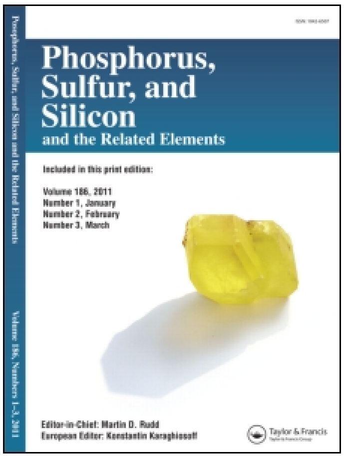
This article was downloaded by:
On: *30 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

NOVEL UNSYMMETRICAL *N,N*-BIS(METHYLENE)BISPHOSPHONIC ACIDS OF α,ω-DIAMINES. PREPARATION AND CHARACTERIZATION OF [[(2-AMINOETHYL)IMINO]BIS(METHYLENE)]BISPHOSPHONIC ACID AND [[(6-AMINOHEXYL)IMINO]BIS(METHYLENE)]BISPHOSPHONIC ACID

Derek Redmore[a]; Balram Dhawan[a]
[a] Petrolite Corporation, St. Louis, MO

To cite this Article Redmore, Derek and Dhawan, Balram(1983) 'NOVEL UNSYMMETRICAL *N,N*-BIS(METHYLENE)BISPHOSPHONIC ACIDS OF α,ω-DIAMINES. PREPARATION AND CHARACTERIZATION OF [[(2-AMINOETHYL)IMINO]BIS(METHYLENE)]BISPHOSPHONIC ACID AND [[(6-AMINOHEXYL)IMINO]BIS(METHYLENE)]BISPHOSPHONIC ACID', Phosphorus, Sulfur, and Silicon and the Related Elements, 16: 3, 233 — 238

To link to this Article: DOI: 10.1080/03086648308080472

URL: http://dx.doi.org/10.1080/03086648308080472

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus and Sulfur, 1983, Vol. 16, pp. 233–238
0308-664X/83/1603-0233/$18.50/0

© 1983 Gordon and Breach, Science Publishers, Inc.
Printed in the United States of America

NOVEL UNSYMMETRICAL *N*,*N*-BIS(METHYLENE)-BISPHOSPHONIC ACIDS OF α,ω-DIAMINES. PREPARATION AND CHARACTERIZATION OF [[(2-AMINOETHYL)IMINO]BIS(METHYLENE)]-BISPHOSPHONIC ACID AND [[(6-AMINOHEXYL)IMINO]BIS(METHYLENE)]-BISPHOSPHONIC ACID

DEREK REDMORE and BALRAM DHAWAN

Petrolite Corporation, St. Louis, MO 63119

(*Received March 8, 1983; in final form May 3, 1983*)

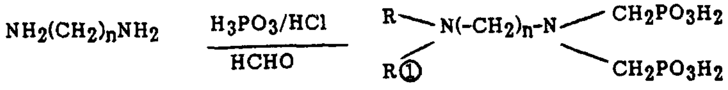
Downloaded At: 10:22 30 January 2011

Reaction of ethylenediamine with phosphorous acid and formaldehyde in molar ratio 1 : 2 : 2 gives [[(2-aminoethyl)imino]bis(methylene)]bisphosphonic acid (**2a**) as the major product. Similarly, reaction of hexamethylenediamine with phosphorous acid and formaldehyde in molar ratio 1 : 2 : 2 yields [[(6-aminohexyl)imino]bis(methylene)]bisphosphonic acid (**2b**) which is isolated either as [[(6-carbobenzoxyaminohexyl)imino]bis](methylene)]bisphosphonic acid (**3b**) or as [[6-(*N*-benzoylamino)hexyl)imino]bis(methylene)]bisphosphonic acid (**4b**). Removal of the carbobenzoxy group with HBr from **3b** or the benzoyl group with HCl from **4b** gives pure [[(6-aminohexyl)imino]bis(methylene)]bisphosphonic acid (**2b**). All compounds were characterized by ^{13}C NMR, ^{31}P NMR and elemental analysis.

Aminophosphonic acids are of interest as the analogs of natural amino acids, chelating agents and important constituents of biological systems. We have been interested in the synthesis of aminophosphonic acids for some time[1] and report here the synthesis and characterization of novel unsymmetrical *N*-*N*-bismethylenebisphosphonic acids of α,ω-diamines.

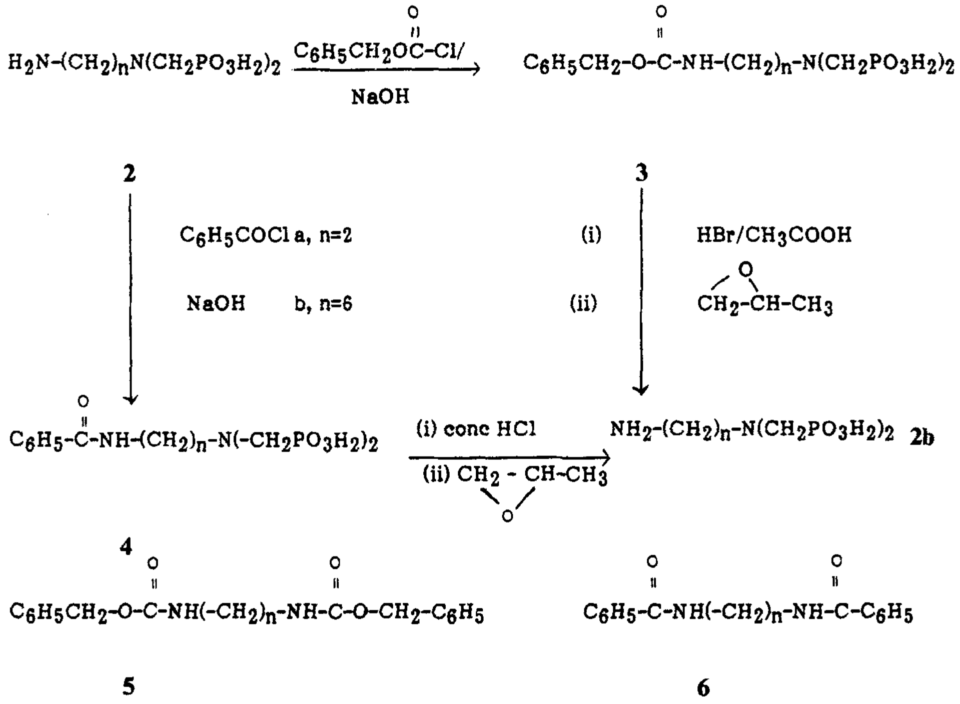
The Mannich-type reaction of amines with formaldehyde and phosphorous acid in strongly acidic solution has been used to prepare many aminomethylenephosphonic acids.[2] Nevertheless the scope and limitations of this process have not been completely elucidated. Moedritzer,[3] in describing elegant routes to aminomethylphosphonic acid and to iminobis(methylenephosphonic) acid, states that amines or ammonia subjected to reaction with less than one equivalent of phosphorous acid per—NH yield mixtures.[4] We describe here results from reactions of primary amines and α,ω-diamines which shed more light on the Mannich-type reactions.

We have found that when an α,ω-diamine is treated with phosphorous acid and formaldehyde in a molar ratio 1 : 2 : 2, respectively, in strongly acidic medium, the two products are [[(ω-aminoalkyl)imino]bis(methylene)]bisphosphonic acid (**2**), the major product, and a tetraphosphonic acid (**1**). For example, when ethylenediamine (0.2 mole) was reacted with phosphorous acid (0.4 mole) and formaldehyde (0.4 mole) in 6N HCl, it gave [[(2-aminoethyl)imino]bis(methylene)]bisphosphonic acid (**2a**) (18.2 g 37%) and ethylenebis(nitrilobismethylene)tetraphosphonic acid (**1a**) (16.4 g, 19%).



1.	$R=R_1=-CH_2PO_3H_2$	a,	n=2
2.	$R=R_1=H$	b,	n=6

When the crude reaction product was carbobenzoxylated, it yielded [[2-(*N*-carbobenzoxyaminoethyl)imino]bis(methylene)]bisphosphonic acid (**3a**) and *N*-*N*′-bis carbobenzoxy ethylenediamine (**5a**) (8–10%) which obviously is formed from the unreacted amine present in the crude product. **3a** was obtained in 58% yield by the carbobenzoxylation of pure (**2a**). Similarly, benzoylation of the crude product yielded [[2-(benzoylaminoethyl)imino]bis(methylene)]bisphosphonic acid (**4a**) and *N*,-*N*′-bisbenzoylethylenediamine (**6a**).



Reaction of hexamethylenediamine with phosphorous acid and formaldehyde in molar ratio 1 : 2 : 2 gave a crude product which contained [[(6-aminohexyl) imino]bis(methylene)]bisphosphonic acid (**2b**) as the major product. Isolation of **2b** from the crude reaction product, however, proved difficult. The crude product was therefore carbobenzoxylated to yield a mixture of [[(6-(carbobenzoxyaminohexyl)imino]bis(methylene)]bisphosphonic acid (**3b**) and *N*-*N*′-bis(carbobenzoxy)hexamethylene diamine (**7b**) from which **7b** could be readily extracted with boiling methanol. Treatment of **3b** with HBr/CH_3COOH then gave **2b** as a white solid. Alternatively, the crude product could be benzoylated to yield [[(6-(benzoylaminohexyl)imino]

Downloaded At: 10:22 30 January 2011

TABLE I

NMR data for **2a**

$$H_2N\text{—}\underset{2}{CH_2}\text{—}\underset{1}{CH_2}\text{—}N[\underset{\alpha}{CH_2}PO_3H_2]_2$$

^{13}C chemical shifts (C—P coupling constants)

pH	C-α	C-1	C-2	^{31}P Chemical shifts
12.1	56.32 (143, 9.5)	56.53 (8.3)	38.33	15.52
8.3	56.57 (144, 8.5)	54.54 (8)	37.98	16.48
4.75	54.76 (150, 7.0)	54.86 (6.7)	38.21	18.75
1.6	53.32 (137, 4.3)	54.09 (3.9)	35.33	8.09

TABLE II

NMR data for **2b**

$$H_2N\text{—}\underset{6}{CH_2}\text{—}\underset{5}{CH_2}\text{—}\underset{4}{CH_2}\text{—}\underset{3}{CH_2}\text{—}\underset{2}{CH_2}\text{—}\underset{1}{CH_2}\text{—}N[\underset{\alpha}{CH_2}PO_3H_2]_2$$

^{13}C chemical shifts (C—P coupling constants)

pH	C-α	C-1	C-2	C-3	C-4	C-5	C-6	^{31}P Chemical shifts
12.2	54.87 (132)	57.46	24.35	26.46	26.46	31.65	41.23	10.5
8.1	54.99 (125, 3.7)	57.22	23.86	25.81	25.81	27.27	40.26	6.52
5.0	53.53 (136)	57.71	24.02	25.81	25.81	27.27	40.34	7.33
1.1	52.47 (137, 3.7)	57.87 (3.7)	23.78	25.81	25.81	27.35	40.42	7.88

bis(methylene)]bisphosphonic acid (**4b**) which on treatment with HCl gave **2b**.

Further characterization of compounds **2a** and **2b** was provided by the ^{31}P and ^{13}C NMR spectra which are summarized in Tables I and II. The phosphorus chemical shifts for **2a** and **2b** show different responses to changes in pH. The change in chemical shift in **2a** from 8 to 17 ppm going from unionized phosphonic acid ($\text{—}PO_3H_2$) to dianion ($\text{—}PO_3^{2-}$)[5] is similar to that observed in NTP (8–18 ppm)[2] and **1a**. On the other hand the ^{31}P chemical shift for **2b** changes little with pH (6–10 ppm) mirroring the behavior of **1b** and **10a**. The carbon spectra of **2a** and **2b** are also influenced by the state of ionization of the phosphonate group but both to the same degree.

DISCUSSION

In light of our earlier results[4] the formation of *N,N*-diphosphonic acids as the predominant product in the reaction of α,ω-diamines with two equivalents of phosphorous acid was unexpected. Upon re-examination of the primary amine reaction with one equivalent of phosphorous acid and formaldehyde we have obtained a different result from that reported earlier.[4] Cyclohexylamine (**8a**) and benzylamine (**8b**) upon reaction with one equivalent of H_3PO_3 and formaldehyde have been found to yield predominantly diphosphonic acids **10a** and **10b**, respectively (monophosphonic acids **9a** and **9b** contain less than 10% of the H_3PO_3

Downloaded At: 10:22 30 January 2011

$$\underset{\mathbf{8}}{RNH_2} \xrightarrow[H_3PO_3/HCHO]{k_1} \underset{\mathbf{9}}{RNHCH_2PO_3H_2} \xrightarrow[H_3PO_3/HCHO]{k_2} \underset{\mathbf{10}}{RN(CH_2PO_3H_2)_2}$$

a. R = $\underline{c}C_6H_{11}$

b. R = $PhCH_2$

SCHEME 1

TABLE III

Amine charged (moles)	Amine recovered	Diphosphonic acid	Monophosphonic acid
8a (0.495)	**8a** (0.205)	**10a** (0.24)	**9a** (trace)
8b (0.50)	**8b** (0.18)	**10b** (0.225)	**9b** (0.05)

Downloaded At: 10:22 30 January 2011

charged). Table III summarizes the results which lead us to conclude that monophosphonic acids **9** react significantly faster than the precursor primary amines **8** with the phosphorous acid/formaldehyde reactant, i.e. $k_2 \gg k_1$.

EXPERIMENTAL

Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee and Petrolite Corporation, Analytical Section. ^{31}P and ^{13}C spectra were obtained with a Jeol FX-60 Spectrometer operating at 24.15 and 15.04 MHz, respectively. The solutions were prepared in D_2O and sodium hydroxide was added to adjust pH. The chemical shift (δ) values are downfield from H_3PO_4 (Cap.) for ^{31}P spectra and from TMS (Cap.) for ^{13}C spectra.

Reaction of Ethylenediamine with Phosphorous Acid and Formaldehyde. To an aqueous solution of phosphorous acid (32.8 g, 0.4 mole, in 100 ml water) was added ethylenediamine (12.0 g, 0.2 mole) and conc. HCl (100 ml). The mixture was heated to 100 ± 5°C and then formaldehyde (40 ml, 0.5 mole, 37%) was added dropwise. After the completion of the addition of formaldehyde, the mixture was heated at reflux for an additional three hours at 100 ± 5°C. The solvent was then removed on a rotary evaporator to yield the crude product as a thick syrup.

Isolation of [1,2-ethanediylbis[nitrilobis(methylene)]tetraphosphonic acid (**1a**) *and [[(2-aminoethyl) imino]bis(methylene)]bisphosphonic acid* (**2a**). The crude product was dissolved in water and allowed to stand where upon the tetraphosphonic acid (**1a**) precipitated as a white solid. The yield was 16.4 g (18.8%), m.p. 214°C. Lit. mp 214°C.[2] C^{13} NMR (D_2O/NaOH, pH = 12.0, TMS Cap.), 53.24 (t, $J_{P-C-N-C} = 4.3$ Hz), 54.72 (dd, $J_{P-C} = 132.5$ Hz, $J_{P-C-N-C} = 4.3$ Hz). The filtrate was then evaporated to a small volume and passed through Dowex 50-W-X-8 Cation exchange resin. The column was eluted with water and phosphonic acid fractions were combined and concentrated. Ethanol was next added to cloudiness and after standing [[(2-aminoethyl)imino]bis(methylene)]bisphosphonic acid[6] (**2b**) precipitated out as white solid. The yield was 18.2 g (36.7%). A crystallization from water-ethanol gave an analytical sample without any loss m.p. 256–258°C. Anal. calcd for $C_4H_{14}N_2O_6P_2$: C, 19.35; H, 5.65; N, 11.29; P, 25.00. Found: C, 19.46; H, 5.65; N, 11.22; P, 25.20.

Carbobenzoxylation of the Crude Product. 7.44 g of crude product (from ethylenediamine, phosphorous acid and formaldehyde) was dissolved in 50 ml 2N sodium hydroxide. The solution was cooled in an ice-bath and benzyl chloroformate (15.3 g) was added dropwise. The pH was maintained between 9–10 by intermittent addition of 4N sodium hydroxide. After stirring for 2.5 h, ether was added and the insoluble material present was collected by filtration. Recrystallization of this solid material from methanol gave *N*,*N*′-bis(carbobenzoxy)ethane-1,2-diamine (**5a**), m.p. 169–170°C. Lit.[7] m.p. 168–169°C. H^1 NMR ($CDCl_3$/TFA/TMS), 3.32 (s, 4 H, $C\underline{H}_2$—NH), 5.12 (s, 4 H, —O—CH_2—Ar), 7.34 (s, 10 H, aromatic). The layers (filtrate) were then separated and the aq. layer was poured over a mixture of 30 ml H_2O, 100 g ice and 30 ml conc. HCl. The mixture was kept in a refrigerator overnight and then filtered to collect a white solid. Recrystallization from water gave [[(2-carbobenzoxyaminoethyl)imino]bis(methylene)] bisphosphonic acid (**3a**) as a white crystalline solid. m.p. 189–190°C. C^{13} NMR (pH – 12.0), 37.27, 54.99 (dd, $J_{P-C} = 126.0$, $J_{\underline{P}-C-N-\underline{C}} = 3$ Hz), 56.90, 68.50, 129.08, 129.66, 130.05, 137.45, 159.40 (> C=O). Anal. calcd for $C_{12}H_{20}N_2O_8P_2$; C, 37.70; H, 5.24; N, 7.33; P, 16.23. Found C, 37.63, H, 5.30; N, 7.42; P, 16.10.

Benzoylation of Crude Product. 12.5 g of crude product (from ethylenediamine, phosphorous acid and formaldehyde) was dissolved in 2N—NaOH (150 ml). The solution was cooled in an ice bath and benzoyl chloride (15.5 g), and 2N—NaOH (100 ml) were added simultaneously. The mixture was stirred for 2.5 hr. and then acidified with dilute HCl to pH 2. Ether was added and the mixture was filtered to collect insoluble material. Recrystallization from acetic acid gave pure *N*,*N*′-bisbenzoyl ethane-1,2-diamine (**6a**) m.p. 254°C. Lit.[8] m.p. 250°C. H^1 NMR (CF_3COOH/TMS), 4.08 (s, 4 H—$C\underline{H}_2$—N), 7.40–7.95 (m, 10 H, aromatic). The aqueous layer (from filtrate) was separated, concentrated and CH_3OH added to precipitate NaCl which was filtered off. The filtrate was evaporated to dryness, dissolved in a small amount of water and passed through Dowex-50-W-X-8 resin. The column was eluted with water and the phosphonic acid fractions were combined. Evaporation of solvent then yielded a thick paste which on crystallization from CH_3OH–water gave [[(2-benzoylaminoethyl)imino]bis(methylene)]bisphosphonic acid (**4a**) as a white solid. m.p. 213–215°C. C^{13} NMR (pH = 11.5); 38.17, 55.19, 56.30 (dd, $J_{P-C} = 142.5$, $J_{\underline{P}-C-N-\underline{C}} = 6$ Hz), 128.56, 129.99, 133.24, 134.80, 171.93 (> C=O). Anal. calcd for $C_{11}H_{18}N_2O_7P_2$; C, 37.50; H, 5.11; N, 7.95; P, 17.61. Found C, 36.78; H, 5.26; N, 7.75; P, 17.70.

Reaction of Hexamethylenediamine with Phosphorous Acid and Formaldehyde. To a solution of phosphorous acid (16.2 g, 0.2 mole) in 50 ml water was added hexamethylenediamine (11.6 g, 0.1 mole) and conc. HCl (50 ml). The mixture was heated to 100 ± 5°C and formaldehyde (18 ml 0.2 mole) was added dropwise with vigorous stirring. After the completion of the addition of formaldehyde, the mixture was refluxed for additional 3 hours. The solvent removal on a rotary evaporator yielded the crude product as an oil.

Benzoylation of the Crude Product. The above crude product was dissolved in 450 ml 2N NaOH. The solution was cooled to 10°C and benzoyl chloride (46.5 g) was added dropwise. During the addition of benzoyl chloride, the pH was maintained at 9–10 with intermittent addition of 4N—NaOH. The mixture was stirred for 2 hr and then acidified with dilute HCl to pH 2. Ether (400 ml) was added. Solid material that remained undissolved in the two layers was collected by filtration and crystallized from methanol to give 6 g of *N*,*N*′-bisbenzoyl hexamethylenediamine (**6b**) m.p. 164–164.5°C. Lit.[9] m.p. 159–160°C. H^1 NMR ($CDCl_3$/TMS) 1.3–1.8 (m, 8 H, $C\underline{H}_2$), 3.3–3.6 (m, 4 H, N—$C\underline{H}_2$), 6.36 (bs, 2 H, N$\underline{H}$—), 7.3–7.9 (m, 10 H), aromatic). The aqueous layer was separated and extracted again with ether. Evaporation of water then gave a white solid which was purified by two recrystallizations from water to obtain [(6-benzoylaminohexyl)imino]bis(methylene)]bisphosphonic acid (**4b**), as a white crystalline solid. The yield was 13.1 g (32%), m.p. 257–259°C. C^{13} NMR (pH = 12), 26.1, 27.5, 29.6, 41.1, 55.8 (dd, $J_{P-C} = 140.5$ Hz, $J_{P-C-N-C} = 7.8$ Hz), 58 (t, $J = 5.8$ Hz), 128, 129.86, 132.97, 134.92, 171.80 (C=O). Anal. calcd for $C_{15}H_{26}N_2O_7P_2$; C, 44.11; H, 6.37; N, 6.86; P, 15.19. Found C, 44.26; H, 6.84; N, 6.76; P, 15.10.

Carbobenzoxylation of Crude Product. A solution of the crude product (from 0.1 mole of 1,6-hexanediamine) in 250 ml 2N—NaOH was cooled to 10°C and benzylchloroformate (76.5 g) was added dropwise. The pH of the reaction mixture was maintained between 9 and 10 by the intermittent addition of 4N—NaOH. The mixture was stirred overnight at room temperature and then extracted with ether (discarded). It was next acidified with dilute HCl to pH 2 and the white precipitate that separated was collected by filtration. It was boiled with CH_3OH—$CHCl_3$ (150 ml, 15 ml) mixture and filtered hot. The CH_3OH—$CHCl_3$ filtrate on cooling deposited *N*,*N*′-bis(carbobenzoxy)hexane-1,6-diamine (**5b**) as white crystalline solid (14%), m.p. 128–129°C. Lit.[10] m.p. 126°C. H^1 NMR ($CDCl_3$/TMS) 1.36 (b, 8 H, CH_2), 3.0–3.3 (m, 4, —N—CH_2), 4.75 (b, 2 H, NH), 5.10 (s, 4 H, —$C\underline{H}_2$O), 7.34 (s, 10 H, aromatic). The residue that was insoluble in hot methanol-chloroform mixture was crystallized from water to obtain [[(6-carbobenzoxyaminohexyl)imino]bis(methylene)]bisphosphonic acid (**3b**) as white crystals (29%), m.p. 191–192°C. C^{13} NMR (pH = 12); 26.30, 27.53, 28.11, 30.38, 42.07, 56.35 (dd, $J_{P-C} = 144.5$, $J_{P-C-N-C} = 9.8$ Hz), 58.31 (t, $J_{P-C-N-C} = 6.8$ Hz), 68.11 (—O—CH_2), 129.01, 129.66, 130.12, 137.97, 159.66 (> C=O). Anal. calcd for $C_{16}H_{28}N_2O_8P_2$; C, 43.83; H, 6.39; N, 6.39; P, 14.15. Found C, 44.20; H, 6.52; N, 6.41; P, 13.80.

Downloaded At: 10:22 30 January 2011

Preparation of [[(*6-Aminohexyl*)*imino*]*bis*(*methylene*)]*bisphosphonic acid* (**2b**).

(a) *By removal of carbobenzoxy group from* **3b** To a stirred solution of 2.19 g (0.005 mole) of **3b** in 25 ml of glacial acetic acid was added 12.5 ml of 48% HBr. and stirring continued for 3–4 hr at r.t. The solvent was removed on a rotary evaporator, the residue was dissolved in 25 ml of ethanol and the solvent was removed again. *The residue was dissolved in 25 ml of ethanol and 2 ml of propylene oxide was added.* A white solid precipitated, was collected by filtration, dissolved in warm water and the solution filtered to remove any suspended material. The filtrate was concentrated to *ca.* 10 ml and then ethanol was added till the precipitation of white solid ceased. After keeping overnight in a refrigerator, the solid was collected by filtration and crystallized again from water–ethanol. The yield was 1.52 g (100%). m.p. 186–188°C. C^{13} (pH −12.25) 25.60, 27.39, 33.03, 41.88, 55.88 (dd, $J_{P-C} = 136$ Hz, $J_{P-C-N-C} 7.0$ Hz), 58.07 (t, $J_{P-C-N-C} = 4.5$ Hz). Anal. calcd for $C_8H_{22}N_2O_6P_2 \cdot H_2O$: C, 29.81; H, 7.45; N, 7.60; P, 19.25; H_2O, 5.59. Found C, 29.46; H, 7.56; N, 8.70; P, 19.70: H_2O, 5.27%.

(b) *By removal of benzoyl group from* **4b** A solution of 2 g of **4b** in 20 ml of conc. HCl was refluxed for 36 hr. Upon cooling benzoic acid precipitated out and was removed by extraction with ether. The aqueous solution was then evaporated to almost dryness, dissolved in ethanol and reevaporated to dryness. The residue was dissolved in ethanol and 2 ml of propylene oxide was added when **2b** separated precipitated as an oil. On seeding, it crystallized to give a white solid which was purified by recrystallization from water–ethanol mixture. This was identical in all respects with the product obtained above by decarbobenzoxylation of **3b**.

Reaction of benzylamine with phosphorous acid and formaldehyde at 1 : 1 : 1 *molar ratio.* To a solution of benzylamine (53.5 g; 0.5 mole) and phosphorous acid (41 g; 0.5 mole) in water (50 ml) and concentrated HCl (50 ml) heated at gentle reflux was added formaldehyde (40 ml; 0.53 mole) during 15 mins. After heating at 100–105° for 2 hrs. the reaction mixture was cooled to room temperature. The solid which separated was filtered washed with cold water and dried; yield 66.3 g, m.p. 254–256° (lit 248°[2]), **10b**, benzyliminodimethylenediphosphonic acid. The filtrate (177 g) was found to contain an additional 1.4 g of **10b** and 13.8 g of the monophosphonic acid **9b**. Basification of the filtrate and extraction with chloroform (3 × 50 ml) yielded benzylamine (19.3 g) bp 180–185°.

Reaction of cyclohexylamine with phosphorous acid and formaldehyde at 1 : 1 : 1 *molar ratio.* To a solution of cyclohexylamine (49.0 g; 0.495 mole) and phosphorous acid (40.1 g; 0.495 mole) in water (50 ml) and concentrated HCl (50 ml) heated at 100° was added formaldehyde (40 ml; 0.53 mole) during 30 mins. After continuing to heat at 100–105° for 2 hrs. the reaction mixture was cooled; basified (KOH) and extracted with chloroform (4 × 50 ml). Evaporation of the chloroform and distillation yielded cyclohexylamine (20.3 g) bp 140–145°. Acidification of the aqueous phase and evaporation gave a phosphonic acid from which KCl was separated by crystallization. The acid solution showed two peaks by ^{31}P NMR 8.06 (**10a**) and very weak 9.60 (**9a**). ^{13}C NMR (pH 7), 28.5, 28.9, 29.9, 53.3 (dd, $J = 145$ Hz, $J = 9.8$), 63.0 (t, $J = 6.5$ Hz).

ACKNOWLEDGMENTS

We acknowledge the assistance of W. S. Paley in early preparations and D. A. Loyet in measurement of NMR spectra.

REFERENCES

1. D. Redmore in "Topics in Phosphorus Chemistry," E. J. Griffith and M. Grayson, Ed., John Wiley & Sons, N.Y. vol. 8, 515 (1976).
2. K. Moedritzer and R. R. Irani, *J. Org. Chem.*, **31**, 1603 (1966).
3. K. Moedritzer, *Synth. Inorg. Met. Org. Chem.*, **2**, 317 (1972), *ibid.*, **3** 75 (1973).
4. Ref 1, footnote 53 cited unpublished work of D. Redmore and F. T. Welge reporting that cyclohexylamine with one equivalent of H_3PO_3 and formaldehyde gave approximately equal amounts of mono- and bismethylenephosphonic acids.
5. For **2a** the pK_a values at 25°C in 0.1 M KNO_3 are 3.02, 5.94, 8.24, 11.03.
6. V. Ya Temkina, S. P. Ivashchenko, N. V. Tsisulnikova and R. P. Lastovskii, *Zh Obshch. Khim.*, **46**, 501 (1976). These authors report the preparation of **2a** from *N*-acetyl ethylenediamine, formaldehyde and phosphorous acid but no melting point is reported.
7. W. B. Lawson, M. D. Leafer, A. Tewes and G. J. S. Rao, *Hoppe–Seyler's, Z. Physio. Chem.*, **349**, 251 (1968); *Chem. Abstr.*, **69** 27754 (1968).
8. S. R. Aspinall, *J. Org. Chem.*, **6**, 895 (1941).
9. V. Prelog, W. Kueng, T. Tomljenovic, *Helv. Chem. Acta*, **45**, 1352 (1962).
10. R. P. Linstead, B. R. Shephard, B. C. L. Weedon, *J. Chem. Soc.*, 2854 (1951).

Downloaded At: 10:22 30 January 2011