mg) at reflux for 2 hr. The alcohol, purified by preparative tlc (EtOAc), had ν_{max} 1640, 1610, 1590, and 1570 cm^{-1}; τ ($CDCl_3$) 8.80 (6 H, singlet), 7.20 (1 H, broad, disappears on shaking the solution with D_2O), 7.00 (4 H, singlet), 5.97 (3 H, singlet), 4.97 (2 H singlet).

Tetrahydroilludinine Methyl Ester (XIII).—Methyl ester XI (100 mg) was hydrogenated at room temperature and atmospheric pressure in 50 ml glacial acetic acid containing reduced platinum oxide catalyst (100 mg) for 2 hr. The solution was made alkaline with sodium bicarbonate and extracted with ethyl acetate, from which the tetrahydro derivative was obtained as a yellow gum. Sublimation and crystallization from petroleum ether afforded the pure ester XIII: mp 83–84°; ν_{max} 1725 and 1575 cm^{-1}; τ ($CDCl_3$) 8.87 (6 H, singlet), 7.13 (4 H, singlet), 6.95 (2 H, multiplet), 6.60 (2 H, multiplet), 61.7 (6 H, singlet), 5.59 (2 H, singlet).

Pyridine Hydrochloride Cleavage and Decarboxylation of Illudinine. Isoquinolinol XIV.—Illudinine (I, 40 mg) was mixed with pyridine hydrochloride (400 mg) and heated in a sealed tube at 220° for 4 hr. The reaction mixture was cooled, dissolved in water, and extracted with ethyl acetate. The extract on evaporation gave isoquinolinol XIV as a reddish residue, which crystallized from methanol: mp 207–210°; ν_{max} 1640, 1612, and 1575 cm^{-1}; τ ($CDCl_3$) 8.84 (6 H, singlet), 7.16 (4 H, singlet), 2.92 (1 H, singlet), 1.61 (1 H, broad), 1.32 (1 H, broad), 0.73 (1 H, broad); mass spectrum M^+ 213. On refluxing with methyl iodide in an acetone–benzene solution, XIV formed the methiodide, mp 230–233° (EtOH).

Action of Ammonia on Illudalic Acid.—Illudalic acid (40 mg) was heated on a steam bath for 10 min with 20 ml of 15% ammonia solution. The solution was evaporated to dryness, extracted with acetic acid and the acetic acid was then removed under reduced pressure. Partition of the residue between water and ethyl acetate (1:10) yielded the isoquinolinol XIV identical with that obtained from II: mp and mmp 208–210°; mass spectrum M^+ 213; ir, nmr, and uv spectra, superimposable.

Registry No.—I, 18508-77-5; II, 18500-63-5; IV, 18508-78-6; VI, 18500-64-6; VII, 18500-65-7; VIII, 18500-66-8; IX, 18508-79-7; methyl ester of IX, 18508-80-8; diacetate of IX, 18508-81-1; X, 18508-82-2; XI, 18500-67-9; XII, 18500-68-0; XIII, 18500-60-2; XIV, 18500-61-3; methiodide of XIV, 18500-62-4.

Acknowledgment.—This work was supported by grants AI-00226 and GM 12150 from the National Institutes of Health. The nmr spectra were done on a Varian A60A nuclear magnetic resonance spectrometer, the purchase of which was made possible by a General Research Support Grant, 5-S01-FRO-5621, to The New York Botanical Garden. The authors are indebted to Drs. A. K. Bose and K. S. Khanchandani of the Stevens Institute for some of the mass spectra. We thank Mr. Francis Manginelli and Mrs. Hulda Holness for technical assistance.

Preparation of N-Carboxy-α-amino Acid Anhydrides by the Reaction of Copper(II)–Amino Acid Complexes with Phosgene

RODNEY D. HAMILTON AND DONALD J. LYMAN

Polymer Chemistry Department, Stanford Research Institute, Menlo Park, California 94025

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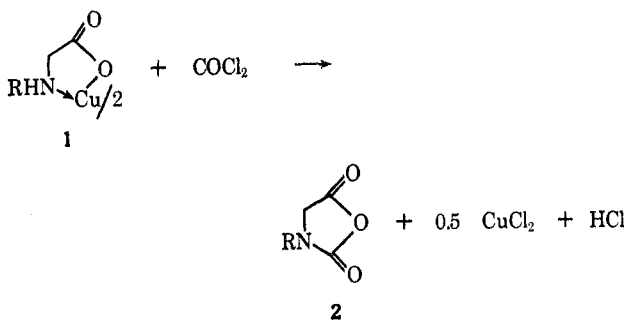
N-Carboxy-α-amino acid anhydrides (2), which are widely used as precursors for polypeptides, are generally prepared by reacting phosgene directly with amino acids, their hydrochlorides, or their sodium salts in an inert, polar solvent.[1] They are also obtained by treatment of N-alkoxycarbonyl-α-amino acids with thionyl chloride,[2] phosphorous pentachloride,[3] and oxalyl chloride,[4] and by the reaction of thionyl chloride or phosgene with the disodium salts of N-carboxy-amino acids.[5]

We have now found that N-carboxy-α-amino acid anhydrides are obtained in good yields when finely ground copper(II)–amino acid complexes (1) are suspended in tetrahydrofuran and treated with phosgene at room temperature for 1–2 hr. The copper atom is expelled as copper(II) chloride. The first



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stage of the reaction probably involves attack by the nitrogen atom on the carbonyl carbon atom of phosgene, even though the nucleophilicity of the nitrogen atom is greatly diminished because of its coordination with copper. Subsequent cleavage of the covalent[6,7] N–Cu bond and ring closure with elimination of copper(II) chloride would lead to 2. The rate of the reaction is related to the nature of the R group, the N–Cu bond, and the solubility of the complex in the solvent. The influence of the metal atom was not studied (the order of stability of complex formation between amino acids and metals is Cu > Ni > Zn > Co > Cd > Fe^{2+} > Mn > Mg).[8]

Preparation of N-carboxyanhydrides of amino acids which are purified only with difficulty might be facilitated by this reaction—*i.e.*, the complex could be prepared, readily purified (in contrast to the amino acid itself), and reacted directly with phosgene to afford the desired N-carboxyanhydride.

Experimental Section[9]

Amino Acid–Copper(II) Complexes.—The general procedure used to prepare these complexes was as follows. The amino acids (0.1 mol) were dissolved in hot water (150 ml for sarcosine and 500 ml of DL-alanine and glycine), and a 10% excess of solid cupric carbonate was slowly added with stirring to give deep blue

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solutions. These solutions were filtered and poured into 1 l. of cold ethanol (for glycine and DL-alanine) or 1 l. of cold butanol (for sarcosine). The blue precipitates were collected, washed with ethanol and ether, and then dried in a vacuum oven (80°) for 24 hr. Further purification was not necessary.

Bis(sarcosino)copper(II) was obtained in 80% yield. *Anal.* Calcd for $C_6H_{12}CuN_2O_4$: C, 30.06; H, 5.04; Cu, 26.51; N, 11.69. Found: C, 30.3; H, 5.17; Cu, 26.60; N, 11.89.

Bis(glycino)copper(II) was obtained in 85% yield. *Anal.* Calcd for $C_4H_8CuN_2O_4$: C, 22.70; H, 3.81; Cu, 30.02; N, 13.24. Found: 22.91; H, 3.88; Cu, 30.00; N, 13.18.

Bis(DL-alanino)copper(II) monohydrate was obtained in 81% yield. *Anal.* Calcd for $C_6H_{12}CuN_2O_4 \cdot H_2O$: C, 27.96; H, 5.48; Cu, 24.65; N, 10.87. Found: C, 28.23; H, 5.49; Cu, 24.70; N, 11.07.

Reaction of Phosgene with Amino Acid–Copper(II) Complexes.—The following general procedure was used. Phosgene was bubbled at a moderate rate for 1 hr into rapidly stirred suspensions of the finely ground copper(II)–amino acid complexes (5 g) in dry tetrahydrofuran (500 ml). The color of the suspensions changed to green, and then to orange-brown as copper(II) chloride precipitated. Rapid stirring was continued for 1 more hr, after which the solvent was evaporated (<50°) under reduced pressure. The residues were extracted with warm benzene, ethyl acetate, and chloroform (for sarcosine, glycine, and DL-alanine, respectively), and the resulting extracts were pressure-filtered under nitrogen through glass wool and coarse fritted glass. The solvents were then removed under reduced pressure (<50°), leaving the crude N-carboxyanhydrides.

Sarcosine N-carboxyanhydride was obtained in 88% yield as an oil, which solidified upon standing. It was recrystallized from chloroform–petroleum ether (bp 30–60°) and had a melting point of 105° (lit.[10] mp 105°). *Anal.* Calcd for $C_4H_5NO_3$: C, 41.74; H, 4.38; N, 12.17. Found: C, 42.13; H, 4.51; N, 12.51.

Glycine N-carboxyanhydride was obtained in 78% yield and was recrystallized twice from acetic anhydride. It decomposed above 100° (lit.[5a] dec pt >100°). *Anal.* Calcd for $C_3H_3NO_3$: C, 35.65; H, 2.99; N, 13.86. Found: C, 35.99; H, 3.01; N, 13.80.

DL-Alanine N-carboxyanhydride was obtained in 90% yield. It was recrystallized from chloroform at −40° and had a melting point of 46° (lit.[11] mp 46°). *Anal.* Calcd for $C_4H_5NO_3$: C, 41.74; H, 4.38. Found: C, 41.81; H, 4.47.

Registry No.—Phosgene, 75-44-5; bis(sarcosino)-copper(II), 18253-88-8; bis(glycino)copper(II), 13479-54-4; bis(DL-alanino)copper(II), 15274-59-6; sarcosine N-carboxyanhydride, 5840-76-6; glycine N-carboxyanhydride, 2185-00-4; DL-alanine N-carboxyanhydride, 1192-73-0.

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Nucleic Acids. VIII.[1] Synthesis and Chemistry of *ara*-Cytidine 2′,5′ Cyclic Phosphate. Phosphate Anisotropy

WILLIAM J. WECHTER

Department of Chemistry, The Upjohn Company, Kalamazoo, Michigan 49001

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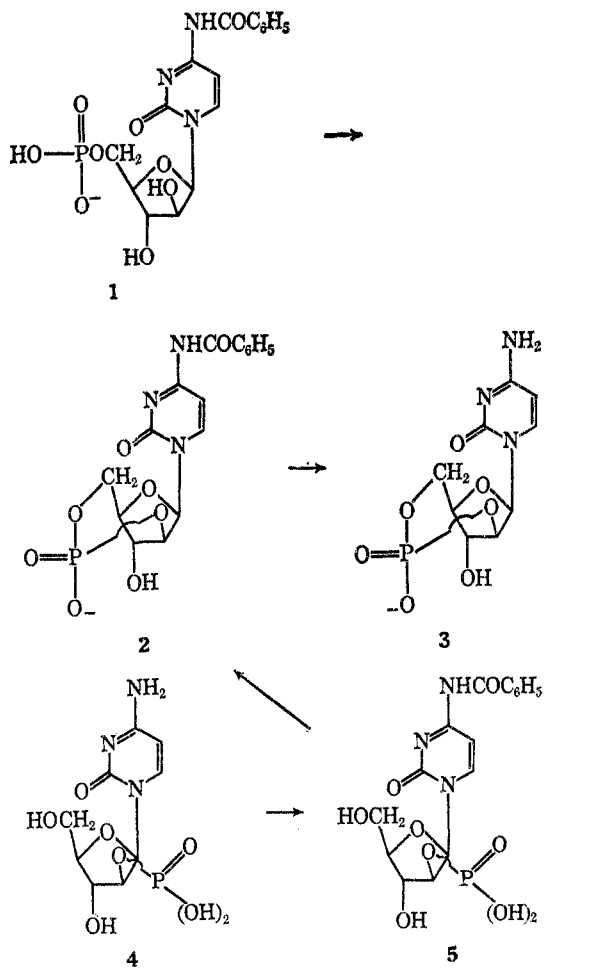
The biological importance of nucleoside 3′,5′ cyclic phosphate esters, particularly of adenosine and uridine,[2] prompted us to investigate the synthesis and chemistry of the cyclic phosphates derived from the cytotoxic[3a,b] antiviral[3c–e] nucleoside *ara*-cytidine[3f] as part of our continuing effort to assess the biodynamic effects of nucleotides and their derivatives.[4] It was also of interest to assign the structure of *ara*-adenosine cyclic phosphate[5] by employing *ara*-cytidine chemistry as a model. The work described herein contributed to the first goal, clarified the structural problem with regard to *ara*-adenosine and led to a further understanding of the contribution of phosphate anisotropy to the nmr spectra of organophosphorus compounds, particularly nucleotides and oligonucleotides.

N^4-Benzoyl-*ara*-cytidine 5′-phosphate[4] (**1**), when cyclized employing dicyclohexylcarbodiimide (DCC), afforded a single crystalline cyclic phosphate (Scheme I). This material, **2**, after removal of the N^4 protecting group, proved to be *ara*-cytidine 2′,5′ cyclic phosphate (**3**), a molecule uniquely unreactive toward acid, base, and the multitude of nucleases present in crude snake venom.[6] Spin decoupling experiments and analysis of

SCHEME I



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