through a short (10 × 1 cm) Vigreux column gave **12c** as a colorless oil, bp 115–117° (0.1 mm), in 27% yield (2.53 g). This sample was dissolved in ethanol (25 ml) and treated with an ethanol solution of dry HCl to give crystalline, ethanol-insoluble **12c**·3HCl (3.68 g), which was reprecipitated from concentrated HCl (36 ml) by addition of ethanol (380 ml). The collected, ethanol-washed product was suction dried under N_2 and dried *in vacuo* (77°, P_2O_5) to give pure **12c**·HCl, mp 262–264° dec, in 84% conversion (3.26 g) from the free base: ν_{max}^{KBr}, cm^{-1}, 1455 (CH bend, strongest band in fingerprint region).

Anal. Calcd for $C_9H_{23}N_3S \cdot 3HCl$: C, 34.31; H, 8.33; Cl, 33.79; N, 13.35; S, 10.20; SH, 10.51. Found: C, 34.25; H, 8.05; Cl, 33.92; N, 13.36; S, 10.17; SH, 10.35.

S-2-[3-[4-Phthalimidobutylamino]propylamino]ethylthiosulfuric Acid (22a) Hydrobromide.—A solution of **21** (4.38 g, 8.05 mmoles), $NaOAc \cdot 3H_2O$ (1.10 g, 8.08 mmoles), and $Na_2S_2O_3 \cdot 5H_2O$ (2.00 g, 8.05 mmoles) in water (8 ml) was heated at 90–95° for 1 hr. The cooled solution deposited a colorless syrup that solidified on refrigeration. The collected, ethanol-washed, and dried (*in vacuo* at 25–30° over P_2O_5) solid (2.84 g) was dissolved in boiling methanol (350 ml). The Norit-treated and filtered (Celite) solution was concentrated on a rotary evaporator to 50 ml while an opaque white gum separated. Ethanol (150 ml) was added and rapid magnetic stirring soon caused the gum to solidify. The collected solid was dried *in vacuo* (25–30°, P_2O_5) to constant weight (2.47 g). Elemental analysis indicated this product to be a monoethanolate of **22a**·HBr.

Anal. Calcd for $C_{17}H_{25}N_3O_5S_2 \cdot HBr \cdot C_2H_5OH$: C, 42.07; H, 5.95; N, 7.75. Found: C, 42.26; H, 5.93; N, 7.79.

Further drying *in vacuo* (P_2O_5) at successive temperatures of 58, 77, and 100° caused a weight loss of ~11% (2.43 to 2.17 g) and afforded **22a**·HBr: yield, 54%; melting point indefinite range above 170°; ν_{max}^{KBr}, cm^{-1}, 1760 (m), 1700 (s) (imide C=O), 1230, 1180, 1010, 615 ($-SSO_3^-$).

Anal. Calcd for $C_{17}H_{25}N_3O_5S_2 \cdot HBr$: C, 41.13; H, 5.28; Br, 16.10; N, 8.46; S, 12.92. Found: C, 40.89; H, 5.20; Br, 15.80; N, 8.59; S, 12.98.

S-2-[3-(4-Phthalimidobutylamino)propylamino]ethylphosphorothioic Acid (22b) Dihydrate.—Pulverized **21** (6.00 g, 11.0 mmoles) was added in portions during 15 min to a stirred suspension of Na_3SPO_3 (1.98 g, 11.0 mmoles) in water (18 ml) and DMF (6 ml). Complete solution resulted and stirring was continued for 1 hr while crystalline product separated. The mixture was stirred with ethanol (180 ml) and the collected, ethanol-washed precipitate was dried *in vacuo* (P_2O_5) at 25–30°: yield 96% (4.79 g); melting point indefinite range above 120°; ν_{max}^{KBr}, cm^{-1}, 1760 (m), 1705 (s) (imide C=O), 1120, 1065, 945, 575 ($-SPO_3^{2-}$).

Anal. Calcd for $C_{17}H_{26}N_3O_5PS \cdot 2H_2O$: C, 45.23; H, 6.70; N, 9.31; P, 6.86; S, 7.10. Found: C, 44.87; H, 6.69; N, 9.21; P, 6.83; S, 6.97.

Registry No.—**1**, 15544-47-5; **3**, 13621-89-1; **4**, 13621-90-4; **5a**·2HBr, 15440-80-9; **5b**, 15440-81-0; **5c**·$4H_3PO_4$, 15544-48-6; **8**, 15440-82-1; **9**, 15440-95-6; **10**, 15440-83-2; **11**, 13621-88-0; **12a**·2HBr, 15440-85-4; **12c**·$3H_3PO_4$, 15440-96-7; **12c**·3HCl, 15440-86-5; **13**, 15440-87-6; **16**, 15440-88-1; **17**, 15440-89-8; **18**, 15544-49-7; **19**, 15440-90-1; **20**, 15440-91-2; **21**, 15544-50-0; **22a**·HBr, 15440-92-3; **22b**, 15440-93-4; 2-aminoethanethiol, 60-23-1; spermine, 71-44-3; spermidine, 124-20-9.

Acknowledgment.—The authors are indebted to Dr. W. J. Barrett, Dr. P. D. Sternglanz, Dr. W. C. Coburn, Jr., and associates of the Analytical and Physical Chemistry Division of Southern Research Institute for microanalytical and spectral determinations. Some of the elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Synthesis of Adenine and 4,5-Dicyanoimidazole from Hydrogen Cyanide in Liquid Ammonia[1]

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Received July 7, 1967

Adenine and 4,5-dicyanoimidazole were formed simultaneously in 22 and 21% yields, respectively, on heating a solution of hydrogen cyanide in excess liquid ammonia. Diaminomaleonitrile was also detected in the reaction mixture at the initial stage. When the reaction mixture was heated with aqueous acid, the hydrolysis products glycine and formamide were isolated. Furthermore, when anhydrous hydrogen cyanide and acetamidine were heated in liquid ammonia, 2-methyl-, 8-methyl-, and 2,8-dimethyladenine and 2-methyl-4,5-dicyanoimidazole, as well as adenine and 4,5-dicyanoimidazole, were formed. Anhydrous hydrogen cyanide was also allowed to react with liquid methylamine and yielded N,N'-dimethylformamidine, 1-methyl-4-methylamino-5-cyanoimidazole and its methylamidino derivative, and 7- and 9-methyl-6-methylaminopurine. From these results, a suggested mechanism by which adenine and 4,5-dicyanoimidazole might be derived is discussed.

Adenine has been synthesized from malononitrile and thiourea,[2] from malononitrile *via* its amidine derivatives,[3] or from hypoxanthine.[4] Oró and Kimball[5] have reported that small amounts of adenine accompany a large quantity of resinous substances when a solution of hydrogen cyanide is heated in excess aqueous ammonia and that, concurrently, formamidine, 4-amino-5-imidazolecarboxamidine, and 4-amino-5-imidazolecarboxamide can be detected as key intermediates leading to the formation of adenine. However, hydrogen cyanide and the postulated intermediate amidines are quite unstable under these conditions. A previous report[1] described the improved synthesis of adenine and the formation of 4,5-dicyanoimidazole under anhydrous conditions. In the present paper we describe our efforts to study this reaction further and to shed light on the route by which these compounds are formed.

Results

Reaction of Hydrogen Cyanide with Ammonia.—Either liquid hydrogen cyanide or a mixture of sodium cyanide and ammonium chloride was heated in liquid ammonia under various conditions in a pressure vessel.

(1) (a) For a preliminary report on this article, see H. Wakamatsu, Y. Yamada, T. Saito, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, **31**, 2035 (1966); (b) presented in part at the 20th Annual Meeting of Chemical Society of Japan, Tokyo, 1967.

(2) A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3109 (1948).

(3) E. Shaw, *J. Biol. Chem.*, **188**, 439 (1950).

(4) A. Bendich, P. J. Russel, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(5) J. Oró and A. P. Kimball, *Arch. Biochem. Biophys.*, **96**, 293 (1962).

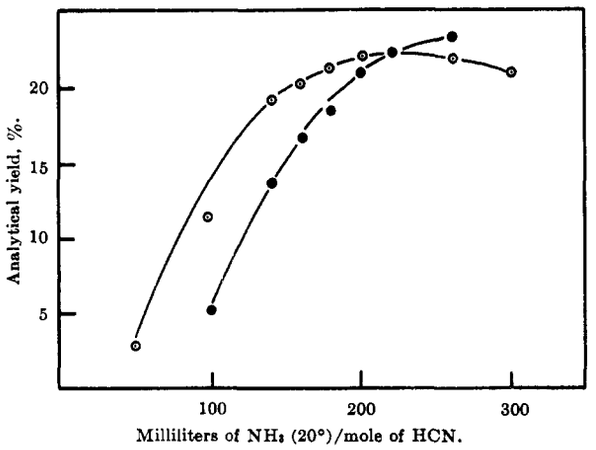


Figure 1.—Effect of the ratio of ammonia to hydrogen cyanide determined in a mixture of hydrogen cyanide and various amounts of ammonia heated at 80° for 20 hr: ⊙, adenine; ●, 4,5-dicyanoimidazole.

Adenine and 4,5-dicyanoimidazole were isolated as described in the preceding paper.[1] In addition to these compounds, diaminomaleonitrile, which had previously been isolated from products obtained by base-catalyzed polymerization of hydrogen cyanide[6] or as an addition product of aminomalononitrile with hydrogen cyanide,[7] was formed during the initial stages of the reaction. In contrast to the result reported by Oró and Kimball, neither 4-amino-5-imidazolecarboxamide nor 4-amino-5-imidazolecarboxamidine was detected in the liquid ammonia system. The acid-treated solution of the reaction mixture, however, contained formamide and glycine, which had been also detected by Oró in the aqueous system.

The influence of the concentration of hydrogen cyanide in liquid ammonia on the yields of adenine and 4,5-dicyanoimidazole based on hydrogen cyanide employed is shown in Figure 1. The yield of adenine reached the maximum when 1 mole of anhydrous hydrogen cyanide was heated in about 200 ml (20°) of liquid ammonia.

The dependency of the yields of adenine and 4,5-dicyanoimidazole on the reaction temperature as well as on the duration is shown in Figure 2. The reaction proceeded much more slowly below 80° and the decomposition of adenine became extensive above 160°. As shown in Figure 2, the preferred range of temperature lay between 100 and 120° under the conditions adopted.

The Effect of Water.—When water was added to the reaction system, the yields of both adenine and 4,5-dicyanoimidazole decreased markedly as shown in Figure 3.

The Reaction in Acetamidine–Hydrogen Cyanide–Ammonia System.—According to the mechanism suggested by Oró, hydrogen cyanide and aminomalononitrile are converted into the corresponding amidines, formamidine and aminomalonodiamidine, by the addition of ammonia to the cyano group, respectively. The latter then condenses with 1 molar equiv of formamidine to form 4-amino-5-imidazolecarboxamidine. In the final step, 4-amino-5-imidazolecarboxamidine condenses further with another molecule of formamidine

(6) T. Völker, *Angew. Chem.*, **72**, 379 (1960).
(7) J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.*, **88**, 3829 (1966).

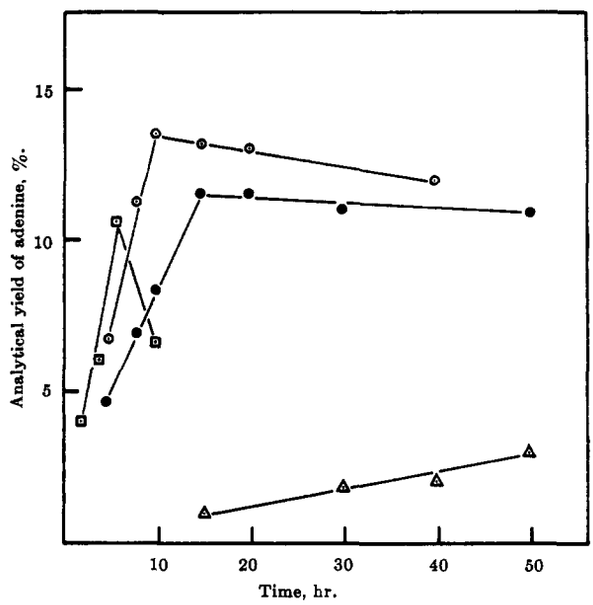
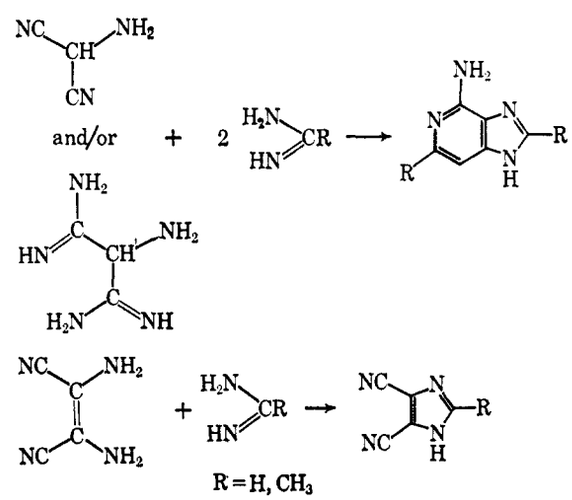


Figure 2.—Effect of reaction temperature determined in a mixture of 44 mmoles of sodium cyanide, 40 mmoles of ammonium chloride, and 60 ml of liquid ammonia heated at various temperatures: △, 80°; ●, 100°; ⊙, 120°; ⊡, 160°.

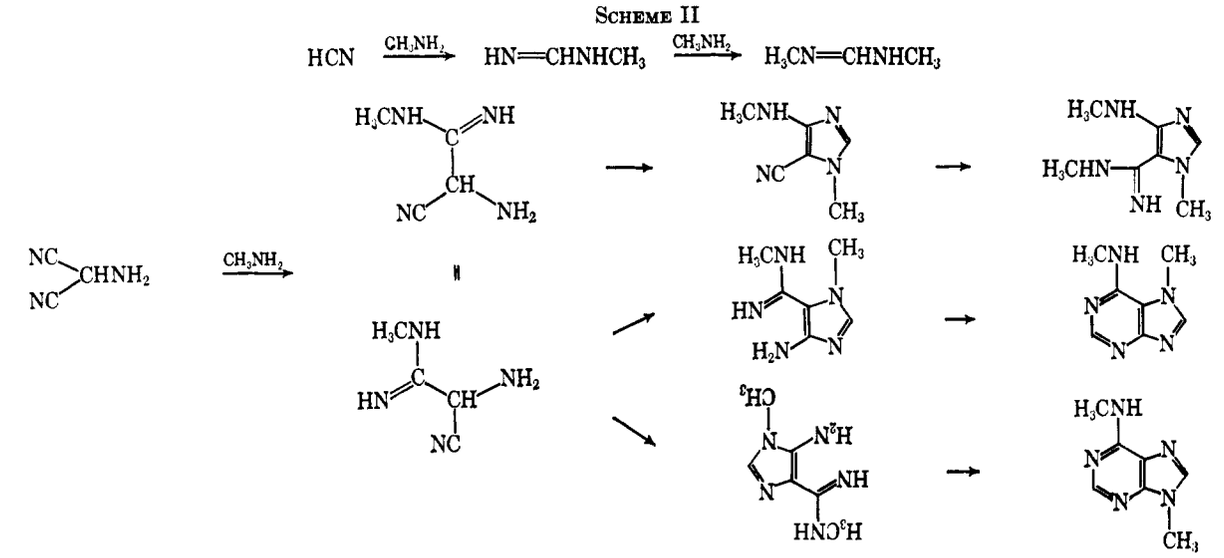
to give adenine. In order to verify the function of formamidine in the anhydrous system, 0.25 equiv of extra formamidine acetate to hydrogen cyanide used was added to a mixture of hydrogen cyanide and liquid ammonia prior to the reaction. However, the yield of adenine increased only slightly compared with the control experiment.

In a further effort to clarify the role which formamidine plays in the cyclization step, the reaction of hydrogen cyanide and acetamidine acetate in liquid ammonia was investigated. If adenine were derived from aminomalononitrile, C-methyl-substituted adenines should be formed when acetamidine is added in place of formamidine. As expected, 2-methyl-, 8-methyl-, and 2,8-dimethyladenine and 2-methyl-4,5-dicyanoimidazole, as well as adenine and 4,5-dicyanoimidazole, were formed on heating a mixture of hydrogen cyanide and acetamidine acetate in liquid ammonia. These results lend some supports to Oró's hypothesis (Scheme I).

SCHEME I



SCHEME II



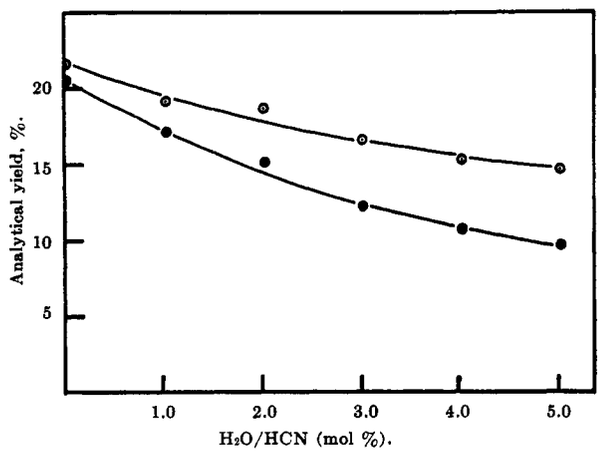


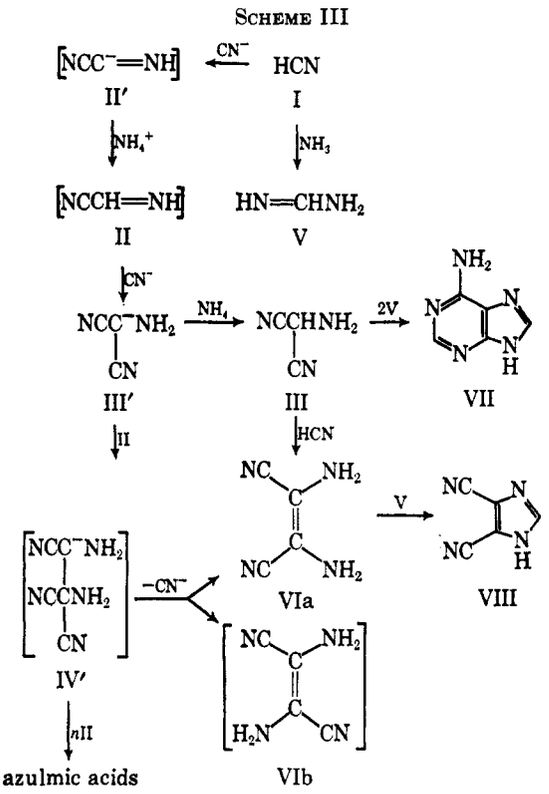
Figure 3.—Effect of water determined in a mixture of 44 mmoles of sodium cyanide and 40 mmoles of ammonium chloride in 8 ml of liquid ammonia heated at 120° for 10 hr in the presence of various amounts of water: ⊙, adenine; ●, 4,5-dicyanoimidazole.

The Reaction of Hydrogen Cyanide with Methylamine.—Although adenine can be considered a pentamer of hydrogen cyanide, no adenine is formed from hydrogen cyanide itself whether or not a polymerization catalyst, such as a small amount of aqueous sodium hydroxide, is present unless ammonia is added. In an approach to demonstrate the effect of ammonia, the reaction of hydrogen cyanide with methylamine was carried out. Heating anhydrous hydrogen cyanide with liquid methylamine in a pressure vessel at 120° for 6 hr gave small amounts of 7- and 9-methyl-6-methylaminopurines, 1-methyl-4-methylamino-5-cyanoimidazole and its methylamidino derivative, and some N, N′-dimethylformamidine. The formation of these methyl-substituted bases can be understood on the basis of Scheme II. Although no direct evidence for the presence of the different amidine-type intermediates, which would serve the various ring-closing condensation reactions, was found in the liquid ammonia system, the results of the reaction of hydrogen cyanide with methylamine might suggest that ammonia plays an indispensable role in the formation of such amidine derivatives.

Discussion

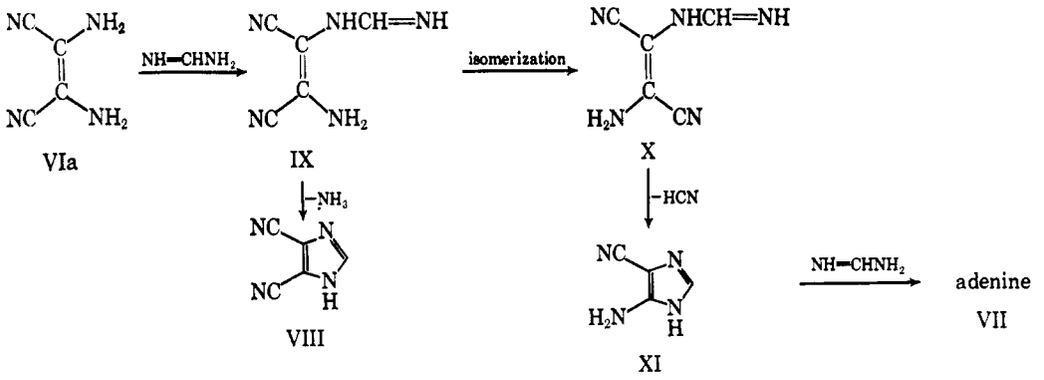
The mechanism of adenine formation *via* aminomalononitrile suggested by Oró in the aqueous system was apparently operative also in the anhydrous system adopted in the present work. The discovery of 4,5-dicyanoimidazole, however, requires another branch shown in Scheme III. Addition of cyanide ion to hydrogen cyanide (I) followed by protonation due to ammonium ion is presumed to give iminoacetonitrile (II), which is converted again into aminomalononitrile anion (III′) by the addition of cyanide ion; the latter constitutes the first branch point.

SCHEME III



In aqueous ammonia solution, most of the hydrogen cyanide may exist in dissociated form. Since aminomalononitrile (III) similarly might exist as an anionic

SCHEME IV



species III′, it would rapidly add to II to give 1,2-diamino-1,1,2-tricyanoethylene anion (IV′) which constitutes the second branch point (*vide infra*). This anion could in turn undergo analogous successive reactions with II and, by further ring closures,[6] afford a large amount of azulmic acids. A very small fraction of anion III′ present in the system appears to undergo protonation to afford III, which may take part in the formation of adenine (VII) according to the process described earlier.

In aqueous ammonia, 4-amino-5-imidazolecarboxamidine postulated as the imidazole-type intermediate on the path toward VII may not be prone to react with formamidine (V); thence it is partly converted into 4-amino-5-imidazolecarboxamide on hydrolysis. Furthermore, the formation of 4-amino-5-imidazolecarboxamidine and 4-amino-5-imidazolecarboxamide under Oró's conditions may in part be due to the fact that formamidine itself, indispensable for the ring closure of 4-amino-5-imidazolecarboxamidine into VII, is readily hydrolyzed to formamide in aqueous solution.

In contrast with the aqueous ammonia system, the dissociation constant of hydrogen cyanide in liquid ammonia has been found to be 1.9×10^{-3} at $-40°$.[8] In this system 4-amino-5-imidazolecarboxamidine may readily condense with V to VII and, since hydrolysis of V cannot take place, 4-amino-5-imidazolecarboxamidine and 4-amino-5-imidazolecarboxamide would not be formed. Moreover, considerable fraction of anion III′ would probably form III with ammonium ion and consequently the yield of VII would be very much higher.

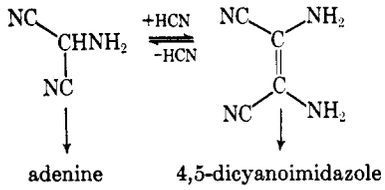
When a solution of diaminomaleonitrile (VIa) and formamidine acetate in liquid ammonia was heated, adenine (VII) and 4,5-dicyanoimidazole (VIII) were formed. Therefore, it may be possible to presume that a precursor of VII is VIa. Scheme IV represents an alternative mechanism.

However, the postulated intermediate (IX) may readily be converted into VIII by direct cyclization prior to the isomerization to X. Although the photoisomerization of VIa into diaminofumaronitrile may be quite reasonable, any thermal isomerization of IX into X has not been proved yet without ultraviolet irradiation. Moreover, it may be considered to be rather difficult to presume the elimination of cyanide anion from the intermediate (X) in the formation of XI by an intramolecular substitution reaction.

On heating a mixture of aminomalononitrile *p*-toluenesulfonate, sodium cyanide, and formamidine acetate in liquid ammonia at 120° for 2 hr, the formation of adenine was proved, but no 4,5-dicyanoimidazole was detected in the reaction mixture.

In an aqueous solution,[7] the cyanation of aminomalononitrile proceeds rapidly to give VIa. In the anhydrous ammonia system, however, such a type of cyanation occurs so slowly that the preferential cyclization of aminomalononitrile takes place to afford adenine exclusively. Therefore, at least in the liquid ammonia system, aminomalononitrile seems to be a direct precursor of adenine.

As an interpretation of the formation of adenine from IVa in the liquid ammonia system, an equilibrium between aminomalononitrile and VIa may be assumed in the presence of cyanide ion.



Among the products which are formed in the anhydrous system, we have also found another compound which is derived from the postulated *trans* isomer of VIa, *i.e.*, "diaminofumaronitrile (VIb)," although its structure has not yet been settled decisively. In order to clarify whether the direct cyanation of II with cyanide ion may also or may not take place in the anhydrous system, aminomalononitrile *p*-toluenesulfonate was treated with sodium cyanide in liquid ammonia and then cyclized with formamidine (see the Experimental Section). Compound VII and 4,5-dicyanoimidazole (VIII) were formed, but no compound derived from VIb was discovered. The formation of VIII may suggest that cyanide addition to the trimer III occurs at least in part even in liquid ammonia. It is evident, however, that the direct cyanation does not result in the formation of hypothetical VIb. As an alternative leading to the assumed *trans* isomer VIb, elimination of cyanide ion from anion IV′, mentioned above as a primary precursor of azulmic acids, might possibly be postulated and consequently IV′ might constitute in the second branch point (*vide ante*). More evidence on the possible existence of tetrameric *trans* isomer VIb will be reported later in detail. Compound VIa might then condense with 1 molar equiv of formamidine to give VIII. The cyclization of VIa to VIII has been substantiated by Woodward[9] under ordinary

(8) E. N. Guryanova and U. A. Pleskov, *J. Phys. Chem.* (USSR), **8**, 345 (1936).

(9) D. W. Woodward, U. S. Patent 2,534,331 (1950).

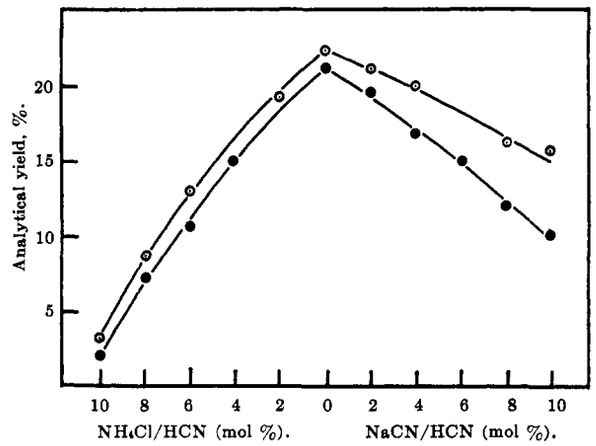


Figure 4.—Effect of the coexistence of acid or base determined in mixtures of 2.7 g of hydrogen cyanide, 20 ml of liquid ammonia, and different amount of sodium cyanide or ammonium chloride heated at 80° for 20 hr in a sealed vessel: ⊙, adenine; ●, 4,5-dicyanoimidazole.

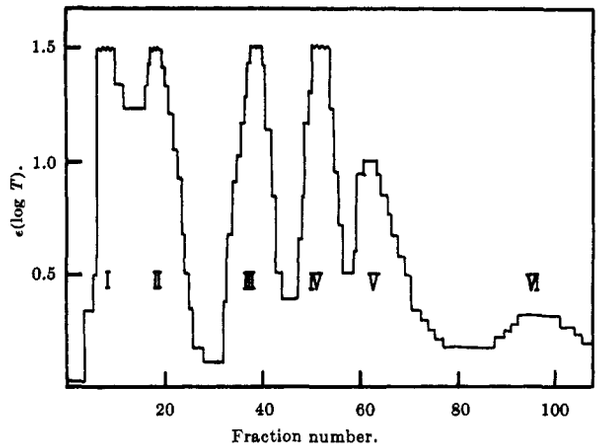


Figure 5.—Ion-exchange column chromatogram of the products: after a water wash, elution was effected with 2 *N* hydrochloric acid; peak I was an unabsorbed part through the column, 4,5-dicyanoimidazole (5%); peak II was obtained by washing the column with water, 2-methyl-4,5-dicyanoimidazole (5%); peaks III–VI were the eluates with 2 *N* hydrochloric acid; peak III, adenine (8%); peak IV, 2-methyladenine (7%); peak V, 8-methyladenine (6%); peak VI, 2,8-dimethyladenine (1.5%).

preparative conditions, *i.e.*, heating a mixture of VIa and ethyl orthoformate in anisole in the presence of sodium methoxide.

In connection with this scheme, the effect of adding an acid or a base on the reactions in the liquid ammonia system was investigated and can be interpreted in manner shown in Figure 4. Since the presence of strong acids, such as ammonium chloride, in liquid ammonia may repress nucleophilic attack of cyanide ion on hydrogen cyanide by inhibiting the dissociation of hydrogen cyanide, the formation of nitrile II, comprising the first step in the reaction sequence, will be prevented. The same should hold for preventing the formation of III in the presence of an acid. By contrast, the presence of the strong bases, such as sodium cyanide, may accelerate the formation of azulmic acids by the similar reason as has been discussed on the possible mechanism in the aqueous system.

Experimental Section[10]

Identification of the Intermediates.—Glycine and formamide were detected in the acid-treated solution of the reaction mixture by the method similar to that described by Oro.[5]

The dark brown residue was obtained by heating 5.4 g of hydrogen cyanide and 24.7 g (40 ml at 15°) of liquid ammonia at 100° for 5 min in a pressure vessel, followed by removing the volatile material from reaction mixture. Diaminomaleonitrile could be isolated from the hot water extract of the residue. The product exhibited mp 178–178.5° and characteristic infrared absorption band due to the cyano group at 2240 cm^{-1}.

Anal. Calcd for $C_4H_4N_4$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.74; H, 4.13; N, 51.98.

The ultraviolet and infrared absorption spectra of the isolated compound were identical with those of an authentic sample.[7]

Effect of Formamidine Added.—A mixture of 2.16 g (44 mmoles) of sodium cyanide, 2.14 g (40 mmoles) of ammonium chloride, and 1.04 g (10 mmoles) of formamidine acetate in 8 ml of liquid ammonia was heated at 120° for 8 hr. The yield of adenine was increased from 21 to 24% based on hydrogen cyanide employed.

Formation of Adenine and 4,5-Dicyanoimidazole from Aminomalononitrile.—A mixture of 12.65 g (50 mmoles) of aminomalononitrile *p*-toluenesulfonate,[7] 3.67 g (75 mmoles) of sodium cyanide, and 32 ml of liquid ammonia was stirred at room temperature in a pressure vessel. After 10 min, 10.4 g (100 mmoles) of formamidine acetate was added in the pressure vessel and the mixture was heated at 120° for 2 hr. Then the volatile materials were removed from the reaction mixture under reduced pressure. Paper chromatographic analysis of the aqueous extract from the residual dark brown solid showed the formation of 1.4 g (21%) of adenine and 0.22 g (4%) of 4,5-dicyanoimidazole.

C-Methyl-Substituted Adenines.—A mixture of 2.7 g (0.1 mole) of hydrogen cyanide, 9.45 g (0.1 mole) of acetamidine hydrochloride, 4.9 g (0.1 mole) of sodium cyanide, and 24.7 g (40 ml at 15°) of liquid ammonia was heated at 120° for 6 hr in a pressure vessel. Then the volatile materials were removed from the reaction mixture under reduced pressure. The residual dark brown solid was extracted several times with hot water. The paper chromatogram of the aqueous extract showed two spots, in addition to those of adenine and 4,5-dicyanoimidazole, under ultraviolet radiation. The combined extract was passed through a column of Dowex 50W (X4, 100–200 mesh, H^+ form) (see Figure 5). 4,5-Dicyanoimidazole was isolated from peak I. The ultraviolet spectra of the compound isolated from peak II showed absorption maximum at 255 mμ in 0.1 *N* hydrochloric acid and 272 mμ in 0.1 *N* sodium hydroxide solution. The infrared absorption spectra of the compound were identical with those of authentic 2-methyl-4,5-dicyanoimidazole.[11] Adenine was found to be contained in peak III. The infrared absorption spectra of the compound obtained from the peak IV were identical with those of authentic 2-methyladenine.[12] The compounds contained in peaks V and VI were found to be 8-methyladenine[13] and 2,8-dimethyladenine, respectively, by the comparison of their infrared absorption spectra with those of respective authentic sample. The authentic 2,8-dimethyladenine was prepared from 2-methyl-4,6-diamino-5-nitrosopyrimidine[12] by a method similar to that described by Koppel.[13]

N-Methyl-Substituted Adenines.—A mixture of 140 g (200 ml) of anhydrous methylamine and 27 g of hydrogen cyanide was put into a 500-ml stainless steel pressure vessel with cooling and heated at 120° for 6 hr. After removing ammonia, methylamine, and unchanged hydrogen cyanide, an oily substance having bp 59° (20 mm) was obtained from the resulting residue by distillation: λ_{max}^{KBr} 3380, 3310, 2920, 2800 cm^{-1}.

Anal. Calcd for $C_3H_8N_2$: C, 49.97; H, 11.18; N, 38.85. Found: C, 49.88; H, 10.69; N, 38.81.

(10) All melting points are uncorrected. Ultraviolet and infrared spectra were measured with a Hitachi EPS-2 and a JASCO Model IR-S recording spectrophotometers, respectively. Paper chromatography was performed on Toyo Roshi No. 51A paper using the ascending technique with a solvent system *n*-C_3H_7OH–NH_3–H_2O (20:12:3, v/v).

(11) U. Tamamushi, *J. Pharm. Soc. Japan*, **55**, 1053 (1935).

(12) E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Am. Chem. Soc.*, **81**, 2442 (1959).

(13) H. C. Koppel and R. K. Robins, *J. Org. Chem.*, **23**, 1457 (1958).

The infrared absorption spectra were identical with those of authentic N,N'-dimethylformamidine.[14] This amidine was isolated in 34% yield based on hydrogen cyanide used. Then the distillation residue was extracted several times with hot water. The two-dimensional paper chromatogram[15] of the aqueous extract showed four spots under ultraviolet radiation. The supernatant solution of this extract was passed through a column of Dowex 50W (X4, 100–200 mesh, H^+ form). Then the column was washed with water and eluted with 0.1 *N* hydrochloric acid. Four peaks were obtained from the column. 1-Methyl-4-methylamino-5-cyanoimidazole of mp 178–178.4° was obtained from peak I.

Anal. Calcd for $C_6H_8N_4$: C, 52.92; H, 5.92; N, 41.15. Found: C, 53.25; H, 5.81; N, 41.38.

The isolated substance showed ultraviolet absorption maxima at 241 and 270 mμ in 0.1 *N* sodium hydroxide solution, which closely resemble those of 4-amino-5-cyanoimidazole. Its infrared absorption spectrum exhibited a characteristic band due to the cyano group at 2220 cm^{-1}, and was identical with that of an authentic sample. Authentic 1-methyl-4-methylamino-5-cyanoimidazole was prepared from 1-methyl-4-amino-5-imidazolecarboxamide[16] by N-methylation with methyl iodide in dilute sodium hydroxide solution, followed by dehydration of the carbamoyl group with phosphoryl chloride. On evaporation of peaks II and III separately, two derivatives of N-methyl-substituted adenine were obtained. The former showed ultraviolet absorption maxima at 265 mμ in 0.1 *N* hydrochloric acid and 270 mμ in 0.1 *N* sodium hydroxide solution and the latter at 280 mμ in 0.1 *N* hydrochloric acid and 277 mμ in 0.1 *N* sodium hydroxide solution. The infrared absorption spectra of these compounds were identical with those of the authentic samples of 6-methylamino-9-methylpurine[17] and 6-methylamino-7-methylpurine,[18] respectively. Attempts to isolate the substance from peak IV were unsuccessful. It was presumed from ultraviolet absorption spectra, however, that the substance was a methylamidino derivative of 1-methyl-4-methylamino-5-cyanoimidazole.

(14) A. Pinner, *Ber.*, **16**, 358 (1883).

(15) First solvent, *n*-C_3H_7OH–NH_3–H_2O (20:12:3, v/v); second solvent, *n*-C_4H_9OH–CH_3CO_2H–H_2O (4:1:1, v/v).

(16) R. K. Robins and R. N. Prasad, *J. Am. Chem. Soc.*, **79**, 6401 (1957).

(17) R. K. Robins and H. H. Lin, *ibid.*, **79**, 490 (1957).

(18) E. C. Taylor and P. K. Loeffler, *ibid.*, **82**, 3147 (1960).

Registry No.—I, 74-90-8; ammonia, 7664-41-7; VII, 73-24-5; VIII, 1122-28-7; N,N-dimethylformamidine, 2304-00-9; 1-methyl-4-methylamino-5-cyanoimidazole, 15353-10-3.

Acknowledgment.—The authors wish to express their sincere thanks to Mr. Shinichi Motozaki, director of this laboratory, for his kind encouragement. The assistance of Mr. Masao Nakamura and Mr. Katsuhide Mokushi throughout this work is also gratefully acknowledged.

Steroid Hormone Analogs. III.[1] The Synthesis and Stereochemistry of C-Nor-D-homoprogesterone Analogs[2]

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Received September 6, 1967

The synthesis is described of the C-nor-D-homo-11-keto-17-hydroxyprogesterone derivatives XX and XXII, which possess the progesterone configuration at each of the ring junctions. Jervine was degraded to the diketone IV by standard procedures. Treatment of IV with ethylidenetriphosphorane under Wittig reaction conditions yielded the geometric isomers, V and VI, and alkaline hydrolysis afforded VII and VIII, respectively. Spectral studies showed (1) that V and VII possess C/D-*trans*, C-18β-(equatorial)-methyl, and C-21-*cis*-methyl configurations and (2) that VI possesses the less stable C/D-*cis* junction and is epimerized at C-12 during alkaline hydrolysis to VIII, with C/D-*trans*, C-18β-(equatorial)-methyl, and C-21-*trans*-methyl configurations. Oppenauer oxidation of VII and VIII gave XI and XII, respectively. Epoxidation of XI gave the isomeric oxides XIII and XIV and chemical and spectral arguments are advanced for assignment of β-epoxide and α-epoxide configurations, respectively. Attempted oxidation of XIII with dimethyl sulfoxide–boron trifluoride etherate gave XVII, which was oxidized with chromic acid–pyridine to XVIII. Oxidation of XI or XII with osmium tetroxide and hydrogen peroxide under neutral conditions yielded the epimeric ketones XX and XXII. Spectral and chemical evidence are adduced for assignment of the C-nor-D-homo-11-keto-17α-hydroxyprogesterone structure for XX and the C-nor-D-homo-11-keto-17β-hydroxyprogesterone structure for XXII.

Recent years have witnessed continuing interest in the modification of the basic steroid skeleton of hormones to seek analogs with enhanced or more specific pharmacological properties. In view of the natural occurrence of the C-nor-D-homo steroid ring system (*e.g.*, in jervine (I)[3,4]), the synthesis of related hormone analogs has been a particularly attractive target.[1,5–9] We described herewith the synthesis of the first C-nor-D-homoprogesterone derivatives which possess the progesterone configuration at each of the ring junctions.

An earlier approach[1] to C-nor-D-homoprogesterone derivatives started from $\Delta^{5,12,17(20)}$-17-ethyletiojervatrien-3β-ol-11-one 3-acetate (II)[3,5,10] and proceeded *via* hydroxylation of the 17,20 double bond. However, the latter approach proved to be impractical, owing largely to the sensitivity of the 17,20 bond to oxidative cleavage in the 12,13-unsaturated derivatives. The approach described in the present work proceeds *via*

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(8) (a) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964); (b) W. F. Johns and I. Laos, *ibid.*, **30**, 123, 4220 (1965).

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(10) The designation etiojervane is used, as in our earlier reports,[1,5] to describe 17aβ-methyl-C-nor-D-homo-18-nor-5α,13β-androstane. It should be noted that the same term has *subsequently* been used to designate two different stereoisomers.[7,8a]