Table I. Characterization of N-Acetyl Esters of the Diastereoisomeric Pairs of 3-Methylprolines and Isoleucines by G.l.p.c.

Compound	Column[a]	Temp., °C.	Retention, min.
N-Acetyl-*trans*-3-methyl-DL-proline ethyl ester (I, R′ = Ac, R = Et)	A	138	5.9
	B	189	7.1
N-Acetyl-*cis*-3-methyl-DL-proline ethyl ester (II, R′ = Ac, R = Et)	A	138	6.8
	B	189	8.1
N-Acetyl-L- (and -DL-) isoleucine ethyl ester (V)	B	158	11.7
N-Acetyl-D- (and -DL-) alloisoleucine ethyl ester	B	158	11.0

[a] A: 3% SE52 on 6-ft. Gaschrom A; B: 3% neopentyl glycol succinate on 6-ft. Gaschrom Z.

bottromycin A.[6] This is the first reported instance of the occurrence of this amino acid in a natural product, although *trans*-4-methyl-L-proline occurs in apples[7] and *cis*-4-methyl-L-proline was isolated from hydrolysates of antibiotic I.C.I. 13,959 from a strain of *Paecilomyces*.[8]

The optical resolution of the *cis*- and *trans*-3-methyl-DL-prolines and their inhibitory effects on the biosynthesis of actinomycin are under study.

(6) S. Nakamura, T. Chikaike, K. Karasawa, H. Yonehara, and H. Umezawa, *J. Antibiot.* (Tokyo), **A18**, 47 (1965); S. Nakamura, T. Chikaike, and H. Umezawa, *ibid.*, **A18**, 60 (1965); S. Nakamura, T. Chikaike, H. Yonehara, and H. Umezawa, *Chem. Pharm. Bull. Japan*, **13**, 599 (1965).

(7) A. C. Hulme and W. Arthington, *Nature*, **170**, 659 (1952); **173**, 588 (1954).

(8) G. W. Kenner and R. C. Sheppard, *ibid.*, **181**, 48 (1958).

A. B. Mauger, F. Irreverre, B. Witkop
National Institute of Arthritis and Metabolic Diseases
National Institutes of Health, Bethesda, Maryland
Received September 3, 1965

Aminomalononitrile and 4-Amino-5-cyanoimidazole in Hydrogen Cyanide Polymerization and Adenine Synthesis[1]

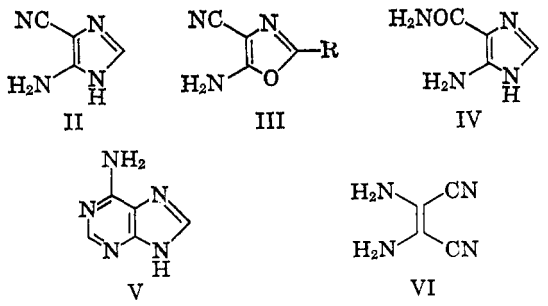
Sir:

The formation of adenine spontaneously in ammoniacal cyanide solutions[2a,b,g] or during the irradiation of dilute aqueous solutions of hydrogen cyanide[2d,e,h,k] has led to much speculation concerning the role of these reactions in the prebiological synthesis of adenine.[2] Several reaction pathways have been considered, but for the most part the evidence remains fragmentary (see particularly ref. 2j, which claims the isolation of aminomalononitrile but gives no details).

We wish to report the preparation of two new "polymers" of hydrogen cyanide, aminomalononitrile (I) and 4-amino-5-cyanoimidazole (II), and to demonstrate their use in the synthesis of heterocyclic compounds[3] and in the study of the mechanism of HCN polymerization[4] and adenine synthesis.[2]

Reduction of oximinomalononitrile[5] with aluminum amalgam in ether–tetrahydrofuran gave a 45–50% yield of I isolated as the *p*-toluenesulfonate, m.p. 180–181°. *Anal.* Calcd. for $C_{10}H_{11}N_3O_3S$: C, 47.41; H, 4.38; N, 16.59. Found: C, 47.20; H, 4.39; N 16.52.[6]

Treatment of I with acid anhydrides yielded the corresponding oxazoles. Thus acetic anhydride in formic acid yielded III (R = H), m.p. 184–186°. *Anal.* Calcd for $C_4H_3N_3O$: C, 44.04; H, 2.77; N, 38.52. Found: C, 43.99; H, 2.93; N, 38.58. Acetic anhydride gave III (R = CH_3), m.p. 153–155°. *Anal.* Calcd. for $C_5H_5N_3O$: C, 48.78; H, 4.09; N, 34.13. Found: C, 48.77; H, 4.35; N, 33.91. Propionic anhydride gave III (R = C_2H_5), m.p. 148–149°. *Anal.* Calcd. for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.32; H, 5.29; N, 30.55. Benzoic anhydride gave III (R = C_6H_5), m.p. 241–243°. The oxazole structure was proved by direct comparison of III (R = C_6H_5) with a sample prepared by a published procedure.[7]



The imidazole ring system could be formed by the condensation of I with formamidine acetate in ethanol to give a 35% yield of II as the *p*-toluenesulfonate, m.p. 168–169° (*Anal.* Calcd. for $C_{11}H_{12}N_4O_3S$: C, 47.13; H, 4.31; N, 20.00. Found: C, 46.90; H, 4.54; N, 19.62), which was also obtained in 15% yield by dehydration of 4-aminoimidazole-5-carboxamide (IV)[8] with thionyl chloride in pyridine. Treatment of II with formamidine acetate in boiling methoxyethanol[9] yielded adenine (V) (68%), m.p. 357–360°.

A brown polymer and diaminomaleonitrile (VI), m.p. 183–185°, result from the treatment of I with aqueous potassium cyanide at pH 9–10. Compound VI is the

(1) This work was supported by Grant GB-3152 from the National Science Foundation.

(2) (a) J. Oro and A. P. Kimball, *Arch. Biochem. Biophys.*, **94**, 217, (1961); (b) *ibid.*, **96**, 293 (1962); (c) *Nature*, **191**, 1193 (1961); (d) *ibid.*, **197**, 802 (1963); (e) *ibid.*, **197**, 971 (1963); (f) J. Oro and J. S. Kamat, *ibid.*, **190**, 442 (1961); (g) C. U. Lowe, M. W. Rees, and R. Markham, *ibid.*, **199**, 219 (1963); (h) C. Ponnamperuma, R. M. Lemmon, R. Mariner, and M. Calvin, *Proc. Natl. Acad. Sci. U. S.*, **49**, 737 (1963); (i) R. M. Kliss and C. N. Matthews, *ibid.*, **48**, 1300 (1962); (j) M. Calvin, "Chemical Evolution," University of Oregon Press, Eugene, Ore., 1961, p. 24; (k) C. Palm and M. Calvin, *J. Am. Chem. Soc.*, **84**, 2115 (1962); (l) for recent reviews, see "The Origins of Prebiological Systems," S. W. Fox, Ed., Academic Press Inc., New York, N. Y., 1965, pp. 137–172, 221–242.

(3) The potential utility of these compounds in heterocyclic synthesis and some attempted preparations are described by A. H. Cook, I. Heilbron, and E. Smith, *J. Chem. Soc.*, 1440 (1949); M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2759 (1958); and W. Ruske and E. Ruske, *Ber.*, **41**, 2505 (1958).

(4) T. Volker, *Angew. Chem.*, **72**, 379 (1960); J. Vaughan, *J. New Zealand Inst. Chem.*, **22**, 149 (1958); W. Ruske and E. Ruske, *Ber.*, **91**, 2496 (1958); W. Ruske, N. Becker, and H. J. Jahn, *Z. Chem.*, 271 (1961); L. E. Hinkel, G. O. Richards, and O. Thomas, *J. Chem. Soc.*, 1432 (1937); H. Bredereck, G. Schmotzer, and H. Becher, *Ann.*, **600**, 87 (1956).

(5) G. Ponzio, *Gazz. chim. ital.*, **61**, 561 (1931).

(6) All new compounds prepared in this work had infrared, ultraviolet, and nuclear magnetic resonance spectra in agreement with the proposed structures. The spectra of known compounds were identical with spectra of authentic samples or with literature spectra.

(7) H. T. Clarke, J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 729.

(8) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **181**, 89 (1949).

(9) This approach to the synthesis of purines was developed by E. C. Taylor; *e.g.*, see E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, **87**, 1995 (1965), and references therein.

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).

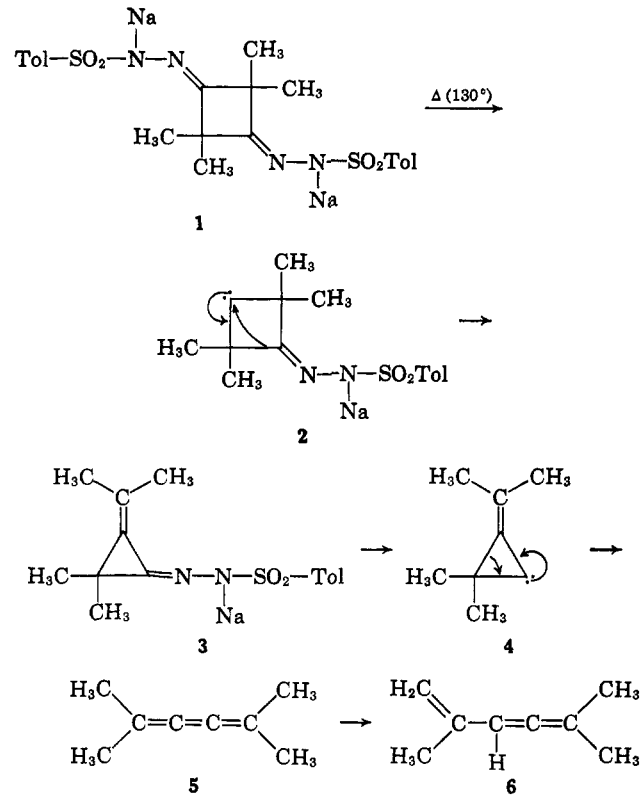
(13) Compound VI has the same R_f value and gives the same color reactions as compound A.[2b]

James P. Ferris, L. E. Orgel
The Salk Institute for Biological Studies
La Jolla, California
Received August 2, 1965

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).