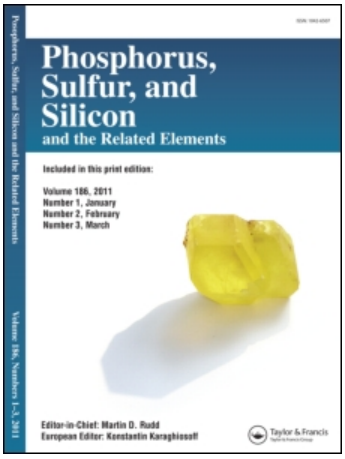

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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Jerzy Szewczyk[a]; Maria Hoffmann[a]
[a] Department of Organic Chemistry, Technical University of Gdañsk, Gdañsk, Poland

To cite this Article Szewczyk, Jerzy and Hoffmann, Maria(1983) 'A NON-SYMMETRICAL DIESTER OF 1-AMINO-1-PHENYLMETHANEPHOSPHONIC ACID. PART I SYNTHESIS AND SEPARATION OF DIASTEREOISOMERS WITH A CHIRAL PHOSPHORUS ATOM', Phosphorus, Sulfur, and Silicon and the Related Elements, 16: 3, 325 — 329
To link to this Article: DOI: 10.1080/03086648308080486
URL: http://dx.doi.org/10.1080/03086648308080486

Phosphorus and Sulfur, 1983, Vol. 16, pp. 325–329
0308-664X/83/1603–0325/$18.50/0

A NON-SYMMETRICAL DIESTER OF 1-AMINO-1-PHENYLMETHANEPHOSPHONIC ACID. PART I SYNTHESIS AND SEPARATION OF DIASTEREOISOMERS WITH A CHIRAL PHOSPHORUS ATOM†

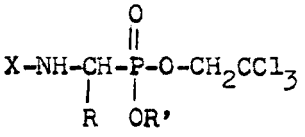
JERZY SZEWCZYK* and MARIA HOFFMANN

Department of Organic Chemistry, Technical University of Gdańsk, 80 952 Gdańsk, Poland

(*Received January 13, 1983; in final form April 16, 1983*)

Synthesis and separation of diastereoisomers of (R)-*N*-phthalyl-1-amino-1-phenylmethanephosphonic acid ethyl-2,2,2-trichloroethyl diester were described. These derivatives were converted to hydrochlorides and then to *N*-carbobenzoxy non-symmetrical diesters. In order to confirm the configuration on α-carbon atom, *N*-phthalyl diester was deprotected to obtain optically active 1-amino-1-phenylmethanephosphonic acid.

Previously we have described[1] the interesting spectroscopic properties of the non-symmetrical diesters of 1-aminoalkanephosphonic acids. These compounds, containing two asymmetrical atoms: carbon and phosphorus, formed the mixture of diastereoisomeric racemates. The analysis of ^{1}H NMR spectra for the mixtures of diastereoisomeric alkyl-2,2,2-trichloroethyl diesters *N*-derivatives of 1-aminoalkanephosphonic acids shows very remarkable differences of spectra for both diastereo isomers.



X = *N*-phthalyl, *N*-carbobenzoxy-, hydrochloride

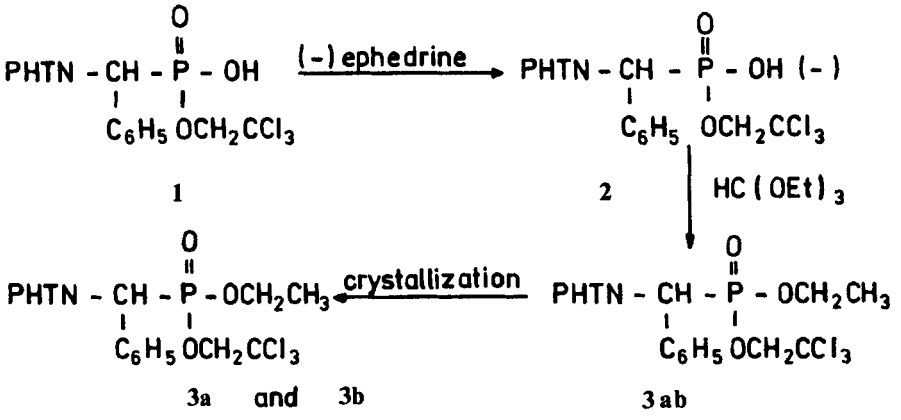
R = CH_3, $CH(CH_3)_2$, C_6H_5

R′ = CH_3, C_2H_5

Chemically equivalent protons, particularly those close to the asymmetric centre, exhibited significant differences of chemical shifts (δ ppm). We have observed that in some cases there is a formation of ABX system for methylene protons of trichloroethyl group. The calculation of this system and the IR data were necessary for the conformational analysis and in consequence, for the determination of configuration of asymmetric phosphorus atom.

We needed pure stereoisomers of non-symmetrical diesters of the derivatives of 1-aminophosphonic acids for the spectroscopic studies. Initially, we have chosen the derivatives of 1-amino-1-phenylmethanephosphonic acid. To obtain the required

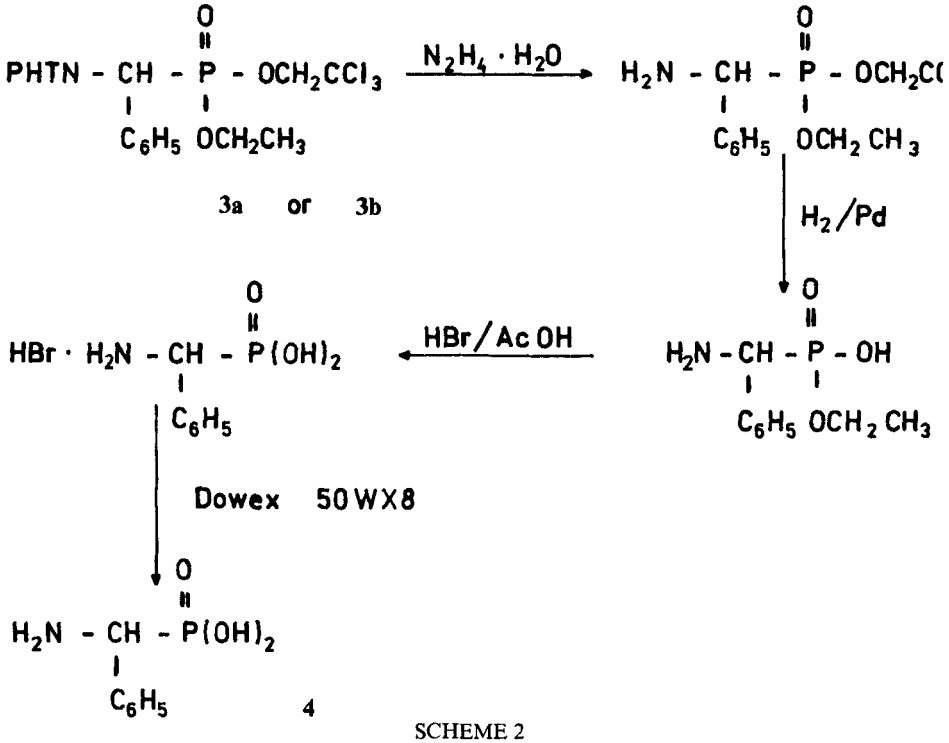
† Part II appears on page 365.



SCHEME 1

compounds we have carried the conversions described below. 2,2,2-Trichloroethyl monoester of *N*-phthalyl-1-amino-1-phenylmethanephosphonic acid **1** was separated to enantiomers by the crystallization of a salt with ephedrine. Then monoester **2** with $[\alpha]_D^{20} = -81.5°$ reacted with ethyl orthoformate yielding the mixture of diastereoisomers **3a** and **3b** which were separated by crystallization to give pure **3a** and **3b**.

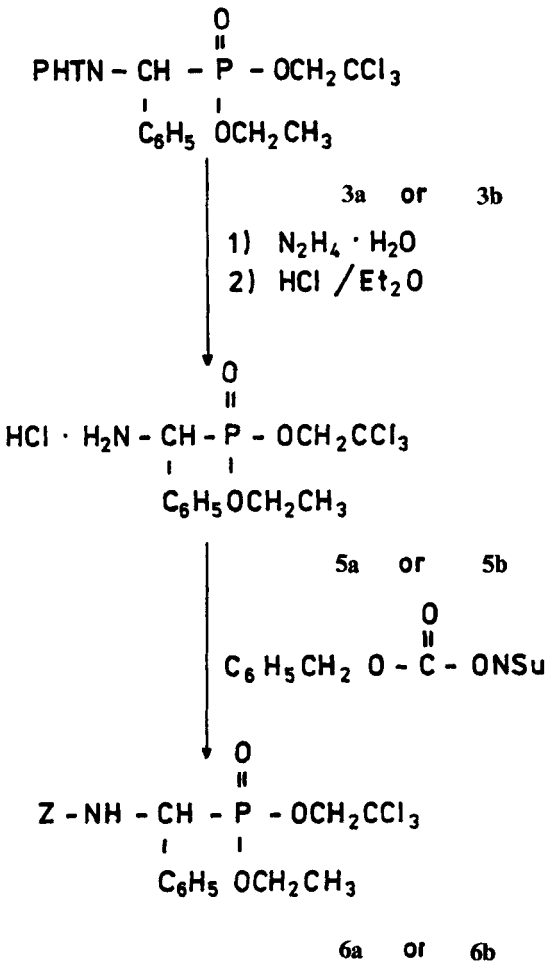
The purity of diastereoisomers was confirmed by ^1H NMR. The next task was to determine the configuration of carbon atom. At first we have removed protections in



SCHEME 2

diastereoisomeric diesters **3a** and **3b**. *N*-phthalyl was removed by the action of hydrazine hydrate; 2,2,2-trichloroethyl ester group was removed hydrogenolytically then we obtained 1-amino-1-phenylmethanephosphonic acid hydrobromide using 45% hydrogen bromide in acetic acid. The cation-exchange chromatography on a Dowex 50WX8 column yielded 1-amino-1-phenylmethanephosphonic acid **4** having $[\alpha]_D^{20} = +16.5°$ and $+16.7°$.

Comparing this result with that of Mastalerz *et al.*[2] we concluded that the configuration of carbon atom is (R). Our attempts to separate other derivatives of ethyl-2,2,2-trichloroethyl diester of 1-amino-1-phenylmethanephosphonic acid were not fully successful so, we made use of the separated diastereoisomers of *N*-phthalyl derivatives **3a** and **3b**. *N*-phthalyl group was removed by the action of 100% hydrazine hydrate and diester hydrochloride **5a** and **5b** were then isolated. **5a** and **5b** reacted then with benzyl–succinimidyl carbonate yielding *N*-carbobenzoxy diesters **6a** and **6b**.



SCHEME 3

These reactions, apart from the synthesis of subsequent derivatives of aminophosphonic acid containing chiral phosphorus atom, yielded the information that the configuration of phosphorus atom is identical in each series of compounds **a** and **b**.

All derivatives were analysed by ^{1}H NMR and IR. The obtained results were the basis for the determination of phosphorus atom configuration. The results of these considerations will be reported later.

EXPERIMENTAL

All m.ps are uncorrected. NMR spectra were recorded on Tesla BS 80 using HMDSO as internal or external standard.

Resolution of 2,2,2-trichloroethyl monoester of N-phthalyl-1-amino-1-phenylmethanephosphonic acid with (-)ephedrine. To a solution of 8.96 g (20 mmole) 2,2,2-trichloroethyl monoester of racemic *N*-phthalyl-1-amino-1-phenylmethanephosphonic acid **1** and 3.48 g (20 mmole) of (-)ephedrine (obtained from 20 mmole of ephedrine hydrochloride) in 61 ml of ethyl acetate, 59 ml of *n*-hexane was added. The reaction mixture was kept at room temperature for 24 hrs. The precipitate was collected by filtration and recrystallized from ethyl acetate *n*-hexane mixture. Yield 4.3 g (35%) the (-)ephedrine salt of *N*-phthalyl-1-amino-1-phenylmethanephosphonic acid 2,2,2-trichloroethyl monoester. M.p. 88–90°C, $[\alpha]_D^{20} = -48.0°$, $c = 1$ in methanol. Found 52.62% C, 4.66% H. Calc. for $C_{27}H_{28}N_2O_6Cl_3P$ 52.81% C, 4.56% H.

4.3 g (2 mmole) of salt described above was dissolved in 50 ml of methanol and 14 mval of Amberlite IR 120 was added. The reaction mixture was stirred at room temperature for 15 min. The Amberlite was filtered off and the filtrate was evaporated to dryness under reduced pressure. The oily residue was crystallized from ethyl acetate. 2.1 g (90%) optically active 2,2,2-trichloroethyl monoester of *N*-phthalyl-1-amino-1-phenylmethanephosphonic acid **2** was obtained, $[\alpha]_D^{20} = -60.8°$, c = 1 in methanol. M.p. 169–171°C.

Diastereoisomers of ethyl-2,2,2-trichloroethyl diester of N-phthalyl-(R)-1-amino-1-phenylmethanephosphonic acid **3a** *and* **3b**. A suspension of 2.24 g (5 mmole) of 2,2,2-trichloroethyl monoester of *N*-phthalyl-(R)-1-amino-1-phenylmethanephosphonic acid in 8 ml of triethyl orthoformate was slowly heated at 80°C. The ethanol and ethyl formate were continually removed by distillation. When all of the precipitate had dissolved the temperature was risen from 80 to 145°C. The solution was refluxed for 20 min. Excess of triethyl orthoformate was evaporated under reduced pressure. The residue was dissolved in 10 ml of benzene and 100 ml of *n*-hexane was added. After standing for 12 hrs the first diastereoisomer **3a** of the ethyl-2,2,2-trichloroethyl diester of *N*-phthalyl-(R)-1-amino-1-phenylmethanephosphonic acid precipitated and was collected by filtration. Yield 690 mg (29%). M.p. 150–151°C, $[\alpha]_D^{20} = -81.5°$, c = 2,8, in chloroform. NMR ($CDCl_3$) 1.21 (t, $J_{HH} = 7$ Hz, 3 H, $OCH_2\underline{CH_3}$); 4.23 (d-q, $J_{HH} = 7$ Hz, $J_{PH} = 7$ Hz, 2 H, OCH_2CH_3); 4.77 (d, $J_{PH} = 7$ Hz, 2 H, OCH_2CCl_3); 5.80 (d, $J_{PH} = 26$ Hz, 1 H, CHP); 7.17–7.95 (m, 9 H, $C_6\underline{H}_5$, $C_6\underline{H}_4$). Found 48.02% C, 3.68% H. Calc. for $C_{19}H_{17}Cl_3NO_5P$ 47.85% C, 3.58% H.

To the filtrate 50 ml of *n*-hexane was added. The precipitate was discarded by filtration. The filtrate was evaporated under reduced pressure and the residue was crystallized from benzene and pentane mixture. 1.1 g (46.5%) of second diastereoisomer **3b** of the diester was obtained. M.p. 75–76°C, $[\alpha]_D^{20} = -48.0°$, $c = 2$ *in chloroform.* NMR ($CDCl_3$) 1.17 (t, $J_{HH} = 7$ Hz, 3 H, $OCH_2\underline{CH_3}$); 4.29 (d-q, $J_{HH} = 7$ Hz, $J_{PH} = 7$ Hz, 2 H, OCH_2CH_3); 4.47 (d, $J_{PH} = 7$ Hz, 2 H, OCH_2CCl_3); 5.87 (d, $J_{PH} = 26$ Hz, 1 H, CHP); 7.17–7.95 (m, 9 H, $C_6\underline{H}_5$, $C_6\underline{H}_4$). Found 47.58% C, 3.74% H. Calc. for $C_{19}H_{17}Cl_3NO_5P$ 47.85% C, 3.58% H.

Deprotection of N-phthalyl-(R)-1-amino-1-phenylmethanephosphonic acid ethyl 2,2,2-trichloroethyl diesters

(a) To a solution of 1.3 g (2.7 mmole) of ethyl-2,2,2-trichloroethyl diester of *N*-phthalyl-(R)-1-amino-1-phenylmethanephosphonic acid **3a** ($[\alpha]_D^{20} = -81.5°$) in 5 ml of anhydrous ethanol, 0.3 ml (6 mmole) of hydrazine hydrate (100%) was added. The mixture was kept at room temperature for 72 hrs. The resulting precipitate was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 10 ml of ethanol, 1 ml of acetic acid and 500 mg of Pd/C were added and hydrogen was passed through the reaction mixture for 72 hrs. Catalyst was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 5 ml of 45% hydrogen bromide in glacial acetic acid and kept at room temperature for 72 hrs. Volatile components of the reaction mixture were evaporated under reduced

pressure and the residue was purified on ion exchange resin Dowex 50WX8 100–200 mesh (H^+ form). 384 mg (76%) of (R)-1-amino-1-phenylmethanephosphonic acid **4** was obtained. M.p. 281–282°C, $[\alpha]_D^{20} = +16.0°$, c = 3.5 in 1 N NaOH.

(b) In identical manner from 1.5 g (3.5 mmole) of diester **3b** ($[\alpha]_D^{20} = -48.0°$) 458 mg (78%) of (R)-1-amino-1-phenylmethanephosphonic acid **4** was obtained. M.p. 282–283°C, $[\alpha]_D^{20} = +16.7°$, c = 4 in 1 N NaOH. (Lit.[2]: R—enantiomer is dextrorotatory.)

Diastereoisomeric hydrochlorides of ethyl-2,2,2-trichloroethyl diesters of 1-amino-1-phenylmethanephosphonic acid **5a** *and* **5b**. To a solution of 720 mg (1.5 mmole) of ethyl-2,2,2-trichloroethyl diester of *N*-phthalyl-(R)-1-amino-1-phenylmethanephosphonic acid **3a** ($[\alpha]_D^{20} = -81.5°$) in 6 ml of anhydrous ethanol 0.08 ml of hydrazine hydrate (100%) was added. The mixture was kept at room temperature for 3 days. The resulting phthalyl hydrazine was filtered off and solution was evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous ether. The precipitate was filtered off. Etheral solution of gaseous hydrochloric acid was added to the filtrate. White hydrochloride of ethyl-2,2,2-trichloroethyl diester of (R)-1-amino-1-phenylmethanephosphonic acid **5a** precipitated and was collected by filtration. Yield 486 mg (84%). M.p. 126–128°C decomp., $[\alpha]_D^{20} = +8.0°$, c = 2 in methanol after crystallization for ethanol and ether mixture. NMR ($CDCl_3$) 1.54 (t, J_{HH} = 7 Hz, 3 H, $OCH_2\underline{CH_3}$); 4.51 (d-q, J_{HH} = 7 Hz, J_{PH} = 7 Hz, 2 H, $O\underline{CH_2}CH_3$); 4.90 (d, J_{PH} = 8 Hz, 2 H, $O\underline{CH_2}CCl_3$); 5.45 (d, J_{PH} = 19 Hz, 1 H, CHP); 7.57–8.12 (m, 5 H, $C_6\underline{H_5}$); 9.32–10.10 (m, 3 H, $N\underline{H_3^+}$). Found 34.26% C, 4.06% H. Calc. for $C_{11}H_{16}Cl_4NO_3P$ 34.46% C; 4.18% H.

In identical manner from 760 mg (1.6 mmole) second diastereoisomer of diester **3b**, 426 mg (69%) of hydrochloride of diester **5b** was obtained. M.p. 128–130°C decomp. $[\alpha]_D^{20} = -7.0°$, in methanol. NMR ($CDCl_3$) 1.35 (t, J_{HH} = 7 Hz, 3 H, $OCH_2\underline{CH_3}$); 4.33 (d-q, J_{HH} = 7 Hz, J_{PH} = 7 Hz, 2 H, $O\underline{CH_2}CH_3$); 5.16 (d, J_{PH} = 9 Hz, 2 H, $O\underline{CH_2}CCl_3$); 5.45 (d, J_{PH} = 18 Hz, 1 H, CHP); 7.59–8.07 (m, 5 H, $C_6\underline{H_5}$); 9.32–10.30 (m, 3 H, NH_3^+). Found 34.52% C, 4.27% H. Calc. for $C_{11}H_{16}Cl_4NO_3P$ 34.46% C, 4.18% H.

Ethyl-2,2,2-trichloroethyl diester of N-carbobenzoxy-(R)-1-amino-1-phenylmethanephosphonic acid **6a** *and* **6b**

(a) To a solution of 486 g (1.26 mmole) of ethyl-2,2,2-trichloroethyl diester of (R)-1-amino-1-phenyl-methanephosphonic acid hydrochloride **5a** ($[\alpha]_D^{20} = +8.0°$), in 25 ml, 50% THF aq, 106 mg of $NaHCO_3$ and 286 mg of benzyl-*N*-hydroxy-succinimidyl carbonate was added at 0°C. The mixture was kept at room temperature for 4 hrs. The THF was evaporated under reduced pressure. The precipitate was collected by filtration and purified by chromatography on silica gel column eluted with benzene–acetone (10 : 1). Yield 495 mg (82%, of product **6a**). M.p. 165–167°C, $[\alpha]_D^{20} = +9.1°$, c = 4 in chloroform. NMR ($CDCl_3$) 1.22 (t, J_{HH} = 8 Hz, 3 H, $OCH_2\underline{CH_3}$); 3.62–4.47 (ABX system, 2 H, $O\underline{CH_2}CCl_3$); 3.92–4.30 (m, 2 H, $OCH_2\underline{CH_3}$); 5.06 (s, 2 H, $\underline{CH_2}$, $C_6\underline{H_5}$); 5.31 (d-d, J_{HH} = 9.5 Hz, J_{PH} = 22 Hz, 1 H, CHP); 6.60–6.95 (m, 1 H, NH); 7.25 (s, 5 H, $C_6\underline{H_5}$). Found 47.61% C, 4.44% H. Calc. for $C_{19}H_{21}Cl_3NO_5P$ 47.75% C, 4.37% H.

(b) In identical manner from 426 mg (1.1 mmole) of second diastereoisomer **5b**, 392 mg (74%) of *N*-carbobenzoxy derivative **6b** were obtained. M.p. 129–130°C, $[\alpha]_D^{20} = 0$, c = 3 in chloroform. NMR ($CDCl_3$) 1.05 (t, J_{HH} = 7 Hz, 3 H, $OCH_2\underline{CH_3}$); 3.60–4.20 (m, 2 H, $\underline{CH_2}CH_3$), 4.20–4.75 (ABX system, m, 2 H, $O\underline{CH_2}CCl_3$); 5.07 (s, 2 H, $\underline{CH_2}$-$C_6\underline{H_5}$); 5.30 (d-d, J_{HH} = 10 Hz, J_{PH} = 22.5 Hz, 1 H, CHP); 6.35–6.75 (m, 1 H, NH); 7.25 (s, 5 H, $C_6\underline{H_5}$). Found 47.85% C, 4.31% H. Calc. for $C_{19}H_{21}Cl_3NO_5P$ 47.74% C, 4.37% H.

ACKNOWLEDGMENT

The Authors wish to thank Polish Academy of Sciences for the financial support by the Grant No. MR-I.12.1.

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