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LETTERS TO THE EDITOR

Asymmetric Synthesis of 1-Hydroxy-2-alkylphosphonic Acids

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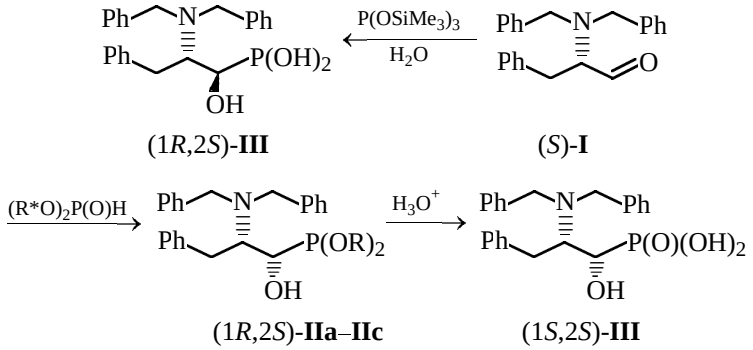
α-Hydroxy-β-aminoalkylphosphonic acids and esters are important biologically active compounds among which interesting medicine preparations and bioregulators have been found [1, 2]. We synthesized chiral compounds of this structure. We found that reaction of dialkyl hydrogen phosphites with (*S*)-*N*,*N*-dibenzylphenylalaninal proceeds stereoselectively and leads to formation of chiral α-hydroxy-β-(dibenzylamino)-γ-phenylpropylphosphonates with (1*S*,2*S*)-configuration. Diastereomeric ratio obtained was 5 : 1 (R = Et) and 9 : 1 (R = Mnt, Brn). Compounds **IIa**–**IIc** were crystallized from acetonitrile, and this allowed us to prepare chemically and optically pure (1*S*,2*S*)-diastereomers of compound **II**, which then were converted to 1-hydroxy-2-aminophosphonic acids (**III**) by hydrolysis with 20% hydrochloric acid in dioxane at 70–80°C.

In contrast, reaction of tris(trimethylsilyl)phosphate with c phenylalaninal resulted in a mixture of hydroxyaminophosphonic acid **III** (1*S*,2*S*)- and (1*R*,2*S*)-diastereomers in a 3 : 1 ratio from which by crystallization from water we isolated optically pure (1*R*,2*S*)-diastereomer. Structure of compounds obtained was confirmed by NMR spectroscopy and elemental analysis.



II, R = Brn = *endo*-borneol (**a**), Mnt = (1*R*,2*S*,3*R*)-menthol (**b**), Et (**c**).

Stereoselectivity of reaction of chiral dibornyl- and dimenthylphosphites with chiral aldehyde **I** is higher than that of achiral diethyl phosphite with **I**. This fact can probably be explained by dual asymmetric induction [3, 4].

Dibornyl 2-(dibenzylamino)-1-hydroxy-3-phenylpropylphosphonate (IIa). To a solution of 0.72 g (2.3 mmol) of aldehyde **I** in 0.7 ml of absolute toluene 0.55 ml (1.55 mmol) of di-*endo*-bornyl phosphite was added. The solution was cooled to 0°C and diazabicycluoundecene (2–3 drops) was added. The reaction mixture was left for 24 h at room temperature. Solvent was then evaporated and residue was passed through a column with silica gel, eluent ethyl acetate–hexane, 1 : 4. R_f 0.3. The product obtained was crystallized from acetonitrile. Yield 77%, mp 171–171.5°C (from acetonitrile). $[\alpha]_D$ –16.6° (*c* 1, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.94 s (3H, CH_3); 0.96 s (3H, CH_3); 1.04 s (3H, CH_3); 1.07 s (3H, CH_3); 1.08 s (6H, CH_3); 2.5 m (2H, PhCH_2C); 3.73 s (1H, PhCH_2N); 3.78 m (1H, CCHN); 4.23 s

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(1H, PhC*H*N); 4.3 s (1H, PhC*H*N); 4.9 m (3H, C*H*O + CHP); 5.9 br (1H, OH); 7.17–7.31 m (15H, ArH). $^{31}P–\{^1H\}$ NMR spectrum (δ_P, ppm, $CDCl_3$): 28.3. Found, %: N 2.15; P 4.26. $C_{43}H_{58}NO_4P$. Calculated, %: N 2.05; P 4.53.

Dimenthyl 2-(dibenzylamino)-1-hydroxy-3-phenylpropylphosphonate (IIb). Prepared similarly to compound **IIa**. Purified by column chromatography on silica gel. $[\alpha]_D$ –27.57° (*c* 6, CCl_4), R_f 0.15 ($CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.72 d (3H, CH_3, $^3J_{HH}$ 6.5); 0.74 d (3H, CH_3, $^3J_{HH}$ 6.5); 0.76 d (3H, CH_3, $^3J_{HH}$ 6.5); 0.77 d (3H, CH_3, $^3J_{HH}$ 6.5); 0.86 d (3H, CH_3, $^3J_{HH}$ 6.5); 0.89 d (3H, CH_3, $^3J_{HH}$ 6.5); 0.8–1.6 m [16H, (CH_2 + CH)]; 2.1 m [1H, $CH(CH_3)_2$]; 3.3 m (2H, CC*H*$_2$Ph); 3.5 m (2H, PhC*H*$_2$N); 3.70 m (1H, CHN); 3.8 m (2H, PhC*H*$_2$N); 4.3 m (1H, CHO); 4.4 m (1H, CHO); 3.62 d (1H, CHP, $^3J_{HH}$ 15,); 4.7 br (1H, OH); 7.1–7.4 m (15H, C_6H_5). $^{31}P–\{^1H\}$ NMR spectrum (δ_P, ppm, $CDCl_3$): 30.29. Found, %: N 2.04; P 4.50. $C_{43}H_{62}NO_4P$. Calculated, %: N 2.04; P 4.50.

Diethyl (2*R*,3*S*)-2-(dibenzylamino)-1-hydroxy-3-phenylpropylphosphonate (IIa). Obtained similarly to compound **IIa**. Purified by column chromatography on silica gel. Yield 50%, mp 127oC (from acetonitrile). $[\delta]_D$ –28° (*c* 1, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.25 t (3H, CH_3, $^3J_{HH}$ 7.1). 1.29 (3H, CH_3, $^3J_{HH}$ 7.1), 1.29 d (3H, CH_3, $^3J_{HH}$ 7.1), 3.15–3.02 m (2H, CH_2), 3.3 m (1H, CHN), 3.5 s (1H, CHN); 3.55, s (1H, CHN); 3.9 s (1H, CHN); 3.95 s (1H, CHN); 4.2 m (5H, CH_2O + CHP); 4.39 br (1H, OH), 7.1–7.3 m (15H, C_6H_5). $^{31}P–\{^1H\}$ NMR spectrum (δ_P, ppm, $CDCl_3$): δ_P 23.85. Found, %: P 6.62. $C_{27}H_{34}NO_4P$. Calculated, %: P 6.62.

(1*S*,2*S*)-2-(Dibenzylamino)-1-hydroxy-3-phenylpropylphosphonic acid. mp 118–120°C (from water). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.9 m (2H, CC*H*$_2$Ph); 3.8 m (4H, PhC*H*$_2$N); 3.70 m (1H, CHC); 4.3 m (1H, CHP); 5.9 br (1H, OH); 7.17–7.31 m (15H, C_6H_5). $^{31}P–\{^1H\}$ NMR spectrum (δ_P, ppm, $CDCl_3$): 17.4. Found, %: P 7.85. $C_{23}H_{26}NO_4P$. Calculated, %: P 7.53.

(1*R*,2*S*)-2-(Dibenzylamino)-1-hydroxy-3-phenylpropylphosphonic acid (III). 0.54 g (1.16 mmol) of hydroxyaminophosphonate was dissolved in 4 ml of dioxin and 4 ml of hydrochloric acid was added. The mixture was heated for 7 h at 70–80oC. Volatile products were removed in a vacuum. Crystalline residue after common treatment and crystallization from water was obtained as colorless crystalline compound. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.9 m (2H, CC*H*$_2$Ph); 3.8 m (4H, PhC*H*$_2$N); 3.70 m (1H, CHC); 4.3 m (1H, CHP); 5.9 br (1H, OH); 7.17–7.31 m (15H, C_6H_5). $^{31}P–\{^1H\}$ NMR spectrum (δ_P, ppm, $CDCl_3$): 17.4.

NMR spectroscopic investigations were performed on a Varian-300 instrument with internal reference TMS (^1H) and external 85% H_3PO_4 in D_2O (^{31}P).

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REFERENCES

1. Hilderbrand, R.L. and Henderson, T.G., *The Role of Phosphonates in Living Systems*, Boca Raton: CRC Press. 1983, p. 5.
2. Shibuya, S., *Yakugaku Zasshi* (The Pharmaceutical Society of Japan), 2004, vol. 124, no. 11, p. 725.
3. Kolodiazhnyi, O.I., *Tetrahedron*, 2003, vol. 59, no. 32, p. 5923.
4. Kolodiazhnyi, O.I., Sheiko, O., and Grishkun, E.V., *Heteroatom. Chem.*, 2000, vol. 11, no. 2, p. 138.