(14) L. V. Hopkins, J. P. Vacik, and W. H. Shelver, *J. Pharm. Sci.*, **61**, 114 (1972). N. S. Kozlov, V. D. Pak, and E. S. Elin, *Tr. Permsk. Gos. Skh. Inst.*, **68**, 34 (1970); *Chem. Abstr.*, **78**, 43698 (1973).
(15) Imines have moderate to low basicity; PhCH=NBu-t has pK_a 6.7 (E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963)).
(16) pK_a for 1-(2-methylpropenyl)pyrrolidine is 8.84: E. J. Stomhuis, W. Maas, and H. Wynberg, *J. Org. Chem.*, **30**, 2160 (1965).
(17) D. Giron-Forest and G. Thomas, *Bull. Soc. Chim. Fr.*, 296 (1972).
(18) J. Zon and P. Mastalerz, *Rocz. Chem.*, **50**, 1403 (1976).
(19) K. Abe and S. Yamamoto, *J. Pharm. Soc. Jpn.*, **73**, 1322 (1953); *Chem. Abstr.*, **49**, 1771 (1955).
(20) "Dictionary of Organic Compounds", Oxford University Press, New York, N.Y., 1965.
(21) G. Darzens, *C. R. Hebd. Seances Acad. Sci.*, **149**, 1001 (1910).
(22) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
(23) T. J. King, *J. Chem. Soc.*, 898 (1951).
(24) R. E. Lutz et al., *J. Org. Chem.*, **12**, 760 (1947).
(25) Supplementary data discloses ^{13}C NMR spectra of *cis*- and *trans*-1-methyl-2-morpholinocyclohexane.

Notes

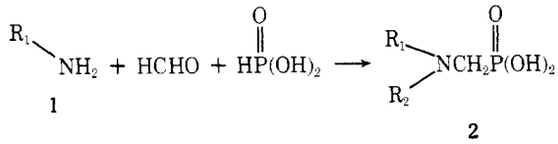
N-Benzyl-α-amino Phosphonic Acids

Derek Redmore

Petrolite Corporation, Tretolite Division, St. Louis, Missouri 63119

June 19, 1977

The Mannich-type reaction of amines with formaldehyde and phosphorous acid is a very useful procedure for the preparation of aminomethylenephosphonic acids.[1] One of the limitations of this procedure is that primary amines (**1**) treated with 1 equiv of formaldehyde and phosphorous acid yield a mixture of mono- and bis(methylenephosphonic) acids (**2a** and **2b**).[2] A further limitation appears to be in the choice of

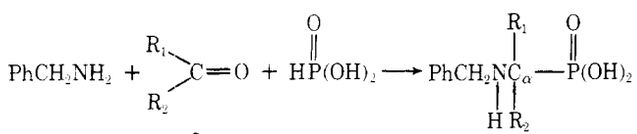


1 **2**

a, $R_2 = H$
b, $R_2 = CH_2P(=O)(OH)_2$

carbonyl component; all examples reported use formaldehyde with one exception in a patent.[3]

In light of the above, the recent report[4] that benzylamine reacts with a series of carbonyl compounds (**3a–d**) to yield



3 **4**

a, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_2CH_3$; $R_2 = H$
d, $R_1 = CH_2CH_3$; $R_2 = CH_3$

monophosphonic acids **4a–d** and, in particular, that best yields are obtained upon reacting 2 equiv of **3** and phosphorous acid for each equivalent of benzylamine is unexpected. Furthermore, the dissociation constants reported for these phosphonic acids are significantly different from those of other α-amino phosphonic acids.[2b] The present work was, therefore, undertaken in an attempt to resolve these discrepancies.

In our hands benzylamine heated with acetone, propionaldehyde or methyl ethyl ketone, and phosphorous acid by the procedure of Szczepaniak[4] yielded white crystalline products. The ^1H NMR spectra of these products showed only two peaks, at δ 4.2 and 7.5, in the ratio 2:5. Basification of these solids liberated benzylamine, showing that the solids were benzylamine salts. Careful examination of the mother liquors from the crystallization by ^{31}P NMR yielded no evidence for the presence of even traces of phosphonic acids. In the case of formaldehyde the only product isolated was the bis(methylenephosphonic) acid **2b** (R_1 = $PhCH_2$–).

Authentic samples of the phosphonic acids **4a–d** were obtained by hydrolysis of the corresponding ethyl or isopropyl esters **5a–d** prepared by the method of Fields.[5] In the hydrolysis of the esters **5b** and **5d**, some degradation was observed resulting in the recovery of benzylamine. The ^{13}C and ^{31}P NMR spectra of the acids **4a–d**, as shown in Table I, provided proof of structure together with other analytical data.

The dissociation constants of the acids **4a–d** were measured by potentiometric titration. Table II summarizes the results of our measurements and includes for comparison the results of Szczepaniak[4] and some other data from the literature for α-amino phosphonic acids.[6] It can be seen that the results from the present study are consonant with results from other workers.[6]

We conclude that the phosphonic acids **4a–d** cannot be prepared by the direct route from phosphorous acid and that the acids, when obtained by an authentic process, yield the expected acid dissociation constants.

Experimental Section

Melting points are uncorrected. The elemental analyses were performed by Clark Microanalytical Laboratories and Petrolite Corpo-

Table I. ^{31}P and ^{13}C NMR Data for α-Amino Phosphonic Acids

Registry no.	Compd	R_1	R_2	δ ^{31}P[a]	δ ^{13}C[b] (J_{C-P}, Hz)		
					C_α	R_1	R_2
49622-09-5	**4a**	H	H	−16.6	53.1 (138)		
49622-10-8	**4b**	CH_3	CH_3	−15.4	59.8 (136)	25.1	25.1
26067-66-3	**4c**	CH_2CH_3	H	−17.3	65.2 (135)	29.9, 18.5	
49622-12-0	**4d**	CH_2CH_3	CH_3	−14.8	62.9 (143)	26.9, 8.4 (6)	19.7

[a] Relative to 85% H_3PO_4 internal reference. [b] Relative to Me_4Si internal reference.

0022-3263/78/1943-0996$01.00/0

Table II. Dissociation Constants of α-Amino Phosphonic Acids

Compd	pK_{a_1}	pK_{a_2}	Ref
4a	3.22	6.16	4
4a	5.40	10.10	This work
4b	3.66	6.29	4
4b	6.02	9.75	This work
4c	3.55	6.33	4
4c	6.00	10.70	This work
4d	3.65	6.23	4
4d	5.53	10.68	This work
$NH_2C(CH_3)_2P(=O)(OH)_2$	6.05	10.43	6
$NH_2CH(Ph)P(=O)(OH)_2$	5.60	9.50	6

ration, Analytical Section. ^1H NMR spectra were obtained with a Varian A-60 spectrometer, ^{31}P and ^{13}C spectra with a Jeol FX-60 spectrometer operating at 24.15 and 15.04 MHz, respectively.

***N*-Benzyliminobis(methylenephosphonic) Acid (2b, R_1 = $PhCH_2$–).** In precisely the manner described[4] benzylamine (0.1 mol) was reacted with phosphorous acid (0.2 mol) and formaldehyde (0.2 mol). The yield of white crystals, virtually insoluble in ethanol, was 14 g. Recrystallization from water yielded pure **2b** (R_1 = $PhCH_2$);[1] mp 257–258 °C; NMR (D_2O) (as sodium salt) δ 3.50 (d, 4, J = 12 Hz, NCH_2P), 4.85 (s, 2, $PhCH_2$), 7.62 (s, 5, PhH).

Anal. Calcd for $C_9H_{15}NO_6P_2$: N, 4.75; P, 21.02. Found: N, 4.64; P, 20.88.

***N*-Benzyl-α-aminomethylphosphonic Acid (4a).** Diethyl *N*-benzyl-α-aminomethylphosphonate (25.7 g, 0.1 mol) was heated under reflux in 18% hydrochloric acid (200 mL) for 2 h. Evaporation of the aqueous acid yielded a gum. Crystallization from ethanol/ether yielded **4a** as its hydrochloride: mp 272–274 °C; NMR (D_2O) δ 3.28 (d, 2, J = 13 Hz, NCH_2P), 4.37 (s, 2, $PhCH_2N$), 7.50 (s, 5, PhH).

Anal. Calcd for $C_8H_{12}NO_3PHCl$: C, 40.42; H, 5.47; N, 5.89; P, 13.05. Found: C, 40.64; H, 5.66; N, 5.63; P, 13.44.

***N*-Benzyl-2-amino-2-propylphosphonic Acid (4b).** Hydrolysis of the corresponding ethyl ester as described above yielded after crystallization the acid **4b**: mp 177–180 °C from ethanol; NMR (D_2O) δ 1.68 (d, 6, J = 12 Hz, CH_3CP), 4.44 (s, 2, $PhCH_2$), 7.55 (s, 5, PhH).

Anal. Calcd for $C_{10}H_{16}NO_3P$: C, 52.40; H, 6.99; N, 6.11; P, 13.54. Found: C, 52.69; H, 7.12; N, 5.78; P, 13.35.

***N*-Benzyl-1-amino-1-propylphosphonic Acid (4c).** As in the case of **4a**, the acid crystallized from ethanol/ether as its hydrochloride: mp 182–184 °C; NMR (D_2O) δ 1.10 (t, 3, J = 7 Hz, CH_3CH_2), 2.0 (m, 2, CH_2CH_3), 3.1–3.6 (m, 1, CHP), 4.43 (s, 2, CH_2Ph), 7.55 (s, 5, PhH).

Anal. Calcd. for $C_{10}H_{16}NO_3P{\cdot}HCl$: N, 5.27; P, 11.68; Cl^-, 13.37. Found: N, 4.90; P, 11.76; Cl^-, 13.37.

Dissolution of the hydrochloride in ethanol and treatment with propylene oxide gave the free acid **4c**, mp 227–228 °C (lit.[7] mp 222–224 °C).

***N*-Benzyl-2-amino-2-butylphosphonic Acid (4d).** The acid was obtained from the corresponding ethyl ester as described above and crystallized from ethanol/ether: mp 125–128 °C; NMR (D_2O) δ 1.13 (t, 3, J = 7 Hz, CH_2CH_3), 1.60 (d, 3, J = 14 Hz, CH_3CP), 1.9–2.3 (m, 2, CH_2), 4.47 (s, 2, CH_2Ph), 7.57 (s, 5, PhH).

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.29; H, 7.40; N, 5.58; P, 12.25.

Registry No.—**2b**, 6056-53-7; **4a** HCl, 64715-31-7; **4a** diethyl ester, 50917-70-9; **4b** diethyl ester, 64715-32-8; **4c** HCl, 64715-33-9; **4c** diethyl ester, 42274-96-4; **4d** diethyl ester, 64740-22-3; benzylamine, 100-46-9; formaldehyde, 50-00-0; phosphorous acid, 13598-36-2.

References and Notes

(1) K. Moedritzer and R. R. Irani, *J. Org. Chem.*, **31**, 1603 (1966).
(2) (a) K. Moedritzer, *Synth. Inorg. Met.-Org. Chem.*, **2**, 317 (1972); **3**, 75 (1973); (b) D. Redmore, *Top. Phosphorus Chem.*, **8**, 515–585 (1976).
(3) R. R. Irani and K. Moedritzer, U. S. Patent 3 288 846 (1966).
(4) W. Szczepaniak and J. Siepak, *Rocz. Chem.*, **47**, 929 (1973).
(5) E. K. Fields, *J. Am. Chem. Soc.*, **74**, 1528 (1952).
(6) J. P. Berry, A. F. Isbell, and G. E. Hunt, *J. Org. Chem.*, **37**, 4396 (1972).
(7) R. Tyka, *Tetrahedron Lett.*, 677 (1970).

N-Iodosuccinimide for the Synthesis of Rose Oxide

S. C. Taneja, K. L. Dhar,* and C. K. Atal

Regional Research Laboratory, Council of Scientific and Industrial Research, Jammu, India

Received April 21, 1977

The use of *N*-iodosuccinimide (NIS) in the synthetic field is less explored than that of *N*-bromosuccinimide (NBS). Djerassi et al.[1,2] have found that NIS is incapable of performing certain free-radical chain iodinations typical of the radical chain brominations brought about by NBS. NIS has been shown to react with enol acetates derived from ketones to give iodo ketones.[2] The mechanism of the reaction seems to be ionic in nature. In another unusual free-radical iodination reaction characteristic of NIS, a vinylic proton is replaced by iodine.[3]

In the present note, we report the use of NIS in the synthesis of rose oxide (III) from citronellol (I) in one step. The synthesis of the same compound from citronellol or citronellyl acetate using NBS is reported to be a multistep process in which allylic bromination is followed by dehydrobromination with a base and finally hydrolysis and cyclization with an acid.[4] With the use of NIS, all these steps are combined into one, giving rose oxide in yields up to 36%. The probable mechanism of the reaction may be represented as shown in Scheme I.

From the above sequence of reactions, it appears that the mechanism involved is similar to that of allylic bromination by NBS. However, in the case of NIS, allylic iodination is immediately followed by dehydroiodination, resulting in the formation of dehydrocitronellols IIa and IIb.[5] The cyclization of dehydrocitronellol to rose oxide is facilitated by iodine, which itself is generated during the course of the reaction.

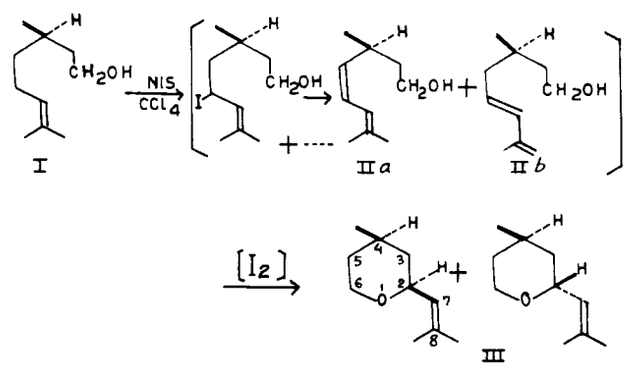
In summary, while the reaction of citronellol with NBS (in CCl_4) gives a bromo derivative of citronellol, the reaction with NIS (in CCl_4) gives rose oxide as the major product. Changing the reaction medium to dioxane and acetic acid gave only a trace amount of rose oxide.

Experimental Section

NIS was prepared by the method of Djerassi and Lenk.[6] A 10-g amount of the citronellol[7] and 22 g of *N*-iodosuccinimide were taken up in 80 mL of CCl_4, and the mixture was refluxed in a water bath for 45 min. The dark violet solution obtained was shaken several times with an aqueous solution of sodium thiosulfate until the iodine was completely removed. It was then washed with distilled water and dried over anhydrous sodium sulfate. The solution was concentrated and subjected to column chromatography on silica gel. Elution with petroleum ether–benzene (10:1) afforded pure rose oxide: 3.6 g (cis/trans, 81:19);[8] bp 48 °C (1.5 mm); $[\alpha]^{20}_D$ +27.5°; ^1H NMR (60 MHz) δ 0.90 (d, J = 8 Hz, 3 H, C-4), 1.52 (d, J = 1.2 Hz, 3 H, C-8), 1.66 (d, J = 1.2 Hz, 3 H, C-8), 3.0–4.0 (m, 3 H, C**H**–O–C$\mathbf{H}_2$), 5.10 (m, 1 H, =CH).

Acknowledgment. We wish to thank Dr. Y. V. Subbarao of the Regional Research Laboratory, Hyderabad, for the ^1H

Scheme I



0022-3263/78/1943-0997$01.00/0