CHEMISTRY LETTERS, pp. 1349-1350, 1978. Published by the Chemical Society of Japan

PREPARATION OF 1-HYDROXY-2-AMINOETHYLPHOSPHONIC ACID AND ITS ALKYL-SUBSTITUTED DERIVATIVES

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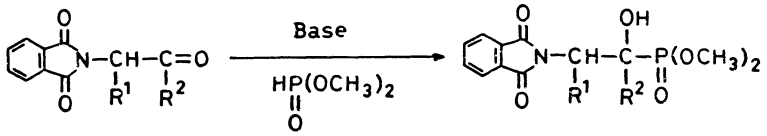
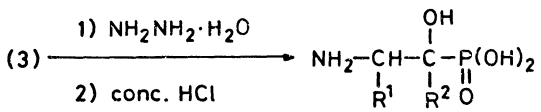
1-Hydroxy-2-aminoethylphosphonic acid, a substance of biochemical interest, and its alkyl-substituted derivatives were prepared for the first time by the reaction of N-(2-oxoethyl)phthalimide and dimethyl phosphite in the presence of base.

Since the discovery of 2-aminoethylphosphonic acid (ciliatine) in a rumen ciliate,[1] natural phosphonic acids have received much attention from biochemists.[2] Although several methods for their preparations have been reported, an earlier effort to prepare 1-hydroxy-2-aminoethylphosphonic acid (1a), isolated from Acanthamoeba castellanii,[3] by a reaction of aminoacetaldehyde with dimethyl phosphite was unsuccessful, because aminoacetaldehyde is unstable in the presence of base or acid.[4] By using N-(2-oxoethyl)phthalimide (2a), as the key intermediate, we prepared (1a) successfully.

The following reaction sequence was employed.

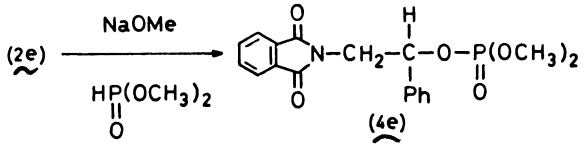


			Yield (%)	Mp (°C)	m/e
(2a)	R^1= H, R^2= H	(3a)	57	148-149	299 (M^+)
(2b)	R^1= H, R^2= Me	(3b)	64	153-154	313 (M^+)
(2c)	R^1= Me, R^2= H	(3c)	67	130-131	313 (M^+)
(2d)	R^1= i-Pr, R^2= H	(3d)	69	oil	341 (M^+)
(2e)	R^1= H, R^2= Ph	(3e)	0	—	—



	Yield (%)	Dec (°C)	^{1}H-NMR (δ) (D_2O-NaOD)
(1a)	21	254-258	2.80 (m,2H,-C<u>H</u>$_2$-), 3.50 (m,1H,-C<u>H</u>(OH)-)
(1b)	33	235-238	1.28 (d,3H,J=11.9Hz,-C<u>H</u>$_3$), 2.64-3.04 (m,2H,-C<u>H</u>$_2$-)
(1c)	30	258-260	1.40 (d,3H,J=6.1Hz,-C<u>H</u>$_3$), 3.59 (m,1H,-C<u>H</u>(OH)-) 3.63 (m,1H,-C<u>H</u>(CH_3)-)
(1d)	36	196-199	1.01 (d,6H,J=6.6Hz,-CH(C<u>H</u>$_3$)$_2$), 2.30 (m,1H,-C<u>H</u>(CH_3)$_2$) 3.20 (m,1H, N-C<u>H</u>-), 3.66 (t,1H,J=8.5Hz,-C<u>H</u>(OH)-)

Treatment of (2)[5] with excess dimethyl phosphite at 50-60°C for 3h in the presence of base (NEt_3 for a,c,d, NaOMe for b,e) gave a solid residue. From the residue was isolated white crystalline product (3) by recrystallization from a mixture of ethanol and benzene.[6] But N-(2-oxo-2-phenylethyl)phthalimide (2e) reacted with dimethyl phosphite to give an isomerized product (4e) instead of N-(2-dimethoxyphosphinyl-2-hydroxy-2-phenyl)phthalimide (3e). Removal of phthaloyl group from (3) was



Yield	Mp(°C)	m/e
80	88-90	357(M^+)

accomplished by the treatment with hydrazine hydrate in refluxing methanol for 1h. Phthalhydrazide was removed by filtration and the compound in the filtrate was hydrolyzed in a refluxing conc.HCl solution for 7h. The reaction mixture was concentrated and the crude product was precipitated by the addition of ethanol. White crystal (1) was obtained by recrystallization from water. Elemental analyses supported the chemical structure of (1).

It is noteworthy that the methine and methylene proton signals of (1a) shifted to a lower magnetic field with an increase of acidity of the solution as shown below. This may be due to the formation of the protonated amino moiety in acidic solution. The ^{1}H-NMR data of (1a) were consistent with those isolated from plasma membranes of Acanthamoeba castellanii.[3]

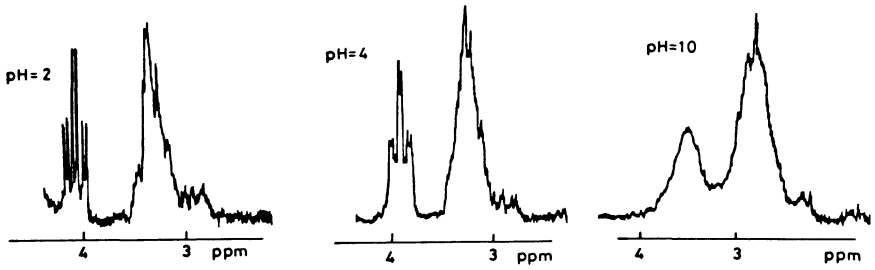


Fig. ^{1}H-NMR Spectra of (1a) in D_2O (DSS as an internal standard)

REFERENCES AND NOTES

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2) T.Hori, M.Horiguchi, "C-P Kagobutsu no Seikagaku", Japan Scientific Societies Press (1978).
3) E.D.Korn, D.G.Deaborn, H.M.Fales, E.D.Sokolski, J. Biol. Chem., 248, 2257 (1973).
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5) N-(2-oxoethyl)phthalimide (2a) and its derivatives (2b) and (2e) were prepared by Gabriel synthesis; the reaction of potassium phthalimide with bromoacetaldehyde dimethyl acetal, bromoacetone, and 2-bromoacetophenone, respectively, followed by the hydrolysis in 8% HCl solution in case of (2a).
The aldehydes (2c) and (2d) were prepared by Rosenmund reduction.
6) N-(1-formyl-2-methylpropyl)phthalimide (3d) was an oily product.

(Received June 23, 1978)