored and the purity of chromatographically separated products was checked by TLC on Silufol plates.

Synthesis of α-amino phosphonates 2 and 15—24 (general procedure). Benzylamine (2 mmol), anhydrous $MgSO_4$ (2 mmol), and ^{t}PcAlCl (0.2 mmol) were added to a solution of a carbonyl compound (2 mmol) in an appropriate solvent (3 mL). The reaction mixture was stirred with a magnetic stirring bar for 3—4 h and then diethyl phosphite (2.4 mmol) was added. The course of the reaction was monitored by TLC (the reaction times are specified in Table 2).

Magnesium sulfate was filtered off and washed with CH_2Cl_2—MeOH (10 : 1, 3×2 mL). The filtrate was concentrated *in vacuo*. The residue was dissolved in a minimum CH_2Cl_2—MeOH (50 : 1) and chromatographed on silica gel (length 15 cm, diameter 1.5—2.0 cm) with CH_2Cl_2—MeOH (50 : 1) as an eluent.

Diethyl 1-benzylamino-2,3-dihydro-1*H*-inden-1-ylphosphonate (2) was obtained from indan-1-one (**1**). The yield was 95%, R_f 0.24 (CH_2Cl_2—EtOH, 35 : 1). Found (%): C, 66.62; H, 7.08; N, 3.81. $C_{20}H_{26}NO_3P$. Calculated (%): C, 66.84; H, 7.29; N, 3.90. ^1H NMR, δ: 1.28, 1.32 (both t, 3 H each, 2 Me, J = 7.0 Hz); 2.34, 2.66, 3.02 (all m, 2 H each, $CH_{2,ring}$); 3.10 (br.m, 1 H, NH); 3.55 (H_A), 3.73 (H_B, AB system, 2 H, CH_2Ph, $^2J_{H,H}$ = 12.7 Hz); 3.85, 4.04, 4.12 (all m, 4 H, 2 OCH_2); 7.26, 7.50 (both m, 9 H, arom.). ^{31}P NMR, δ: 27.82. ^{13}C NMR, δ: 16.48, 16.59 (both d, Me, $^3J_{C,P}$ = 6.1 Hz); 30.65, 32.12 ($CH_{2,ring}$); 46.93 (d, CH_2Ph, J = 12.3 Hz); 59.68 (d, $C(1)_{ring}$, $^1J_{C,P}$ = 154.1 Hz); 62.74, 63.34 (both d, OCH_2, $^2J_{C,P}$ = 7.7 Hz); 124.5, 125.69, 126.55, 126.93, 128.24, 128.36, 128.45, 140.66, 145.04 (C_{arom}). IR, ν/cm^{-1}: 1245 (P=O); 3330, 3480 (NH).

Diethyl 1-hydroxy-2,3-dihydro-1*H*-inden-1-ylphosphonate, a minor product (5%) in the synthesis of compound **2**, R_f 0.22 (CH_2Cl_2—EtOH, 35 : 1). Found (%): C, 57.23; H, 7.11. $C_{13}H_{19}O_4P$. Calculated (%): C, 57.78; H, 7.04. ^1H NMR, δ: 1.30 (t, 6 H, 2 Me, J = 7.0 Hz); 2.21, 2.80, 3.02 (all m, 2 H each, $CH_{2,ring}$); 3.60 (br.m, 1 H, OH); 4.04, 4.14 (both m, 4 H, 2 OCH_2); 7.28, 7.33, 7.59 (all m, 9 H, arom.). ^{31}P NMR, δ: 24.91. IR, ν/cm^{-1}: 1230 (P=O); 3300 (OH).

Recycling of the catalyst recovered in 95% yield by chromatography of the reaction mixture. Benzylamine (2 mmol), anhydrous $MgSO_4$ (2 mmol), and the recovered phthalocyanine catalyst (0.19 mmol) were added to a solution of indan-1-one (2 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 3 h, diethyl phosphite (2.4 mmol) was added, and stirring was continued for an additional 15 h. Subsequent workup was done according to the general procedure. The yield of α-amino phosphonate **2** was 93—95%.

Diethyl 9-benzylamino-9*H*-fluoren-9-ylphosphonate (15) was obtained from fluorenone **3**. The yield was 40%, R_f 0.26 (CH_2Cl_2—EtOH, 35 : 1). ^1H NMR, δ: 1.11, 1.27 (both t, 6 H, 2 Me, J = 7.0 Hz); 2.35 (br.m, 1 H, NH); 3.55 (H_A), 3.78 (H_B, AB system, 2 H, CH_2Ph, $^2J_{H,H}$ = 13.4 Hz); 3.85, 3.94, 4.06 (all m, 4 H, OCH_2); 7.18, 7.27, 7.42, 7.73, 7.80 (all m, 13 H, arom.). ^{31}P NMR, δ: 23.09. ^{13}C NMR, δ: 16.08, 16.28 (both d, Me, $^3J_{C,P}$ = 6.3 Hz); 51.03 (d, CH_2Ph, J = 18.8 Hz); 59.41 (d, $C(1)_{ring}$, $^1J_{C,P}$ = 154.2 Hz); 62.60, 62.80 (both d, OCH_2, $^2J_{C,P}$ = 7.9 Hz); 126.94, 127.74, 128.16, 128.19, 128.30, 128.51, 136.53, 139.16 (C_{arom}). IR, ν/cm^{-1}: 1250 (P=O); 3300, 3470 (NH). MS, m/z: 408 $[M]^+$.

Diethyl 9-hydroxy-9*H*-fluoren-9-ylphosphonate, a minor product (10%) in the synthesis of compound **15**, R_f 0.22 (CH_2Cl_2—EtOH, 35 : 1). ^1H NMR, δ: 1.07 (t, 6 H, 2 Me, J = 7.0 Hz); 3.65 (br.m, H, OH); 3.85, 3.92 (both m, 4 H, OCH_2); 7.31, 7.39 (both t, 2 H each, arom., J = 7.3 Hz); 7.64, 7.90 (both d, 2 H each, arom., J = 7.3 Hz). ^{31}P NMR, δ: 21.06. ^{13}C NMR, δ: 16.13 (d, Me, $^3J_{C,P}$ = 4.7 Hz); 63.70 (d, OCH_2, $^2J_{C,P}$ = 6.3 Hz); 80.58 (d, $C(1)_{ring}$, $^1J_{C,P}$ = 162.0 Hz); 119.87, 126.15, 127.66, 129.52, 140.68, 143.18 (C_{arom}). IR, ν/cm^{-1}: 1250 (P=O). MS, m/z: 318 $[M]^+$; 180 $[M - P(O)(OEt)_2]^+$; 152 $[M - CHOP(O)(OEt)_2]^+$; 105 $[C_6H_4CHO]$; 76 $[C_6H_4]$; 45 [OEt].

Diethyl 9*H*-fluoren-9-yl phosphate, a minor product (10%) in the synthesis of compound **15**, R_f 0.30 (CH_2Cl_2—EtOH, 35 : 1). ^1H NMR, δ: 1.36 (t, 6 H, 2 Me, J = 7.0 Hz); 4.19 (q, 4 H, OCH_2); 6.24 (d, 1 H, ring, $^3J_{H,P}$ = 8.9 Hz); 7.31, 7.40 (both t, 2 H each, arom., J = 7.3 Hz); 7.63, 7.73 (both d, 2 H each, arom., J = 7.6 Hz). ^{31}P NMR, δ: 0.41. ^{13}C NMR, δ: 15.97 (d, Me, $^3J_{C,P}$ = 7.8 Hz); 63.95 (d, OCH_2, $^2J_{C,P}$ = 6.3 Hz); 78.02 (d, $C(1)_{ring}$, $^2J_{C,P}$ = 6.3 Hz); 119.84, 125.79, 127.71, 129.54, 140.33,

141.71 (C_{arom}). IR, ν/cm^{-1}: 1220 (P=O). MS, *m/z*: 318 $[M]^+$; 180 $[M - P(O)(OEt)_2]^+$; 152 $[M - CHOP(O)(OEt)_2]^+$; 121 $[P(OEt)_2]$; 105 $[C_6H_4CHO]$; 76 $[C_6H_4]$.

Diethyl 9-benzylamino-9,10-dihydroanthracen-9-ylphosphonate (16) was obtained from anthrone (**4**). The yield was 20%, R_f 0.30 (CH_2Cl_2—EtOH, 35 : 1). ^{1}H NMR, δ: 1.12, 1.27 (both t, 6 H, 2 Me, J = 6.8 Hz); 2.27 (br.m, 1 H, NH); 3.56 (H_A), 3.78 (H_B, AB system, 2 H, CH_2Ph, $^2J_{H,H}$ = 13.1 Hz); 3.72 (m, 2 H, $CH_{2,ring}$); 3.99, 4.05 (both m, 4 H, OCH_2); 7.26, 7.34, 7.51, 7.80, 7.92 (all m, 13 H, arom.). ^{31}P NMR, δ: 23.00. ^{13}C NMR, δ: 16.12, 16.53 (both d, Me, $^3J_{C,P}$ = 6.3 Hz); 35.60 (d, $CH_{2,ring}$, J = 5.2 Hz); 51.09 (d, CH_2Ph, J = 18.8 Hz); 59.44 (d, $C(1)_{ring}$, $^1J_{C,P}$ = 154.2 Hz); 62.65, 62.83 (both d, OCH_2, $^2J_{C,P}$ = 7.9 Hz); 126.35, 127.55, 128.35, 128.48, 129.05, 129.61, 131.90, 132.03, 133.15, 140.35 (C_{arom}). IR, ν/cm^{-1}: 1250 (P=O); 3300, 3470 (NH). MS, *m/z*: 421 $[M]^+$.

Diethyl 9-hydroxy-9,10-dihydroanthracen-9-ylphosphonate, a minor product (15%) in the synthesis of compound **16**, R_f 0.21 (CH_2Cl_2—EtOH, 35 : 1). ^{1}H NMR, δ: 0.95 (t, 6 H, 2 Me, J = 7.3 Hz); 3.70 (br.m, 1 H, OH); 3.82, 3.90, (both m, 4 H, OCH_2); 6.83 (m, 2 H, arom.); 7.39 (m, 4 H, arom.); 7.82 (m, 2 H, arom.). ^{31}P NMR, δ: 21.28. IR, ν/cm^{-1}: 1250 (P=O).

Diethyl 9,10-dihydroanthracen-9-yl phosphate was obtained in the synthesis of compound **16**. The yield was 25%, R_f 0.35 (CH_2Cl_2—EtOH, 35 : 1). ^{1}H NMR, δ: 1.35 (t, 6 H, 2 Me, J = 7.3 Hz); 4.13 (q, 4 H, OCH_2); 4.32 (m, 2 H, $CH_{2,ring}$); 5.92 (d, 1 H, ring, J = 9.2 Hz); 6.83 (m, 2 H, arom.); 7.40 (m, 4 H, arom.); 7.93 (m, 2 H, arom.). ^{31}P NMR, δ: 6.90. IR, ν/cm^{-1}: 1220 (P=O).

Tetraethyl [9,10-bis(benzylamino)-9,10-dihydroanthracen-9,10-diyl]bis(phosphonate) (17) was obtained from 9,10-anthraquinone (**5**). The yield was 75%, R_f 0.22 (CH_2Cl_2—EtOH, 35 : 1). ^{1}H NMR, δ: 1.12, 1.27 (both t, 12 H, 4 Me, J = 7.0 Hz); 2.32 (br.m, 2 H, NH); 3.55 (H_A), 3.79 (H_B, AB system, 4 H, CH_2Ph, $^2J_{H,H}$ = 12.7 Hz); 3.95, 3.99, 4.04 (all m, 8 H, 4 OCH_2); 7.25, 7.30, 7.36, 7.42 (all m, 18 H, arom.). ^{31}P NMR, δ: 25.08. ^{13}C NMR, δ: 16.14, 16.33 (both d, Me, $^3J_{C,P}$ = 6.3 Hz); 51.08 (d, CH_2Ph, J = 17.3 Hz); 59.47 (d, $C(1)_{ring}$, $^1J_{C,P}$ = 154.2 Hz); 62.65, 62.84 (both d, OCH_2, $^2J_{C,P}$ = 7.7 Hz); 126.99, 127.79, 128.24, 128.37, 128.59, 135.60, 139.21 (C_{arom}). IR, ν/cm^{-1}: 1250 (P=O); 3320, 3470 (NH). MS, *m/z*: 662 $[M]^+$.

Tetraethyl [1,4-bis(benzylamino)cyclohexa-2,5-diene-1,4-diyl]bis(phosphonate) (18) was obtained from 1,4-benzoquinone (**6**). The yield was 50%, R_f 0.22 (CH_2Cl_2—EtOH, 35 : 1). ^{1}H NMR, δ: 1.12, 1.27 (both t, 12 H, 4 Me, J = 7.0 Hz); 2.33 (br.m, 2 H, NH); 3.54 (H_A), 3.80 (H_B, AB system, 4 H, CH_2Ph, $^2J_{H,H}$ = 13.3 Hz); 3.94, 3.99, 4.07 (all m, 8 H, 4 OCH_2); 7.26, 7.30, 7.36, 7.42 (all m, 14 H, arom.). ^{31}P NMR, δ: 23.06. ^{13}C NMR, δ: 16.12, 16.31 (both d, Me, $^3J_{C,P}$ = 5.9 Hz); 51.10 (d, CH_2Ph, J = 17.6 Hz); 59.49 (d, $C(1)_{ring}$, $^1J_{C,P}$ = 153.7 Hz); 62.68, 62.86 (both d, OCH_2, $^2J_{C,P}$ = 6.6 Hz); 127.01, 127.81, 128.23, 128.36, 128.58, 135.6, 139.2 (C_{arom}, C=C, ring). IR, ν/cm^{-1}: 730 (C=CH, ring); 1250 (P=O); 1400 (C=CH, ring); 1655 (C=C); 3040 (C=CH); 3320, 3470 (NH). MS, *m/z*: 562 $[M]^+$.

Diethyl 4-hydroxyphenyl phosphate was obtained as a by-product in the synthesis of compound **18**. The yield was 50%, R_f 0.35 (CH_2Cl_2—EtOH, 35 : 1). ^{1}H NMR, δ: 1.35 (t, 6 H, 2 Me, J = 7.1 Hz); 4.19 (m, 4 H, OCH_2); 6.58, 6.91 (both m, 2 H each, arom.). ^{31}P NMR, δ: −5.89. ^{13}C NMR, δ: 16.00 (d, Me, $^3J_{C,P}$ = 6.7 Hz); 64.69 (d, OCH_2, $^2J_{C,P}$ = 6.1 Hz); 116.23, 120.66, 143.02, 149.21 (C_{arom}). IR, ν/cm^{-1}: 1200 (Ar—OH); 1270 (P=O); 3270 (OH).

Diethyl (1-benzylamino-1-cyclopropylethyl)phosphonate (19) was obtained from cyclopropyl methyl ketone **7**. The yield was 60%, R_f 0.43 (CH_2Cl_2—EtOH, 35 : 1). Found (%): C, 61.51; H, 8.61. $C_{16}H_{26}NO_3P$. Calculated (%): C, 61.74; H, 8.36. ^{1}H NMR, δ: 0.50 (m, 4 H, 2 $CH_{2,ring}$); 1.12 (d, 3 H, Me, J = 16.5 Hz); 1.25 (m, 1 H, CH_{ring}); 1.33, 1.36 (both t, 6 H, 2 Me, J = 7.0 Hz); 3.97 (br.m, 2 H, CH_2Ph); 4.19 (m, 4 H, OCH_2); 7.23, 7.31 (both m, 5 H, arom.). ^{31}P NMR, δ: 29.53. ^{13}C NMR, δ: 0.39, 0.47, 1.00 (all s, C_{ring}); 15.37 (d, Me, J = 4.7 Hz); 16.53, 16.59 (both br.s, Me); 47.03 (s, CH_2Ph); 55.21 (d, C(1), $^1J_{C,P}$ = 149.4 Hz); 62.05 (s, OCH_2); 126.65, 128.01, 128.15, 141.22 (C_{arom}). IR, ν/cm^{-1}: 1250 (P=O); 3330, 3480 (NH).

Diethyl 2-benzylamino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylphosphonate (20) was obtained from camphor (**8a**). The yield was 30%, R_f 0.19 (CH_2Cl_2—EtOH, 35 : 1). Found (%): C, 66.47; H, 7.86; N, 3.05. $C_{21}H_{34}NO_3P$. Calculated (%): C, 66.49; H, 8.97; N, 3.69. ^{1}H NMR, δ: 0.96, 0.98, 1.00 (all s, 9 H, 3 Me, ring); 1.12, 1.21, 2.32 (all m, 7 H, ring); 1.27, 1.35 (both t, 6 H, 2 Me, J = 7.3 Hz); 2.28 (br.m, 1 H, NH); 3.55 (H_A), 3.78 (H_B, AB system, 2 H, CH_2Ph, $^2J_{H,H}$ = 13.3 Hz); 4.05, 4.49, 4.69 (all m, 4 H, 2 OCH_2); 7.26, 7.42 (both m, 5 H, arom.). ^{31}P NMR, δ: 20.49, 21.26, 22.12. ^{13}C NMR, δ: 15.78, 15.97 (both d, Me, $^3J_{C,P}$ = 6.1 Hz); 22.89, 23.44, 23.70 (all s, 3 Me, ring); 50.73 (d, CH_2Ph, J = 17.3 Hz); 58.46 (m, C_{ring}); 59,61 (d, $C(1)_{ring}$, $^1J_{C,P}$ = 154.2 Hz); 60.01, 62.27 (both m, C_{ring}); 70.77, 70.85 (both br.d, OCH_2); 126.57, 127.33, 127.88, 128.36, 135.45, 138.91 (C_{arom}). IR, ν/cm^{-1}: 1240 (P=O); 3320, 3340, 3420 (NH).

***tert*-Butyl 4-benzylamino-4-(diethoxyphosphoryl)piperidine-1-carboxylate (21)** was obtained from *N*-Boc-piperidone (**9**). The yield was 99%, R_f 0.31 (CH_2Cl_2—EtOH, 35 : 1). Found (%) C, 58.96; H, 8.31. $C_{21}H_{35}N_2O_5P$. Calculated: C, 59.15; H, 8.22. ^{1}H NMR, δ: 1.33 (t, 6 H, 2 Me, J = 7.0 Hz); 1.45 (s, 9 H, 3 Me, Boc); 1.82, 1.88 (both m, 4 H, 2 $CH_{2,ring}$); 3.23 (m, 4 H, 2 $NCH_{2,ring}$); 3.88 (br.m, 1 H, NH); 3.92 (d, 2 H, CH_2Ph, J = 3.3 Hz); 4.15 (q, 4 H, 2 OCH_2); 7.27, 7.35 (both m, 5 H, arom.). ^{31}P NMR, δ: 28.68. ^{13}C NMR, δ: 16.59, 16.71 (both d, Me, $^3J_{C,P}$ = 6.4 Hz); 28.40 (s, Me, Boc); 29.39 (br.s, 2 $CH_{2,ring}$); 38.07 (br.s, 2 $NCH_{2,ring}$); 47.23 (s, CH_2Ph); 54.32 (d, $C(1)_{ring}$, $^1J_{C,P}$ = 144.6 Hz); 61.85, 62.01 (d, OCH_2, $^2J_{C,P}$ = 8.0 Hz); 79.41 (s, C, Boc); 127.00, 128.12, 128.38, 140.82 (C_{arom}); 154.84 (C=O, Boc). IR, ν/cm^{-1}: 1250 (P=O); 1695 (C=O); 3320, 3480 (NH).

Diethyl 3-benzylamino-2-oxo-2,3-dihydro-1*H*-indol-3-ylphosphonate (22) was obtained from isatin (**10**). The yield was 90%, R_f 0.21 (CH_2Cl_2—EtOH, 50 : 1). Found (%): C, 60.92; H, 6.33. $C_{19}H_{23}N_2O_4P$. Calculated (%): C, 60.96; H, 6.19. ^{1}H NMR, δ: 1.12, 1.27 (both t, 6 H, 2 Me, J = 6.9 Hz); 2.56 (br.m, 1 H, NH); 3.56 (H_A), 3.73 (H_B, AB system, 2 H, CH_2Ph, $^2J_{H,H}$ = 13.1 Hz); 3.80, 3.96, 4.07 (all m, 4 H, 2 OCH_2); 7.26, 7.42 (both m, 9 H, arom.). ^{31}P NMR, δ: 23.86. ^{13}C NMR, δ: 16.08, 16.27 (both d, Me, $^3J_{C,P}$ = 4.6 Hz); 51.04 (d, CH_2Ph, J = 18.3 Hz); 59.41 (d, $C(1)_{ring}$, $^1J_{C,P}$ = 152.6 Hz); 62.60, 62.77 (both d, OCH_2, $^2J_{C,P}$ = 6.1 Hz); 127.20, 128.03, 128.43, 128.55, 128.72, 128.80, 135.68, 139.33 (C_{arom}); 159.91 (s, C=O). IR, ν/cm^{-1}: 1250 (P=O); 1750 (C=O); 3330, 3460 (NH).

Diethyl 3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-ylphosphonate, a minor product (10%) in the synthesis of compound **22**, R_f 0.15 (CH_2Cl_2—EtOH, 50 : 1). ^{1}H NMR, δ: 1.19, 1.23 (both t, 6 H, 2 Me, J = 6.9 Hz); 4.02 (q, 4 H, 2 OCH_2); 7.30, 7.33, 7.45,

7.48 (all s, 4 H, arom.). ^{13}C NMR, δ: 16.40, 16.48 (both d, Me, $^{3}J_{C,P}$ = 4.6 Hz); 63.18, 63.52 (both d, OCH_2, $^{2}J_{C,P}$ = 7.2 Hz); 70.76 (d, $C(1)_{ring}$, $^{1}J_{C,P}$ = 159.8 Hz); 125.41, 127.15, 127.26, 126.06, 128.26, 136.82 (C_{arom}); 159.92 (s, C=O). ^{31}P NMR, δ: 21.93. IR, ν/cm^{-1}: 1240 (P=O); 1740 (C=O); 3330, 3280 (OH).

3-Benzylamino-3-diethoxyphosphoryl-17-(1-benzylamino-1-diethoxyphosphoryl-2-hydroxyethyl)-10β-methylgonane-11β,17α-diol (23) was obtained from pregnane **11**. The yield was 40%, R_f 0.15 (CH_2Cl_2—EtOH, 35 : 1). ^{1}H NMR, δ: 0.67 (m, pregnane); 1.06 (s, 3 H, Me, pregnane); 1.30, 1.39 (both t, 12 H, 4 Me, J = 7.0 Hz); 1.00, 1.20, 1.26, 1.32, 1.44, 1.74, 1.98, 2.17, 2.35, 2.43, 3.35 (all m, pregnane); 3.87 (H_A), 4.12 (H_B, AB system, 4 H, CH_2Ph, $^{2}J_{H,H}$ = 12.4 Hz); 4.04, 4.14, 4.21 (all m, 8 H, OCH_2); 7.27, 7.34 (both m, 10 H, arom.). ^{31}P NMR, δ: 20.94, 25.59. IR, ν/cm^{-1}: 1240 (P=O); 3320, 3480 (NH).

Tetraethyl [1,2-bis(benzylamino)-1,2-diphenylethane-1,2-diyl]bis(phosphonate) (24) was obtained from benzil (**14**). The yield was 30%, R_f 0.15 (CH_2Cl_2—EtOH, 50 : 1). ^{1}H NMR, δ: 1.12, 1.27 (both t, 12 H, 4 Me, J = 7.0 Hz); 2.90 (br.m, 2 H, NH); 3.56 (H_A), 3.80 (H_B, AB system, 4 H, CH_2Ph, $^{2}J_{H,H}$ = 13.3 Hz); 3.95, 4.07, 4.15 (all m, 8 H, 4 OCH_2); 7.26—7.67 (m, 20 H, arom.). ^{31}P NMR, δ: 21.94. IR, ν/cm^{-1}: 1250 (P=O); 3320, 3460 (NH). MS, m/z: 664 $[M]^+$.

2-Benzylimino-1,2-diphenylethyl diethyl phosphate was obtained as a by-product in the synthesis of compound **24**. The yield was 20%, R_f 0.22 (CH_2Cl_2—EtOH, 50 : 1). ^{1}H NMR, δ: 1.14, 1.28 (both t, 6 H, 2 Me, J = 7.0 Hz); 3.89, 4.17 (both m, 4 H, OCH_2); 4.62 (d, 2 H, CH_2Ph, J = 5.7 Hz); 6.62 (d, 1 H, $^{3}J_{H,P}$ = 8.0 Hz); 7.28—7.90 (m, 15 H, arom.). ^{31}P NMR, δ: −2.54. IR, ν/cm^{-1}: 1270 (P=O); 1690 (C=N).

4-(Benzylamino)pent-3-en-2-one (25) was obtained from acetylacetone (**12**). The yield was 99%, R_f 0.26 (CH_2Cl_2—EtOH, 50 : 1). ^{1}H NMR, δ: 1.90 (s, 3 H, Me); 2.03 (s, 3 H, COMe); 4.44 (d, 2 H, CH_2Ph, J = 6.2 Hz); 5.04 (s, 1 H, CH); 7.25, 7.33 (both m, 5 H, arom.). IR, ν/cm^{-1}: 1720 (C=O); 3300 (NH).

Ethyl 2-benzylaminocyclopent-1-ene-1-carboxylate (26) was obtained from oxo ester **13**. The yield was 50%, R_f 0.59 (CH_2Cl_2—EtOH, 35 : 1). ^{1}H NMR, δ: 1.27 (t, 3 H, Me, J = 7.0 Hz); 1.80 (m, 2 H, $CH_{2,ring}$); 2.53 (t, 4 H, $CH_{2,ring}$, J = 7.3 Hz); 4.15 (q, 2 H, OCH_2); 4.38 (d, 2 H, CH_2Ph, J = 6.3 Hz); 7.25, 7.32 (both m, 5 H, arom.); 7.77 (br.m, 1 H, NH). IR, ν/cm^{-1}: 1740 (C=O); 3300 (NH).

We are grateful to Prof. L. G. Tomilova for provided samples of phthalocyanines.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 05-03-33054), the Council on Grants of the President of the Russian Federation (Program for State Support of Leading Scientific Schools of the Russian Federation, Grant NSh-2552.2006.3), the Ministry of Education and Science (Target Program "Development of Scientific Potential of High School", Grant RNP.2.1.1.7779), and the Russian Academy of Sciences (Basic Research Grants 1-OKhNM RAN and 10-OKhNM RAN).

References

1. R. P. Sheridan, *J. Chem. Inf. Comput. Sci.*, 2002, **42**, 103.
2. B. Bioulac, E. De Tingui, J. D. Vincent, and E. Neuzil, *Gen. Pharmacol.*, 1978, **10**, 121.
3. T. Murakawa, H. Sakamoto, S. Fukada, T. Konishi, and M. Nishida, *Antimicrob. Agents Chemother.*, 1982, **21**, 224.
4. J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, L. W. Lambert, L. J. Nisbet, and P. S. Ringrose, *Nature*, 1978, **272**, 56.
5. F. R. Atherton, M. J. Hall, C. H. Hassall, L. W. Lambert, W. J. Lloyd, A. V. Lord, P. S. Ringrose, and D. Westmacott, *Antimicrob. Agents Chemother.*, 1983, **24**, 552.
6. M. P. Lambert and F. C. Neuhaus, *J. Bacteriol.*, 1972, **110**, 978.
7. V. P. Kukhar and H. R. Hudson, *Aminophosphonic and Aminophosphinic Acids*, Ed. V. P. Kukhar, J. Wiley and Sons, 2000.
8. J. Uziel and J. P. Genêt, *Zh. Org. Khim.*, 1997, **33**, 1605 [*Russ. J. Org. Chem.*, 1997, **33** (Engl. Transl.)].
9. R. A. Cherkasov and V. I. Galkin, *Usp. Khim.*, 1998, **67**, 940 [*Russ. Chem. Rev.*, 1998, **67** (Engl. Transl.)].
10. V. Y. Pavlov, M. M. Kabachnik, E. V. Zobnina, V. Timofeev, I. O. Konstantinov, B. G. Kimel, G. V. Ponomarev, and I. P. Beletskaya, *Synlett.*, 2003, 2193.
11. M. M. Kabachnik, E. V. Zobnina, and I. P. Beletskaya, *Zh. Org. Khim.*, 2005, **41**, 517 [*Russ. J. Org. Chem.*, 2005, **41** (Engl. Transl.)].
12. E. D. Matveeva, T. A. Podrugina, E. V. Tishkovskaya, and N. S. Zefirov, *Synlett.*, 2003, 2321.
13. N. S. Zefirov, E. D. Matveeva, and T. A. Podrugina, *Abstr. 230th ACS National Meeting (Washington, Aug. 28—Sept. 1, 2005)*, Washington (DC, United States), 2005, ORGN-118.
14. E. D. Matveeva, T. A. Podrugina, M. V. Prisyajnoy, and N. S. Zefirov, *Proc. Int. Symp. on Advances in Synthetic, Combinatorial and Medicinal Chemistry*, Moscow (Russia), 2004, p. 130.
15. E. D. Matveeva, T. A. Podrugina, M. V. Prisyajnoy, and N. S. Zefirov, *Tezisy dokladov Mezhdunarodnoi nauchno-tekhnicheskoi konferentsii "Perspektivy razvitiya khimii i prakticheskogo primeneniya alitsiklicheskikh soedinenii"* [*Abstr. Int. Scientific and Technical Conf. "The Prospects of Progress in the Chemistry and Practical Applications of Alicyclic Compounds"*], Samara, 2004, p. 203 (in Russian).
16. V. P. Kukhar and V. A. Solodenko, *Usp. Khim.*, 1987, **56**, 1504 [*Russ. Chem. Rev.*, 1987, **56** (Engl. Transl.)].

Received February 16, 2006;
in revised form June 20, 2006