Tetrahedron Letters No.36, pp. 3147-3150, 1970. Pergamon Press. Printed in Great Britain.

SIMPLE SYNTHESIS OF 2-AMINOETHYLPHOSPHONIC ACID AND RELATED COMPOUNDS

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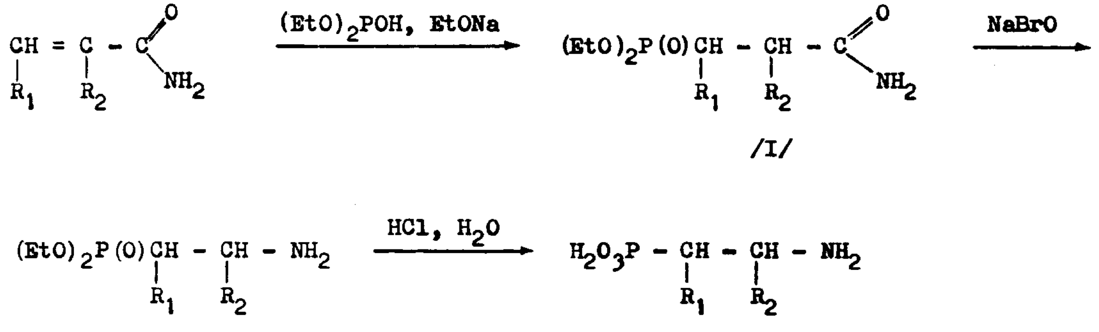
(Received in UK 22 June 1970; accepted for publication 2 July 1970)

2-Aminoethylphosphonic acid, a substance of considerable biochemical interest, is known since 1946 and several methods for its preparation are described in the literature (1-4). However, the number of known structural analogues of this compound is very small (5-8), although such analogues are interesting as substrates for biochemical studies in enzyme systems involved in the metabolism of 2-aminoethylphosphonic acid. In the course of our studies on aminophosphonic acids a simple, essentially two-step method was developed for the preparation of 2-aminoethylphosphonic acid and related compounds from unsaturated amides:



$$\underset{R_1}{CH}=\underset{R_2}{C}-C(O)NH_2 \xrightarrow{(EtO)_2POH,\ EtONa} (EtO)_2P(O)\underset{R_1}{CH}-\underset{R_2}{CH}-C(O)NH_2 \xrightarrow{NaBrO}$$

/I/

$$(EtO)_2P(O)\underset{R_1}{CH}-\underset{R_2}{CH}-NH_2 \xrightarrow{HCl,\ H_2O} H_2O_3P-\underset{R_1}{CH}-\underset{R_2}{CH}-NH_2$$

(not isolated)

/II/

Ia, IIa $R_1 = H, R_2 = H$ **Ic, IIc** $R_1 = CH_3, R_2 = H$

Ib, IIb $R_1 = H, R_2 = CH_3$ **Id, IId** $R_1 = C_6H_5, R_2 = H$

Thus, a mixture of diethyl hydrogen phosphonate (0.11 mole) and unsaturated amide (0.1 mole) was heated to 60-70° and the exothermic reaction was initiated by dropwise addition of 5 ml of 3 M ethanolic sodium ethoxide. The reaction was completed by heating for 1 hour at 110°. To isolate crystalline diethyl 2-carbamylphosphonates (I) the mixture was diluted with ethanol, neutralized with conc. HCl, filtered and the solvent was removed at reduced pressure. The residue solidified and was recrystallized from benzene or benzene-cyclohexane (3:1) to yield pure carbamylphosphonates listed in Table 1.

Hofmann degradation of the carbamylphosphonates followed by acid hydrolysis yielded 2-aminophosphonic acids listed in Table 2. The acids were isolated by standard procedures and purified by crystallization from ethanol-water mixtures. The isolation of carbamylphosphonates is not necessary if only aminophosphonic acids are desired. Yields of pure acids exceeding 70% were achieved when crude reaction mixtures obtained after the addition of diethyl hydrogen phosphonate to unsaturated amides were treated with sodium hypobromite in alkaline solution.

Carbamylphosphonates and aminophosphonic acids reported here are new except for compounds Ia and IIa.

The success of our approach depended upon the development of an efficient procedure for the preparation of 2-carbamylphosphonates from α, β unsaturated amides. Pertinent literature data are surprisingly scarce and only two examples could be found. Harvey (9) obtained diethyl 2-carbamylethylphosphonate (Ia) from acrylamide and triethyl phosphite in phenol. The reaction is general but of little value for preparative purposes because the large excess of phenol renders the isolation of pure amides difficult.

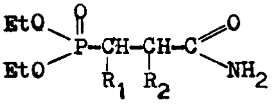
Pudovik and Jarmuchametova (10) erroneously described diethyl 2-carbamyl-2-methylethylphosphonate (Ib) as a liquid of b. p. 146-7°/13 mm Hg and n_D^{20}= 1.4361, obtained by diethyl hydrogen phosphonate addition to the amide of methacrylic acid. The addition was carried out in the presence of sodium ethoxide as catalyst. The product was isolated by distillation of crude reaction mixture. Reinvestigating the addition of diethyl hydrogen phosphonate to the amide of methacrylic acid we have established that the product described by Pudovik and Jarmuchametova is in all respects, including IR and NMR spectra, identical with diethyl 2-cyano-2-methylethylphosphonate, prepared from the nitrile of methacrylic acid in a similar reaction and described earlier by Pudovik (11). Evidently the initially formed diethyl 2-carbamyl-2-methylethylphosphonate was dehydrated to corresponding nitrile during distillation.

Dehydration of diethyl 2-carbamyl-2-methylethylphosphonate upon distillation was confirmed by distillation of pure amide isolated by crystallization as described in this communication. Distillation at 4 mm Hg yielded pure nitrile almost quantitatively. At lower pressures mixtures of the amide and nitrile were obtained but even at 4×10^{-4} mm Hg dehydration of the amide was significant.

Pure diethyl 2-carbamylethylphosphonate prepared from acrylamide was similarly dehydrated to the nitrile upon distillation.

Table 1

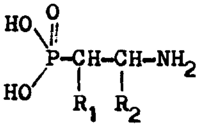
Diethyl esters of 2-carbamylphosphonic acids



R_1	R_2	Yield %	M.p °C	% N calc.	% N found	% P calc.	% P found
H	H	75	74-6	6.70	6.83	14.81	15.20
H	CH_3	80	75-7	6.28	6.43	13.88	13.20
CH_3	H	75-80	72-6	6.28	6.35	13.88	14.25
C_6H_5	H	76-81	135-6	4.91	5.24	10.86	10.32

Table 2

2-aminophosphonic acids



R_1	R_2	Yield %	M.P. °C	% N calc.	% N found	% P calc.	% P found
H	H	75	271-8	11.20	11.62	24.77	24.78
H	CH_3	85	278-84	10.07	10.10	22.27	22.15
CH_3	H	80	282-6	10.07	9.87	22.27	22.93
C_6H_5	H	75	274-6	6.96	6.92	15.40	15.31

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