hydrogen had been taken up (2450 ml. corresponded to two molar equivalents of hydrogen), and further uptake was very slow. The catalyst was then separated and the filtrate was evaporated to dryness under reduced pressure, redissolved in acetone (25 ml.), and filtered to remove sodium hydroxide. Evaporation of the acetone gave 7.93 g. of crude crystalline 6-chloro-1,2,3,4-tetrahydroquinoline,[19] which was dissolved directly in 55 ml. of dry toluene. To this solution was added benzaldehyde (10.6 ml.) and glacial acetic acid (1 ml.), and the mixture was allowed to reflux 41 hr. under a Dean–Stark trap. The toluene was removed under reduced pressure and the residue was extracted with four 50-ml. portions of hot *n*-heptane. The heptane extracts yielded 9.56 g. of dark sirup, of which 1.03 g. was dissolved in benzene and chromatographed on 33 g. of Woelm alumina (activity I). From the later 1:10 ether–benzene fractions and the pure ether fractions 256 mg. of crude crystalline 3-benzyl-6-chloroquinoline was obtained. An analytical sample, recrystallized four times from ether, had m.p. 91.5–92°. The yield, based on the weight of 6-chlorotetrahydroquinoline, was 20%.

Anal. Calcd. for $C_{16}H_{12}NCl$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.90; H, 4.80; N, 5.57.[20]

The ultraviolet spectrum of the product [λ_{max} 265–270 (unresolved multiplet), 296, 302, 309, 315, 323 mμ, ϵ_{max} 4350, 3140, 2750, 4030, 3140, 5950] closely resembled that of 6-chloroquinoline [λ_{max} 272 (broad), 292, 298, 306, 312, 319 mμ, ϵ_{max} 4300, 2950, 2500, 3300, 2600, 4400].

4-Benzylisoquinoline.—A solution of 5.00 g. of 1,2,3,4-tetrahydroisoquinoline (Eastman White Label) and 1.5 ml. of acetic acid in 80 ml. of dry toluene was heated at reflux for 48 hr. under a Dean–Stark trap. About 2 ml. of aqueous phase collected. Removal of solvent under reduced pressure left 13.5 g. of thick red oil, which was extracted with five 50-ml. portions of hot heptane. The heptane extract was allowed to stand overnight, then decanted from precipitated gums and decolorized with charcoal. Evaporation under reduced pressure left 5.68 g. of yellow oil which partially crystallized. Crystalline material, washed with ether and recrystallized from acetone, had m.p. 119.5–120°. Authentic 4-benzylisoquinoline, prepared in 3.7% yield by a small-scale adaptation of the method of Avramoff and Sprinzak,[21] had m.p. 119.5–120° after three recrystallizations from acetone. A mixture melting point was undepressed, and the infrared spectra of the two samples potassium bromide disk) were superimposable.

The ultraviolet spectrum of 4-benzylisoquinoline had λ_{max} 265 (sh), 274, 285, 298, 310, 318, 323 mμ, ϵ_{max} 4480, 5130, 4270, 2070, 3910, 3870, 5480. A homogeneous sample of the decolorized reaction mixture exhibited the three longest wave length bands, from which it was determined that 4-benzylisoquinoline was produced in 34% yield from tetrahydroisoquinoline. About one third of the material was collected crystalline and ether-washed.

N-Benzyl-1,2,3,4-tetrahydroisoquinoline (3.87 g.), prepared from tetrahydroisoquinoline and benzyl chloride in pyridine solution, was treated with benzaldehyde (4 ml.) and acetic acid (1.5 ml.) in precisely the same manner as described above for tetrahydroisoquinoline. No water collected in the Dean–Stark trap, and recovery of the N-benzyl derivative was quantitative. The infrared spectrum of N-benzyltetrahydroisoquinoline (chloroform solution) exhibited a number of strong bands absent from the spectrum of 4-benzylisoquinoline. In particular, the band at 2800 cm.$^{-1}$ has intensity proportional to concentration. From this it was determined that N-benzyltetrahydroisoquinoline constituted no more than 6% of the noncrystalline portion of the decolorized reaction mixture of tetrahydroisoquinoline and benzaldehyde, and was thus formed in less than 3% yield in that reaction.

1,2,3,4-Tetrahydroquinoline and Benzaldehyde.—Treatment of tetrahydroquinoline with benzaldehyde under the conditions affording 4-benzylisoquinoline from tetrahydroisoquinoline gave only polymeric material. When the heating period was decreased to 15 hr. a small amount (less than 5% of the initial weight of tetrahydroquinoline) of crystalline material was isolated from the heptane extract. It was recrystallized from acetone and, on the basis of its melting point (151–152°) and infrared spectrum (N–H band at 3440 cm.$^{-1}$ in carbon tetrachloride solution) was assigned the same structure as Einhorn's compound[16] (6,6′-benzalbistetrahydroquinoline, m.p. 152–153°).

Spectra.—Ultraviolet spectra in 95% ethanol were determined using the Cary Model 14 recording spectrophotometer.

Acknowledgment.—The authors are grateful to Dr Cope for assistance in completing this project.

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[19] J. von Braun, A. Petzold, and J. Seeman, *Ber.*, **55**, 3779 (1922).

[20] Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.

[21] M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 4090 (1956).

The Reaction of Chloroacetaldehyde with Cyanide Ion in Aqueous Medium

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Received October 15, 1962

When an aqueous solution of chloroacetaldehyde (I) is added to an excess of aqueous sodium cyanide at 0°, 2-chloro-1-cyanoethyl acetate (II) is obtained in 90% yield. A study of this reaction indicates that the cyanohydrin of I dehydrohalogenates to acetyl cyanide, which then acetylates the conjugate base of more cyanohydrin to yield II.

Introduction

The reaction of an equimolar quantity of an aldehyde with cyanide ion in water normally will give the conjugate base of the corresponding aldehyde cyanohydrin. However, certain aldehydes have been shown to undergo reactions in the presence of cyanide ion which do not lead to cyanohydrins. The best known and most thoroughly studied example of what may be termed an atypical reaction of an aldehyde with cyanide ion is the benzoin condensation. In this reaction the cyanide ion sufficiently increases the acidity of the hydrogen of the —CHO group by converting the aldehyde to a mixture of cyanohydrin and its conjugate base so that this aldehydic hydrogen now alpha to a nitrile becomes easily removable in the presence of a base.[1] This appears to be a crucial step in the formation of a benzoin from the corresponding aldehyde.

The rearrangement of β-formyl acrylic acid to succinic acid has also been shown to be cyanide ion-catalyzed.[2] The proposed mechanism as in the benzoin condensation again incorporates the ability of the cyanide ion to increase greatly the acidity of the hydrogen of the —CHO group.

The interesting cyanide ion-catalyzed decomposition of β,β-dicarbethoxypropionaldehyde into diethyl malonate and ethyl acetate is another example of a reaction whose mechanistic explanation depends on the increased acidity of the aldehydic hydrogen. In this latter case the anion formed fragments to give a more stable anion; the aldehyde is converted to an ester.

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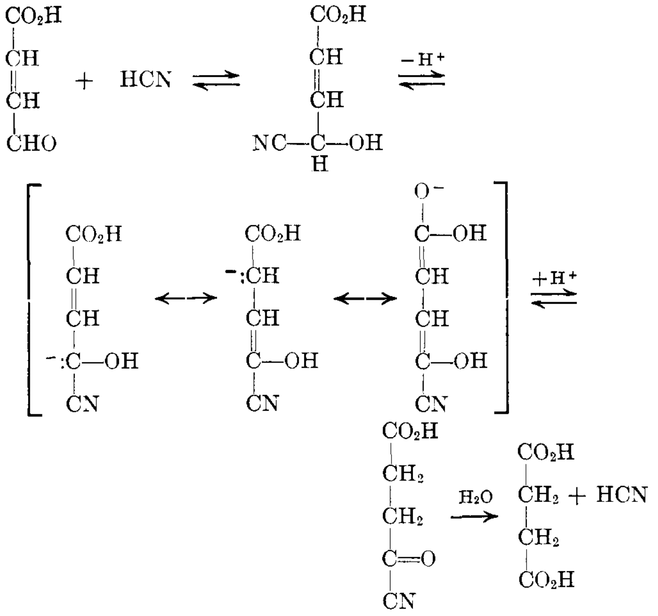
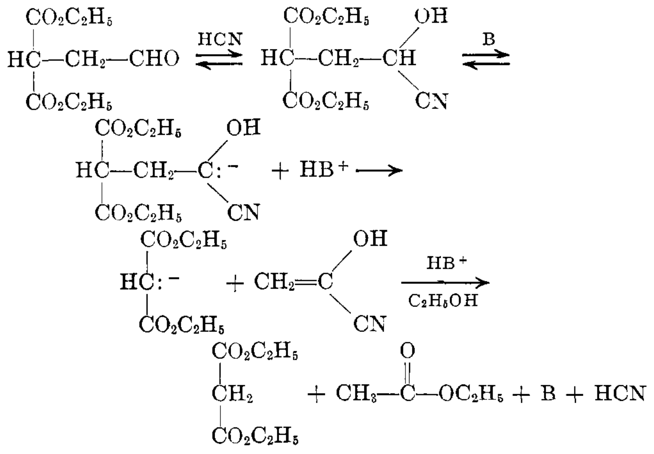
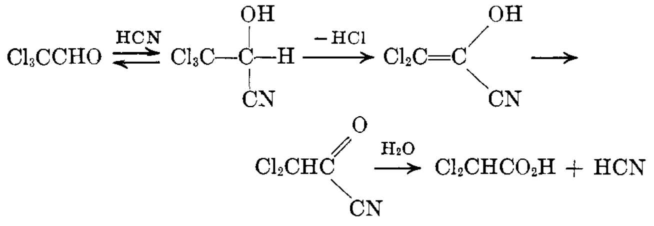
[1] For pertinent references see J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 257.

[2] V. Franzen and L. Fikentsher, *Ann.*, **623**, 68 (1959).





As early as 1873[3,4] it was observed that cyanide ion caused α-chloroaldehydes to undergo unusual reactions. In aqueous solution these aldehydes were converted to acids containing one less chlorine atom in the alpha position by the action of cyanide ion. The most thoroughly studied reaction of this type is the cyanide ion-catalyzed transformation of chloral to dichloroacetic acid.[5] The mechanism generally accepted today was proposed, along with an alternate route, almost fifty years ago.[6] In 1931, Lapworth argued convincingly by analogies for the mechanism now favored.[7] Again, as in the previous examples, a necessary step in the postulated mechanism is the cyanide ion's ability to labilize the aldehydic hydrogen.



$$Cl_3CCHO \underset{}{\overset{HCN}{\rightleftharpoons}} Cl_3C{-}C(OH)(H)(CN) \xrightarrow{-HCl} Cl_2C{=}C(OH)(CN) \longrightarrow Cl_2CHC(=O)CN \xrightarrow{H_2O} Cl_2CHCO_2H + HCN$$

However, this mechanism has not been fully verified in spite of recent work projected toward this goal. Fodor and Katritzky[8] showed that, when chloral deuteriohydrate reacts with sodium cyanide in deuterium oxide, no CH is found in the product, dichloroacetic acid. This indicates that, if an epoxide intermediate is formed, it cannot rearrange to dichloroacetyl cyanide by an intramolecular hydride shift. However, an epoxide intermediate is not ruled out.

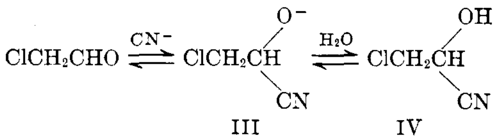
In 1958 another mechanism was proposed for this reaction but later experimentally refuted.[9,10]

We have now found another unusual aldehyde–cyanide ion reaction. When aqueous chloroacetaldehyde is added slowly to an aqueous solution of sodium cyanide at 0°, a 90% yield of 2-chloro-1-cyanoethyl acetate is isolated.[11] A mechanism for this reaction is proposed which is consistent with the experimental evidence to be presented.

Results and Discussion

Addition of aqueous chloroacetaldehyde to an equimolar or preferably excess aqueous sodium cyanide solution, as in the preparation of a cyanohydrin, gives an unexpectedly vigorous exothermic uncontrollable reaction which finally leads to a black tarry mass. With proper temperature control, however, and slow addition of chloroacetaldehyde, the major product isolated is not acetic acid, as one might anticipate, but 2-chloro-1-cyanoethyl acetate (II) in 90% yield along with the cyanohydrin of I in 8% yield and a very small amount of acetic acid (<2%). Starting material I is thus roughly 100% accounted for. On a 0.10-molar scale the reaction can be completed in less than five minutes; the acetate begins to separate as a light yellow oil after about half of I has been added if the reaction temperature is kept at 0°. A sample of II prepared from the reaction of acetic anhydride with 3-chlorolactonitrile had an infrared spectrum, boiling point, refractive index, and n.m.r. spectrum identical with II prepared by the reaction studied.

Strong evidence in the literature supports the formation of a cyanohydrin as the initial step in this reaction. It is a fact well documented that the carbonyl–cyano-



$$ClCH_2CHO \overset{CN^-}{\rightleftharpoons} \underset{\text{III}}{ClCH_2CH(O^-)(CN)} \overset{H_2O}{\rightleftharpoons} \underset{\text{IV}}{ClCH_2CH(OH)(CN)} \qquad (1)$$

hydrin equilibrium is a very rapid reaction for simple aldehydes, especially in the presence of base.[12] The pH of the aqueous cyanide ion solution is approximately

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[3] O. Wallach, *Ber.*, **6**, 114 (1873).

[4] F. D. Chattaway and H. Irving, *J. Chem. Soc.*, 1038 (1929).

[5] A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 181.

[6] A. Kötz and K. Otto, *J. prakt. Chem.*, **88**, 531 (1913).

[7] W. Cocker, A. Lapworth, and A. T. Peters, *J. Chem. Soc.*, 1382 (1931).

[8] G. Foder and A. R. Katritzky, *Chem. Ind.* (London), 1530 (1961).

[9] The suggestion was made (D. J. Cram and G. S. Hammond, "Organic Chemistry," J. Wiley and Sons, Inc., New York, N. Y., 1959, p. 255) that a necessary step may be incorporation of cyanide ion onto the product in the chloral transformation. A subsequent rebuttal was based on ^{14}C experiments.[10] However, it should be noted that the chloral transformation to dichloroacetic acid is published in "Organic Syntheses," ref. 5. Only a *catalytic amount* of cyanide ion is used.

[10] C. Rosenblum, C. Taverna, and N. L. Wendler, *Chem. Ind.* (London), 718 (1960).

[11] R. M. Nowak, U. S. Patent 2,915,549 (December 1, 1959).

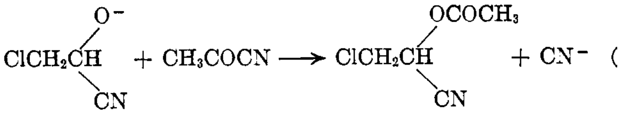
[12] Some pertinent references discussing the rate of the carbonyl–cyanohydrin equilibrium are: A. Lapworth, *J. Chem. Soc.*, 995 (1903); 2533 (1928); W. J. Jones, *ibid.*, 1560 (1914); J. W. Baker and M. L. Hemming, *ibid.*, 191 (1942).

12. Under these conditions chloroacetaldehyde cyanohydrin (IV) will form in a few seconds.

It was shown that IV can be formed easily and swiftly in 85% yield under nonbasic conditions by adding aqueous sodium cyanide to an equimolar solution of I and acetic acid in water. Here the pH of the solution never gets more basic than pH of 5.3. It was also shown that when IV was slowly added to an aqueous sodium cyanide solution at 0°, acetate II was formed in 90% yield. The reaction proceeded at an equivalent rate but much less exothermally than in the preparation of II from I. About 8% cyanohydrin was also reisolated. When IV reacted in ether at 20° with an equimolar quantity of triethylamine, dehydrohalogenation occurred smoothly over a sixty-minute interval, as evidence by the precipitation of triethylamine hydrochloride. Three products were isolated. They were α-acetoxyacrylonitrile (V) (66% yield), II (6% yield), and 1,1-dicyanoethyl acetate (VI) (12% yield). Compound V arises from dehydrochlorination of II formed during the reaction. This dehydrochlorination was studied under the same reaction conditions. An 80% yield of V was obtained from II at 30° within sixty minutes using triethylamine as base.[13] Both V and II were expected products. However, VI was the most interesting of the three products for its isolation is a strong indication that acetyl cyanide (VII) is present in the solution. It is well known that acetyl cyanide can be made to dimerize under the conditions used to yield VI.[14]

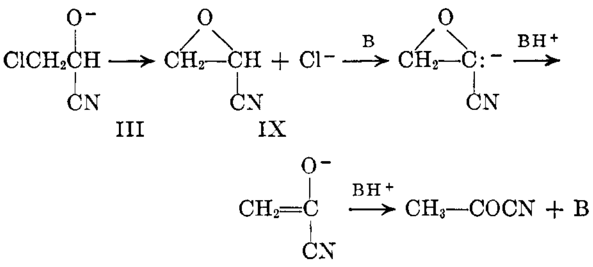
It is concluded from the above work that the reaction proceeds through the cyanohydrin and that another possible intermediate is VII.

The assumption that acetyl cyanide is an intermediate in the reaction was next tested. Bartlett has shown that VII solvolyzes rapidly in methanol.[14] In fact VII is almost as reactive an acylating agent as acetyl chloride or acetic anhydride. If VII is an intermediate in the reaction, path 2 should be a general reaction for the formation of 1-cyanoalkyl acetates from aldehydes. This we have found to be true. This reaction was tried with acetaldehyde. An equimolar quantity of VII was added slowly to an aqueous solution of acetaldehyde and excess sodium cyanide. The same time and temperature interval as in the studied reaction to produce II was followed. A 92% yield of 1-cyanoethyl acetate (VIII) was isolated along with 5% cyanohydrin. The use of chloroacetaldehyde in this reaction gives no useful information regarding path 2 since I in the presence of sodium cyanide forms II without addition of VII.



$$\mathrm{ClCH_2CH(O^-)(CN)} + \mathrm{CH_3COCN} \longrightarrow \mathrm{ClCH_2CH(OCOCH_3)(CN)} + \mathrm{CN^-} \quad (2)$$

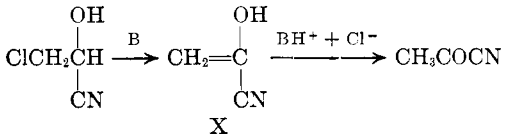
If VII is an intermediate, as the above reaction strongly suggests, there are two logical paths to its formation. One possibility is through an epoxide intermediate.



(3)

To test this hypothesis glycidonitrile (IX) was prepared by the method of Payne.[15,16] Glycidonitrile then was added to an aqueous solution of sodium cyanide and acetaldehyde. If IX is an intermediate in the reaction, VIII should be formed. No VIII could be isolated. A small amount of IX was recovered on work-up along with a trace of an unidentified liquid. Even allowing the reaction to proceed twice as long as the chloroacetaldehyde cyanide reaction did not destroy all the IX. Glycidonitrile was next added to an aqueous sodium cyanide solution to determine whether under reaction conditions similar to that used to form II, acetic acid would form as would be anticipated if IX rearranged to VII. The reaction mixture was not analyzed for products. Instead Duclaux values were run on the acidified reaction mixture. Potentiometric titration of the distillate indicated that no acetic acid had been formed. Path 3 is therefore eliminated as the major source of VII.

A second possible path to VII is *via* dehydrohalogenation of IV followed by tautomerization. Support for this proposal was obtained by running the studied reaction in deuterium oxide.



$$\mathrm{ClCH_2CH(OH)CN} \xrightarrow{B} \underset{\mathrm{X}}{\mathrm{CH_2{=}C(OH)CN}} \xrightarrow{BH^+ + Cl^-} \mathrm{CH_3COCN} \quad (4)$$

Due to the difficulty of preparing anhydrous I, a concentrated aqueous solution was used instead. When diluted with deuterium oxide, the solution contained 0.17, 0.30, and 1.2 moles of I, water, and deuterium oxide, respectively. This solution was added to a solution of 0.17 mole of sodium cyanide and 1.3 moles of deuterium oxide. Deuterium content in purified II was analyzed by mass spectrometry.

It was first shown by mass spectrometry that II does not exchange with deuterium oxide under the reaction conditions, so that any deuterium found in II must have entered before or during the reaction. Any exchange of starting material before dehydrohalogenation should fortunately show up in the chloromethyl group of II. The deuterium data in Table I show that only 9.6% of the chloromethyl groups contain deuterium, indicating that exchange of I before the formation of II was not rapid. However, 55% of the methyl groups of II were found to contain at least one deuterium.

It can be shown easily that while the deuterium found in the chloromethyl group is a statistical distribution based on simple exchange of $\mathrm{ClCH_2}$— with solvent, the

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[13] Heinrich Lange, U. S. Patent 2,266,771 (July 29, 1939).

[14] Bartlett states that acetyl cyanide is an active acetylating agent rapidly hydrolyzed by water. In methanol at room temperature the carbonyl absorption for the cyanide at 331 mμ is half gone in 40 sec. In water, hydrolysis is even faster. In a highly basic aqueous solution its hydrolysis must be exceedingly fast; see P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.*, **78**, 5575 (1956).

[15] G. B. Payne, *ibid.*, **81**, 4901 (1959).

[16] We gratefully acknowledge a sample of glycidaldehyde supplied by G. B. Payne of the Shell Development Company, Emeryville, Calif. We also heartily agree with Dr. Payne when he points out the *violent decomposition* that glycidaldehyde oxime will undergo if left to stand at room temperature for much longer than 1 hr.

TABLE I

MASS SPECTROMETRY ANALYSIS OF 2-CHLORO-1-CYANOETHYL ACETATE PREPARED IN DEUTERIUM OXIDE[a]

Ion	Parts[b]	Ion	Parts[b]
$ClCH_2\overset{+}{C}HCN$	100	CH_3CO^+	100
$ClCHD\overset{+}{C}HCN$	10	CH_2DCO^+	110
$ClCD_2\overset{+}{C}HCN$	0.6	CHD_2CO^+	13

[a] See ref. 17. [b] Each undeuterated moiety has been arbitrarily set equal to 100.

deuterium in the methyl group is far from that predicted by exchange with solvent.

The deuterium data are consistent with a mechanism shown by paths 1 followed by 4, then 2, with the following stimulations: dehydrohalogenation must be either a concerted mechanism or loss of chloride ion must at least be fast enough so as not to allow exchange of the aldehydic hydrogen (this means that the deuterium content found in the $ClCH_2\overset{+}{C}HCN$ moiety is also found in X before tautomerization); acetylation of III by VII must be rapid compared to exchange with solvent or enolization; and a deuterium isotope effect of 8.3 is encountered presumably at the tautomerization step.[18,19] This isotope effect is consistent with what is known about deuterium isotope effects at a carbon adjacent to a carbonyl in the presence of strong base.[20] Table II compares the observed values for deuterium distribution in the methyl group and the values predicted based on the proposed mechanism.

TABLE II

OBSERVED AND PREDICTED DEUTERIUM CONTENT IN THE METHYL GROUP

Ion	Observed, %[a]	Predicted, %
CH_3CO^+	44.8	44.8
CH_2DCO^+	49.4	50.1
CHD_2CO^+	5.8	4.8
CD_3CO^+	[b]	~0.3

[a] Calculations in this column are based on Table I. [b] A small peak at mass 46 could not be determined accurately due to the complexity of the cracking pattern, but is consistent with <0.5% CD_3CO^+.

To obtain the predicted values in Table II, enol X with a deuterium distribution identical to the $ClCH_2\overset{+}{C}HCN$ moiety in Table I was calculated to pick up a ratio of hydrogen to deuterium such that the observed and predicted CH_3CO^+ moiety concentration in Table II coincided. The mono- and dideuterated moieties could then be compared with the observed results. The good agreement between observed and predicted values in Table II strongly supports the postulated mechanism.

To add further support to a concerted E2 elimination of hydrogen chloride rather than a two-step E2 elimination, a solution of acetaldehyde was allowed to exchange in a solution of deuterium oxide and sodium cyanide under conditions similar to which I was converted to II.[21] However, the reaction time was five times as long. Then acetyl chloride was swiftly added as a method of efficiently and rapidly isolating acetaldehyde cyanohydrin (XI). Ether extraction and fractionation gave a 20% yield of 1-cyanoethyl acetate. It was determined by n.m.r. spectroscopy that, while the methyl group from the acetaldehyde had become highly deuterated, 100-CD_3, 66.2-CHD_2, and 15.8-CH_2D for every 1.1-CH_3, neither the proton spectrum nor the deuterium spectrum gave the slightest indication that deuterium exchange had taken place at the aldehydic hydrogen. There was, as expected, no indication of exchange at the acetate methyl. This great difference in the rate of loss of proton from XI and from IV indicates that loss of hydrogen chloride from IV must follow a concerted E2 mechanism, that is, that carbanion formation cannot be the rate-determining step in loss of hydrogen chloride from IV. While XI would be expected to undergo exchange *via* a carbanion intermediate, if IV also passes through a carbanion intermediate the great acceleration in rate must be accounted for merely by the inductive effect of one β-chlorine atom. This is unreasonable, as Pearson has pointed out.[22] Rather, a proton is removed from IV with greater ease due to the simultaneous departure of the chloride ion and double bond formation.

Experimental[23]

3-Chlorolactonitrile (IV).—To 588 g. (3.0 moles) of 40% aqueous chloroacetaldehyde was added slowly 183 g. (3.05 moles) of glacial acetic acid. To this solution was added, keeping the temperature between −10° and +5°, 147 g. (3.0 moles) of sodium cyanide dissolved in 500 ml. of water. Stirring was continued 1 hr. after addition was complete. The cyanohydrin (IV) then was extracted with ether. The ether solution was

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(17) Mass spectrometry analysis of either the acetate or methyl ions might be expected to give the same results. This, however, was not the case. The $CH_3^+/CH_2D^+/CHD_2^+$ ratio was found to be 100/97/6.8, respectively. The discrepancy between the methyl and acetyl cations is assumed to be due to a deuterium isotope effect in the cleavage reaction during spectral analysis. The methyl cation should, therefore, be least accurate since the broken bond is closest to the methyl group. The ratio of peak heights of CH_3CO^+ to CH_3^+ is roughly 22 to 1 indicating CH_3CO^+ as the major cracking route. The acetyl cation was, therefore, accepted as giving the most reliable data.

(18) The temperature varied from −10 to 0° during the experiment and the ratio of water to deuterium oxide (determined by n.m.r.) was known only to an accuracy of ±5%.

(19) A maximum isotope effect for the O–H bond at 0° is 12.6. See K. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

(20) Pocker found that CD_3CHO reacted 7.4 times slower than acetaldehyde in an aldol condensation; see Y. Pocker, *Chem. Ind.* (London), 599 (1959).

(21) While it is logical to postulate a concerted E2 elimination, since the carbanion formed by proton loss can be resonance stabilized by —C≡N, a two-step E2 elimination appears as a possibility. Pertinent references to the study of two-step *vs.* one-step E2 eliminations can be found in E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, N. Y., 1959, pp. 478–480.

(22) Weinstock, Bernardi, and Pearson have estimated that the inductive effect of a chlorine atom in the beta position of an ethyl ketone increases by roughly 15 times the rate of ionization of the chlorethyl over the ethyl ketone. Substitution of a —C≡N for the $\rangle$C=O would not be expected to change this value greatly even though $\rangle$C=O stabilizes the negative charge in the alpha position better than —C≡N; see J. Weinstock, J. L. Bernardi, and R. G. Pearson, *J. Am. Chem. Soc.*, **80**, 4961 (1958); R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953).

(23) Melting points and boiling points are uncorrected. The infrared spectra were run on a Beckman-IR5 infrared spectrophotometer. A modified Westinghouse 90° sector type magnetic mass spectrometer with a heated inlet was used. Gas chromatography was run on a 3-ft. by 0.25-in. stainless steel column packed with 15% Dow polyglycol E-4000 (polyethylene glycol; 4000 molecular weight) on 42/60-mesh acid-washed Chromosorb. A high carrier gas rate at 151° was used. N.m.r. 30-Mc. spectra were run on a high resolution n.m.r. spectrometer described by E. B. Baker and L. W. Burd, *Rev. Sci. Instr.*, **28**, 313 (1957). N.m.r. 60- and 9.2-Mc. spectra were run on a high resolution n.m.r. spectrometer described by E. B. Baker and L. W. Burd, *ibid.*, to be published. Line positions were measured with respect to a separate water sample by interchanging sample and reference.

dried, concentrated, and fractionated through a 12-in. Vigreux column to yield 225 g. (71%) of IV, b.p. 88–90° (2.5 mm.), $n^{35}\text{D}$ 1.4565. Infrared spectrum showed characteristic absorption at 3400 cm.$^{-1}$ and 2240 cm.$^{-1}$. N.m.r. spectrum at 30 Mc.: At a 20 volume % solution of IV in deuterium oxide, the —CH_2Cl protons are a slightly broadened doublet (splitting 5.0 ±0.1 c.p.s.) centered at −26.8 c.p.s. from the water reference. The CH proton is a pair of doublets (splittings of 4.8 and 5.2 c.p.s.) centered at +8.1 c.p.s. The unlike $>$CH—CH_2— splittings indicate strongly hindered rotation about this C—C bond. The —OH proton is a single line at −1 c.p.s. due to fast exchange with deuterium oxide. On the neat sample —OH exchange is much slower and OH/CH splitting of about 5 to 6 c.p.s. appears. The —OH proton lies at −1 c.p.s. and the CH at +8 c.p.s.

Anal. Calcd. for C_3H_4ClNO: C, 34.12; H, 3.79; Cl, 33.65; N, 13.27. Found: C, 34.42; H, 3.88; Cl, 33.54; N, 13.16.

2-Chloro-1-cyanoethyl Acetate (II) from Chloroacetaldehyde and Sodium Cyanide.—To a solution of 98 g. (1.95 moles) of sodium cyanide dissolved in 300 ml. of water was added slowly 389.5 g. (2.0 moles) of 39.3 ± 0.1% (aldehyde assay) aqueous chloroacetaldehyde. The temperature of the reactants was controlled between −10 and 0°. Addition time was 20 min. After an additional 5 min. of stirring, the solution was extracted with four 150-ml. portions of ether which were combined and dried over anhydrous sodium sulfate. After flashing the ether at 60° (20 mm.), 139 g. of a mixture of acetate (II) and cyanohydrin (IV) was obtained. N.m.r. indicated 8% cyanohydrin in the mixture while infrared with use of standards showed 7%. Fractionation gave a 90% yield of acetate (II), b.p. 65° (1 mm.), $n^{35}\text{D}$ 1.4355, along with 5–7% of IV. N.m.r. spectrum of pure I at 30 Mc.: CH_3CO (−76.0 ± 0.2 c.p.s.), $CH_2ClCCNO$ (doublet centered at −25.5 ± 0.2 c.p.s., splitting 5.0 ± 0.2 c.p.s.) and CHCNO (triplet centered at +24.3 ± 0.2 c.p.s., splitting 4.9 ± 0.2 c.p.s.). The spectrum is in complete agreement with II.

Anal. Calcd. for $C_5H_6ClNO_2$ (II): C, 40.68; H, 4.06; Cl, 24.07; N, 9.50. Found: C, 40.76; H, 4.11; Cl, 24.24; N, 9.62.

The aqueous layer remaining after ether extraction was acidified to pH 3 and continuously extracted with ether for 20 hr. The infrared spectrum of the product after removal of the ether was identical with acetic acid with the exception of a strong bond at 3450 cm.$^{-1}$ indicating the presence of water. N.m.r. was used to determine that the 13.5 g. of solution was a mixture of water and acetic acid in a mole ratio of 1.5 to 1. There was no indication in the n.m.r. spectrum of a $>CH_2$. Neutral equivalent calculated for the above mixture: 87; found: 86. Material balance based on 1.95 moles of chloroacetaldehyde is 1.76 moles of II plus 0.08 to 0.09 mole of IV plus 0.12 mole of acetic acid for a total of 1.97 moles of I accounted for.

2-Chloro-1-cyanoethyl Acetate (II) from 3-Chlorolactonitrile and Acetic Anhydride.—A mixture of 20 g. of cyanohydrin (IV), excess acetic anhydride, and 5 drops of pyridine was allowed to stand for 24 hr. Fractionation gave 24 g. (86%) of II. The infrared spectrum, refractive index, and b.p. of II were identical with II prepared from I and sodium cyanide in aqueous solution.

2-Chloro-1-cyanoethyl Acetate (II) Prepared in Deuterium Oxide.—Anhydrous chloroacetaldehyde is not only difficult to obtain but also difficult to store due to a great tendency to trimerize and polymerize. To avoid the problem of preparing a pure sample of I a 40% aqueous solution of I was continuously extracted with ether. The ether was then dried over sodium sulfate and concentrated. A 71% aqueous solution of I was obtained. This solution was shown by n.m.r. to contain 0.17 mole of chloroacetaldehyde and 0.30 mole of water. To this was added 1.2 moles of deuterium oxide. The resultant solution was added to a solution 0.17 mole of sodium cyanide dissolved in 1.3 moles of deuterium oxide. The reaction was run as described above with the exception that addition took only 1 min. and the product was extracted with ether just 9 min. later. The 2-chloro-1-cyanoethyl acetate isolated by fractionation was shown to be at least 99.8% pure by gas chromatography. Mass spectrometric analysis of this sample is tabulated in Table I.

Exchange of II in Deuterium Oxide–Sodium Cyanide Solution.—A sample of pure II was stirred in a solution of sodium cyanide–deuterium oxide. The concentration of each material approximated the concentration found in the preparation of II from I and cyanide. After 15 min. at 0° II was extracted with ether and fractionated. Infrared and refractive index indicated II had been recovered. Mass spectrometric analysis indicated that on the basis of 100 parts of $CH_3C{=}O^+$ and 100 parts of $C_3H_3NCl^+$ only 0.6 and 0.4 parts of $CH_2DC{=}O^+$ and $C_3H_2DNCl^+$, respectively, were found. Thus II does not significantly exchange under the conditions of the reaction.

Glycidonitrile (IX).—Prepared by the method of G. B. Payne, *J. Am. Chem. Soc.*, **81**, 4901 (1959).

***α*-Acetoxyacrylonitrile (V) *via* Dehydrohalogenation of 2-Chloro-1-cyanoethyl Acetate.**—To 295 g. (2.0 moles) of 2-chloro-1-cyanoethyl acetate in 2000 ml. of dry ether was added slowly 202 g. (2.0 moles) of triethyl amine diluted with 100 ml. of ether. The reaction temperature was kept below 30°. After addition, the solution which now contains a copious precipitate of amine hydrochloride was stirred an additional 6 hr. To the solution was added excess dilute aqueous hydrochloric acid to both dissolve the amine hydrochloride and neutralize any unreacted amine. Without a thorough acid wash the product will fractionate as an amber liquid instead of a colorless liquid. To the ether solution was added a pinch of *t*-butylcatechol as a polymerization inhibitor. The ether solution then was concentrated and fractionated through a 12-in. column packed with 0.25-in. Berl saddles to give 202 g. (91%) of V, b.p. 65° (12 mm.); $n^{35}\text{D}$ 1.4191. An 80% yield of V can be obtained if the reaction is run for only 1 hr. Identifying infrared absorption peaks are found at 2232, 1774, and 1636 cm.$^{-1}$. Other strong bands are found at 1370, 1190, 970, 923, 874, and 673 cm.$^{-1}$.

Anal. Calcd. for $C_5H_5NO_2$ (V); C, 54.05; H, 4.50; N, 12.61. Found: C, 54.28; H, 4.34; N, 12.39.

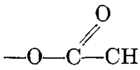
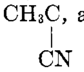
Dehydrohalogenation of 3-Chlorolactonitrile (IV) with Triethylamine.—To a stirred solution of 55 g. (0.55 mole) of triethylamine in 200 ml. of dry ether was added 53 g. (0.50 mole) of 3-chlorolactonitrile. After 15 min. the reaction became noticeably exothermic and a flocculant precipitate of amine hydrochloride began to form. The mixture was kept at 25° and stirred for a total of 1 hr. Water was added to dissolve the amine hydrochloride salts. The solution was acidified to pH 3 and extracted with ether. The ether was dried and then flashed to give 26 g. of a liquid which was examined by gas chromatography. Gas chromatography indicated 18.2 g. (66% of *α*-acetoxyacrylonitrile, 2.2 g. (6%) of II, and 4.2 g. (12%) of what was proved to be 1,1-dicyanoethyl acetate (VI). The over-all yield based on cyanohydrin was 84%. N.m.r. spectrum of VI at 30 Mc.: a sharp peak at −79 ± 0.5 c.p.s. and a broad peak at −83 ± 0.5 c.p.s.; m.p. 69.5–70.5° (69.4–70.2° reported by Bartlett[18]).

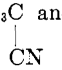
Anal. Calcd. for $C_6H_6N_2O_2$ (VI): C, 52.1; H, 4.35; N, 20.3. Found: C, 51.98; H, 4.21; N, 20.12.

1-Cyanoethyl Acetate (VIII).—To 200 ml. of water and 98 g. (2.0 moles) of sodium cyanide was added slowly 44 g. (1 mole) of acetaldehyde. Then, while the reaction temperature was kept at −10 to 0°, 94 g. (1.2 moles) of acetyl chloride was added dropwise with vigorous stirring. The addition reaction was very exothermic. After addition was complete stirring was continued for 2–3 min. To the solution was added 100 ml. of water to dissolve the sodium acetate. The product was extracted with ether and concentrated to give 113 g. (95% yield), $n^{35}\text{D}$ 1.3960 of crude product. Fractionation gave a 90% yield of VIII, b.p. 68° (8 mm.), $n^{35}\text{D}$ 1.3948. Infrared and n.m.r. spectra are consistent with VIII. If acetic anhydride is used instead of acetyl chloride, the yields are equally good. An excess of sodium cyanide is necessary for optimum yields. When equimolar cyanide and aldehyde was used, the yield of VIII was only about 55–65%.

Anal. Calcd. for $C_5H_7NO_2$ (VIII): C, 52.17; H. 4.35; N, 20.29. Found: C, 51.98; H, 4.21; N, 20.00.

Exchange Reaction of Acetaldehyde in Deuterium Oxide–Sodium Cyanide.—To a solution of 8.35 g. (0.17 mole) of sodium cyanide in 20 g. of deuterium oxide was added slowly at 0° 7.0 g. (0.16 mole) of acetaldehyde in 5 g. of deuterium oxide. The solution was kept between −10 and 0° for 25 min. Then 13.5 g. (0.2 mole) of acetyl chloride was added within a 2-min. interval. An oil formed almost immediately. The solution was twice extracted with ether. The combined ether fractions were concentrated and fractionated. A 20% yield of deuterated VIII was obtained. The major component was a high boiling residue probably arising from an aldol condensation. The infrared spectrum of this material was consistent with 1-cyano-3-acetoxybutyl acetate. This material was not further identified. Purified VIII from the reaction was studied with n.m.r.

The proton spectrum shows a large sharp peak at −180 c.p.s. due to nondeuterated  $-O-\overset{O}{\overset{\|}{C}}-CH_3$, a broad doublet at −212 c.p.s. due to partially deuterated  $\underset{CN}{\underset{|}{CH_3C}}$, and a broad triplet at +13 c.p.s. due to CH.

Spin decoupling at the D frequency of 9.211569 Mc. and high power sharpens both the CH_3C and  $\underset{CN}{\underset{|}{CH}}$. The CH_3 is separable into three doublets corresponding to CHD_2, CH_2D, and CH_3. These are shifted 1 c.p.s. from each other due to a small isotopic effect on the chemical shift. Their relative areas, on a molar basis, should correspond to the amounts of each present.

The CH is split by the deuterated methyls into a seven line pattern corresponding to 1/8 CH_3, 1/4 CH_2D, (1/2 CHD_2 + 3/8 CH_3), (CD_3 + 1/2 CH_2D), (1/2 CHD_2 + 3/8 CH_3), 1/4 CH_2D, and 1/3 CH_3. The integral curve gives on a normalized basis: 100 CD_3, 66.2 CHD_2, 15.8 CH_2D, ~1.1 CH_3. This corresponds well with the ratios 100 CHD_2, 47.7 CH_2D, 5.0 CH_3 in the CH_3 spectrum allowing for an apparent line shape assymetry.

The CH_3 spectrum shows no trace of a line near the center of the pattern which would be expected if there were any deuterium at the CH position.

The deuterium spectrum shows a large line due to the CD_3, CHD_2, and CH_2D and a small line near the deuterium oxide reference point. In the proton spectrum the CH_3 and CH are separated by 225 c.p.s. or 3.74 p.p.m. Multiplying 3.74 p.p.m. by the deuterium frequency of 9.211 Mc. we obtain 34.5 c.p.s. for the CD_3 to CD separation which is not near the position of the small line found. It is concluded that there is no CD in VIII and that the small line is probably deuterium oxide impurity.

Acknowledgment.—The author expresses his gratitude to Dr. J. P. Heeschen and Dr. E. B. Baker of The Dow Chemical Company who ran and interpreted the n.m.r. spectra, to Mr. R. S. Gohlke of The Dow Chemical Company who ran and interpreted the mass spectrometric analysis, and to Mr. R. A. Nyquist who helped interpret the infrared spectra. The author especially appreciates the helpful suggestions of Professor J. W. Crump of Albion College, Albion, Michigan.

Pteridines. I. Synthesis of Some 6-Alkyl-7-aminopteridines from Nitrosopyrimidines

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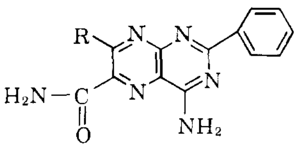
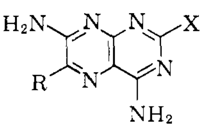
Received October 11, 1962

Compounds with methylenes activated by acyl groups react with 4,6-diamino-5-nitroso-2-phenylpyrimidine in the presence of sodium cyanide with incorporation of cyanide, loss of acylate, and cyclization to form 6-substituted 7-aminopteridines. The principles involved in this process were modified to permit the synthesis of six 6-alkyl-7-aminopteridines.

The diuretic activity displayed by 4,7-diamino-2-phenyl-6-pteridinecarboxamide (I) and related compounds[2] prompted us to undertake the synthesis for biological screening of a series of compounds bearing alkyl groups in the 6-position (III). Although a number of 6-aryl-7-aminopteridines (IV) have been prepared through condensation of arylacetonitriles with appropriate 4-amino-5-nitrosopyrimidines,[3] compounds of type III have not been reported. While the methylene group of an arylacetonitrile is sufficiently acidic to form an anion and react with a 4-amino-5-nitrosopyrimidine in the presence of basic catalysts, the α-methylene of a simple alkylnitrile cannot form an anion under similar conditions because it is a weaker acid than a 4-amino-5-nitrosopyrimidine. Reaction in the latter case therefore fails.

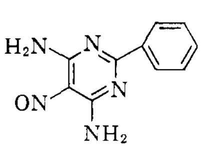


I. R = NH₂
II. R = phenyl

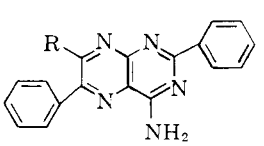


III. R = alkyl
IV. R = aryl

A solution to the problem of preparing compounds of type III came about in unexpected fashion. It was found that, although 4,6-diamino-5-nitroso-2-phenylpyrimidine (V) condenses with phenylacetaldehyde and phenylacetone in the presence of potassium acetate to give the pteridines VI and VII, the reactants condense in each case in the presence of sodium cyanide to give only the 7-aminopteridine (VIII). Compound VIII is also produced when V reacts with phenylacetonitrile in the presence of sodium cyanide.



V



VI. R = H
VII. R = CH₃
VIII. R = NH₂

In similar fashion, benzoylacetamide reacts with V in the presence of potassium acetate to produce 4-amino - 2,7 - diphenyl - 6 - pteridinecarboxamide (II). With sodium cyanide as the condensing agent, the reactants yield I.

In the synthesis of VIII from phenylacetaldehyde or phenylacetone, and in the synthesis of I from benzoylacetamide, an acyl group is lost and a nitrile incorporated at appropriate stages in the process. Kröhnke[4]

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[2] (a) J. Weinstock, U. S. Patent 2,963,478 (1960); (b) E. C. Taylor, U. S. Patent 2,963,479 (1960); (c) E. C. Taylor and J. Weinstock, U. S. Patent 2,963,480 (1960); (d) J. Grannells and J. Weinstock, U. S. Patent 2,963,481 (1960); (e) T. S. Osdene and E. C. Taylor, U. S. Patent 2,975,180 (1961).

[3] R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).

[4] F. Kröhnke, *Chem. Ber.*, **80**, 298 (1947).