Suppose equilibrium measurements are based on observations of a property to which only B contributes and the presence of C is unsuspected. The apparent equilibrium constant is then

$$K_{app} = \frac{b_e}{a_0 - b_e} = \frac{K_1}{1 + K_1K_2} \quad (2)$$

where a_0 is the total concentration and b_e is the equilibrium concentration of B. Differentiation with respect to temperature gives

$$\Delta H_{app} = \frac{\Delta H_1 - K_1K_2\Delta H_2}{1 + K_1K_2} \quad (3)$$

A calorimetric experiment would give for the observed heat of reaction per mole of A originally present

$$\Delta H_{obs} = \frac{K_1(1 + K_2)\Delta H_1 + K_1K_2\Delta H_2}{1 + K_1 + K_1K_2} \quad (4)$$

If the calorimetric experiment were performed under conditions where A is completely reacted ($K_1 >> 1$)

$$\Delta H_{obs} = \Delta H_1 + \frac{K_2}{1 + K_2}\Delta H_2 \quad (5)$$

It is obvious that with arbitrary values of the various quantities, equations 3 and 4 can give very different results. For example, if $\Delta H_1 = K_1K_2\Delta H_2$, $\Delta H_{app} = 0$ and $\Delta H_{obs} = \Delta H_1$. Similarly, if only C is observed

$$K_{app} = \frac{c_e}{a_0 - c_e} = \frac{K_1K_2}{1 + K_1} \quad (6)$$

and

$$\Delta H_{app} = \frac{\Delta H_1}{1 + K_1} + \Delta H_2 \quad (7)$$

It is evident, in view of these considerations, that it is not necessarily surprising to find apparent reaction heats deduced from indirect equilibrium measurements which do not agree with heats determined calorimetrically.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

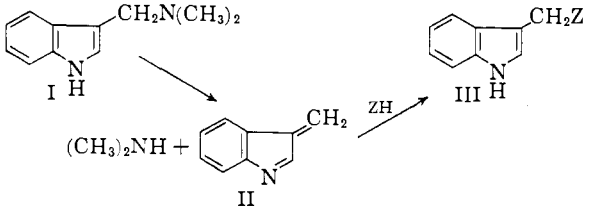
Synthesis and Reactions of α-Cyanogramine[1]

BY PHILIP N. JAMES[2] AND H. R. SNYDER

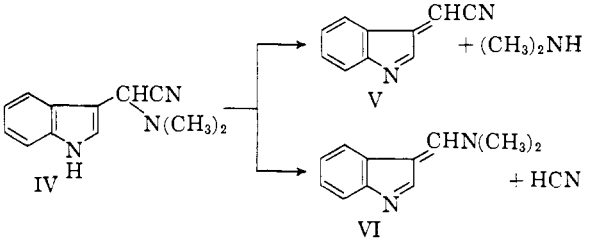
RECEIVED JUNE 26, 1959

The synthesis of α-cyanogramine from indole-3-aldehyde by the Strecker reaction is reported. This compound does not undergo the simple alkylation reactions characteristic of gramine, but does exchange its dimethylamino group with piperidine and does release dimethylamine on pyrolysis. It is easily converted to the parent aldehyde by hydrolysis, reduced to gramine by lithium aluminum hydride, converted to 3-dimethylaminomethylene-3H-pseudoindole by strong, non-aqueous bases, and converted to a yellow crystalline solid, which is not a simple alkylation product, by diethyl nitromalonate. Its reaction with methyl iodide is complex, tetramethylammonium iodide being the only product isolated. It forms an unstable monopicrate which decomposes to dimethylamine picrate on attempted recrystallization. The significance of these reactions in relation to a proposed mechanism for carbon–carbon alkylations with gramine is discussed.

There is now ample evidence for the elimination–addition mechanism of reactions in which Mannich bases of the gramine (3-dimethylaminomethylindole, I) type serve as alkylating agents.[3] The reactive intermediate appears to be 3-methylene-3H-pseudoindole (II), which is formed in the presence of a reagent such as an active methylene compound that immediately adds to it to form the alkylation product III.



α-Cyanogramine (IV) would appear to offer an interesting alternative to the loss of dimethylamine, for a 3H-pseudoindole could arise by the elimination of either the secondary amine or hydrogen cyanide. The present work was undertaken to search for evidence of the two different eliminations.



α-Cyanogramine was prepared from indole-3-aldehyde by a modification of the Strecker reaction.[4] It proved to be much less stable than gramine, decomposing not far above 100° and undergoing hydrolysis to indole-3-aldehyde even in neutral solution. Its sensitivity precludes its use in many reactions which find valuable synthetic applications with gramine.[5] The thermal decomposition occurred with the loss of dimethylamine (70% yield, isolated as the phenylthiourea) and the formation of a red-brown gum which resisted all attempts at separation into pure sub-

(1) Abstracted in part from a Thesis submitted by Philip N. James to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1957.

(2) National Science Foundation Fellow, 1955–1957.

(3) J. D. Albright and H. R. Snyder, THIS JOURNAL, **81**, 2239 (1959).

(4) For a discussion of methods of synthesis of α-aminonitriles, see V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," A.C.S. Monograph Series No. 105, Reinhold Publishing Corp., New York, N. Y., 1947, Ch. 10.

(5) See J. H. Brewster and E. L. Eliel, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 99.

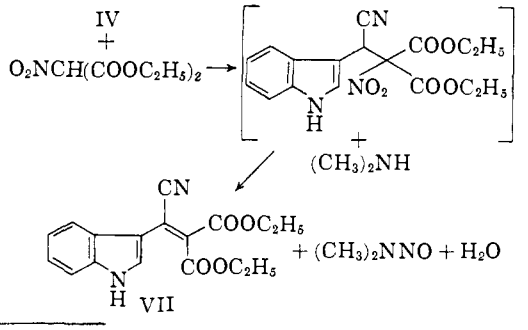
stances. The hydrolysis to indole-3-aldehyde is catalyzed either by weak acids or by bases; strong acids convert IV to resinous materials which cannot be hydrolyzed to indole-3-aldehyde. It seems likely that attack by base proceeds through removal of the proton from the indole nitrogen atom followed by loss of cyanide ion to give VI, hydrolysis of which leads to the aldehyde. Hydrolysis with weak acids probably proceeds by salt formation on the dimethylamino group, loss of dimethylamine and a proton to give V, and finally hydrolysis to the aldehyde. In the presence of strong acids V or one of its precursors evidently polymerizes.

Alkylations of sodium cyanide, malonic ester, 1-nitropropane, 2-nitropropane and nitromalonic ester by IV were attempted. Simple alkylation was not observed in any instance, and a crystalline product was isolated only from the reaction with nitromalonic ester. That reaction produced dimethylnitrosamine and a yellow solid of the composition $C_{17}H_{16}N_2O_4$.

The compound $C_{17}H_{16}N_2O_4$ is insoluble in water, dilute acids and dilute bases. It does not react with bromine in carbon tetrachloride solution on standing overnight. When treated with ethanolic sodium ethoxide, a deep red solution is formed. The compound reacts with methyl iodide in the presence of base to form a new compound, $C_{18}H_{18}N_2O_4$. Exhaustive hydrogenation (atmospheric pressure) of the C_{18}-compound resulted in the consumption of 1.6 moles of hydrogen, but a number of products was formed. The predominant product, separated by chromatography, was obtained in approximately 75% yield as a viscous, pale yellow oil.

The infrared spectrum of $C_{17}H_{16}N_2O_4$ showed the presence of ester carbonyl, nitrile and indole N–H atomic groupings. Its ultraviolet spectrum was consistent with the presence of the 3-vinylindole chromophore.[6] The ultraviolet spectrum of $C_{18}H_{18}N_2O_4$ was nearly identical with that of $C_{17}H_{16}N_2O_4$, and its infrared spectrum indicated the presence of the same atomic groupings with the exception of indole N–H. The ultraviolet spectrum of the principal C_{18}-hydrogenation product indicated that the indole chromophore alone was present, and its infrared spectrum was much less complex in the double bond region than that of its C_{18}-parent, though the carbonyl and nitrile regions were nearly identical for the two compounds.

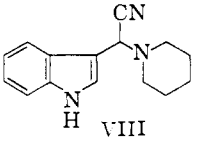
On the basis of this evidence, the structure VII



VII

was assigned to $C_{17}H_{16}N_2O_4$. Analogy with the reaction between gramine and diethyl nitromalonate[7] suggests the path shown in the equation. Reports of the base-catalyzed loss of a nitro group as nitrous acid are rare in the literature, and this is the first such case in which an aliphatic double bond is generated in this manner.

One reaction which parallels the corresponding process on gramine is amine exchange.[8] When α-cyanogramine is heated with piperidine, amine exchange occurs smoothly. The same product (VIII) is obtained in excellent yield by replacing dimethylamine with piperidine in the Strecker reaction on indole-3-aldehyde. *t*-Butylamine failed to react in either the amine exchange or the Strecker reaction.



VIII

α-Cyanogramine reacted with methyl iodide, but the only product isolated was tetramethylammonium iodide. When gramine is treated with methyl iodide under ordinary conditions, the result is disproportionation to an equimolar mixture of tetramethylammonium iodide and diskatyldimethylammonium iodide.[9] In this Laboratory, Lovejoy was able to control the disproportionation by operating at low temperatures or in the presence of weak acids.[10] These methods failed to suppress the formation of tetramethylammonium iodide in the reaction of methyl iodide with α-cyanogramine, suggesting that this reaction occurs by a different path.

Treatment of α-cyanogramine with picric acid resulted in the formation of an unstable picrate (m.p. 238–241°) which was converted to dimethylamine picrate (m.p. 161–163°) upon recrystallization from ethanol.

In all of the experiments described above the dimethylamino group was removed from the molecule in forming the reaction products. The reactions can all be explained on the basis of the intermediate formation of the cyanomethylene pseudoindole following the loss of dimethylamine. In the following experiments, the attacking reagent is strongly basic, so that attack on the hydrogen atom attached to the indole nitrogen atom would be expected. The result of such an attack would be the elimination of cyanide anion, forming the dimethylaminomethylene pseudoindole.

α-Cyanogramine reacts with lithium aluminum hydride to produce gramine in 87% yield, and 71% of the theoretical amount of cyanide ion was detected by titration of aqueous extracts of the reaction mixture. It is possible that part of the organic material lost was converted to skatole by further reduction of gramine. The action of lith-

(6) (a) W. E. Noland and D. N. Robinson, *J. Org. Chem.*, **22**, 1134 (1957); (b) G. N. Sausen, V. A. Engelhardt and W. J. Middleton, THIS JOURNAL, **80**, 2818 (1958).

(7) D. I. Weisblat and D. A. Lyttle, THIS JOURNAL, **71**, 3080 (1949).

(8) E. E. Howe, A. J. Zambito, H. R. Snyder and M. Tishler, *ibid.*, **67**, 38 (1945).

(9) C. Schöpf and J. Thesing, *Angew. Chem.*, **63**, 377 (1951).

(10) E. R. Lovejoy, Ph.D. Thesis, University of Illinois, Urbana, 1953.

ium aluminum hydride on gramine appears not to have been reported, but other chemical reducing agents do convert it to skatole.[11] Reduction of α-cyanogramine by this method probably involves the intermediate production of the pseudoindole VI, which is then further reduced by the reagent.

Treatment of α-cyanogramine with a variety of other strong bases, such as sodium hydride, sodium and sodium ethoxide, gave inconclusive results, but treatment with sodium triphenylmethyl in absolute ether resulted in the formation in good yield (about 70%) of 3-dimethylaminomethylene-3H-pseudoindole (VI), m.p. 155–160° The product was identified by comparison of its infrared spectrum with that from an authentic sample prepared by the method of Smith.[12] The spectra were indistinguishable.[13]

The available evidence suggests that the two different pseudoindoles structurally possible from α-cyanogramine are actually involved in reactions of this compound. Under acidic conditions, or in the presence of reagents capable of reacting with amines, the cyanomethylene-pseudoindole is formed, while under strongly basic conditions, the dimethylaminomethylene-pseudoindole is formed. The latter pseudoindole is relatively stable, and is capable of isolation. The former pseudoindole is unstable under all conditions investigated. A consideration of resonance structures for the two pseudoindoles confirms these observations. In addition, a comparison of resonance structures for the unsubstituted 3-methylene-3H-pseudoindole with those for the substituted pseudoindoles leads to the prediction that it would be intermediate in stability.

These considerations, supported by the experimental evidence in this report, suggest that electron-withdrawing groups tend to decrease, and electron-donating groups increase, the stability of the 3-methylene-3H-pseudoindole system. Alkylation reactions of α-substituted gramines depend upon the comparative reactivity of the substituted pseudoindole system toward addition of the compound to be alkylated and toward all other competing reactions. The electronic[14] effects of hydrogen in the methylene position of this pseudoindole system seem to be more favorable in this respect than either the cyano group or the dimethylamino group.

(11) A. P. Terentyev, N. A. Dzbanovsky and N. A. Favorskaya, *J. Gen. Chem. (U.S.S.R.)*, **23**, 2151 (1953).

(12) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(13) Both materials appeared to contain approximately 50% of the pseudoindole and 50% of indole-3-aldehyde (see Experimental). Hydrolysis of the pseudoindole occurred with remarkable ease and rapidity at elevated temperatures, though at room temperature in the crystal state the rate was slow. At 80°, the moisture present in the atmosphere and adsorbed on equipment was sufficient to effect appreciable hydrolysis. Once formed, the aldehyde was impossible to remove from the pseudoindole by recrystallization from benzene. Apparently, either cocrystallization or molecular complex formation was responsible for the difficulty, for the mixture had widely different solubility properties from the aldehyde itself, both in chloroform and in benzene.

(14) It could be argued that steric effects are also important, but H. R. Snyder and D. S. Matteson [THIS JOURNAL, **79**, 2217 (1957)] have accomplished alkylation reactions with a compound closely related to α-methylgramine, suggesting that electronic effects are far more important.

Experimental[15]

α-Cyanogramine.—In a 100-ml. round-bottomed flask were placed, in the order named, 1.7 g. (0.034 mole) of sodium cyanide in 4 ml. of water, 3.0 g. (0.037 mole) of dimethylamine hydrochloride in 6 ml. of water and 14 ml. of a 25% aqueous solution of dimethylamine (equivalent to 0.078 mole of dimethylamine). With shaking, 5.0 g. (0.034 mole) of indole-3-aldehyde[16] and 12 ml. of 95% aqueous ethanol were added. The flask was stoppered with a lightly greased ground glass stopper, and the stopper was tightly secured with friction tape. The flask was immersed in a water-bath maintained at about 60° for 6 hours. At the end of the reaction period, the flask was cooled under the tap, and the contents diluted to 100 ml. with water. The product was collected on a filter, washed with water and air-dried; the yield of α-cyanogramine was 6.7 g. (98%), m.p. 115–118° with extensive decomposition (m.p. obtained by introducing the sample at 105° and heating at the rate of 2° per minute until melting was complete). Recrystallization from benzene caused no improvement in the melting point. The infrared spectrum of the compound in Nujol showed bands characteristic for the N–H bond of the indole nucleus (2.95 μ) and for the nitrile group (4.47 μ).

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.18; H, 6.59; N, 21.10. Found: C, 72.24; H, 6.47; N, 21.29.

Pyrolysis of α-Cyanogramine.—One gram (0.005 mole) of α-cyanogramine was placed in a 50-ml. round-bottomed flask fitted with a nitrogen inlet tube and connected to a trap cooled by a mixture of solid carbon dioxide and acetone. The cold trap was connected to a gas washing tube containing a solution of an excess of phenyl isothiocyanate in 50 ml. of diethyl ether. The system was flushed thoroughly with nitrogen, and an oil-bath preheated to 180° was placed around the flask. A stream of nitrogen was passed through the system during the pyrolysis. After gas evolution had ceased (about 2 minutes), the heating bath was removed, but the nitrogen stream was allowed to continue for about 10–15 minutes. At the end of this time, the gas washing tube was disassembled and the white crystals which had been deposited in the ether solution were collected on a filter, washed with ether, and air-dried. The yield of N,N-dimethyl-N′-phenylthiourea was 0.63 g. (70%), m.p. 135–136° (lit.[17] 135°). A mixed melting point with an authentic sample showed no depression.

The dark, gummy residue from the pyrolysis could not be induced to deposit crystals from any of a variety of solvents.

Hydrolysis of α-Cyanogramine.—The hydrolysis experiments with α-cyanogramine are summarized in Table I.

Reaction between α-Cyanogramine and Diethyl Nitromalonate.—α-Cyanogramine (15.1 g., 0.076 mole), 32.1 g. (0.157 mole) of diethyl nitromalonate[7] and 300 ml. of xylene were placed in a 500-ml. round-bottomed flask fitted with a mechanical stirrer, a Dean–Stark receiver, and a nitrogen inlet tube. The solution was heated under reflux for 2 hours in an atmosphere of nitrogen, at the end of which time no further collection of water in the Dean–Stark receiver was observed. A total of 1.4 ml. (100%) of water had collected.

The deep red solution was allowed to cool to room temperature, then was extracted with four 200-ml. portions of water, then five 200-ml. portions of a 10% aqueous solution of sodium carbonate, and finally dried over anhydrous magnesium sulfate.

The aqueous extracts were saturated with anhydrous potassium carbonate. The oily layer which separated was removed, and the aqueous solution was extracted with ether. The oily material and the ether extracts were combined, dried over anhydrous magnesium sulfate, and the ether was removed by distillation. The oily residue which remained was distilled, b.p. 148–151° (752 mm.). The pale yellow oil, which weighed 3.3 g. (59%), was identified by means of its boiling point (lit.[18] 149–150° (755 mm.)) and

(15) All melting points are corrected. Microanalyses were performed by Mr. Joseph Nemeth and his associates and by the Microchemical Laboratory, University of California, Berkeley.

(16) P. N. James, *Org. Syntheses*, **39**, 30 (1959).

(17) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., ed. 4, 1956, p. 288.

(18) H. H. Hatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 212.

TABLE I

HYDROLYSIS OF α-CYANOGRAMINE

Experiment	1	2	3	4	
α-Cyanogramine, mg.	499	502	532	500	199
Other reagent (5 ml. used)	5% NaOH	5% HCl	5% HCl	H_2O (*p*H 7)	99% HOAC
Temp., °C.	B.p.	B.p.	25	B.p.	B.p.
Time	1 min.	1 min.	11 days	1 min.	5 min.
Indole-3-aldehyde,[a] mg. (% yield)	300(82)	...	trace	230(63)	[b]
CN^- (determined by titration[19]) % yield	99	0	...	38	...
Other product, mg.	...	437[c]	[d]	[e]	...

[a] Indole-3-aldehyde was identified by its melting point and a mixed melting point with an authentic sample. [b] The yield of aldehyde was not determined in this case, but a significant amount was produced. [c] This material had no definite melting point, and boiling it with 5 ml. of a 5% aqueous solution of sodium hydroxide for 2 hours failed to convert it to indole-3-aldehyde. [d] This material had no definite melting point, and its weight was not determined. [e] Some unreacted α-cyanogramine was recovered.

comparison of its infrared spectrum with that reported[20] for dimethylnitrosamine. The principal absorption bands in the spectrum occur at 3.40, 5.92, 6.75, 6.89, 7.09, 7.58, 7.75, 9.52, 11.84 and 14.67 μ.

The sodium carbonate extracts were combined and acidified to *p*H 1 with concentrated hydrochloric acid. The oil which separated was removed, and the aqueous solution was extracted with five 200-ml. portions of toluene. The oil and the toluene extracts were combined and dried over anhydrous magnesium sulfate. After removal of the toluene by distillation at reduced pressure, the oily residue was distilled, 8.5 g. of the nitro ester being recovered in this way.

The dried xylene solution was passed through a column containing 350 g. of activated alumina. Development of the column with benzene and ether resulted in the elution of a yellow substance. The eluate was dried over anhydrous magnesium sulfate, and the solvent was removed by distillation, yielding 10.2 g. (43%) of a yellow crystalline solid melting at 125–126°. Recrystallization from carbon tetrachloride produced material melting at 126.0–126.8° after a change in crystal structure over the range 120.8–121.5°. Recrystallization of a small sample from a mixture of benzene and cyclohexane produced material sufficiently pure for analysis, m.p. 128–128.5°. The ultraviolet spectrum showed absorption at the following λ_{max}^{EtOH} (log ε): 212 mμ (4.38), 276 (3.86), 284 (3.79), 393 (3.93). The principal infrared absorption bands ($CHCl_3$) occur at 2.93 (indole N–H), 3.30, 3.33, 4.45 (C≡N), 5.82 (C=O), 6.16, 6.27, 6.33, 6.57, 6.67, 6.82, 6.89, 7.01, 7.30, 7.50, 7.68, 8.05, 8.75, 9.02, 9.34, 9.72, 9.83, 11.05 and 11.60 μ.

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97; mol. wt., 312; OC_2H_5, 28.86. Found: C, 65.42; H, 5.44; N, 8.82, mol. wt. (Rast), 305; OC_2H_5, 28.00.

Methylation of $C_{17}H_{16}N_2O_4$.—To a solution of about 50 mg. (2 millimoles) of sodium in 25 ml. of absolute ethanol at 0° was added 550 mg. (1.75 millimoles) of $C_{17}H_{16}N_2O_4$. The yellow solid dissolved instantly, producing a clear, deep ruby solution. Methyl iodide (2.5 g., 18 millimoles) was added, and the solution was swirled to ensure thorough mixing, then allowed to stand at 0° for 15 minutes. The ruby solution was heated under very gentle reflux for 45 minutes, during which time the color changed gradually to a light yellow. The solution was concentrated to dryness, and the yellow solid remaining was treated with ether. Most of the material was soluble in ether, but there remained a white solid insoluble in ether, but soluble in water. The ether solution was concentrated to dryness, and the residue was recrystallized from cyclohexane, yielding 490 mg. (86%) of a yellow crystalline solid, m.p. 75–79°. Successive recrystallizations from cyclohexane produced material melting at 80.8–81.4°. A small sample was further recrystallized to analytical purity. The ultraviolet spectrum showed absorption at the following λ_{max}^{EtOH} (log ε): 218 mμ (4.55), 278 (4.00), 399 (4.12); and was qualitatively similar in shape to that of $C_{17}H_{16}N_2O_4$. The principal infrared absorption bands ($CHCl_3$) occur at 3.30, 3.35, 4.47 (C≡N), 5.84 (C=O), 6.20, 6.30, 6.35, 6.55, 6.80, 6.90, 7.02, 7.20, 7.32, 7.52, 7.70, 8.04, 8.58, 8.80, 9.10, 9.35, 9.56, 9.72, 11.20 and 11.63 μ. No absorption occurred in the N–H stretching region.

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.09; H, 5.37; N, 8.49.

Hydrogenation of $C_{18}H_{18}N_2O_4$.—A solution of 15 mg. (0.046 millimole) of $C_{18}H_{18}N_2O_4$ in 95% ethanol containing 15 mg. of 5% palladium-on-charcoal as a catalyst was hydrogenated at atmospheric pressure at room temperature. The compound took up 1.6 moles of hydrogen in 18 hours. The catalyst was removed by filtration and the filtrate was concentrated to dryness yielding a pale yellow viscous oil. The oil was dissolved in benzene and submitted to chromatography on alumina. Benzene eluted the principal product which appeared as a yellow band on the column. The benzene solution was concentrated to dryness, and the residue was dissolved in 95% ethanol, the solution being brought to a total volume of 500 ml. The ultraviolet spectrum was qualitatively similar to that of indole, showing absorption at the following λ_{max} (optical density): 220 mμ (1.31), 284 (0.24), 294 (0.20). The principal infrared absorption bands ($CHCl_3$) occur at 3.30, 3.35, 3.42, 4.46 (C≡N), 5.80 (C=O), 6.18, 6.44, 6.78, 6.90, 7.31, 7.51, 7.69, 7.97, 8.50, 8.65, 9.13, 9.39, 9.83 and 11.65 μ. No absorption occurs in the N–H stretching region, and the absorption in the double bond region (6.0–6.6 μ) is markedly weaker than that in $C_{18}H_{18}N_2O_4$.

α-Cyanogramine Picrate.—A solution of 1.035 g. of α-cyanogramine in 20 ml. of absolute ethanol and a solution of 1.124 g. of picric acid in 20 ml. of absolute ethanol were filtered and mixed. A bright yellow precipitate formed immediately. The flask was stoppered and allowed to stand for 2 days, during which time partial crystal formation occurred. The precipitate was collected on a filter and washed several times with previously filtered absolute ethanol (*ca.* 150 ml.). The washed crystals were dried in an Abderhalden apparatus and submitted for analysis (m.p. 242–243°).

Anal. Calcd. for $C_{18}H_{16}N_6O_7$: C, 50.47; H, 3.76; N, 19.62. Found: C, 51.67; H, 3.86; N, 17.64.

As indicated below, recrystallization from ethanol caused the decomposition of this picrate; the analysis serves only to show that it is a monopicrate rather than a dipicrate.

Dimethylamine Picrate from α-Cyanogramine.—A solution of 0.102 g. (0.509 millimole) of α-cyanogramine in 5 ml. of absolute ethanol was mixed with a solution of 0.117 g. (0.510 millimole) of picric acid in 5 ml. of ethanol. Upon mixing the solutions, a yellow crystalline solid separated. The suspension was heated to boiling and allowed to cool. Solution of the picrate did not occur. The yellow crystals were collected on a filter, m.p. 237.5–241°, then treated with 50 ml. of boiling ethanol. The crystals dissolved slowly. When solution had occurred, the yellow solution was concentrated to a volume of 5 ml. under a stream of nitrogen and then allowed to cool. The yellow crystals which formed melted at 149–154°. Recrystallization in the same manner from ethanol yielded yellow crystals which melted at 161–163°, mixed m.p. with an authentic sample of dimethylamine picrate, 161.5–163°.

Reaction between α-Cyanogramine and Methyl Iodide.—A mixture of 2.28 g. (0.016 mole) of methyl iodide and 3.0 g. (0.015 mole) of α-cyanogramine in 10 ml. of absolute ethanol was allowed to stand at room temperature for 23 hours.

(19) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Co., New York, N. Y., 3rd ed., 1952, pp. 458, 546.

(20) C. E. Looney, W. D. Phillips and E. L. Reilly, THIS JOURNAL, **79**, 6141 (1957).

The solid which formed was collected on a filter and washed with 10 ml. of absolute ethanol followed by 10 ml. of absolute ether. Recrystallization from absolute ethanol yielded 2.38 g. (79%) of tetramethylammonium iodide, m.p. 241–270° dec.

Anal. Calcd. for $C_4H_{12}NI$: I, 63.1; N, 6.97. Found: I, 66.3; N, 7.04.

The ethanolic filtrate remaining after collecting tetramethylammonium iodide was concentrated to dryness, and the gummy residue was dissolved in ether. The ether solution was filtered, and the salt-free filtrate showed a greenish fluorescence. Concentration of the ether solution yielded a bright yellow gum which was not further investigated.

Attempts to suppress the disproportionation reaction by carrying out the methylation at low temperatures and in the presence of solid carbon dioxide were unsuccessful.

α-Cyano-3-piperidinomethylindole. Method A. The Strecker Reaction.—In a 50-ml. round-bottomed flask were placed, in the order named, 1.1 ml. of concentrated hydrochloric acid, 10 ml. of water, 3.1 g. (0.037 mole) of piperidine, 0.6 g. (0.012 mole) of sodium cyanide, 1.5 g. (0.010 mole) of indole-3-aldehyde and 10 ml. of 95% aqueous ethanol. The flask was closed with a lightly greased ground glass stopper, and the stopper was tightly secured with friction tape. The flask was immersed in a water-bath maintained at about 60° for 6 hours. At the end of the reaction period, the flask was cooled under the tap and its contents poured into 150 ml. of water. The product was collected on a filter, washed with water and air-dried. The yield of α-cyano-3-piperidinomethylindole was 2.4 g. (100%), m.p. 148–150°, with extensive decomposition, when introduced into the apparatus at 140°. Recrystallization from benzene caused no improvement in the melting point. The infrared spectrum of the compound in Nujol showed bands characteristic for the N–H bond of the indole nucleus (3.27 μ) and for the nitrile group (4.50 μ).

Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.46; H, 7.15; N, 17.32.

Method B. Amine Exchange with α-Cyanogramine.—A solution of 500 mg. of α-cyanogramine in 2 ml. of piperidine was heated under reflux in an atmosphere of nitrogen. After a period of about 2 hours the reaction mixture was concentrated to dryness. Addition of a few drops of low-boiling petroleum ether with stirring induced crystallization of the residue. The crystals were collected on a filter, then recrystallized from benzene. The resulting colorless crystals melted with extensive decomposition at 138–141° when introduced into the apparatus at 105°. A mixed melting point with authentic α-cyano-3-piperidino-methylindole, prepared by the Strecker reaction (method A), showed no depression. The infrared spectra of the compounds prepared by method A and by method B were identical.

3-Dimethylaminomethylene-3H-pseudoindole from α-Cyanogramine.—To a solution of 2.6 g. of α-cyanogramine in ether which had been freshly distilled from lithium aluminum hydride was added 100 ml. of a 0.1 *M* solution of triphenylmethylsodium in ether. The addition was complete in 6 hours, and after 30 hours, the suspension was filtered, and the clear filtrate was concentrated to dryness. The gummy residue was treated with absolute ether and the resulting solid material was filtered, yielding 1.3 g. (72%) of crude 3-dimethylaminomethylene-3H-pseudoindole, m.p. 149–160° (lit.[12] 152–154°). Recrystallization from benzene–cyclohexane yielded fine, pale orange needles. These needles appeared to be an intimate mixture of the pseudoindole and indole-3-aldehyde, the uniform crystal structure apparently being formed by cocrystallization. Under the microscope the two compounds of the mixture could be seen to melt independently. The pseudoindole melted at 155–160°, and at this temperature the crystal structure changed abruptly, revealing the characteristic crystal structure of indole-3-aldehyde mixed with the liquid pseudoindole. The crystals of aldehyde melted at 195–197°. Several recrystallizations from dry benzene failed to remove the aldehyde. The infrared spectrum of this sample was identical in all respects with that of 3-dimethylaminomethylene-3H-pseudoindole prepared according to Smith's procedure and also contaminated with approximately the same amount of indole-3-aldehyde. Both spectra are significantly different from the spectrum of pure indole-3-aldehyde.

Anal. Calcd. for a mixture of 58% 3-dimethylaminomethylene-3H-pseudoindole, $C_{11}H_{12}N_2$, and 42% indole-3-aldehyde, C_9H_7NO: C, 75.78; H, 6.11; N, 13.50. Found: C, 76.06; H, 5.83; N, 12.80.

Gramine from α-Cyanogramine.—An ether solution of 1.003 g. (5.04 millimoles) of α-cyanogramine was added over a period of 0.5 hour to a slurry of 0.134 g. (0.0134 equivalent) of lithium aluminum hydride in ether. The mixture was allowed to stand for 0.5 hour, then heated under reflux for 10 min. Ethyl acetate (2 ml.) was added to decompose the excess lithium aluminum hydride, and the ether solution was poured into a 5% aqueous solution of sodium hydroxide. The ether layer was separated and the aqueous layer was extracted several times with ether. The ether extracts were combined and dried over anhydrous magnesium sulfate, then filtered and concentrated to dryness. The solid residue was fractionally crystallized from benzene and petroleum ether, yielding about 0.1 g. of an unidentified solid and 0.75 g. (87%) of gramine, m.p. 129–131°, mixed m.p. with an authentic sample 130–132.5°. The aqueous solution remaining after extraction of the organic product with ether was titrated with a standard solution of silver nitrate, indicating the presence of 71% of the theoretical amount of cyanide ion.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

The Conversion of Alkyl Halides to the Next Higher Homologous Phosphonates[1]

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Two methods for the conversion of alkyl halides to phosphonates having an additional methylene group [$RX \rightarrow RCH_2PO(OR')_2$] are described.

The wide distribution of phosphate in biological systems and the specificity of action shown by many naturally occurring organic phosphates makes them interesting targets for chemotherapeutic approaches to anticancer, antiviral and antibacterial agents. For this reason we have been interested in preparing phosphonic acid analogs of bio-active organic phosphates.

Burger and co-workers have prepared theophyllinyl alkylphosphonic acids,[2a] phosphonic acid esters of ribose and glucopyranosyl purine derivatives,[2b] and the phosphonic acid analog of glucose-6-phosphate.[3] Jensen and co-workers also have been active in the synthesis of "phosphonate analogs of biologically important phosphate com-

(1) For the previous paper in this series see F. Kagan and R. D. Birkenmeyer, THIS JOURNAL, **81**, 3026 (1959).

(2) (a) J. R. Parikh and A. Burger, *ibid.*, **77**, 2386 (1955); (b) J. R. Parikh, M. E. Wolff and A. Burger, *ibid.*, **79**, 2778 (1957).

(3) B. S. Griffin and A. Burger, *ibid.*, **78**, 2336 (1956).