most prominent low molecular weight product formed during the polymerization of HCN.

Our major interest in these compounds is concerned with their significance in the prebiological syntheses of amino acids[2f,g] and adenine and other heterocyclics under primitive earth conditions. Our preliminary experiments have shown the following.

(1) I is converted to II by formamidine acetate in aqueous solution.[10] A certain amount of 4-aminoimidazole-5-carboxamide (IV) is formed in these experiments, presumably by hydrolysis of I prior to its condensation to II (see below).

(2) II is converted to adenine by treatment with formamidine acetate in aqueous solution. Trace amounts of IV are formed only after prolonged reaction time.

(3) II is almost certainly Oro's compound B which appears early in the course of HCN–NH_3 polymerizations,[11,12] prior to the appearance of 4-aminoimidazole-5-carboxamide or the corresponding 5-carboxamidine. Our results support Oro's general reaction sequence leading to adenine formation,[2ac] as well as portions of the mechanistic pathways suggested by others,[2i,j] but still leave many details undecided.

(4) VI is almost certainly Oro's compound A,[12,13] and the polymer formed by the treatment of aminomalononitrile with cyanide ion has the same infrared spectrum as the HCN polymer. These results are in agreement with aminomalononitrile being an intermediate in HCN polymerization.[4]

We believe that our results make it plausible that I is a key intermediate in HCN polymerizations and perhaps in prebiological organic synthesis. We are investigating in detail the reactions of I and II with OH^-, NH_3, CN^-, formamidine, etc., to determine the range of pH, temperature, and reagent concentrations in which adenine synthesis is possible. We are also investigating the synthesis of amino acids and other biologically important heterocyclic systems from I.

Acknowledgment. We are indebted to D. Trentham for a number of valuable suggestions and to R. Mancuso for technical assistance.

(10) Oro detected the presence of formamidine in the ammonia–cyanide solutions.[2b]

(11) Compound II has the same R_f value and gives the same color reactions as compound B.[2b]

(12) These identifications have been suggested tentatively: J. Oro, *Proc. Lun. Plan. Expl. Colloq.*, 3, 9 (1963).

(13) Compound VI has the same R_f value and gives the same color reactions as compound A.[2b]

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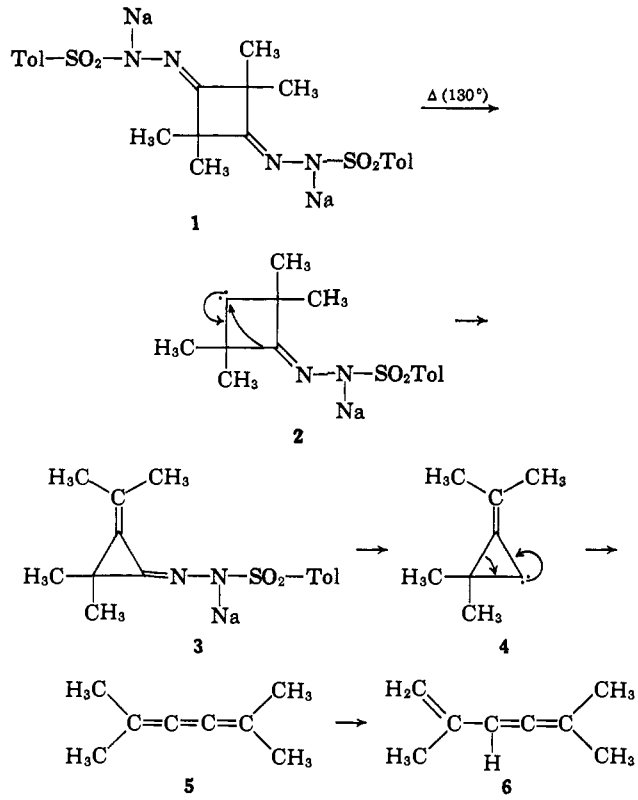
Cumulene Synthesis *via* a Carbenoid Decomposition[1]

Sir:

Carefully controlled thermal decomposition[2] of the preformed disodium salt **1** of tetramethyl-1,3-cyclobutanedione di-*p*-tosylhydrazone gives a good yield of the interesting cumulene **5**.[3] The decomposition combines the ring contraction[4] of cyclobutylidene **2** and ring opening of cyclopropylidene **3**.[5] The product **5**



is sensitive to air, base, and acid, but can be stored at −20° in degassed solutions.[6] If **1** is generated and decomposed *in situ* using either sodium methoxide or sodium hydride,[7] the major product (>60%) of a complex mixture is the rearranged allene **6**. Isomer **6** was also formed in runs where **1** was not thoroughly dried or when insufficiently purified[8] solvents were used.[4a] The isomerization of **5** to **6** can be carried out on solutions of pure **5**. At 130°, even tosylhydrazone (incompletely converted to 1) is sufficiently acidic to effect the transformation. Therefore, compound **6** was formed whenever insufficient or excess sodium methoxide was used in the preparation of precursor **1**.[9]

It has recently been reported[10] that **5** can be prepared by the low-temperature metal halide exchange treatment of dibromide **7**.[11] Although this would seem to

(1) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

(2) (a) L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959); (b) J. W. Powell and M. C. Whiting, *Tetrahedron*, 7, 305 (1959).

(3) (a) W. Krestinski, *Chem. Ber.*, **59**, 1932 (1926); (b) L. Skatteböl, *Tetrahedron*, **21**, 1357 (1965).

(4) (a) J. A. Smith, H. Shechter, J. Bayless, and L. Friedman, *J. Am. Chem. Soc.*, **87**, 659 (1965); (b) L. Friedman and H. Shechter, *ibid.*, **82**, 1002 (1960).

(5) (a) W. von E. Doering and P. LaFlamme, *Tetrahedron*, **2**, 75 (1958); (b) W. M. Jones, M. H. Grasley, and W. S. Brey, *J. Am. Chem. Soc.*, **85**, 2754 (1963).

(6) Analytical data and spectral properties are in accord with all proposed structures.

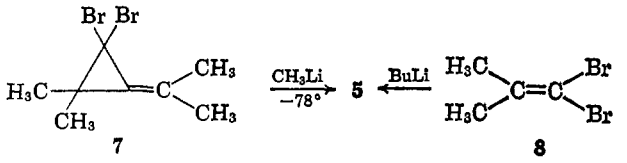
(7) D. M. Lemal and A. J. Fry, *J. Org. Chem.*, **29**, 1673 (1964).

(8) Decompositions were run in either triglyme or tetraglyme. Sufficient purification was achieved by distilling from sodium and redistilling a center fraction from lithium aluminum hydride.

(9) An unusual fragmentation reaction occurs when the ditosylhydrazone is heated with lithium hydride. The major volatile product, 2,4-dimethyl-1,3-pentadiene, has lost a carbon atom as cyanide. The formation can be rationalized on the basis of fragmentation, elimination, and radical decomposition of the intermediate diazosulfone, $(CH_3)_2C{=}C(N{=}NSO_2Tol){-}C(CH_3){=}CH_2$.

(10) L. Skatteböl, *Tetrahedron Letters*, 2175 (1965).

(11) J. Meinwald, J. W. Wheeler, A. A. Numetz, and J. S. Liu, *J. Org. Chem.*, 30, 1038 (1965).



indicate that cyclopropylidene **4** is being formed in the metal halide exchange reaction, we have found isomeric, as yet unidentified, products when the reaction is run at 0°. Cumulene **5** is also formed from **8**.[12] The interesting features of further carbene addition to both the terminal[10,12] and central[12] double bonds of **5** have been noted and the present synthesis of the cumulene should facilitate further studies.[13]

(12) G. Kobrich and H. Heinemann, *Angew. Chem.*, 77, 590 (1965).

(13) NOTE ADDED IN PROOF. After submission of this article, G. Maier, *Tetrahedron Letters*, 3599 (1965), reported the synthesis of 5 from solvent-free decomposition of **1**. We experienced no difficulty in solvent decompositions when the product was removed as formed. We also favor the above stepwise decomposition over the intermediacy of a highly unstable dicarbene.

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Studies on the Hydrolysis of Cyclophosphamide. I. Identification of N-(2-Hydroxyethyl)-N′-(3-hydroxypropyl)ethylenediamine as the Main Product[1]

Sir:

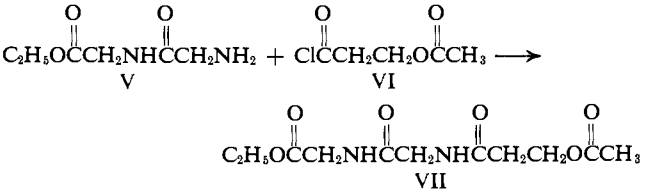
Cyclophosphamide (2H-1,3,2-oxaphosphorine, 2-[bis-(2-chloroethyl)amino]tetrahydro-2-oxide) (I), which was designed as a "transport" form of di(2-chloroethyl)-amine (norHN2),[2] is a known potent inhibitor of experimental tumors in animals that is now used clinically in certain types of human cancer. The compound is biologically inactive *per se* and becomes biologically active only upon appropriate activation *in vivo*. The nature of the activation process, which was presumed to involve release of norHN2, is still not clearly understood although a number of studies have been made.[3-7]

We report here the isolation and characterization of N-(2-hydroxyethyl)-N′-(3-hydroxypropyl)ethylenediamine (III) as the main hydrolytic product from cyclophosphamide[8] (I) when an aqueous solution (2%) of I was heated under reflux for 72 hr. The dioldiamine III was isolated directly as a crystalline dihydrochloride in 40% yield, m.p. 106–108°. *Anal.* Calcd. for $C_7H_{18}N_2O_2 \cdot 2HCl$: C, 35.73; H, 8.57; N, 11.91; Cl, 30.13. Found: C, 35.61; H, 8.60; N, 11.78; Cl, 30.02; Cl (ionic), 29.97. III was also obtained in 70% yield when isolated from the reaction mixture as a dipicrate, m.p. 209–211° (aqueous methanol). *Anal.* Calcd. for $C_7H_{18}N_2O_2 \cdot 2C_6H_3N_3O_7$: C, 36.77; H, 3.92; N, 18.10. Found: C, 36.53; H, 4.09; N, 18.08.

The identity of this hydrochloride and picrate of III was established on the basis of comparison of melting point, mixture melting point, R_f value (for the dihydrochloride, 0.16 in 1-propanol:water, 8:1), and infrared absorption spectra with authentic samples obtained through independent synthesis.

The mother liquor yielded a very small amount of another hygroscopic product, m.p. 147–151° (presoft), with R_f value 0.10 (1-propanol:water, 8:1), identical with that of an authentic sample of 1-(3-hydroxypropyl)-piperazine (IV). *Anal.* Calcd. for $C_7H_{16}N_2O \cdot H_3PO_4 \cdot HCl$: C, 30.2; H, 7.3; N, 10.1; P, 11.1. Found: C, 30.6; H, 7.4; N, 10.2; P, 11.1. The picrate of this product was found to be identical with the picrate derived from a synthetic sample of IV in respect to melting point, mixture melting point, and infrared absorption spectrum.

The dioldiamine III was synthesized by treating β-acetoxypropionyl chloride[9] (VI) with glycylglycine ethyl ester hydrochloride (V) (Schotten-Baumann) to give the acetoxydiamido ester VII in about 60% yield, m.p. 138–140° (ethyl acetate). *Anal.* Calcd. for $C_{11}H_{18}N_2O_6$: C, 48.16; H, 6.61; N, 10.21. Found: C, 48.4; H, 6.4; N, 10.3. The desired base III was obtained from VII by $LiAlH_4$ reduction, yield 56%, oil, b.p. 150–155° (0.1 mm.). *Anal.* Calcd. for $C_7H_{18}N_2O_2$: C, 51.82; H, 11.18; N, 17.27. Found: C, 52.0; H, 11.0; N, 17.2. The dihydrochloride had m.p. 108–110° (2-propanol). The dipicrate, m.p. 210–212° (aqueous methanol).



1-(3-Hydroxypropyl)piperazine (IV), prepared by alkylation of the known N-benzylpiperazine with 3-bromo-1-propanol and subsequent catalytic (10% Pd–C) hydrogenolysis, was isolated as the dihydrochloride, m.p. 233–236° (95% ethanol). *Anal.* Calcd. for $C_7H_{16}N_2O \cdot 2HCl$: Cl, 32.72; N, 12.90. Found: Cl, 32.7; N, 12.9. The compound gave a dipicrate, m.p. 249–251° (aqueous methanol), corresponding closely to the reported value,[10] m.p. 252–253° dec. (water).

From the formation of these compounds it appears that an initial intramolecular alkylation of the type I → II takes place followed by subsequent hydrolysis of the amide (N–P) and ester (O–P) bonds and in the case of the minor product IV a second N-alkylation, at some stage in the process. This suggestion is supported from paper and vapor phase chromatography of the samples taken from the reaction mixture intermittently, where the presence of breakdown products bis(2-hydroxyethyl)amine, 3-hydroxypropylamine, or bis(2-chloroethyl)amine was not indicated, and from the fact that an equimolar mixture of 3-hydroxypropylamine and bis(2-chloroethyl)amine heated to reflux

(1) Supported by a research grant (CA-02130) from National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

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(8) Kindly supplied by Dr. Harry B. Wood, Jr., Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

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