OPTICALLY ACTIVE α-AMINOETHYLPHOSPHONIC ACIDS AND THEIR ETHYL ESTERS

Yu. P. Belov, V. A. Davankov, and S. V. Rogozhin

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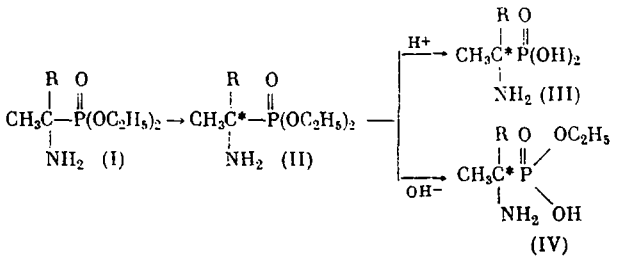
α-Aminophosphonic acids (APA), being analogs of natural α-aminocarboxylic acids, have attracted increasing attention [1-5]; they have also been prepared in optically active form in recent years [6-8]. Here we describe a series of optically active substituted α-aminoethylphosphonic acids and their ethyl esters.

The racemic diethyl α-aminophosphonates (I), synthesized by the Fields–Kabachnik–Medved' method [9-11], were resolved by crystallization with optically active acids into the optical antipodes (II); acid (total) hydrolysis or alkaline (partial) hydrolysis gave the APA (III) and their acid esters (IV) in optically active form:



We found that the yield of aminophosphonates from the condensation of NH_3 with aliphatic ketones and diethyl phosphite can be increased to 50-70% if the reactants are introduced into the reaction not simulta-

TABLE 1. Racemic Aminophosphonates, $CH_3C(NH_2)P(O)(OC_2H_5)_2$

R	Yield, %	bp, deg C (p, mm Hg)	n_D^{20}	d_4^{20}	mp of the picrate, deg C (dec.)	Found / Calculated, % † C	H	N	P
C_2H_5	53–56	65(1)	1,4419	1,0351	165–166	–	–	–	–
	36 *	87–88(5) *	1,4397 *	1,0381 *	166 *				
C_4H_9	49–53	84(1)	1,4448	0,9989	155–156	41,1 / 41,2	5,7 / 5,8	11,8 / 12,0	6,6 / 6,7
i-C_4H_9	≤ 60	76(1)	1,4420	1,0013	163–164	40,7 / 41,2	6,1 / 5,8	12,0 / 12,0	6,5 / 6,7
C_6H_{13}	67	72($5\cdot10^{-3}$)	1,4459	0,9778	160–161	43,5 / 43,7	6,2 / 6,3	11,4 / 11,3	–
C_6H_5	32–33	103($5\cdot10^{-3}$)	1,5078	1,1820	171–172	44,6 / 44,4	4,9 / 4,7	12,5 / 12,7	6,4 / 6,4
	32 *				174–175 *				

* From [11].

† Picrates.

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TABLE 2. Resolution of $CH_3C(R)(NH_2)P(O)(OC_2H_5)_2$ into Optical Antipodes by Crystallization with Dibenzoyl-d-tartaric Acid from Ether–Methanol

R	mp, deg C (dec.)	Acid dibenzoyl-d-tartrate $[\alpha]_D^{20}$ p.i., MeOH	Found / Calculated, % C	H	N	P	Optical activity of the aminophosphonate derived from the salt, $[\alpha]_\lambda^{20}$ at λ, nm 589	578	546	436	365
C_2H_5	137–138	−75,7	54,9 / 55,0	6,1 / 6,0	2,3 / 2,5	5,6 / 5,5	+2,2	+2,3	+2,5	+3,6	+3,9
C_4H_9	127–129	−72,9	56,3 / 56,5	6,6 / 6,4	2,5 / 2,4	–	+2,9	+3,0	+3,4	+5,0	+6,4
i-C_4H_9 *	–	−68,1	–	–	–	–	−1,4	–	–	–	–
C_6H_{13} *	140	−70,3	57,3 / 57,8	6,8 / 6,7	2,6 / 2,3	4,8 / 5,0	+1,9	+2,0	+2,2	+3,1	+2,6
C_6H_5 †	112 (fus.) 141 136 (fus.)	+2,5	47,2 / 47,2	6,4 / 6,4	3,5 / 3,4	7,8 / 7,6	−31,4	−33,0	−38,3	−74,5	−139

*Salts crystallize with difficulty.

†Resolved by crystallization of the acid d-tartrate from methanol.

TABLE 3. Optical Active Aminophosphonic Acids (Monohydrates), $CH_3C(R)(NH_2)P(O)(OH)_2 \cdot H_2O$

R	mp, deg C (dec.)	Found / Calculated, % C	H	N	P	Optical activity $[\alpha]_\lambda^{20}$ at λ, nm 589	578	546	436	365	solvent, concentration
C_2H_5	250–251	28,4 / 28,1	8,5 / 8,2	7,9 / 8,2	–	+4,8	+5,0	+5,6	+9,7	+15,3	5 *N* HCl (2,3)
C_4H_9	247–248	36,1 / 36,2	8,9 / 9,0	7,4 / 7,0	15,8 / 15,6	+3,0	+3,1	+3,3	+6,5	+10,7	5 *N* HCl (1,0)
						−4,5	−4,9	−5,8	−11,9	−23,9	1 *N* NaOH (1,0)
C_6H_5	216–217	44,0 / 43,8	6,3 / 6,4	6,4 / 6,4	13,7 / 14,2	+10,2	+10,6	+12,1	+20,6	+32,2	5 *N* HCl (1,4)
						−54,4	−57,0	−66,4	−130	−242	1 *N* NaOH (1,6)

neously, as in [11], but sequentially, in the above order (NH_3 was bubbled through continuously). Reaction with an aliphatic-aromatic ketone (acetophenone) [11] is more difficult than with aliphatic ketones. Simultaneous and sequential introduction of reactants are not accompanied by evolution of heat during the reaction; the yield of aminophosphonate is 32-33% (Table 1).

Of all the possible mechanisms of condensation of ketones, amines, and dialkyl phosphites [9, 12-15] the most probable is Fields's well-substantiated scheme [9]

1) ketone + amine → intermediate

2) intermediate + dialkyl phosphite → (I)

The increase in yield of aliphatic aminophosphonates when reactants are introduced sequentially also supports this scheme. The increased yield of (I) when diethyl phosphite is added to the reaction mixture after saturation of the ketone with NH_3 can be attributed to the suppression of side reactions, such as the direct reaction of diethyl phosphite with the ketone [16, 17].

Vacuum distillation of (I) is accompanied by partial decomposition, which particularly affects the most branched representative – diethyl α-amino-α-isobutylethylphosphonate. The synthetic aminophosphonates (Table 1) were characterized as the picrates.

Resolution of (I) into optical antipodes followed our published procedure [6], namely crystallization of their acid salts with optically active dicarboxylic acids. Use of d-tartaric acid is most convenient for resolution of diethyl α-amino-α-phenylethylphosphonate. The other aminophosphonates were resolved with dibenzoyl-d-tartaric acid. The properties of the acid salts and the optical activity of the derived aminophosphonates (II) are summarized in Table 2. The aminophosphonates (II) were subsequently used for the synthesis of dissymetric adsorbents containing the corresponding APA groups following our earlier work [18]; the adsorbents were used to resolve racemates into optical antipodes by ligand-exchange chromatography.

Acid and alkaline hydrolysis [11, 19] of several aminophosphonates (II) gave the optically active APA's (III) and their acid esters (IV) respectively (Table 3).

EXPERIMENTAL

Synthesis of Racemic Diethyl α-Aminophosphonates. Methyl alkyl ketone (or acetophenone) (5-200 g) in a flask was saturated for 10-20 min with dry NH_3. After addition of diethyl phosphite (equimolar quantity), NH_3 was bubbled through for 2-5 h until the exothermal reaction ceased (the temperature of the mixture reached 35-60°C); the mixture was then heated for a further 3-6 h, while its temperature gradually increased to 85°C. (The exothermal reaction does not occur with acetophenone.)

At the end of the reaction a powerful current of inert gas was passed through the mixture to remove NH_3, whereupon absolute ether was added until precipitation of ammonium monoethylphosphate ceased [11]. The precipitate was removed. The filtrate was concentrated and vacuum-distilled. To prepare the picrates the distilled or crude product was dissolved in absolute ether and mixed with excess ethereal picric acid. The precipitate was separated and crystallized from ethanol (Table 1).

Optically Active Diethyl α-Aminophosphonates. (−)-Diethyl α-amino-α-phenylethylphosphonate. A solution of racemic diethyl α-amino-α-phenylethylphosphonate (224 g) in absolute ether (130 ml) was mixed with a solution of d-tartaric acid (81.7 g) in methanol (260 ml). The resulting acid tartrate (yield 52%) was recrystallized six times from methanol in 75-85% yield at each stage. The melting point and optical activity after four, five, and six crystallizations were identical, which we adopted as the criterion for terminating the resolution procedure. The acid tartrates were suspended in absolute methanol and saturated with NH_3. Excess absolute ether was added to the resulting solution without discontinuing the flow of ammonia. The resulting precipitate was removed. Concentration of the filtrate on a rotary evaporator gave in quantitative yield (−)-diethyl α-amino-α-phenylethylphosphonate (Table 2).

The other aminophosphonates (I) were resolved by crystallization with dibenzoyl-d-tartaric acid [20] in 1:1 ratio from a mixture of absolute ether with a small quantity of methanol. The aminophosphonates were isolated similarly in 85-95% yield from their acid dibenzoyl-d-tartrates and were additionally purified by vacuum distillation (Table 2).

Optically Active α-Aminophosphonic Acids were prepared by heating aminophosphonates (II) with HCl (1:1) for 3-7 h on a boiling-water bath followed by removal of residual HCl with propylene oxide. Elemental analysis of the APA after recrystallization from aqueous ethanol corresponded to the monohydrate (Table 3).

(+)-Monoethyl Hydrogen α-Amino-α-ethylethylphosphonate. The corresponding diester (Table 2) gave the (+)-monoethyl ester after 6 h reflux with 1.5 N NaOH in 80% ethanol [19]. After reprecipitation with ether from methanolic solution it had mp 209°C; $[\alpha]_{\lambda}^{20}$ (λ, nm): +2.1° (589), +2.2° (578), +2.6° (546), +4.4° (436), +6.7° (365) (5N HCl, p 2.4). Found: C 40.1; H 8.8; N 7.8; P 17.1%. $C_6H_{16}NPO_3$. Calculated: C 39.8; H 8.8; N 7.7; P 17.1%.

CONCLUSIONS

1. We have synthesized a series of optically active substituted α-aminoethylphosphonic acids and their ethyl esters.

2. The yield of products from the condensation of aliphatic ketones with diethyl phosphite and ammonia depends on the order of introduction of the reactants into the reaction.

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