Products from Cyanoethylation of 2-Octanone[1]

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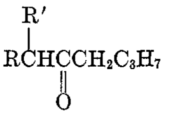
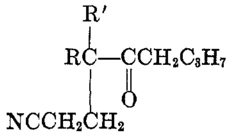
2-Octanone has been cyanoethylated with solid KOH as catalyst, in dimethoxyethane (DME) as reaction solvent, and with KOH solution in *tert*-butyl alcohol; both mono- and dicyanoethylated products have been examined. No product of cyanoethylatian in the terminal position (on methyl) could be detected. In DME as solvent, there were obtained 3-(β-cyanoethyl)-2-octanone (**3**) and a small amount of 3,3-bis(β-cyanoethyl)-2-octanone (**4**), but the principal product was **5** resulting from cyclization of **4**. In *tert*-butyl alcohol as solvent, under a variety of conditions, none of **4** could be isolated, only **3** and **5**. Mass spectrometry was of significance in establishing the structure of **5**, and interesting fragmentation patterns were observed. Acid-catalyzed hydrolysis of cyclic product **5** yielded none of the expected diketone, only an acidic product which proved to be the keto diacid which would result from hydrolysis of the open-chain keto dinitrile **4**. Acid-catalyzed methanolysis of **5** yielded an initial product whose structure was established as the hemiketal (**9**) of the keto nitrile which would result from hydrolysis of the imino group in **5**. This structure exhibits two hydroxyl absorptions and two carbonyl absorptions in the ir, one set of which is ascribed to the chelated structure possible when carbonyl and hydroxyl are cis to each other. Methanolysis of the intermediate hemiketal **9** to keto diester **8** proceeded much more rapidly with HCl catalysis than with H_2SO_4 catalysis. Among additional compounds reported in the literature which have two β-cyanoethyl groups on a single carbon, 1,1,1-tris(β-cyanoethyl)acetone has been examined by mass spectrometry and found to exist in a cyclic structure (**11**).

In an earlier investigation[2] in this laboratory, monocyanoethylation of unsymmetrical ketones of the general formula **1** was examined. That investigation



$$R\overset{R'}{C}H\underset{\underset{O}{\|}}{C}CH_2C_3H_7$$

1



$$R\overset{R'}{\underset{NCCH_2CH_2}{C}}-\underset{\underset{O}{\|}}{C}CH_2C_3H_7$$

2

was limited to a single solvent and catalyst system, a solution of potassium hydroxide in commercial *tert*-butyl alcohol. Dicyanoethylation products were not examined; indeed, the analytical devices then available were taxed to the limit in separation and identification of the isomeric monocyanoethylation products. Nevertheless, under the conditions employed, the evidence was convincing that cyanoethylation favors the more substituted isomer **2**, unless steric hindrance becomes sufficient to interfere with the substitution giving a quaternary carbon in the product. Extremes examined were 2-methyl-3-heptanone (**1**, $R = R' = CH_3$), which gave 87% of the monocyanoethylation product as structure **2**, and 6-ethyl-5-decanone ($R = C_4H_9$, $R' = C_2H_5$), which gave only 25% of structure **2**. Preference for substitution at the tertiary carbon was attributed to the greater acidity of the hydrogen at that position; however, under the equilibrium conditions used for the reactions in that investigation, preference for the more substituted position could result from lower energy of the more branched structure. If this latter explanation be correct, steric interference would still cause a shift to the less substituted side of the carbonyl group. In the careful investigations of House and coworkers,[3] the more substituted hydrogen has proved to be the more acidic as presumed by us;[2] however, the ratio of ions reported by these investigators[4] for open-chain structures was much less favorable to the more substituted hydrogen than observed by us[2] for cyanoethylation of 2-methyl-3-heptanone.

In follow-up of work begun[5,6] nearly twenty years ago, Jolly has recently[7] pointed out that the enormous basicity of potassium hydroxide can be realized, without loss of activity due to solvation of the hydroxide ion, by use of a suspension of solid potassium hydroxide in a nonhydroxylic solvent (rather than a solution of the base in a hydroxylic solvent). This increase may amount to considerably more than ten powers of ten; for example, in dimethyl sulfoxide as solvent, solid potassium hydroxide converts more than 90% of triphenylmethane to its anion. In view of our success in improvement of KOH-catalyzed cyanoethylations[8] by replacement of the long-used aqueous or alcoholic solvents[9] with solid KOH in DME, we have undertaken an investigation of the cyanoethylation of unsymmetrical ketones in DME as solvent and in *tert*-butyl alcohol as solvent. Large differences in results obtained in the two solvents have been observed for *n*-alkyl *sec*-alkyl ketones; however, other unexpected complications have caused us to confine the present report to cyanoethylation of a methyl *n*-alkyl ketone, 2-octanone.

In cyanoethylations of methyl *n*-alkyl ketones reported by Bruson and Riener,[9] a large preference for substitution at the secondary position was reported; however, the principal analytical device applied was isolation of a product obtained in dominant amount. More recently, House and Trost[4] examined the actual distribution of anions between the methyl and methylene positions in 2-heptanone, using potassium tri-

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[1] Grateful acknowledgment is made for support of this investigation by a grant from the Research Corporation. The high-resolution mass spectra were determined on a CEC 21-110B instrument provided by a departmental grant from the National Science Foundation.

[2] J. Cason and M. P. Chang, *J. Org. Chem.*, **21**, 449 (1956).

[3] H. O. House, *Rec. Chem. Progr.*, **28**, 98 (1967).

[4] H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

[5] W. L. Jolly, *J. Phys. Chem.*, **58**, 250 (1954).

[6] Early work by Cram and coworkers was directed toward the great increase in base strength of alkoxides in dimethyl sulfoxide as solvent; *e.g.*, D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Amer. Chem. Soc.*, **83**, 3688 (1961).

[7] W. L. Jolly, *Inorg. Chem.*, **6**, 1435 (1967); *J. Chem. Educ.*, **44**, 304 (1967).

[8] After some 25 years of futile efforts to discover the cause of erratic results in cyanoethylations (low yields, no reaction at all, etc.), we followed the recommendations of Professor Jolly and have obtained consistent, high-yield results by complete elimination of hydroxylated solvents. For cyanoethylation of 2-ethylhexanal, *cf.* J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry", 3rd ed, Prentice-Hall, Englewood Cliffs, N. J., 1970, pp 351, 355.

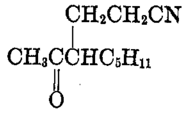
[9] Most procedures have derived from those reported by H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, **64**, 2850 (1942).

phenylmethide in DME. Under equilibrium conditions, as normally assumed to occur in Michael condensations, they reported that about 42% of the anion is terminal, *i.e.*, results from removal of hydrogen from methyl. In view of this ion distribution, we were surprised to discover that no evidence could be secured, in our investigations of 2-octanone, for any cyanoethylation on methyl, under a variety of experimental conditions. Both mono- and dicyanoethylation products were examined by gas chromatography. The components responsible for all peaks in the gc tracing amounting to more than about 1% of the total were collected and examined by mass spectrometry. In a Michael condensation with cyclic ketones, House and coworkers[10] also found a higher ratio of substitution in the more substituted position than expected from their studies of anion distribution. In this instance, however, the discrepancy was not large, and it seems reasonable to explain it, as they did,[10] by the more rapid loss in a second cyanoethylation of the product substituted at the secondary position. Only monocyanoethylation products were examined. In our work with 2-octanone, however, both mono- and dicyanoethylation products were examined, and there was no detectable amount of substitution on methyl in any product.

A plausible explanation of the large difference in substitution pattern between our cyanoethylations and the ion distributions reported[4] involves the large steric requirements of the bases used by House and coworkers, as well as the higher rate of reaction of the more substituted anion.[11] The base used by us, hydroxide, which is perhaps the smallest available, would give a very rapid removal of the more hindered but more acidic secondary hydrogen, much more rapid than would be observed in determination of kinetic acidity with the large base.[4] Rapid reaction of the anion with acrylonitrile would then give the observed preference for the methylene position, in the initial forward reaction. Our investigations of reversibility of the cyanoethylations, using *n*-alkyl *sec*-alkyl ketones, indicated essentially no reversal in *tert*-butyl alcohol, very slow reversal in DME. Evidence of the influence of the steric factor is also found in acid-catalyzed formation of enol acetates, as reported most recently by House and coworkers.[11] Whereas formation of enol acetates of 2-heptanone *via* the anions produced under equilibrating conditions with a large base gave about 58% internal acetates, acid-catalyzed formation of the enol acetates from the ketone and isopropenyl acetate yielded[11] about 84% internal enol acetates.

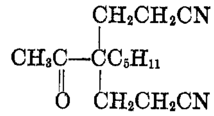
Even with severe discrimination in favor of the internal anion on account of use of a very small base, exclusive reaction of acrylonitrile at the internal position must also depend on a substantially higher rate of reaction of the more substituted anion. This higher rate of reaction at the more hindered position has been ascribed[11] to a decrease in state of aggregation of the enolates caused by the steric interference of additional branching. The decision that the obviously present hindrance would interfere with one reaction more than the other seems to us difficult to reach. On the other hand, especially in reaction with the minimally hindered acrylonitrile, hindrance at the secondary position rather than the primary one should not tend to greatly increase the energy at the transition state. The more branched *product* is of substantially lower energy, however, and, if the transition state is well along the reaction coordinate toward the product, then the substitution at the internal position should, indeed, have the lower-energy transition state, and this product would be formed at a higher rate. This explanation seems especially plausible in conjugate addition to a small linear, highly reactive molecule such as acrylonitrile.

When cyanoethylation was carried out with KOH catalysis in dry DME, only one monocyanoethylation product, **3**, was observed in gc and only one dicyanoethylation product, **4**. The largest peak in the gc tracing occurred at longer retention time than the peak from **4**, at the point where the alternate dicyanoethylation product was expected; however, the mass spectrum of the product responsible for this peak revealed that this is not the second dicyanoethylation product. As discussed subsequently, this principal product of the reaction proved to be cyclization product, **5**. Since **5** is formed by reaction of an anion of **4** (formula **6**), it might be presumed that use of *tert*-butyl alcohol as solvent, greatly decreasing the basicity of KOH, would lead to a larger yield of **4**, less further reaction to **5**. Experiment revealed that *none* of **4** could be detected with *tert*-butyl alcohol as solvent, whether after a few minutes of reaction time, a few hours, or overnight. Addition of increments of water to the *tert*-butyl alcohol also failed to yield any of product **4**. The principal effect of water addition was slowing of the rate of reaction, as would be expected on account of the decrease in basicity of hydroxide which results from solvation by water.



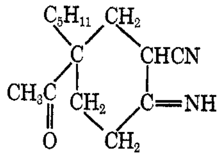
$$CH_3\underset{\underset{O}{\|}}{C}\overset{\overset{CH_2CH_2CN}{|}}{C}HC_5H_{11}$$

3

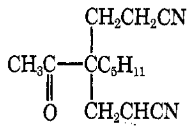


$$CH_3\underset{\underset{O}{\|}}{C}-\overset{\overset{CH_2CH_2CN}{|}}{\underset{\underset{CH_2CH_2CN}{|}}{C}}C_5H_{11}$$

4



5



$$CH_3\underset{\underset{O}{\|}}{C}-\overset{\overset{CH_2CH_2CN}{|}}{\underset{\underset{CH_2CHCN}{|}}{C}}C_5H_{11}$$

6

Actually, the rate of formation of ion **6** from dinitrile **4** is probably not directly involved in conversion of **4** to the cyclic product **5**, because ion **6** is the initial product of reaction of acrylonitrile with the anion of 3-(β-cyanoethyl)-2-octanone (**3**). Furthermore, less than 0.1 molar equiv of KOH was used for the reactions. It follows that appearance of **4** as a product of the reaction must depend on competitive reactions of anion **6** with some acidic species (such as 2-octanone) and intramolecular reaction to give an anion of the cyclic product **5**. Although use of the acidic *tert*-butyl alcohol as solvent increases the concentration of a possible reactant with ion **6**, it would also greatly reduce the basicity of this ion by solvation, an effect known to be quite large in the case of hydroxide ion.[7] This could increase the lifetime of anion **6** and thus increase the probability of its reaching the proper conformation for cyclization.

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[10] H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).

[11] H. O. House, M. Gall, and H. D. Olmstead, *ibid.*, **36**, 2361 (1971).

Given the proper conformation, reaction to give the six-membered ring should occur rapidly even with the solvated anion **6**. Alternate explanations may be evolved which depend on the fact that in DME an amount of the anion of **5** equivalent to the KOH consumed will be present at the conclusion of the reaction, whereas at least part of this anion would react with *tert*-butyl alcohol if it is present as solvent. Such explanations are discounted by the observation that increase of KOH to a full equivalent in *tert*-butyl alcohol solvent results in no appearance of dinitrile **4** in the reaction product. Excess of acrylonitrile also yields none of **4**.

The mass spectrum of the cyclic product, **5**, provided conspicuous evidence that this is not the alternate dicyanoethylation product, for the most abundant ion in the spectrum is *m/e* 43, and mass measurement showed it to be acetyl, CH_3CO. Of course cyanoethylation at methyl would obviate the possibility of acetyl as a cleavage product. The fragmentation pattern presented by this mass spectrum (*cf*. Table I) is unlikely to initially suggest the true structure; however, it bears no resemblance to an open-chain dicyanoethylation product such as **4**, in which the only ions in abundances greater than 17% are *m/e* 43 (100%), C_5H_{11} (71, 63%), and $C_9H_{12}N_2O$ from β cleavage (164, 54%). The very abundant ion at *m/e* 152 ($C_{10}H_{18}N$) would hardly be predicted, and it was especially surprising when the study of metastable ions revealed that the route to this highly abundant ion (152) is *via* initial loss of C_2H_2N (40), followed by loss of C_2H_2O (42). Nevertheless, analysis of the data reveals that the observed ions result from logical fragmentation pathways presented in part in Chart I.

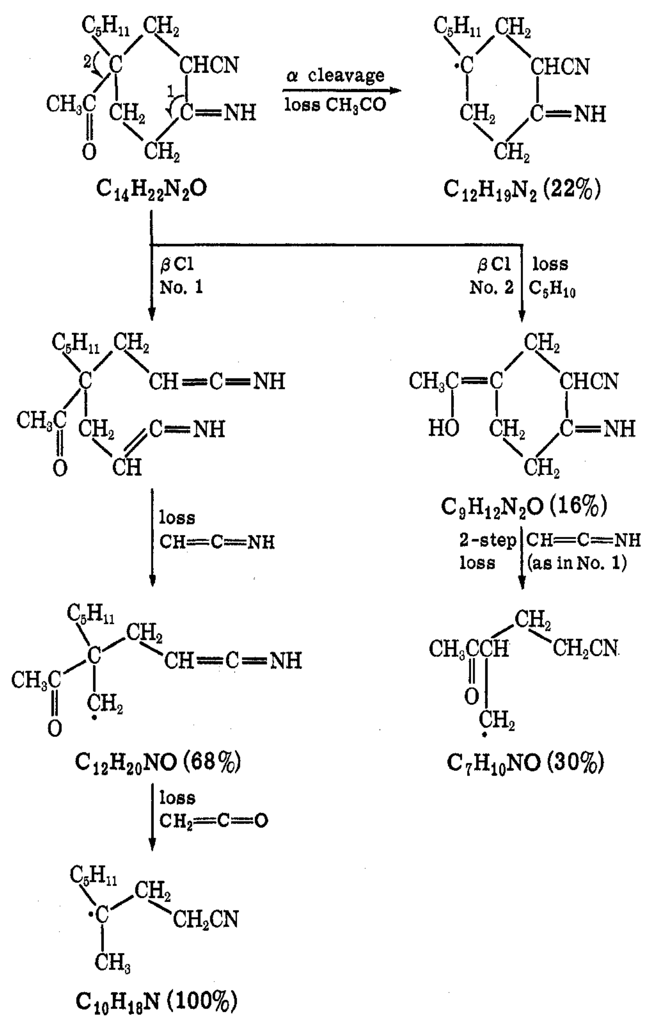
TABLE I

PARTIAL MASS SPECTRUM OF CYCLIZATION PRODUCT 5

Ion formula	Mass[a]	Per cent
CH_3CO	43	>100[b]
C_5H_9	69	20
C_5H_{11}	71	7
$C_6H_{10}N$	96	26
$C_7H_{13}O$	113	11
$C_7H_{10}NO$	124	30
$C_8H_{11}N_2$	135	14
$C_8H_{12}N_2$	136	11
$C_9H_{16}N$	138	4
$C_9H_{17}O$	141	5
$C_9H_{12}N_2$	148	13
$C_{10}H_{18}N$	152	100
$C_9H_{12}N_2O$	164	17
$C_9H_{12}N_2$	191	22
$C_{12}H_{20}NO$	194	68
$C_{14}H_{22}N_2O$ (M)	234	28

[a] All ions in this table were mass measured at high resolution by one of us (C. W. K.) on a CEC 21-110B instrument; *cf*. ref 1. [b] More meaningful comparisons with the fragmentation patterns from other structures, or spectra acquired on other instruments, become possible when the inordinately abundant ion of *m/e* 43 is not used as the base peak.

CHART I



It may be noted that the three initial cleavage reactions shown in Chart I involve one classical α cleavage (separation of the acetyl group) and two β cleavages which yield the most abundant ions. It is apparent that there are possible two additional β cleavages involving the carbonyl group, and these can lead (by fragmentations similar to those in β cleavages no. 1 and no. 2) to ions $C_9H_{17}O$ (*m/e* 141) and $C_9H_{16}N$ (*m/e* 138). The minor abundance of these ions is consonant with fragmentations consistently observed by us in cyanoethylation products from ketones. If the γ hydrogen which must rearrange in a β cleavage is also α to a cyano group, that β cleavage is quite minor or not observable at all (<1% in **4**). The loss of C_2H_2N in both prominent pathways initiated by a β cleavage is rather surprising, in that this might be presumed to be CH_2-CN, a logical fragment for loss from the open-chain product, **4**. In reality, this cleavage is absent or negligible in **4**: M − 40 (*m/e* 191) is only 2%, and M − 43 − 40 (*m/e* 151) is <1%. The loss of C_2H_2N from structure **5** becomes possible after a hydrogen is transferred by β cleavage at cyano. Subsequent bond rupture to lose CH=C=NH may be regarded as an extended α cleavage.

The minimal occurrence of a β cleavage involving rearrangement of hydrogen α to the imino structure depicted in **5** suggests that the imino structure is present, rather than the isomeric vinyl amine structure, **7**. This is contrary to observations reported[12] for the imine derived from an open-chain β-keto ester; however, spectral data also support structure **5**. Whereas

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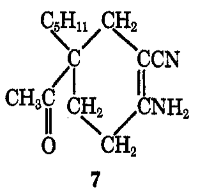
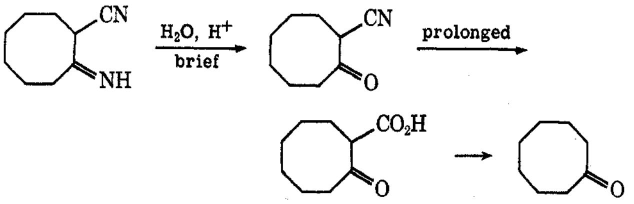
(12) B. Witkop, *J. Amer. Chem. Soc.*, **78**, 2873 (1956). In neutral solution the characteristic spectrum was observed for the vinyl amine structure, whereas in dry acid solution the spectrum became that of the β-imino ester cation (broad absorption at 4.97 μ, trivial absorption at 6–6.2 μ).



7

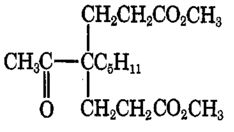
the β-amino ester[12] exhibited in the ir strong absorption at 6.16 μ, characteristic of the carbon–carbon double bond, and a doublet at 2.85 and 2.99 μ for the two NH absorptions, our cyclic product was entirely clear of absorption in the 6.0–6.7-μ region and there was a single absorption at 2.91 μ. Also observed for **5** was the expected absorption at 4.44 (nitrile) and 5.87 μ (carbonyl). Absence of the carbon–carbon double bond in the cyclic product was also demonstrated by the uv spectrum—no absorption above 200 nm with an extinction coefficient as great as 50. The nmr spectrum is consistent with structure **5**, but less definitive than the uv and ir absorption, for the resonance line for the single hydrogen α to cyano in **5** is blended into the downfield edge of the unsplit peak (δ 2.1) for the three hydrogens α to carbonyl. However, the downfield side of the methyl spike is spread and triplet splitting is just visible. This location for hydrogen α to cyano is established by the nmr spectrum of the monocyanoethylation product, **3**, in which the triplet for the two hydrogens α to cyano (centered at δ 2.18) is just resolved from the methyl spike and the tracing stands out above that representing the single hydrogen α to carbonyl.

When the solvolytic behavior of cyclic product **5** was examined, interesting anomalies were observed in comparison with the observations of Ziegler and coworkers[13] on similar compounds without ring substituents. These investigators utilized the products from cyclization of dinitriles as an entry to cyclic ketones of ring sizes difficult to secure in other ways. For cyclooctanone, the hydrolytic sequence was as follows.



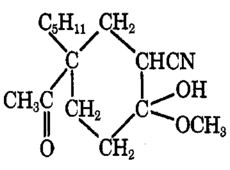
On account of facile hydrolysis of the imino structure and slow hydrolysis of cyano, the intermediate keto nitrile could be readily isolated, but more prolonged acid-catalyzed hydrolysis gave a good yield of cyclic ketone. In the case of structure **5**, acid-catalyzed hydrolysis yielded only acidic products, and esterification of this acid yielded the open-chain diester **8**, which would result from methanolysis of the dicyanoethylation product, **4**.

In order to give products more readily examined by gc and mass spectrometry, **5** was methanolized with acid catalysis. There proved to be rather slow formation of an intermediate, which was converted to diester **8** sufficiently rapidly to maintain a relatively low concentration of the intermediate. The intermediate was difficult to separate from both starting material **5** and



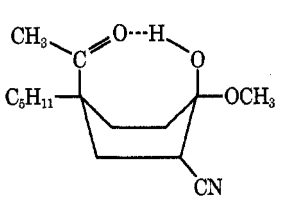
$\mathrm{CH_3C(=O)-C(C_5H_{11})(CH_2CH_2CO_2CH_3)_2}$

8



9

8 by gc; however, after a few hours of reaction time it was possible to separate samples of the intermediate containing only small amounts of **8**. The molecular ion of the intermediate (*m/e* 267) was in very low abundance, always less prominent than the ion of *m/e* 269, assigned to the fragment resulting from loss of methoxy (31) from impurities of diester **8**, whose molecular weight is 300. It proved possible to mass measure the molecular ion of the intermediate, in spite of its low abundance, and the formula assigned was $C_{15}H_{25}NO_3$. The most abundant ion in this mass spectrum was *m/e* 225 (M − 75), which results from loss of acetyl (43) and methanol (31); thus the methanolysis has introduced a methoxy group. This is supported by the prominent ion (31%) of *m/e* 236 (M − 31). Further, the second most abundant ion (45%) was *m/e* 185 (M − 82), resulting from loss of the same fragments which yield the base peak for cyclic product **5**; hence, retention of the ring system and cyano group of **5** is strongly indicated. The ir spectrum also showed that the nitrile had persisted (4.45 μ), and the 6–6.5-μ region remained clear, but there were observed *two* strong carbonyl absorptions (5.75, 5.86 μ) and *two* weak hydroxyl absorptions (2.92, 3.17 μ). There was no significant absorption in the uv above 200 nm, as in **5**, and the nmr spectrum also was similar to that of **5** except that there appeared a spike representing three hydrogens at the position observed (δ 3.3) when methyl is attached to oxygen, as in methyl esters. Since the nitrile group remains present, a methyl ester cannot be present to account for the methoxy revealed by both mass spectrum and nmr spectrum. This combination of spectral characteristics and molecular formula restricts the structure to two geometric isomers of the hemiketal **9**. The isomer with acetyl and hydroxyl cis to each other, in the flexible form shown in structure **9f**, is subject to



9f

rather strong chelation, hence the second hydroxyl absorption at longer wavelength and the second carbonyl absorption at shorter wavelength.

Isolation of the hemiketal **9** by work-up of the reaction mixture using water, followed by gc at about 200°, seems surprising; however, this structure differs from the hemiketal form of a keto sugar only in that the ether oxygen is not in the ring. Stability of this structure, accompanied by severe hindrance to hydrolysis of the nitrile group, is probably responsible for the occurrence of ring opening at a much more rapid rate than solvolysis of the nitrile. Further, the sharp contrast in chemical behavior between the unsub-

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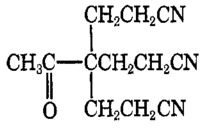
[13] K. Ziegler, H. Eberle, and H. Ohlinger, *Justus Liebigs Ann. Chem.*, **504**, 94 (1933).

stituted imino nitriles of Ziegler and coworkers[13] and our structure **5** must be ascribed to presence of the quaternary carbon in **5** and the effect thereof on the geometry of the ring.

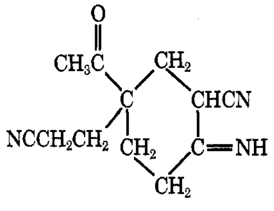
Although we have been unable to discover conditions which yield a significant amount of dicyanoethylation product **4**, it is practical to convert the cyclic product **5** to the open-chain keto diester **8**. Methanolysis with dry hydrogen chloride as catalyst yields the diester uncontaminated with starting material or the intermediate hemiketal. On the other hand, if sulfuric acid is used as catalyst, large amounts of the intermediate hemiketal **9** remain after 96 hr of heating under reflux. With dry methanol as solvent, gc analysis indicates about equal amounts of intermediate and diester. Addition of 2% of water to the methanol solvent almost doubled the ratio of diester; however, the intermediate was eliminated only by shift to hydrogen chloride catalysis.

Since we were able to obtain none of dicyanoethylation product **4** from the Michael reaction in wet or dry *tert*-butyl alcohol., and a minor amount of it in dry DME, it seems probable that other products reported in the literature with two cyanoethyl groups on one carbon actually have a cyclic structure analogous to **5**. Bruson and Riener[9] reported several products of the requisite structure, of which one was the tricyanoethylation product of acetone, described as structure **10**.



$$\underset{\underset{O}{\|}}{CH_3C}—\overset{\overset{CH_2CH_2CN}{|}}{\underset{\underset{CH_2CH_2CN}{|}}{C}}CH_2CH_2CN$$

10



11

The cyclized structure would be **11**. The mass spectrum of a sample of this compound, prepared in *tert*-butyl alcohol solvent according to Bruson and Riener, proved definitive in establishing the actual structure as that in **11**, not the open-chain structure **10**. An analysis of the data is presented in Table II, wherein are considered the two prominent ions in the fragmentation termed β cleavage No. 1 (Chart I), and the fragments from the dominant α cleavage shown in Chart I. It is apparent that the least abundant ion in the observed spectrum, of the four reported in Table II, is that predicted as least abundant for structure **11**, but most abundant in structure **10**. Also observed in the spectrum is an abundance for the ion of *m/e* 135 about twice that for the ion of *m/e* 177, in excellent agreement with the prediction for structure **11**.

TABLE II

MASS SPECTROMETRIC ANALYSIS OF STRUCTURE OF THE TRICYANOETHYLATION PRODUCT OF ACETONE

Ion (*m/e*)	Analogous ion in Table I, Chart I	Predicted ion abundance,[a] % 10	11	Obsd ion abundance,[a] %
M − 82 (135)	$C_{10}H_{18}N$ (152)	6	23	29
M − 43 (174)	$C_{12}H_{19}N_2$ (191)	13	6.5	1
M − 40 (177)	$C_{12}H_{20}NO$ (194)	2	13	16

[a] As per cent of base peak, *m/e* 43 (CH_3CO), in each instance.

Experimental Section[14]

Cyanoethylation of 2-Octanone. A. Preparative Procedures.—To a solution of 0.5 g of KOH pellets in 48 ml of *tert*-butyl alcohol (dried by distillation from sodium), stirred in an atmosphere of nitrogen, 24.5 g of 2-octanone was added in one portion. After this stirred solution had been warmed to 55°, 12.1 g (1.2 molar equiv) of acrylonitrile[15] was added as rapidly as consistent with keeping the temperature in the range 55–60° by cooling; time of addition is not important. After completion of addition, the reaction mixture was stirred for 2 hr as the temperature was maintained at 55–60° by warming. After the cooled reaction mixture had been acidified with 6 *N* HCl, it was diluted with 200 ml of water, and the products were extracted with benzene. The washed and dried benzene solution was either diluted to a measured volume for analysis by gc, or distilled to leave a residue which was distilled from a small Claisen flask at reduced pressure.

In a typical run, analysis by gc (10-ft column, 10% SE-30, 198°, 30-psi He pressure) showed yields of 9.7 g of recovered 2-octanone, 8.2 g (24%) of **3-(β-cyanoethyl)-2-octanone** (**3**), and 6.0 g (13%) of cyclic product **5**. With the ratio of acrylonitrile used, 2-octanone is not the limiting reagent for formation of **5**, but was used for comparison purposes in per cent yield calculation. Retention times for 2-octanone, **3**, and **5** were 15 sec, 68 sec, and 13 min. The 2-octanone peak was so narrow that accurate area measurement was not possible. Distillation gave ready separation of 2-octanone, bp ~56° (10 mm), **3**, bp ~160° (10 mm), and **5**, bp in the range of 200–220° (3 mm). The cyclic product must be distilled in lots no greater than 15 g, with rapid elevation of the bath to 280° and warming of the side neck of the Claisen flask to promote rapid distillation. Slower distillation causes extensive decomposition. Purification and characterization of the cyclic product is given below. For determination of the mass spectrum of **3**, a sample was collected from gc: *m/e* (rel intensity) α cleavage 43 (100), 138 (5); β cleavage (minus C_5H_{10}) 111 (55); molecular ion, 181 (3).

Anal. Calcd for $C_{11}H_{19}NO$: mol wt, 181.1467. Found: mol wt, 181.1468.

In a preparation carried out as above, but favoring cyclic product **5** by use of 2.4 equiv of acrylonitrile, yields determined as before by gc were 5 g (21%) of recovered 2-octanone, 2.6 g (7%) of **3**, and 13.3 g (30%) of **5**. Use of still larger ratios of acrylonitrile did not improve the yield significantly or consume all of the 2-octanone.

3,3-Bis(β-cyanoethyl)-2-octanone (**4**) could be obtained only in DME as solvent, and in small amount isolable by gc. In the process which is probably best applicable to securing this product, procedure was as described for use of *tert*-butyl alcohol solvent, with the following quantities: 7.7 g of 2-octanone, 4.1 g (1.3 equiv) of acrylonitrile, 19.2 ml of DME (dried over molecular seives), and 0.19 g of KOH (pellets rapidly crushed and added to reaction mixture). The best time interval for obtaining **4** was determined by withdrawing 3-ml aliquots at appropriate times, working up as described for runs using *tert*-butyl alcohol as solvent, analyzing by gc, and using collected samples for establishment of response factors. Representative data follow (Table III).

TABLE III

Time, hr	Products in 3-ml aliquot, g 3	4	5
0.25	0.8	0.02	0.01
0.5	1.3	0.03	0.04
1	1.3	0.02	0.2
4	1.3	0.02	0.2

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[14] Microanalyses and low-resolution mass spectra were determined by the Analytical Laboratory, University of California, Berkeley. The mass spectra were recorded on a CEC Model 21-103C instrument, with inlet heated to about 180° and ionizing voltage at 70 eV. The instrument had been equipped with narrower slits and an ion multiplier and otherwise modified to give unit resolution to about 600. High-resolution mass spectra were determined as described in Table I, footnote *a*. Ir spectra were recorded on a Perkin-Elmer instrument, Model 137, and the uv spectra on a Perkin-Elmer Model 202 instrument. Gas chromatography was on an Aerograph Model A-90P.

[15] There appears to be considerable loss of acrylonitrile by polymerization during the Michael condensation, and this loss is increased if old, partly polymerized samples of acrylonitrile are used. Material used for the procedures reported in these investigations was distilled and then stored in the presence of a few crystals of hydroquinone.

Thus, a short reaction time is probably a small advantage; after 30 min the entire reaction mixture contained about 250 mg of product **4**.

A sample of **4** for mass spectrum was collected by gas chromatography (10 ft × 0.375 in. column, 10% SE-30, 200°, He flow rate 200 cc/min): retention times 14 min for **4**, 22 min for **5**; mass spectrum *m/e* (rel intensity) α cleavage 43 (100), 191 (13); β cleavage (minus C_5H_{10}) 164 (54); C_5H_{11} 71 (63); β cleavage involving γ hydrogen which is β to cyano, <1%; molecular ion, M, 234 (3).

Anal. Calcd for $C_{14}H_{22}N_2O$: mol wt, 234.1732. Found: mol wt, 234.1739. Calcd for $C_{13}{}^{13}CH_{22}N_2O$: mol wt, 235.1766. Found: mol wt, 235.1780.

When the same procedure was used for reaction in DME solvent to which 4% of water had been added, *none* of **4** was detectable by gc.

B. Analytical Runs.—Small runs were carried out to determine effect of time and of addition of water in *tert*-butyl alcohol as solvent. The procedure was the same as that described for the preparative run using 1.2 equiv of acrylonitrile except that 4.1 g of 2-octanone was used and aliquots were withdrawn at appropriate times. Since comparative data only were desired, the ratio of areas of the respective peaks in gc was divided by the ratio of response factors, in order to determine ratio of amounts at each time. As before, data for 2-octanone are only approximate, on account of the very short retention time. The trend of the data is indicated in a run in dry *tert*-butyl alcohol (Table IV).

TABLE IV

	Product ratios		
Time, hr	2-Octanone	3	5
0.5	1.3	1.2	3.8
1	1.1	1.1	4.7
2	1	1.2	5.3
4	1	1.3	5.0
8	1	1.5	4.3
24	1	1.5	4.2

A similar trend was observed when 4, 10, or 20% of water was added to the butanol solvent; however the reaction is slowed markedly by addition of water, and the ratio of octanone surviving increases because more acrylonitrile is lost by polymerization or reaction with solvent. With addition of 20% of water to the solvent, after 4 hr the ratio of the three components in the order shown in the tabulation was 1:0.23:0.15. Use of a larger ratio of KOH fails to increase the ratio of 2-octanone reacting with acrylonitrile. It may be noted that excessive reaction time appears to destroy the cyclic product **5**.

In addition to peaks representing the compounds included in the tabulation, there were also three small peaks, of which only one was as large as 1% of the total peak area. This latter peak was absent when dry *tert*-butyl alcohol was solvent, and became about 1.5% of the peak area with 4–10% water present and about 5% of the peak area with 20% water present. Mass spectrometry of the sample collected from this peak showed it to be not a reaction product from 2-octanone, probably a product from reaction of acrylonitrile with solvent.

Characterization of Cyclic Product 5.—Crude, distilled cyclic product **5** was a syrup which crystallized on storage overnight in the refrigerator. After two crystallizations from 95% ethanol, 5.57 g of distillate yielded 2.71 g of fine white crystals, mp 43–44.5°, and a second crop of 1 g, mp 41–43°. Further crystallization gave a maximum melting point of 44.0–44.5°.

Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.8; H, 9.4; N, 12.0; mol wt, 234.1732. Found: C, 72.1; H, 8.8; N, 12.1; mol wt, 234.1739.

The more significant features of the mass spectrum of **5** are assembled in Table I.

Solvolysis of Cyclic Product 5. A. Isolation of Intermediate Hemiketal 9.—A solution of 0.835 g of pure **5**, mp 44.0–44.5°, in 5.76 ml of methanol (dried with Mg) and 0.23 ml of concentrated H_2SO_4 was heated under reflux in an oil bath at about 110° for 6 hr. The cooled reaction mixture was worked up by dilution with water and extraction with benzene. The extract was washed with water and 1 *N* NaOH, solvent was evaporated, and the residue was dissolved in 5 ml of benzene for gc on a 0.25 in. × 10 ft column, 10% SE-30, temperature 210°. The gc tracing showed three extensively overlapping peaks with retention times of 4.2, 5, and 6.3 min. About three-fourths of the area (as extrapolated) was in the third peak, while the second peak was barely detectable as a hump in the valley between the two major peaks. Attempted separation on other partitioning agents was less satisfactory.

The third peak in the gc tracing was shown by coinjection to be that for starting material, **5**, while the first peak was shown by collection and examination to be that of **9**; the collected sample was contaminated by diester **8** (the center minor peak), as well as **5**. For analytical examination, the first two-thirds of the first peak was collected, then reinjected and collected again to separate small amounts of the other two compounds, using a 0.375 in. × 20 ft column, SF-96.

Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.4; H, 9.4; N, 5.2; mol wt, 267.1834. Found: C, 67.15; H, 9.5; N, 5.1; mol wt, 267.1832.

Significant features, especially for analytical purposes, of the mass spectra of **5**, **8**, and **9** are assembled in Table V and designation of fragments lost to give the ions is found in the footnotes to the table. The ions of *m/e* 257 and 269, although of small abundance in the spectrum for **9**, suggest that our best sample of hemiketal is contaminated with significant amounts of the diester **8**; however, the elementary analysis does not reveal this.

TABLE V

COMPARATIVE MASS SPECTRAL DATA

	Ion	Relative abundance, %		
m/e	formula	**5**	**9**	**8**
152	$C_{10}H_{18}N$	*100[a]	19	5
153		14	25[b]	20
164	$C_9H_{12}N_2O$	*17[c]	32[d]	2.5
185			45[a]	37[e]
192	$C_{12}H_{18}NO$	5	*100[f]	2
193			21[g]	38
194	$C_{12}H_{20}NO$	*68[h]	33[i]	8
197	$C_{10}H_{15}NO_3$		*18[c]	20
225	$C_{13}H_{21}O_3$		46	*100[f]
234	$C_{14}H_{22}N_2O$	*28 (M)	1	
236	$C_{14}H_{22}NO_2$		*31[j]	1
257	$C_{14}H_{25}O_4$		7	*26[k]
267	$C_{15}H_{25}NO_3$		*2 (M)	
269	$C_{15}H_{25}O_4$		3	*7[j]
300	$C_{16}H_{28}O_5$			*1 (M)

[a] Formulas given for those ions which have been mass measured, as indicated in each instance by the asterisk. M − 40 (CH_2CN) − 42 (CH_2CO). [b] M − 32 (CH_3OH) − 40 (CH_2CN) − 42 (CH_2CO). [c] M − 70 (C_5H_{10}), β cleavage. [d] M − 32 (CH_3OH) − 71 (C_5H_{11}). [e] M − 73 ($CH_2CO_2CH_3$) − 42 (CH_2CO). [f] M − 32 (CH_3OH) − 43 (CH_3CO). [g] M − 31 (CH_3O) − 43 (CH_3CO). [h] M − 40 (CH_2CN). [i] M − 31 (CH_3O) − 42 (CH_2CO). [j] M − 31 (CH_3O). [k] M − 43 (CH_3CO).

B. Formation of Keto Diester 8.—Dry HCl from a cylinder was passed into 5.76 ml of dried methanol until 10% by weight had been absorbed, then 0.835 g of **5** was added. The reaction mixture, protected by a drying tube, was heated under reflux for 4 days, then worked up as described in A above. Gc on the 10-ft SE-30 column at 219° revealed a single band (except for a small band in edge of solvent) with a retention time of 4.2 min. An analytical sample was collected from the gc. The fragmentation pattern for this product was quite different from that of the cyclic products (Table V).

Anal. Calcd for $C_{16}H_{28}O_5$: mol wt, 300.1937. Found: mol wt, 300.1936.

Near absence of the ion of *m/e* 192 in the mass spectrum of **8** (Table V) demonstrates that this hydrolytic procedure eliminates the intermediate hemiketal **9**.

When the same solvolytic procedure (dried methanol, heating time 4 days) was used except that catalysis was by 0.23 ml of concentrated H_2SO_4, gc in the same column at 217° gave two overlapping peaks of equal height, with retention times of 5 and 5.7 min. Mass spectra of samples collected from each peak demonstrated that the first peak contains **8** and the second peak **9**, the *opposite order of emergence* than that observed when the charge for gc consisted to about 75% of the starting material **5** (*cf.* A above). This obnoxious behavior was observed in five runs as here described, and in gc of several samples from two runs as in A.

When the solvolytic procedure differed from that just described by addition of 2% of water to the solvent, rate of conversion of the intermediate was accelerated; the first peak in gc (identified as **8** by mass spectrum) was of approximately twice the height of the second.

Two samples of diester **8** were hydrolyzed to acid, which was reesterified to give the original ester, as an additional confirmation that **8** is not the hemiketal of the cyclic β-keto ester. For this purpose, 50 mg of **8** collected from gc was heated under reflux for 18 hr with 2 ml of a solution prepared from 4.3 ml of concentrated H_2SO_4, 7.3 ml of glacial acetic acid, and 7.6 ml of water. The reaction product, which was acidic, was esterified as in A except that reaction time was 4 hr. Gc of the product on the column used for the above analyses, at 198°, gave three peaks in the tracing, not overlapping significantly, with retention times of 6.3, 10, and 12.5 min, with areas (in the same order) in the approximate ratio of 4:3.5:1. The first peak proved to be the diester **8** (mass spectrum), while the compounds giving longer retention times were not encountered in other phases of this work, and have not been investigated.

One sample of cyclic product **5** was hydrolyzed in aqueous acid as described for hydrolysis of the diester **8**, above. The product of hydrolysis, which was entirely acidic material, was esterified as described just above. Gc showed two peaks of short retention time and a major peak of retention time expected for **8**; mass spectrum of the collected product verified this identity.

Cyanoethylation Product from Acetone (11).—Application of cyanoethylation to acetone in DME solvent, with solid KOH as catalyst, yielded a red, waxy material, from which no homogeneous product could be isolated. The procedure previously described[9], using a solution of KOH in *tert*-butyl alcohol, yielded the product described by Bruson and Riener, but in about one-fourth the yield. Our recrystallized sample consisted of colorless crystals, mp 149–154° (lit.[9] mp 154°).

Registry No.—**3**, 34917-90-3; **4**, 34886-35-6; **5**, 34886-36-7; **8**, 34886-37-8; **9**, 34886-38-9; **11**, 34886-39-0; 2-octanone, 111-13-7.

The Synthesis and Properties of 2-(2-Cyanoethylidene)-1,3-dithiane and Its Isomeric Ketene Thioacetal[1a]

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The preparation of 2-formyl-1,3-dithiane from 2-lithio-1,3-dithiane and dimethylformamide is reported. Wittig reaction of this versatile aldehyde gave, under different conditions, both "normal" coupling (**1**) and the rearranged ketene thioacetal **6**. Base-catalyzed treatment of **1** gave exclusively **6**, indicating the thermodynamic preference for the ketene thioacetal structure. Alkylation of **1** or **6** *via* its lithio salt gave only products derived from the carbanion α to the cyano group (**11**); yet at equilibrium the conjugation of the double bond favored the ketene thioacetal structure. These results suggest that there is considerable relief of ring strain when the 2 position is sp^2 hybridized. A further effect to account for these results may lie in enhanced overlap by 3p orbitals with the 2p orbitals of carbon when two adjacent sulfur atoms are present.

The synthetic utility of 1,3-dithianes as nucleophilic acylating agents is now well documented[2] by a variety of transformations leading to aldehydes and ketones. As part of another study, it was necessary to prepare 2-(2-cyanoethylidene)-1,3-dithiane (**1**) as a highly functionalized intermediate for further synthesis. The most direct approach seemed to involve the Wittig coupling of cyanomethylphosphorane (**2**) with 2-formyl-1,3-dithiane (**3**, R = H). Although 2-methyl-2-formyl-1,3-dithiane (**3**, R = Me) has been reported[2] from 2-lithio-2-methyl-1,3-dithiane (**4**, R = Me) and dimethylformamide, there was no mention of the preparation of **3** (R = H). The latter synthesis proved to be less than straightforward. When the lithio salt of 1,3-dithiane **4** (R = H) was treated with dimethylformamide, a complex mixture was obtained. However, when the previously prepared lithio dithiane was added to excess dimethylformamide at −10°, a viscous oil was isolated which exhibited both hydroxyl and formyl bands in the infrared. Distillation of this material afforded 2-formyl-1,3-dithiane in 81% yield. Thus, the viscous crude product is considered to be the dimer **5** arising from an aldol-type process which underwent thermal reversal to the desired product. The formyl dithiane slowly dimerized at room temperature although it is quite stable at −20° for several days.

When the formyl dithiane was added to a THF solutaining 1.1 equiv of cyanomethylphosphorane **2**,[3] the product was not the desired olefin **1** but instead the isomeric ketene thioacetal **6** (Figure 1, top). This product is undoubtedly the result of an isomerization by excess base (phosphorane or butyllithium from which it was prepared) present in the reaction medium. Base-catalyzed or thermal (∼200°) equilibration attempts did not lead to any detectable quantities of the cyanovinyl dithiane **1**. The Wittig reaction was repeated using 0.9 equiv of the phosphorane so that no excessive base would be present. Indeed, this resulted in a 63% yield of the cyanovinyl dithiane **1** completely devoid of any isomeric material. To confirm the base-catalyzed lability of **1**, it was treated with 0.2 equiv of sodium ethoxide in ethanol at −20° and allowed to stand overnight at this temperature. Recovery after neutralization provided pure **6**. The isomerization was carried out at low temperature due to the instability of dithiane anions at ambient temperatures,[2] resulting in extensive decomposition of **1**. These results may be interpreted by assuming that the presence of *two* adjacent sulfur atoms causes sufficient 3p–2p π overlap in **6** to outweigh the 2p–2p π overlap in **1**. The importance of

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[2] For an excellent review on this subject, see D. Seebach, *Synthesis*, **1**, 17 (1969).

[3] G. Schiemenz and E. Engelhard, *Ber.*, **94**, 578 (1961).