Synthesis of N-phosphorylated derivatives of bis(2-chloroethyl)amine

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Some asymmetric N-bis(2-chloroethyl)triamidophosphates **III a–c** were synthesized by subsequent nucleophilic displacement at the phosphoryl centre. The yields of target compounds were dependent on the sequence of displacement and temperature of reactions. N-[N'-bis(2-chloroethyl)amido-N''-morpholido]-phosphoryl-*cis*(or *trans*)-4-amidocyclohexanecarboxylic acids **III d, e** were prepared by hydrogenolysis of N-4-benzyloxycarbonylcyclohexyltriamidophosphate derivatives **III b, c** in the presence of Pd/C catalyst in quantitative yields. The structure of obtained compounds was confirmed by ^{1}H and ^{31}P NMR spectroscopy.

Key words: amidophosphates, bis(2-chloroethyl)amine, ^{31}P NMR, ^{1}H NMR

INTRODUCTION

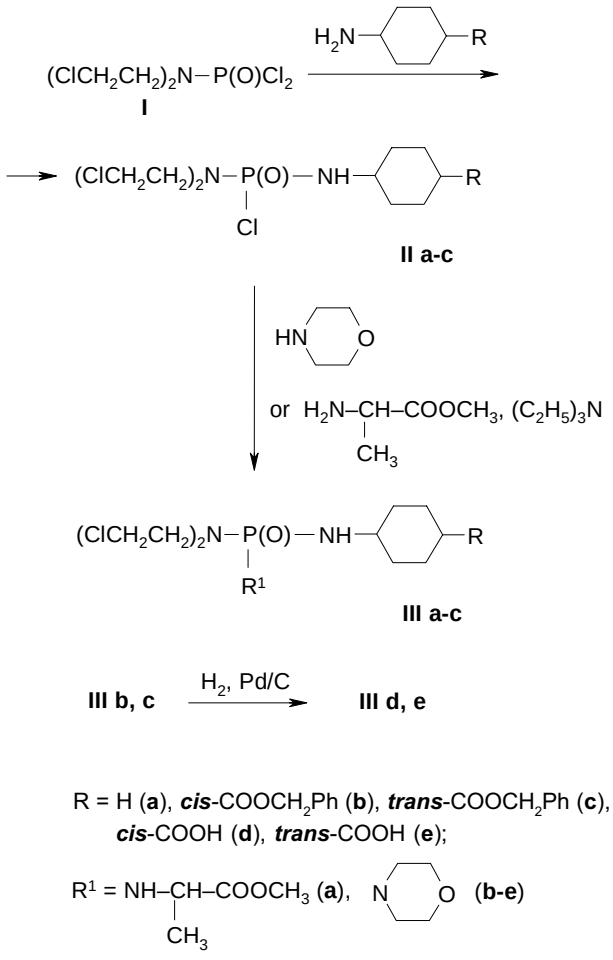
Amides of phosphoric acid display a wide spectrum of biological activity [1–6]. The metabolism, activation and action of the phosphoramidic mustards, with the emphasis on the roles that chemical modeling has and will play in the development in this important class of drugs, were an object of interest also [7]. Some chiral, racemic amidophosphates can act as chiral recognition reagents with respect to the optically active acids, acting via the hydrogen bonding interaction or via the inclusion effects [8].

RESULTS AND DISCUSSION

We report the synthesis of a series of triamidophosphates carrying as an essential structural feature the N-bis(2-chloroethyl) substituent based on phosphoryl chloride as a common starting material **I**. The synthetic pathway used in obtaining the title triamidophosphate is summarized in Scheme.

Preparation of target compounds involved three subsequent nucleophilic displacements at the phosphoryl centre. The order of the nucleophilic reagents introduced into phosphorus is, however, important, and we found that best yields were always obtained when bis(2-chloroethyl)amino group was substituted for the first chlorine atom in $POCl_3$. The triamidophosphate **III a–c** could be obtained via two routes, however, for these products best results were obtained, if the cyclohexylamino (or its derivative) group was substituted for the second chlorine atom in $POCl_3$. The second step was very dependent on the reaction temperature. The optimal temperature was –5–0 °C, while attempts to carry out the reaction at

Scheme



R = H (**a**), ***cis***-$COOCH_2Ph$ (**b**), ***trans***-$COOCH_2Ph$ (**c**), ***cis***-COOH (**d**), ***trans***-COOH (**e**);

R^1 = NH–CH–$COOCH_3$ (**a**), N O (**b-e**)
CH3

higher temperatures led to the formation of side products.

The triamidophosphates **III b, c** were converted to the triamidophosphates **III d, e** by hydrogenolysis using Pd/C catalyst.

The structures of synthesized compounds **III a–e** were confirmed by an elemental analysis and study of their ^{1}H and ^{31}P NMR spectra. The ^{31}P NMR spectra exhibited single signals (δ_P between 14.35 and 17.59 ppm), which were in the range characteristic of amidophosphates [9].

It is of interest to note that in the ^{31}P NMR spectra of **IIIb** and **IIIc** containing cis- and trans-1,4-substituted cyclohexyl ring the phosphorus nuclei resonate *ca*. 0.5 ppm to the lower field when the configuration is *cis* than when it is *trans*. The ^{1}H NMR spectra showed the expected signals for the particular group.

Two bond and three bond coupling constants to phosphorus were observed ($^{2}J_{P–N–H}$ = 9.4–9.6 Hz and $^{3}J_{P–N–C–H}$ = 10 Hz).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Experimental analyses data (C, H, Cl, N, P) of all obtained compounds **III a–e** were summarized in Table. ^{1}H NMR spectra were recorded on a Hitachi R-22 NMR spectrometer (Japan, 90 MHz, 35 °C), using hexamethyldisiloxane (HMDS) as an internal reference (δ = 0.05 ppm) in deuteriochloroform. Chemical shifts are reported in ppm relative to TMS (δ = 0 ppm). Signals are expressed as s (singlet), d (doublet), m (multiplet), b (broad). Single chemical shift values refer to midpoints of multiplets, if the signals of the respective protons are clearly discernible. In the case of overlapping multiplets the overall range is given. $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Bruker HX-90E spectrometer (Germany) at 36.43 MHz, 25 °C relative to external 85% H_3PO_4 in deuteriochloroform and are reported as chemical shifts (δ) in ppm. The values of optical rotation were measured on a Perkin-Elmer spectropolarimeter. The completion of reactions and the purity of the obtained compounds were controlled by the TLC method on sheets coated with Al_2O_3 of grade II activity in a benzene–ether–methanol system, 4:2:1. The spots were detected by iodine vapour or Waskovski–Kostetski reactant.

Chloro-N-bis(2-chloroethyl)-N'-cyclohexyldiamidophosphate IIa and chloro-N-bis(2-chloroethyl)-N'-cis(or trans)-(4-benzyloxycarbonyl)cyclohexyldiamidophosphate II b, c. A solution of 5.7 ml (50 mmol) of cyclohexylamine or 11.65 g (50 mmol) of *cis*(or *trans*)-4-(benzyloxycarbonyl)cyclohexylamine [11] in 100 ml of abs. ether was added dropwise to a stirred and cooled (–5–0 °C) solution of 6.47 g (25 mmol) of dichloro-N-bis(2-chloroethyl)amidophosphate **I** [10] in 200 ml of abs. ether. The mixture was stirred for 1 h at this temperature, for 2 h at r.t. and allowed to stand at 0 °C for 10–12 h. The precipitate of hydrochloride of cyclohexylamine or *cis*(or *trans*)-4-(benzyloxycarbonyl)cyclohexylamine was filtered off. The filtrate was concentrated and immediately used without further purification for synthesis of **III a–c**.

S-(-)-N-bis(2-chloroethyl)-N'-cyclohexyl-N"-(1-methoxycarbonylethyl)-triamidophosphate IIIa. A solution of 3.49 g (25 mmol) of L-alanine methyl ester hydrochloride and 7.0 ml (50 mmol) of triethylamine in 100 ml of abs. ether was added dropwise to a stirred solution of 25 mmol of chloro-N-bis(2-chloroethyl)-N'-cyclohexyldiamidophosphate in 100 ml of abs. ether at –5 °C. The reaction mixture was stirred for 2 h and was allowed to stand at 0 °C for 35 h. The triethylamine hydrochloride precipitate was filtered off. The filtrate was concentrated under reduced pressure to a volume of 50 ml and cooled.

Table. **Characteristics of synthesized compounds III a–c**

Compound	Yield, %	M.p., °C, solvent	Molecular formula	Found, % / Calculated, %				
				C	H	Cl	N	P
IIIa	48	100–103 abs. ethyl ether	$C_{14}H_{28}Cl_2N_3O_3P$	41.55 41.59	6.78 6.98	17.56 17.54	10.44 10.39	7.38 7.66
IIIb	28	104–105 abs. ethyl ether	$C_{22}H_{34}Cl_2N_3O_4P$	52.24 52.18	6.59 6.77	13.20 14.00	8.20 8.30	5.95 6.12
IIIc	20	122–124 abs. ethyl ether	$C_{22}H_{34}Cl_2N_3O_4P$	52.37 52.18	6.79 6.77	13.80 14.00	8.22 8.30	5.40 6.12
IIId	82	114–116 $CHCl_3$/ethyl ether	$C_{15}H_{28}Cl_2N_3O_4P$	44.16 43.28	6.58 6.78	16.60 17.03		7.67 7.44
IIIe	98	100–102 $CHCl_3$/ethyl ether	$C_{15}H_{28}Cl_2N_3O_4P$	43.21 43.28	6.65 6.78	16.99 17.03		7.41 7.44

The solid was recrystallized from abs. ether to yield 4.65 g (48%) of white crystals. After two recrystallizations from abs. ether $[\alpha]_D^{20}$ (1%, ethanol) = –10.43 °.

^{1}H NMR, δ 1.37 (3H, d, CH_3); 0.80–2.13 (10H, m, $(CH_2)_5$-cyclohex.); 2.44 (1H, bt, N<u>H</u>-cyclohex.); 3.01 (1H, t, J_{HP} = 9.6, N<u>H</u>-CH); 3.00 (1H, m, C<u>H</u>NH); 3.41 (4H, m, $2CH_2N$); 3.59 (4H, m, $2CH_2Cl$); 3.69 (3H, s, CH_3O), 3.98 (1H, m, J_{HP} = = 10.0, CHCO).

^{31}P NMR, δ 14.35.

N-Bis(2-chloroethyl)-N'-*cis*-4-benzyloxycarbonylcyclohexyl)-N"-morpholidodiamidophosphate IIIb was prepared from 25 mmol of **IIb** and 4.35 ml (50 mmol) of morpholine as described for **IIIa**.

^{1}H NMR, δ 1.12–2.32 (8H, m, $(CH_2)_4$-cyclohex.); 2.47 (1H, m, CHCO); 2.54 (1H, t, J_{HP} = 9.6, NH); 3.13 (4H, m, $N(CH_2)_2$-morph.); 3.38 (4H, m, $N(CH_2)_2$); 3.62 (8H, m, $2CH_2O$, $2CH_2Cl$); 5.12 (2H, s, CH_2OCO); 7.33 (5H, s, C_6H_5).

^{31}P NMR, δ 17.56

N-Bis(2-chloroethyl)-N'-(*trans*-4-benzyloxycarbonylcyclohexyl)-N"-morpholidodiamidophosphate IIIc was prepared from 25 mmol of **IIc** and 4.35 ml (50 mmol) of morpholine as described for **IIIa**.

^{1}H NMR, δ 0.80-2.47 (10H, m, C_5H_9, NH); 3.14 (4H, m, $2CH_2$N-morph.); 3.39 (4H, m, $2CH_2N$); 3.64 (4H, m, CH_2OCH_2); 5.13 (2H, s, CH_2OCO); 7.34 (5H, s, C_6H_5).

^{31}P NMR, δ 16.98

N-[N'-bis(2-chloroethyl)amido-N"-morpholido]-phosphoryl-*cis*-4-aminocyclohexanecarboxylic acid IIId. A solution containing 1.26 g (2.5 mmol) of **IIIb** in 200 ml of abs. methanol was introduced into a hydrogen flask followed by 0.6 g of 5% Pd/C catalyst. The mixture was hydrogenated at initial pressure. After 180 min the theoretical amount of hydrogen was consumed. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was recrystallized from chloroform/ethyl ether, 1:2, by cooling.

^{1}H NMR, δ 1.25-2.15 (8H, m, $(CH_2)_4$-cyclohex.); 2.25–2.55 (2H, m, CHCONH); 3.17 (4H, m, $N(CH_2)_2$-morph.); 3.41 (4H, m, $N(CH_2)_2$); 3.63 (8H, m, $2CH_2O$, $2CH_2Cl$).

N-[N'-bis(2-chloroethyl)amido-N"-morpholido]-phosphoryl-*trans*-4-aminocyclohexanecarboxylic acid IIIe was prepared from 1.26 g (2.5 mmol) of **IIIc** as described for **IIId**.

^{1}H NMR, δ 0.90-2.23 (9H, m, $(C_5H_9$-cyclohex.); 2.50 (1H, t, J_{HP} = 9.4, NH); 2.95 (1H, m, CHN); 3.11 (4H, m, $(CH_2)_2$N-morph.); 3.36 (4H, m, $N(CH_2)_2$); 3.56 (8H, m, $2CH_2O$, $2CH_2Cl$).

CONCLUSIONS

1. The asymmetric derivatives of N-bis(2-chloroethyl)triamidophosphates were obtained by subsequent nucleophilic displacement at the phosphoryl centre.

2. N[N'-bis(2-chloroethyl)amido-N''-morpholido]phosphoryl-*cis*(or *trans*)-4-aminocyclohexanecarboxylic acid was synthesized by hydrogenation of N-4-benzyloxycarbonylcyclohexyltriamidophosphate derivatives in the presence of Pd/C catalyst.

Received 5 February 2001
Accepted 30 April 2001

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BIS(2-CHLORETIL)AMINO N-FOSFORILINTŲ DARINIŲ SINTEZĖ

S a n t r a u k a

Sintezuoti nauji asimetriniai N-fosforilinti bis(2-chloretil)amino dariniai **III a–c** nuoseklaus nukleofilinio pavadavimo prie fosforilo centro būdu. Nustatyta, kad norimų junginių išeigos priklauso nuo pakaitų įvedimo sekos ir reakcijos temperatūros. N[N'-Bis(2-chloretil)amido-N''-morfolido]fosforil-***cis***(arba ***trans***)-4-aminocikloheksankarboksirūgštys buvo gautos hidrinant cikloheksankarboksirūgščių benzilesterio darinius **IIIb, c** esant Pd/C katalizatoriui. Gautų junginių struktūra patvirtinta ^{1}H ir ^{31}P MBR spektroskopijos metodais.

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СИНТЕЗ ПРОИЗВОДНЫХ N-ФОСФОРИЛ-БИС(2-ХЛОРЭТИЛ)АМИНА

Р е з ю м е

Методом последовательного фосфорилирования аминов хлорангидридом амидофосфорных кислот в присутствии реагирующего амина или Et_3N как акцепторов HCl синтезирован ряд несимметричных триамидов бис(2-хлорэтил)амидофосфорной кислоты. Выход целевых соединений зависит от порядка прибавления реагирующих аминов, а также от температуры реакции. N[N'-Бис(2-хлорэтил)фмидо-N''-морфолидо]-фосфорил-цис(или транс)-4-аминоциклогексанкарбоновые кислоты получены при гидрировании производных бензилового эфира циклогексанкарбоновых кислот **III b, c** в присутствии Pd/C катализатора. Структура полученных соединений подтверждена методами ^{1}H и ^{31}P ЯМР спектроскопии.