Some data concerning the equilibrium between *t*-phosphines and aqueous formaldehyde have been obtained.

$$R_3P + HCHO + H_2O \rightleftharpoons R_3\overset{+}{P}CH_2OH\ \bar{O}H$$

When tributylphosphine was added to a neutral solution of formaldehyde in alcohol–water, approximately 1 mol of hydroxide ion was produced (by titration). However, triphenylphosphine or THP produced no increase in pH. The above equilibrium, therefore, lies far to the right for tributylphosphine but far to the left for THP and triphenylphosphine.

Our finding that neutralization of tetrakis and the reaction of THP with formaldehyde produces a mixture of THP and THP hemiacetal makes questionable the structure of THPOH.[15-17] The synthesis,[10] from phosphine and aqueous formaldehyde, most likely proceeds through the intermediacy of THP. The syrup isolated was identified by elemental analyses, reaction with hydrochloric acid, and reaction with phosphorus pentachloride.[10c] These same results, however, would be

$$PH_3 + 4HCHO + H_2O \longrightarrow (HOCH_2)_4PCl \xleftarrow{HCl} (HOCH_2)_4POH \xrightarrow{PCl_5} (ClCH_2)_4PCl$$

obtained from a more probable mixture of hydrated hemiacetals of THP, for example, approximated by

$$(HOCH_2)_2PCH_2OCH_2OH \cdot H_2O$$

Experimental Section

The nmr spectra were recorded on a Varian Associates Model HA-100 spectrometer at 40.47 MHz; chemical shifts are in parts per million from external phosphoric acid reference. Chemical shifts are accurate to about 0.5 ppm and integrated areas to about 5%.[18] The initial scans were run at a sweep rate of 1.2 ppm/sec, covering the range of −75 to +50 ppm, and the analytical scans were run at a sweep rate of 0.5 ppm/sec.

Materials.—The THPO and THP were gifts of our sample preparation laboratory and were prepared by methods of Gordon.[19a,b] The THPO analyzed for greater than 98% purity by ^{31}P nmr spectroscopy. The THP analyzed for about 52% THP and 48% of a mixture of phosphine oxides, mainly THPO (see Table I). The formaldehyde was a Fisher Scientific product, 40% aqueous formaldehyde. The tetrakis was plant grade material, mp 141–143° (lit.[1] mp 151°).

The Neutralization of Tetrakis by Sodium Hydroxide in Methanol and in Water.—The following solutions were prepared: 2.16 *M* aqueous tetrakis, 2.89 *M* methanolic tetrakis, 2.95 *M* aqueous sodium hydroxide, and 3.21 *M* methanolic sodium hydroxide. The concentration of tetrakis was determined by titration with standard sodium hydroxide to a phenolphthalein end point, and the concentration of sodium hydroxide was determined by titration with standard hydrochloric acid. To a small volume of the tetrakis solution in a test tube was added the calculated volume of base. The tube was stoppered under nitrogen, shaken well, and after allowing about 1 hr for equilibration the ^{31}P nmr spectrum was obtained. In methanol solution the chemical shifts were tetrakis, −27.6; THP, +24.8; and other phosphine, +29.1. In aqueous solution the chemical shifts were tetrakis, −26.5; THP, +24.8; other phosphine, +27.7; and THPO −48. Results of these experiments are shown in Figures 1 and 2. Owing to the high noise level no attempt was made to investigate coupling constants by ^{31}P magnetic resonance spectroscopy. However, the residue obtained by neutralization of an ethanolic water solution of tetrakis, removal of salt, and careful evaporation of solvent to constant weight was investigated by proton magnetic resonance spectroscopy. The spectrum, taken in deuterioacetone with tetramethylsilane as an internal reference, showed a singlet at 4.74 ppm (area 1.0), the THP methylene protons as a doublet at 4.18 ppm (J_{P-H} = 6.6 MHz) above the broad hydroxyl peak (total area approximately 9.5), and a complex pattern (approximate area 2.8) centered about 4.08 ppm and partly overlapping the THP doublet. The 4.74-ppm singlet is in the region expected for OCH_2O.[20]

The Reaction of Formaldehyde with THPO and with THP.—The following solutions were prepared using oxygen-free water, oxygen-free 40% aqueous formaldehyde, and maintaining a nitrogen atmosphere: 50% THPO in 40% aqueous formaldehyde, 50% THP in 40% aqueous formaldehyde, 50% THPO in water, 50% THP in water. After allowing about 1 hr for equilibration the ^{31}P nmr spectra were determined. Results are shown in Table I.

The Reaction of *t*-Phosphines with Formaldehyde as Determined Titrimetrically.—An *ca.* 0.3 *M* stock solution of tributylphosphine (Carlisle Chemical Works) was prepared by dissolving 6 ml of the phosphine in about 100 ml of denatured alcohol. A 10-ml aliquot of this dissolved in alcohol required 50.5 ml of 0.101 *N* aqueous iodine, corresponding to a concentration of 0.252 *M*. A 10-ml aliquot of the stock solution was added to a solution of 5 ml of 40% formaldehyde in 20 ml of 2B alcohol which had been made just neutral to phenolphthalein. The pink phenolphthalein color immediately appeared. The solution was swirled a few minutes, 20 ml of distilled water was added, and then it was titrated with 0.1012 *M* hydrochloric acid. A total of 24.50 ml of acid was required to discharge the phenolphthalein color, corresponding to a concentration of 0.248 *M* for the stock tributylphosphine solution.

When THP and triphenylphosphine were similarly treated, they did not produce a phenolphthalein color.

Registry No.—Tetrakis, 16980-25-9; THP, 2767-80-8; THPO, 1067-12-5; formaldehyde, 50-00-0.

Acknowledgment.—The author thanks the spectroscopy laboratory of Hooker Chemical Corporation, in particular Dr. James Colson, for invaluable assistance in obtaining and interpreting the ^{31}P nmr spectra.

(15) One wonders whether THPOH can exist as a stable compound. A pentacovalent structure seems unlikely in view of the greater stability of quadruple- over quintuple-bonded phosphorus[16] and the hydrolytic instability of oxyphosphoranes.[17] An ionic structure also seems unlikely in that it would contain both a strong base and a moderately strong acid.

(16) J. R. Van Wazer, "Phosphorus and Its Compounds," Vol. I, Interscience Publishers, Inc., New York, N. Y., p 73.

(17) F. Ramirez, International Union of Pure and Applied Chemistry, Organic Chemistry Division Special Symposium on Organo Phosphorus Compounds, Heidelberg, Germany, 1964, p 368.

(18) J. Colson and A. Davis, "Quantitative Analysis by ^{31}P NMR," presented at the Applied Spectroscopy Meeting, Chicago, Ill., June 1967.

(19) (a) I. Gordon, U. S. Patent 3,076,034 (1963); (b) I. Gordon and G. M. Wagner, U. S. Patent 3,257,460 (1966).

(20) High Resolution NMR Spectra Catalog, Vol. 2, Varian Associates, 1963, spectra no. 437 and 445.

A New Synthesis of Lysine

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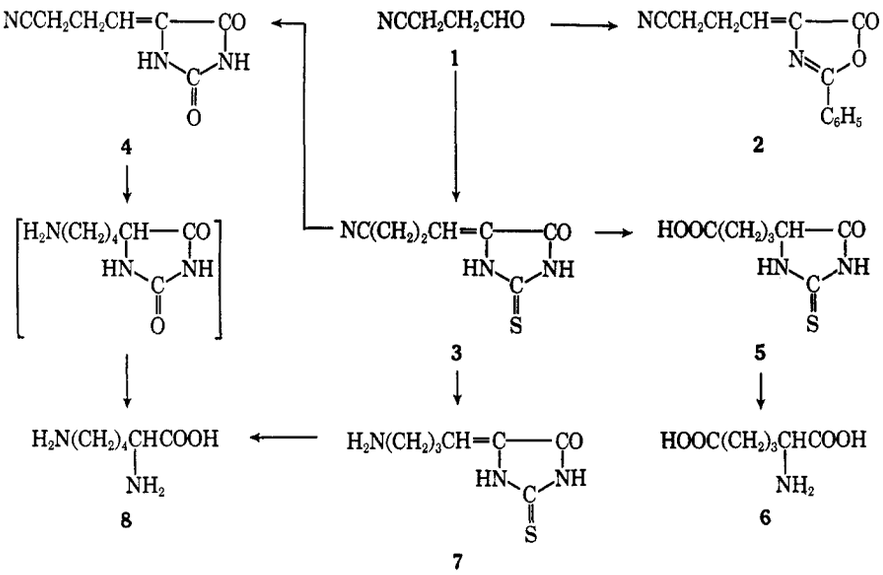
Numerous papers have been published on the synthesis of lysine.[1] The present paper reports a new method of synthesis of lysine starting from β-cyano-

(1) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961, p 2097.

SCHEME I



propionaldehyde (β-CPA) (1) which is a synthetic intermediate developed lately.[2]

As the first step of the synthesis, the condensation of 1 with hippuric acid, hydantoin, rhodanine, or 1-acetyl-2-thiohydantoin was examined. The condensation of 1 and hydantoin or rhodanine was attempted in various ways without success and the erlenmeyer reaction with hippuric acid gave 2-phenyl-4-(3-cyanopropylidene)-oxazol-5-one (2) in only 15% yield. On the other hand, the reaction of 1 and 1-acetyl-2-thiohydantoin, carried out in the presence of piperidine, gave 5-(3-cyanopropylidene)-2-thiohydantoin (3) in about 55% yield as a result of condensation and deacetylation. Consequently, 3 was chosen as the intermediate of choice in the synthesis of lysine.

Catalytic hydrogenation of 3 was tried over a platinum black but the reaction did not proceed at all, probably because the sulfur in 3 acted as a catalyst poison. Accordingly, 3 was converted into 5-(3-cyanopropylidene)hydantoin (4) by the method of Boyd, *et al.*[3] The hydantoin (4) was then subjected to catalytic hydrogenation, followed by hydrolytic cleavage of the hydantoin ring with phosphorus, iodine, and hydroiodic acid. However, the yield of lysine thus obtained was extremely low.

The reduction of 3 with phosphorus and hydroiodic acid was also unsuccessful. The nitrile group of 3 underwent hydrolysis in preference to reduction and 3 was converted into 5-(3-carboxypropyl)thiohydantoin (5), which was hydrolyzed to α-aminoadipic acid (6).

Therefore, the nitrile group of 3 alone was first reduced by lithium aluminum hydride, and 5-(4-aminobutylidene)thiohydantoin (7) was isolated as the picrate. After this picrate was converted into the hydrochloride *via* the method of Rice,[4] the reduction of the double bond and the hydrolysis of the ring were carried out with phosphorus, iodine, and hydroiodic acid. Lysine was then obtained as the monopicrate in about 65% yield.

(2) (a) J. Kato, H. Wakamatsu, R. Iwanaga, and T. Yoshida, *Kogyo Kagaku Zasshi*, **64**, 2139 (1961); (b) J. Kato, H. Wakamatsu, R. Iwanaga, and T. Yoshida, *ibid.*, **64**, 2142 (1961); (c) S. Motoki, S. Satsumabayashi, and I. Tajima, *Bull. Chem. Soc. Jap.*, **37**, 646 (1964); (d) S. Motoki, S. Satsumabayashi, and H. Kusano, *ibid.*, **38**, 922 (1965); (e) S. Motoki, S. Satsumabayashi, and T. Masuda, *ibid.*, **39**, 1519 (1966); (f) S. Satsumabayashi and S. Motoki, *ibid.*, **40**, 2872 (1967).

(3) W. J. Boyd and W. Robson, *Biochem. J.*, **29**, 542 (1935).

(4) E. E. Rice, *J. Biol. Chem.*, **131**, 1 (1939).

Experimental Section

2-Phenyl-4-(3-cyanopropylidene)oxazol-5-one (2).—A mixture of 1 (16.6 g, 0.2 mol),[2c] hippuric acid (36.0 g, 0.2 mol), basic lead acetate (113.2 g, 0.2 mol), and acetic anhydride (200 ml) was stirred at room temperature for 40 hr and then poured into ice–water (200 ml). The crude, pale brown product that precipitated was recrystallized from acetone: mp 127–128°; yield, 6.6 g (14.6%).

Anal. Calcd for $C_{13}H_{10}O_2N_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.80; H, 4.65; N, 12.41.

5-(3-Cyanopropylidene)-2-thiohydantoin (3).—To a hot solution of 1 (10.0 g, 0.12 mol) and 1-acetyl-2-thiohydantoin[5] (15.8 g, 0.1 mol) in 50% ethanol (50 ml), 6.8 g (0.08 mol) of piperidine was added slowly and the reaction mixture was refluxed for 2 hr. The precipitate was recrystallized from methanol to give 10.1 g of 3: mp 211–212°; yield, 55.8% (based on acetylthiohydantoin).

Anal. Calcd for $C_7H_7ON_3S$: C, 46.41; H, 3.90; N, 23.20. Found: C, 46.20; H, 4.16; N, 23.51.

5-(3-Cyanopropylidene)hydantoin (4).—According to Boyd's method,[3] 6.4 g of 4 was obtained from 9.1 g (0.05 mol) of 3: mp 207–208° (from water); yield, 77.2%.

Anal. Calcd for $C_7H_7O_2N_3$: C, 50.91; H, 4.27; N, 25.45. Found: C, 50.95; H, 4.29; N, 25.70.

Lysine (8) from 4.—A compound 4 (4.1 g, 0.025 mol) in ethanol (200 ml) was hydrogenated in the presence of 0.5 g of platinum black for about 40 hr. After the catalyst and the solvent were removed, the white powder obtained was heated at 130° (bath temperature) for 5 hr with phosphorus (1.4 g), iodine (4.5 g), and 20 ml of hydroiodic acid (57% solution). Phosphorus was filtered off and the filtrate was treated with an anion exchange resin (Amberlite IRA-400). The solution was then concentrated to about 10 ml and lysine was isolated as the monopicrate (0.3 g) from the solution: mp 228–230°; yield, 3.2% (based on 4).

Anal. Calcd for $C_{12}H_{17}O_9N_5$: C, 38.40; H, 4.57; N, 18.66. Found: C, 38.12; H, 4.61; N, 18.68.

5-(3-Carboxypropyl)-2-thiohydantoin (5).—A mixture of 3 (4.5 g, 0.025 mol), phosphorus (4 g), and hydroiodic acid (60 ml) was heated for 5 hr. Phosphorus was filtered off, and the filtrate was concentrated to about 10 ml. The precipitate was recrystallized from water to yield 3.5 g (69.5%), mp 175°.

Anal. Calcd for $C_7H_{10}O_3N_2S$: C, 41.58; H, 4.99; N, 13.86. Found: C, 41.61; H, 5.01; N, 13.88.

α-Aminoadipic Acid (6).—A mixture of 5 (2 g, 0.01 mol), iodine (2.5 g), and 10 ml of hydroiodic acid was heated for 5 hr. The solution was then concentrated to about 5 ml, and the white

(5) J. B. Johnson and B. H. Nicolet, *J. Amer. Chem. Soc.*, **33**, 1973 (1911).

crystals that precipitated were recrystallized from water to yield 1.1 g (68.0%), mp 205–206°.

Anal. Calcd for $C_6H_{11}O_4N$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.43; H, 7.01; N, 8.90.

5-(4-Aminobutylidene)-2-thiohydantoin (7).—A solution of **3** (4.5 g, 0.025 mol) in tetrahydrofuran (200 ml) was treated with 3 g of lithium aluminum hydride in the usual manner. After the reaction was completed, 150 ml of 10% hydrochloric acid was added. Picric acid was then added to the aqueous layer. Picrate of **7** was obtained and recrystallized from water to yield 4.3 g (41.2%), mp 250° dec.

Anal. Calcd for $C_{13}H_{14}O_8N_6S$: C, 37.68; H, 3.41; N, 20.28. Found: C, 37.46; H, 3.57; N, 20.44.

Lysine (8) from 7.—By Rice's method, the picrate of **7** (4.1 g, 0.01 mol) was converted into about 10 ml of an aqueous solution of the hydrochloride of **7**. Phosphorus (1.5 g), 57% hydroiodic acid (15 ml), and iodine (3 g) were added to this solution, and the mixture was refluxed for 5 hr. After phosphorus was filtered off, the filtrate was passed through an anion exchange resin (Amberlite IRA-400) and concentrated to about 10 ml. By the addition of picric acid, 2.5 g of lysine monopicrate was obtained to yield 66.7%, mp 208°.

Anal. Calcd for $C_{12}H_{17}O_9N_5$: C, 38.40; H, 4.57; N, 18.66. Found: C, 38.62; H, 4.77; N, 18.81.

The product was also identified as dihydrochloride by the agreement of R_f value on paper chromatography.

Registry No.—**2**, 17190-64-6; **3**, 17190-65-7; **4**, 17190-66-8; **5**, 13593-99-2; **6**, 542-32-5; **7** picrate, 17190-69-1; **8** monopicrate, 6150-71-6.

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The Addition of Oxime Anions to Dienophiles

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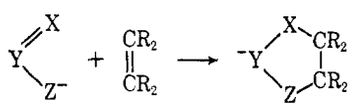
The concerted thermal cycloaddition of allylic anions to double bonds is predicted to be a facile process[1] (eq 1), but no unambiguous examples of it appear to



(1)

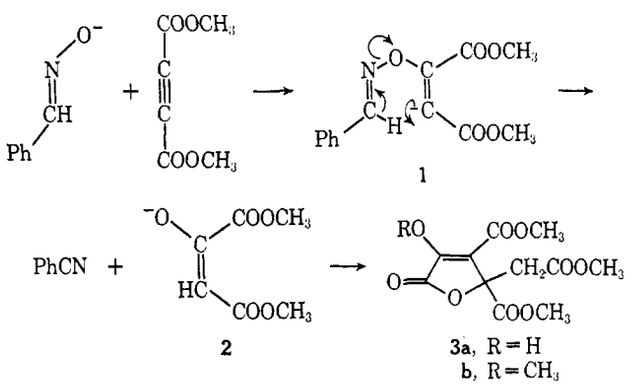
have been reported. There are, however, many examples of a formally analogous process in which the central atom of the allylic system is a positively charged nitrogen (eq 1, Y = RN^+). These reactions have been formulated as 1,3-dipolar additions.[2] Alternatively, these reactions may be regarded as examples of 4 + 2 electrocyclization.[3] In the former view, the positive charge plays an essential role in the reaction process, while in the latter view the positive charge is incidental and plays no role in the electronic process leading to new bond formation.

We sought to gain more information about the effect of the positive charge in this process by examining the reaction of oxime anions with dienophiles (eq 1, X = CR_2; Y = N; Z = O). The analogous 1,3-dipolar addition reaction, the addition of nitrones to dienophiles (eq 1, X = CR_2; Y = RN^+; Z = O) occurs readily to form isoxazolidines.[4]

It was found that the dry sodium salt of *syn*-benzaldoxime reacted exothermically with dimethyl acetylenedicarboxylate at room temperature in the absence of solvent. The major products of the reaction were benzonitrile and an acidic substance which could be isolated as a methyl derivative after treatment of the reaction mixture with diazomethane. This methyl derivative was identified from its spectral characteristics as the previously unreported methyl ether of oxalocitric anhydride trimethyl ester **3b**, and its identity was confirmed by independent preparation from authentic **3a**.

The formation of these products is rationalized in Scheme I. Initial Michael addition of the oxime anion to the dienophile is proposed. The proton abstraction by the resulting anion **1** has analogy in the reactions of anions formed by addition of other nucleophiles to dimethyl acetylenedicarboxylate.[5] The formation of **3a** from the anion of dimethyl oxaloacetate **2** has been reported.[6]

SCHEME I



The same products were formed when the reaction was carried out in aprotic solvents or when dimethyl acetylenedicarboxylate, benzaldehyde *syn*-oxime, and potassium t-butoxide were refluxed in t-butyl alcohol. With sodium methoxide in methanol, unreacted oxime and dimethyl 2,2-dimethoxysuccinate were isolated. In no case was isoxazoline formation or any evidence for concerted cycloaddition observed.

The reaction of dimethyl acetylenedicarboxylate with the sodium salt of acetone oxime, in which nitrile formation by proton abstraction is not possible, yielded a resinous solid from which no low molecular weight products could be isolated.

The reaction of the sodium salt of *syn*-benzaldoxime with maleic anhydride occurred at 115°. The major products were benzonitrile and sodium maleate. Since the reactants were stable separately at 115°, and since no other source of oxygen was present, the transfer of hydroxyl must have occurred by addition of the oxime

(1) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2048 (1965).

(2) R. Huisgen, R. Graskey, and J. Sauer, in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1964, pp 806–878.

(3) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968); R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968); R. Huisgen and H. Gotthardt, *Chem. Ber.*, **101**, 1059 (1968).

(4) See ref 2, pp 861–867; R. Graskey, R. Huisgen, and H. Leiterman, *Tetrahedron Lett.*, No. 12, 9 (1960).

(5) J. B. Hendrikson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964).

(6) A. Michael and H. D. Smith, *Ann.*, **363**, 36 (1908).