

NOVEL SYNTHESIS OF α -AMINOPHOSPHONIC ACIDS

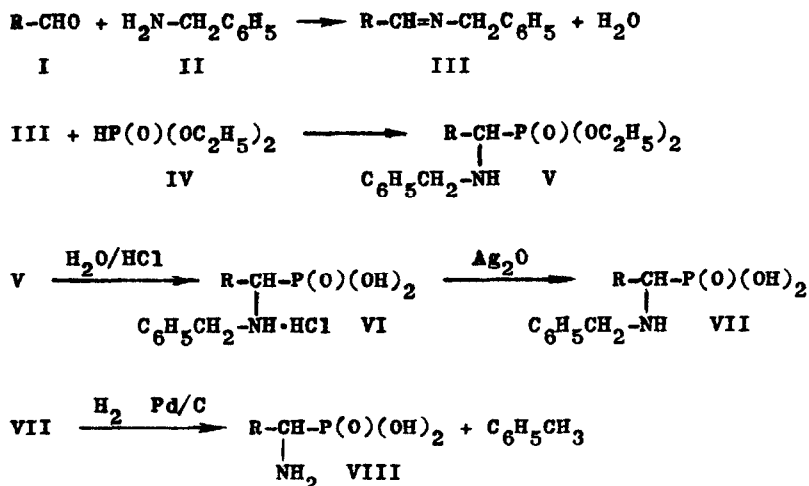
Roman Tyka

Institut of Organic and Physical Chemistry, Technical University
Wrocław (Poland)

(Received in UK 6 January 1970; accepted for publication 21 January 1970)

Simultaneous addition of ammonia and diethyl hydrogen phosphonate to aldehydes and ketones as described by Kabachnik (1-4) followed by hydrolysis of the addition product appears to be the simplest of present methods for the preparation of α -aminophosphonic acids (5-10). Unfortunately, the yields obtained by this method are usually low and the purity of products is often not satisfactory. Much more readily proceeds the addition of dialkyl hydrogen phosphonates to Schiff's bases as described by Fields (11), yielding N-substituted α -aminophosphonic acids upon hydrolysis of the intermediate esters. The readily available N-substituted α -aminophosphonic acids would be useful for the preparation of the biologically more interesting aminophosphonic acids with free amine group if a procedure could be found for the removal of substituent from the nitrogen atom. In this respect the benzyl group appeared to be most promising as benzylamine forms Schiff's bases readily and the hydrogenolysis of N-benzylaminoderivatives is known to generate free amino group (12,13).

We wish to report a general procedure for the preparation of α -aminophosphonic acids starting with Schiff's bases prepared from aldehydes and benzylamine. The addition of diethyl hydrogen phosphonate followed by hydrolysis yielded N-benzyl- α -aminophosphonic acids which upon hydrogenolysis formed α -aminophosphonic acids:



When ethyl hydrogen alkylphosphonites $\text{R}'\text{-P(OH)(OC}_2\text{H}_5)_2$ were substituted for diethyl hydrogen phosphonate corresponding α -aminophosphinic acids $\text{RCH-P(O)(OH)NH}_2\text{R}'$ were obtained.

The conditions of reactions are as follows: the equimolar mixture of N-benzylaldimine (III) obtained after (11) and diethyl hydrogen phosphonate (IV) was heated for 0.5 hour at a temp. of 100-140° (the progress of the reaction was controlled by thin layer chromatography) and the reaction mixture was hydrolysed by boiling with concentrated hydrochloric acid for 8 hours. The resulting solution was filtered, evaporated to dryness and the residue was dissolved in water. The chloride ions were removed by treatment with moist Ag_2O and the solution was concentrated to a small volume. Pure N-benzyl- α -aminophosphonic acids crystallized from the solution upon treatment with ethanol. Hydrogenolysis of the N-benzyl- α -aminophosphonic acids (VII) in glacial acetic acid with 50% Pd/C (14) as catalyst yielded the desired α -aminophosphonic acids. It is to be noted that the esters of N-benzyl- α -aminophosphonic acids are resistant to hydrogenolysis.

The structures of products were confirmed by elemental analysis, chemical properties and infrared spectra. The results obtained are summarized in the Tables.

TABLE 1. N-Benzyl- α -aminophosphonic acids $\text{R}-\underset{\text{NHCH}_2\text{C}_6\text{H}_5}{\text{CH}}-\text{P}(\text{O})(\text{OH})_2$

R	M.p. °C	Yields %	Analysis							
			Calc:				Found:			
			C	H	N	P	C	H	N	P
CH ₃	236-8	58	50.20	6.50	6.50	14.40	49.91	6.21	6.66	14.11
C ₂ H ₅	222-4	55	52.42	7.02	6.11	13.52	52.43	7.37	6.16	13.50
n-C ₃ H ₇	214-6	65	54.29	7.46	5.75	12.74	54.03	7.25	5.91	12.45
n-C ₄ H ₉	205-7	65	56.01	7.84	5.44	12.01	56.17	7.62	5.59	11.83
C ₆ H ₅	236-7	70	60.62	5.81	5.05	11.18	60.31	5.72	5.30	11.45

TABLE 2. α -Aminophosphonic acids $\text{R}-\underset{\text{NH}_2}{\text{CH}}-\text{P}(\text{O})(\text{OH})_2$

R	M.p. °C	Yields %	Analysis							
			Calc:				Found:			
			C	H	N	P	C	H	N	P
CH ₃	272-4	95	19.20	6.45	11.2	24.80	18.92	6.21	11.41	25.00
C ₂ H ₅	264-6	93	25.90	7.20	10.11	22.31	25.65	7.11	10.22	22.21
n-C ₃ H ₇	262-4	94	31.27	7.85	9.15	20.26	31.01	8.02	9.12	19.95
n-C ₄ H ₉	269-7	92	35.91	8.38	8.37	18.54	35.62	8.42	8.51	18.91
C ₆ H ₅	280-2	93	44.91	5.38	7.48	16.56	44.80	5.19	7.51	16.67

TABLE 3. N-Benzyl- α -aminophosphonic acids $\text{R}-\underset{\text{NHCH}_2\text{C}_6\text{H}_5}{\text{CH}}-\text{P}(\text{O})(\text{R}')(\text{OH})$

R	R'	M.p. °C	Yields	Analysis							
				Calc:				Found:			
				C	H	N	P	C	H	N	P
CH ₃	C ₆ H ₅	232-3	43	65.44	6.59	5.09	11.26	65.21	6.62	5.19	11.12
C ₂ H ₅	C ₆ H ₅	252-3	38	66.40	6.97	4.84	10.71	66.29	6.75	5.12	10.47
n-C ₃ H ₇	C ₆ H ₅	204-5	39	67.29	7.30	4.61	10.22	67.03	7.00	4.68	9.89
n-C ₄ H ₉	C ₆ H ₅	175-6	35	68.11	7.59	4.41	9.77	67.82	7.41	4.60	10.01
C ₆ H ₅	C ₆ H ₅	252-3	58	71.21	5.97	4.15	9.19	71.13	5.62	4.33	9.28
n-C ₃ H ₇	C ₂ H ₅	164-5	41	61.14	8.68	5.48	12.14	60.80	8.49	5.67	12.29
C ₆ H ₅	C ₂ H ₅	212-3	57	66.42	6.97	4.84	10.71	66.19	6.59	4.81	10.52

TABLE 4. α -Aminophosphinic acids $R-\underset{\text{NH}_2}{\text{CH}}-\text{P}(\text{O})(\text{R}')(\text{OH})$

R	R'	M.p. °C	Yields %	A n a l y s i s							
				C a l c :				F o u n d :			
				C	H	N	P	C	H	N	P
CH ₃	C ₆ H ₅	262-9	92	51.88	6.53	7.56	16.74	51.61	6.61	7.81	16.51
C ₂ H ₅	C ₆ H ₅	265-6	91	54.26	7.08	7.02	15.56	54.09	6.93	7.25	15.33
n-C ₃ H ₇	C ₆ H ₅	245-7	94	56.30	7.55	6.56	14.53	56.03	7.67	6.89	14.21
n-C ₄ H ₉	C ₆ H ₅	244-5	95	58.13	7.98	6.16	13.64	58.00	8.15	6.41	13.92
C ₆ H ₅	C ₆ H ₅	246-7	93	63.16	5.71	5.66	12.54	62.86	5.40	5.93	12.39
C ₆ H ₅	C ₂ H ₅	232-3	93	54.27	7.08	7.03	15.56	54.11	6.88	7.09	15.65

Acknowledgement

The author is very indebted to Dr. Przemysław Mastalerz for the helpful discussions and suggestions.

REFERENCES

1. M.I.Kabachnik and T.Ya.Medved, Dokl.Akad.Nauk SSSR, 83, 689 (1952); Chem.Abstr., 47, 2724 (1953).
2. T.Ya.Medved and M.I.Kabachnik, Dokl.Akad.Nauk SSSR, 84, 717 (1952); Chem.Abstr., 47, 3226 (1953).
3. M.I.Kabachnik and T.Ya Medved, Izv.Akad.Nauk SSSR, Otd.Khim.Nauk, 868 (1953); Chem.Abstr., 49, 840 (1955).
4. T.Ya.Medved and M.I.Kabachnik, Izv.Akad.Nauk SSSR, Otd.Khim.Nauk, 314 (1954); Chem.Abstr., 48, 10541 (1954).
5. M.E.Chalmers and G.M.Kosolapoff, J.Am.Chem.Soc., 75, 5278 (1953).
6. N.Kreutzkamp and G.Cordes, Ann.Chem., 623, 103 (1959).
7. J.R.Chambers and A.F.Isbell, J.Org.Chem., 29, 832 (1964).
8. K.D.Berlin, R.T.Claunch, and E.T.Gaudy, J.Org.Chem., 33, 3090 (1968).
9. K.D.Berlin, N.K.Roy, R.T.Claunch, and D.Bude, J.Am.Chem.Soc., 90, 4494 (1968).
10. H.Hoffmann, and H.Förster, Monatsh., 99, 380 (1968).
11. E.K.Fields, J.Am.Chem.Soc., 74, 1528 (1952).
12. E.Baer, H.Basu, and B.C.Pal, Canad.J.Biochem., 45, 1467 (1967).
13. H.Dahn and U.Solms, Helv.Chim.Acta, 35, 1162 (1952).
14. R.P.Linstead and S.L.S.Thomas, J.Chem.Soc., 1127 (1940).