pure acid XI, m.p. 94–96° dec. A mixture melting point with an authentic sample of XI (lit.[2] m.p. 94–96°) was not depressed. The infrared spectra of the two samples were identical.

Acid XI (2.1 g., 0.01 mole) was heated in an oil bath at 110–115° until carbon dioxide evolution had ceased, to give 1.6 g. (98%) of benzoylacetone, m.p. 58–60°.

Acid XI (2.1 g., 0.01 mole) was heated on the steam bath with 20 g. of polyphosphoric for 1.5 hr. The resulting dark red mixture was poured onto 200 g. of crushed ice to precipitate a solid which was collected by filtration and digested with hot absolute ethanol. There was obtained 1.7 g. (90%) of lactone VII, m.p. 258–259° dec., which was identified by mixture melting point and by comparison of infrared spectra with an authentic sample of VII, m.p. 254–256° dec.[17]

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(17) Melting of lactone VII was accompanied by considerable decomposition which evidently resulted in the lower melting point (241–244°) reported in ref. 2.

An Unusual Reaction Product from Epichlorohydrin and Sodium Cyanide

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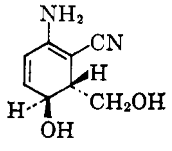
The major product arising from the reaction of epichlorohydrin and unbuffered potassium cyanide solution, aside from water-soluble polymers, is shown, largely by physical means, to be *trans*-3,4-dihydro-2-cyano-3-hydroxymethyl-4-hydroxyaniline (I). A seven-step mechanism for its formation is proposed.

The reaction of potassium cyanide in aqueous solution with epichlorohydrin was first investigated by Pazschke[1] in 1870, although undoubtedly this same system was under study indirectly, when Simpson[2] treated 1,3-dichloropropanol-2 with 2 equiv. of this salt, exactly a century ago.

In the interim other investigators have examined this reaction and have shown that the nature of the products is dependent on the pH at which the system is maintained. At neutral pH the chief product is 4-chloro-3-hydroxybutyronitrile,[3] whereas at pH 9–9.5 the major component is 3-hydroxyglutaronitrile[4] accompanied by small amounts of 4-chloro-3-hydroxybutyronitrile and 4-hydroxycrotononitrile. With an unbuffered potassium cyanide solution (pH 11.5–12.5) small amounts of the two latter substances were isolated[3] together with 2,5-biscyanomethyl-1,4-dioxane[3,5,6] in yields of 10% or less.

However, under the latter conditions, the material (I) which is produced in greatest amount, apart from water-soluble polymer, appears to have been missed by previous workers. Failure to observe it, can be traced to the fact that it is water soluble and can only be isolated from the reaction mixture by prolonged continuous extraction with ethyl acetate. Obtained in this manner I crystallized from ethanol as cubic, lemon yellow crystals, m.p. 154°, having a molecular weight of 166 and the empirical formula, $C_8H_{10}N_2O_2$. Acetylation was trouble free and gave a pale yellow diacetate (II). Catalytic reduction, equally facile, led to a colorless dihydro derivative (III) and acetylation of this substance or hydrogenation of II led to the same dihydrodiacetate (IV). In an attempt to deduce the structure of I by chemical means a number of other reactions, including acid hydrolysis, various oxidations, and diazotization, were tried, but quite consistently, if starting material were not recovered, irresolvable syrups or tars were obtained. Rather than persist with chemical failure we turned to a study of the spectroscopic properties of the compounds I–IV in the hope that this would provide an answer. The data, presented below, has permitted the assignment of the structure *trans*-3,4-dihydro-2-cyano-3-hydroxymethyl-4-hydroxyaniline to I.



I

Infrared Evidence.—The infrared spectrum[7] of I showed bands at 2.90, 2.99 (sharp), and 3.09 μ, indicative of both hydroxyl and amino groups, while a strong absorption at 4.56 μ characterized a highly unsaturated nitrile. Bands at 6.01, 6.11, and 6.34–6.35 μ could be ascribed to double bond and/or imine functions whereas those at 9.40, 9.65, and 9.90 μ were characteristic of C–O stretching vibrations. Lastly a weak absorption at 12.85 μ suggested *cis* ethylenic hydrogens but its unusual sharpness mitigated against this geometry.

In the spectrum of the diacetate (II) a triplet of sharp bands at 2.91, 2.99, and 3.08 μ, highly characteristic of an unsaturated amino group in the solid state, confirmed the presence of this function. A number of the bands already observed for I were apparent in the spectrum of II but in the latter the appearance of two peaks at 5.76 and 5.80 μ indicated the presence of two different types of acetate groups.

The spectra of the dihydro derivatives (III and IV) were interesting in that they showed the nitrile group absorption to be unchanged at 4.55 μ despite the fact the band for *cis*-ethylenic hydrogen atoms at 12.85 μ was now absent. The high position of absorption of the nitrile group in all these compounds, together with the fact that the amine group did not acetylate under the mild conditions used, indicated the presence of a Ziegler–Thorpe system, while the loss of color on hydrogenation suggested that the latter group in I was conjugated with a double bond. Taken as a whole then, the above information permitted the partial formulas,

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(1) F. O. Pazschke, *J. prakt. Chem.*, [2] **1**, 97 (1870).

(2) M. Simpson, *Ann.*, **133**, 74 (1864).

(3) C. C. J. Culvenor, W. Davies, and F. G. Haley, *J. Chem. Soc.*, 3123 (1950).

(4) F. Johnson, J. P. Panella, and A. C. Carlson, *J. Org. Chem.*, **27**, 2241 (1962).

(5) W. Hartenstein, *J. prakt. Chem.*, [2] **7**, 297 (1873).

(6) A. van Dormael, *Trav. lab. chim. gen., Univ. Louvain*, 34 (1942–1947).

(7) All infrared spectra were run as Nujol mulls unless otherwise stated.

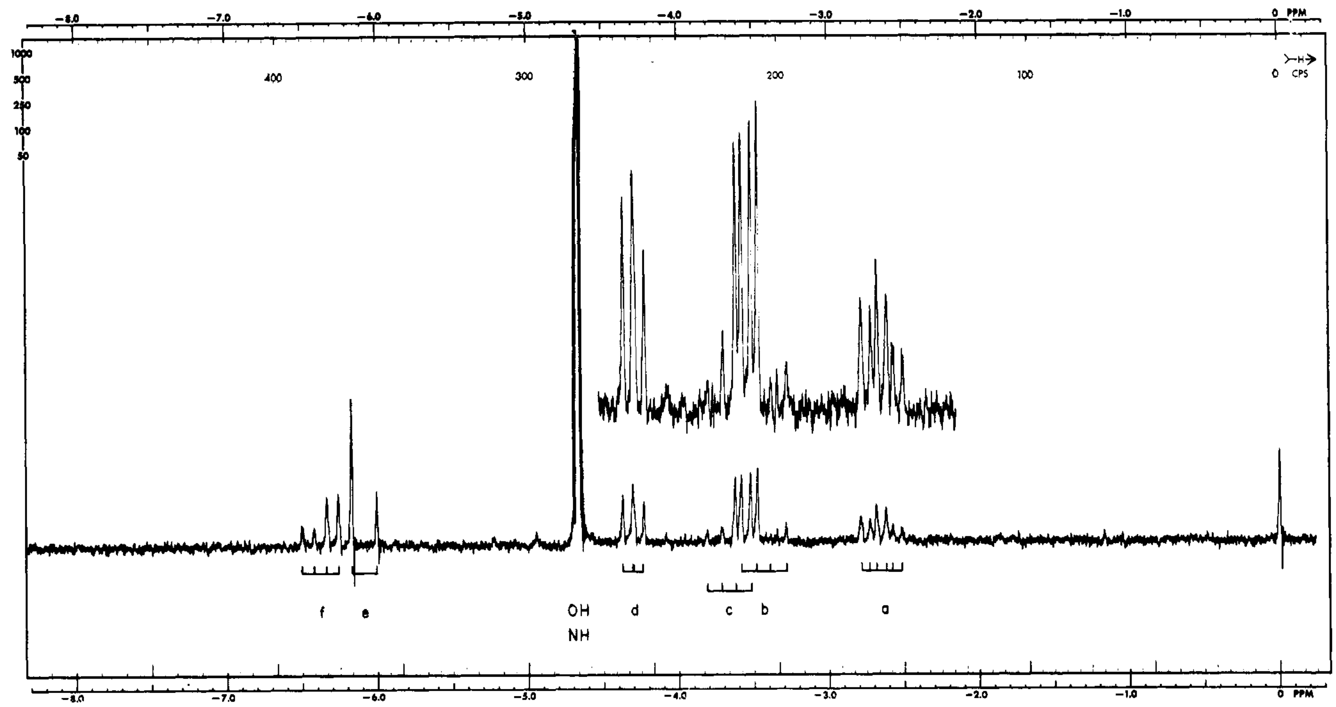


Fig. 1.—Proton n.m.r. spectrum of dialcohol I in deuterium oxide (60 Mc.).

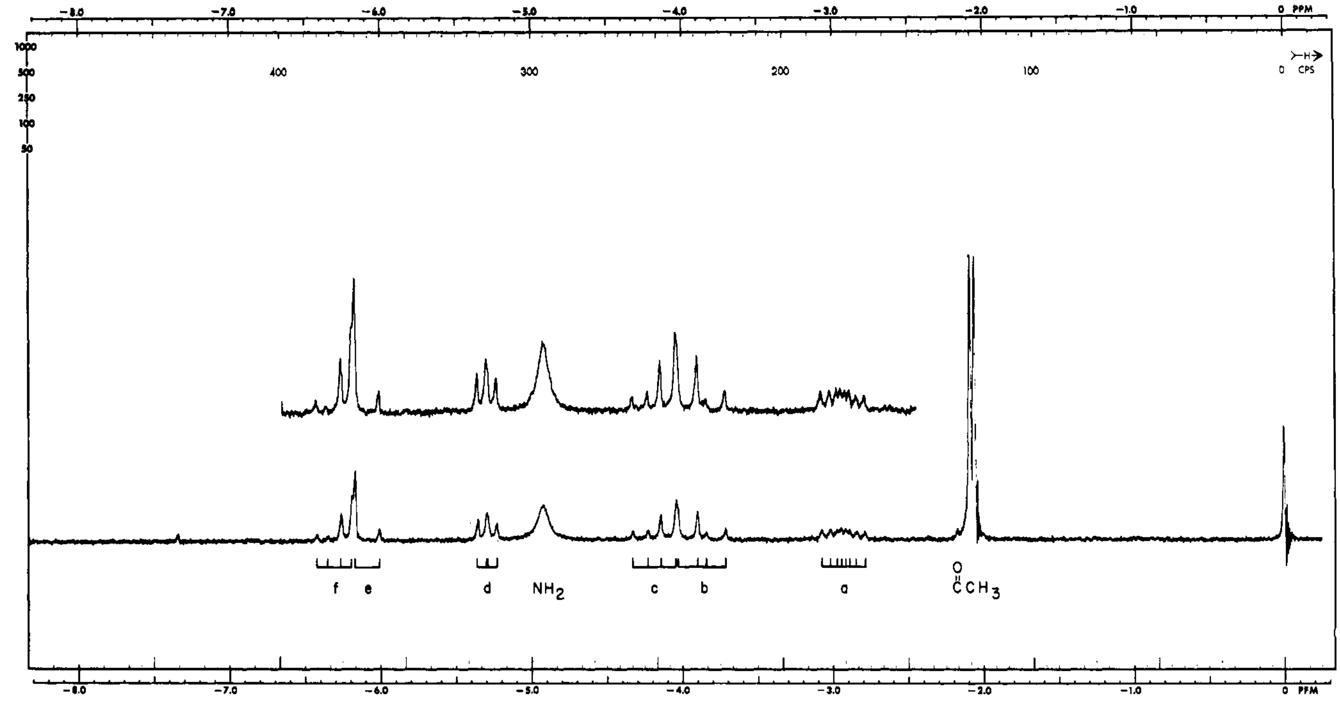
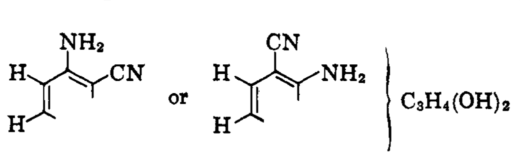


Fig. 2.—Proton n.m.r. spectrum of diacetate (II) in deuteriochloroform (60 Mc.).

seen below, to be written for I. Since all of the hetero atoms in I now were accounted for, I had to be a carbocycle, but whether this was a five-, six-, or seven-membered ring remained unanswered. However, further information on this point was forthcoming from the n.m.r. spectra of I and II.



N.m.r. Evidence.[8]—The spectrum of I (Fig. 1) was obtained in D_2O because of the lack of solubility of this substance in organic solvents. However the spectra of the diacetate proved the clearest and most useful and these were recorded in deuteriochloroform (Fig. 2), in trifluoroacetic acid[9] (Fig. 3), and in acetone. In

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[8] The n.m.r. spectra were obtained with a Varian Associates A-60 analytical spectrometer. The analyses are first order unless otherwise noted.

[9] The parameters assigned to the diacetate in trifluoroacetic acid solution are based on the stronger spectrum seen immediately after preparation of the solution.[10] When trifluoroacetic acid is added to the deuteriochloroform solution of II, the spectrum becomes blurred and shows a change toward that in the acid. Two separate species were not apparent. Thus it seems certain that the trifluoroacetic acid solution at first contains the same molecule as the deuteroichloroform solution and that interconversion between the two forms is fast.

[10] The spectrum slowly disappears owing to decomposition of the molecule.

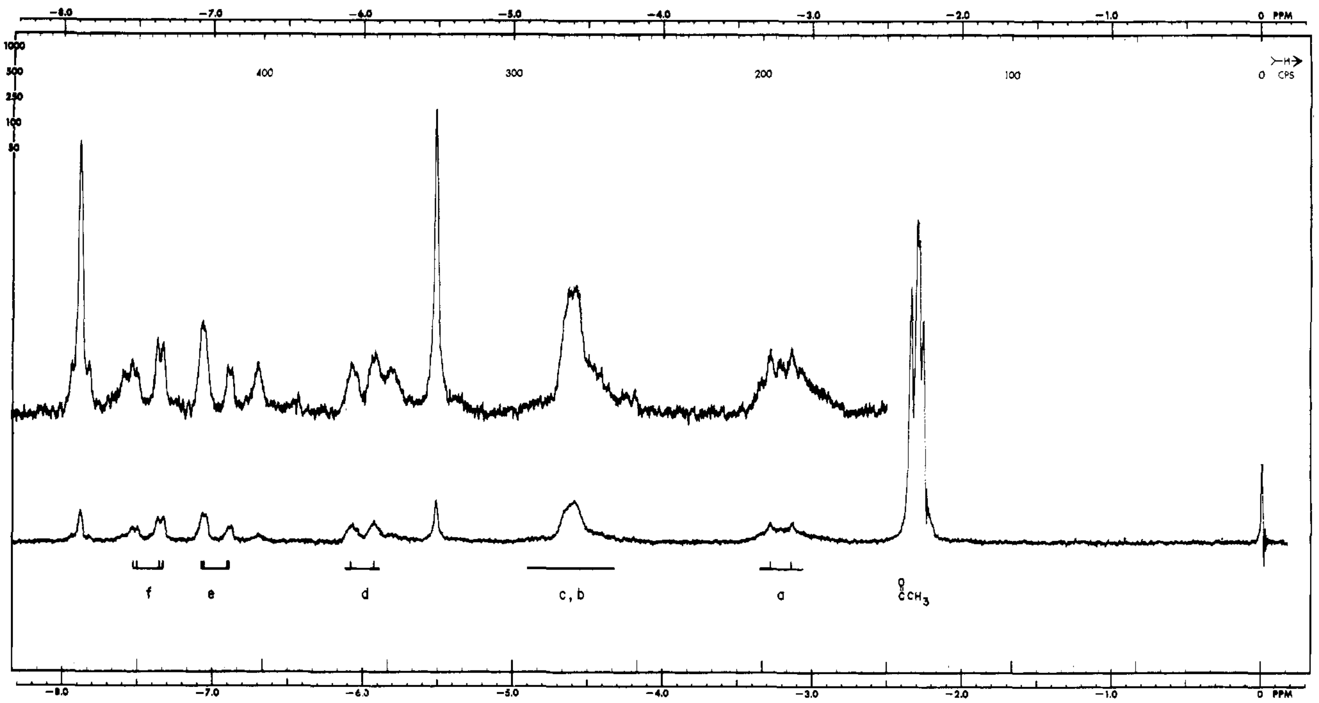


Fig. 3.—Proton n.m.r. spectrum of diacetate (II) in trifluoroacetic acid (60 Mc.).

these spectra the individual protons are labeled a, b, c, d, e, and f and their chemical shifts and nonzero coupling constants are listed in Tables I and II.

TABLE I

Proton	Chemical shift (shielding), p.p.m.[a]			
		Diacetate (II)		
	I in D_2O[b]	In acetone	In $CDCl_3$	In CF_3COOH
a	−2.65	−2.87	−2.95	−3.22
b	−3.48[c]	−3.83[c]	−3.89[c]	−4.6
c	−3.62[c]	−4.13[c]	−4.15[c]	
d	−4.30	−5.32	−5.32	−6.03
e	−6.10[c]	−6.27[c]	−6.10[c]	−7.00
f	−6.33[c]	−6.33[c]	−6.25[c]	−7.50
NH(OH)	−4.67	−5.90	−5.08	
CH_3CO			−2.05 −2.08	−2.32 −2.34

[a] Relative to internal TMS; accurate to ±0.02 p.p.m. [b] Internal reference is CH_3 of $(CH_3)SiCH_2CH_2CH_2SO_3Na$. [c] Calculated as AB of an ABX spectrum (J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959).

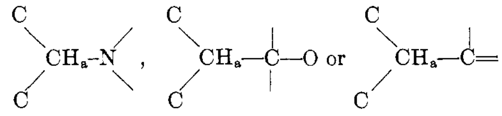
TABLE II

Proton coupling	Nonzero coupling constant, c.p.s.[a]			
		Diacetate (II)		
	I in D_2O	In acetone	In $CDCl_3$	In CF_3COOH
J_{ab}	+6.4	+8.1[b]	+8.1[b]	3–4
J_{ac}	+6.0	+5.9[b]	+5.9[b]	4–3
J_{ad}	3.8	3.05	3.5	9
J_{af}	0.5	<1	<1	...
J_{bc}	11.2	11.1	11.1	...
J_{de}	−0.5	1.7	<0.5	⩽1
J_{df}	+5.0	3.05	3.5	1–2
J_{ef}	9.8	...	10.0	10

[a] Accurate to ±0.1 c.p.s. [b] Calculated as J_{ax} and J_{bx} of an ABX spectrum. Algebraic signs are relative and apply only within the appropriate ABX group.

As the general spectral features and proton distributions are essentially the same for the CH protons of I and its diacetate (II), it may be assumed that no bonds have broken (except OH) upon acetylation. The CH protons of II can then be characterized in the following manner.

Proton a.—This is coupled ostensibly to four other protons. Three coupling constants are typical of vicinal, but not of geminal positions in rings of intermediate size.[11,12] The fourth coupling J_{af} is small and could be vicinal (dihedral angle ~90°) or longer range but is unlikely to be geminal. The latter seems even less probable because H_a is shifted 1 p.p.m. from the next nearest proton. The position of H_a is typical of hydrogen on a trisubstituted sp^3 carbon and suggests the following structures. The first possibility can be excluded by the normal shift of H_a in trifluoroacetic acid, relative to most of the other protons in the molecule. The previously cited infrared evidence also mitigates against it.



Protons b and c.—The coupling between them is 11.1 c.p.s., both see H_a as the only vicinal proton (based on coupling constants),[11,12] and they have similar chemical shifts. Therefore we conclude that H_b and H_c are geminal. Their positions in the spectrum are typical of RCH_2O– but their magnetic environments are nonidentical as indicated by their dissimilar chemical shifts, and different couplings to H_a.

Proton d.—Its shift indicates it to be olefinic or on a tetrahedral carbon atom bearing two electron-withdrawing groups. The strong deshielding that occurs upon acetylation of I indicates that the carbon bearing this proton also bears a secondary hydroxyl.[12] The

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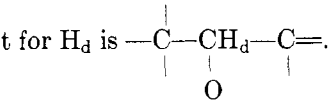
(11) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(12) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p. 84.

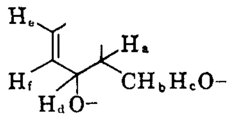
couplings to H_a and H_f are typical vicinal values[11,12] for dihedral angles of $\leqslant 60°$ or $\geqslant 120°$ in acetone and chloroform, and of $\sim 0°$ or $\sim 180°$ in trifluoroacetic acid. A likely environment for H_d is



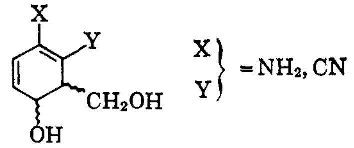
$-\underset{|}{\overset{|}{C}}-\underset{\underset{O}{|}}{CH_d}-\underset{|}{C}=$.

Protons e and f.—Their chemical shifts are typical of olefins which are conjugated and/or which have deshielding groups attached. The 10-c.p.s. coupling between them is typical of *cis*-oriented ethylenic protons.[13] On the basis of their coupling constants, H_f is vicinal to H_d, whereas H_e probably has no vicinal proton. The system H_d. H_e, and H_f, then would be $-CH_e{=}CH_fCH_d<$.

Thus chemical shifts and coupling constants of the protons a to f together suggest that I and II contain the fragment



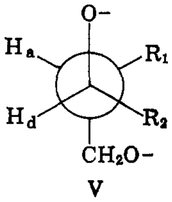
in which H_e and H_f are the *cis* olefinic protons of the conjugated fragment deduced earlier from the infrared spectra. Therefore, the gross molecular structure for I is



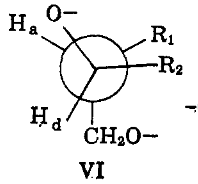
but preferably with $X = NH_2$ and $Y = CN$ in view of the strong shift which the olefinic protons undergo in trifluoroacetic acid.

In addition to the above information it was also possible to deduce the stereochemistry of the saturated carbon atoms from the observed coupling constants of J_{ad} and an examination of Drieding molecular models of I.

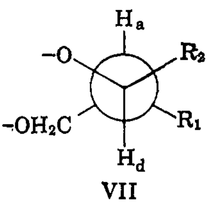
Six of the possible conformers about the bond between the tetravalent ring carbons are shown as Newman projections (V to X) in which VI and IX represent eclipsed conformers. Structures V to VII correspond to the *trans* conformation and VIII to X are *cis*.



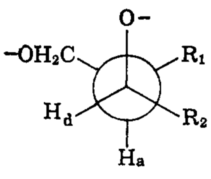
V



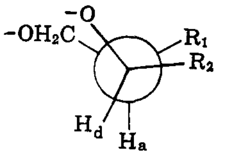
VI



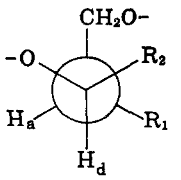
VII



VIII



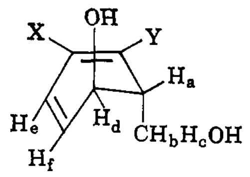
IX



X

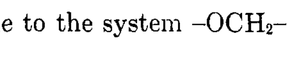
The fact that J_{ad} approximates 3 to 4 c.p.s. for I in D_2O and for II in acetone and deuteriochloroform indicates sizable contributions from V and VI if the substituents are *trans* oriented or from VIII and X if *cis*. For II in trifluoroacetic acid, $J_{ad} = 9$ c.p.s.; thus conformer VII predominates if these hydrogens are *trans* or IX predominates if they are *cis*. A Dreiding model of this cyclohexadiene ring suggests that the most stable conformation has an 18–22° dihedral angle between the two double bonds and that rotation about the bond between the tetravalent carbons will allow extensive staggering of the latters' remaining bonds. Thus conformers V, VII, VIII, and X appear to be the most stable, whereas VI and IX in which the ring is planar would seem to be prohibited because of severe ring strain. In addition one could expect IX to exhibit strong steric repulsion between the eclipsed substituents.

These observations, then, strongly support a *trans* configuration and a major conformation of the dialcohol (I) would be XI. It should be noted that the ring hydroxyl (acetoxyl) and hydroxymethyl (acetoxymethyl) substituents must spend a major fraction of the time *trans* diaxial in D_2O, acetone, or deuteriochloroform, whereas these groups become diequatorial in the diacetate (II) when the latter is in trifluoroacetic acid.



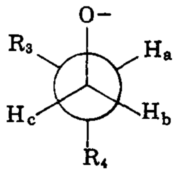
XI

While it provides little in the way of structural evidence the n.m.r. analysis would not be complete without a consideration of the coupling constants, J_{ab} and J_{ac}. These are due to the system

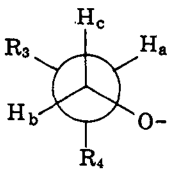


$-OCH_2{-}HC{<}^{R_3}_{R_4}$

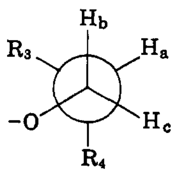
in which there are certain restrictions about the C–C bond. The three conformers are shown below where R_3 and R_4 represent the remainder of the ring. With completely free rotation about the C–C bond all forms (XII to XIV) would be equally populated so that $J_{ab} \approx J_{ac}$. This appears to be the case for the dialcohol (I) in D_2O. However, for the diacetate (II) in acetone or deuteriochloroform $J_{ab} = 8.1$ c.p.s. and $J_{ac} = 5.9$ c.p.s. indicating the relative populations of XIII > XII >> XIV, since *trans* vicinal couplings are ~ 10 c.p.s. and gauche couplings ~ 3 c.p.s. Although the shifts of H_b and H_c are not expected to be the same because the acetoxymethyl group is attached to an asymmetric carbon, the hindered rotation undoubtedly also contributes to their dissimilar shifts.



XII



XIII



XIV

In trifluoroacetic acid J_{ab} and J_{ac} of the diacetate (II) become smaller suggesting a greater contribution from

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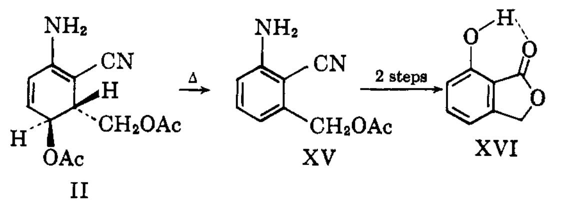
[13] W. Brügel, T. Ankel, and F. Krückeberg, *Z. Electrochem.*, **64**, 1121 (1960).

conformer XIV. An alternative explanation for the lower J_{ab} and J_{ac} values in trifluoroacetic acid may be in the conformational change of the ring which makes the acetoxymethyl group equatorial. It has been observed in cyclohexanone[14] that an axial methyl group is coupled more strongly to the equatorial ring proton than an equatorial methyl is coupled to an axial proton.

Electron Impact Study.—A full analysis of the mass spectral curves of I and II will not be given here. It is sufficient to say that the fragmentation patterns were in agreement with the above deductions. The most important features of the spectra, to our ends, were the presence of a small but significant molecular ion peak at m/e = 166 for I, and an almost complete absence of this type of peak for II at m/e = 250. These facts, coupled with the appearance of an intense peak in the latter's spectrum at m/e = 190, demonstrated a very facile loss of acetic acid from II and corroborated well with the previous conclusion that the ring acetoxyl and its vicinal hydrogen are *cis* to one another in II. This molecular elimination of acetic acid which can be regarded as a thermal rather than an electron impact effect pointed the way to completing the structure proof. Simply heating II to 210° led to a very vigorous and quantitative evolution of 1 equiv. of acetic acid. The residue, on cooling, crystallized readily and led to an 83% yield of a material (XV) whose infrared spectrum indicated it to have a 1,2,3-trisubstituted benzene ring (12.70 μ), an aromatic nitrile (4.46 μ), an amino group (2.89, 2.95, and 3.05 μ), and an aliphatic ester function (5.78 μ). Unambiguous proof that XV had the structure assigned to it was obtained by acid hydrolysis followed by diazotization when the phenolic lactone XVI was obtained. Comparison of this with an authentic specimen prepared according to Blair, *et al.*,[15] confirmed its identity. Thereby the structure of I was established.



II XV XVI

The failure to effect easy conversion of I to an aromatic system under ionic conditions deserves some comment. Two major reasons offer a ready explanation. (a) In neither of the two conformations of I do the ring hydroxyl and the hydrogen of the adjacent saturated carbon atom assume the necessary *trans* coplanar orientation necessary for facile acid-catalyzed elimination of water. Such resistance to elimination has already been observed[16] with (+)-*trans*-2,3-dihydro-3-hydroxyanthranilic acid,[17] some of which could be recovered after standing for 6 hr. in concentrated hydrochloric acid at 60°. (b) The complexity of I itself suggests that alternate reactions could take place before the molecule assumes the necessary form for aromatization. This was borne out when the reaction product of I with concentrated hydrochloric acid was rescrutinized. Besides a considerable amount of tar there was isolated a very small quantity of 7-hydroxyphthalide. This fact coupled with the hydrolytic stability of the amino group in 7-aminophthalide to acid (see above) strongly suggests that hydrolysis of the amino group in I must have taken place prior to aromatization.

Mechanism of Formation of I.—The formation of I from potassium cyanide and epichlorohydrin at first presented quite a puzzle since the reaction mixture at one stage or another contained a variety of substances. However, the incorporation of additional epichlorohydrin at a late stage in the formation of I was precluded when it was found that I could be prepared by the action of sodium methoxide on 4-chloro-3-hydroxybutyronitrile. Thus it appeared extremely likely that I arose from two C_4 moieties. The vital clue was obtained when it was observed that the 4-hydroxycrotononitrile isolated from the reaction mixture was essentially all-*trans*. The absence of the *cis* form seemed most unusual and we concluded that this latter substance was in all likelihood primarily responsible for the generation of I. Scheme I, outlined below, embodies our ideas about the formation of I by the action of potassium cyanide on epichlorohydrin.

Although this sequence requires seven discreet steps it successfully surmounts the two most serious obstacles that arose in formulating a mechanism for the formation of I: (a) the mode of formation of the Ziegler–Thorpe group which, we initially thought, had to come from a base-catalysed condensation of two $-CH_2CN$ groups and (b) the stereochemistry of the groups on the saturated carbon atoms of the ring.

Several assumptions have been made in this scheme. that the rate of formation of XVIII must be out line slower than the Diels–Alder reaction leading to XIX; otherwise one could expect the formation of little or none of I. Second, it has been assumed that *trans*-4-hydroxycrotononitrile cannot participate in a Diels–Alder reaction[18] with XVIII. While we have not been able to demonstrate this conclusively by employing 2-aminofuran, we have found that *trans*-4-hydroxycrotononitrile does not react with either 2-acetaminofuran[19] or 2-methoxyfuran at or slightly above room temperature.[20] Finally, it has been assumed that base-catalyzed epimerization of the hydrogen atom α to the nitrile group in XIX takes place. This would accommodate the further rearrangement to I which would perhaps require this hydrogen atom to be *trans* to the oxygen bridge.

The postulation that 2-aminofuran is an intermediate in this reaction has not readily lent itself to scrutiny since this substance is unknown in the free state and previous attempts to prepare it from derivatives have met with uniform failure.[20] However attempts are now being made to prepare the unknown *cis*-4-hydroxycrotononitrile by an alternate route with a view

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(14) F. Johnson and N. A. Starkovsky, *Tetrahedron Letters*, 1173 (1962).

(15) J. Blair, J. J. Brown, and G. T. Newbold, *J. Chem. Soc.*, 708 (1955).

(16) J. R. D. McCormick, J. Reichenthal, U. Hirsch, and N. D. Sjolander, *J. Am. Chem. Soc.*, **84**, 3711 (1962).

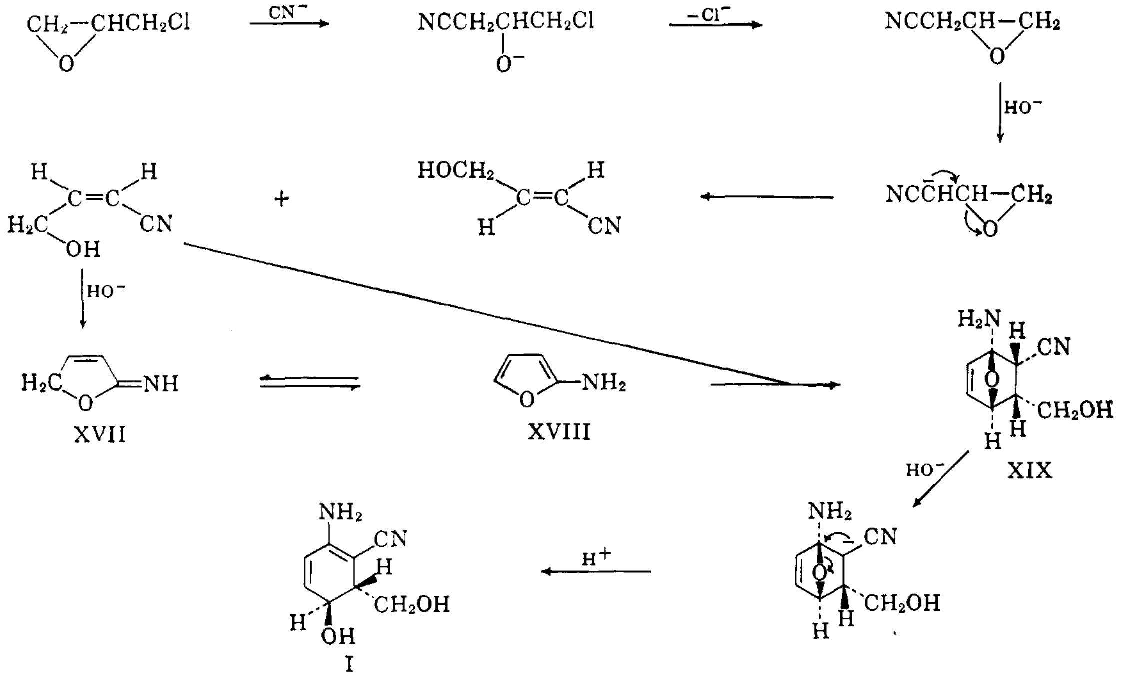
(17) We have confirmed the *trans* nature of the hydrogen atoms on the saturated carbons in this molecule, from its n.m.r. spectrum. In D_2O the splitting constant is 6.3 c.p.s. and this suggests that the hydrogen atoms have considerable axial character implying that the amino and hydroxyl functions are in equatorial positions.

(18) Without a violation of Alder's rule one could not expect this particular reaction to lead to I. Rather, the product would be the *cis* form of I. The latter we have never observed in our reactions.

(19) These experiments were carried out by Dr. R. P. Stein.

(20) H. M. Singleton and W. R. Edwards, Jr., *J. Am. Chem. Soc.*, **60**, 540 (1938).

Scheme I



to proving or disproving the postulated reaction pathway.

The ready accessibility of I coupled with its polyfunctionality makes it appear very attractive as a starting material for the synthesis of a number of natural products. Studies designed to explore the versatility of this material are underway.

Experimental

Melting points were determined on a Fisher-Johns melting point block and are not corrected. Infrared spectra were recorded on a Baird spectrophotometer Model No. 4-65, and mass spectra were obtained using a Bendix Time-of-Flight spectrometer, Model No. 12-100. Epichlorohydrin as supplied by Eastman Kodak was used without further purification.

***trans*-3,4-Dihydro-2-cyano-3-hydroxymethyl-4-hydroxyaniline** (I). A.—To a 2-l. flask containing a magnetically stirred solution of sodium cyanide (100 g., 2.04 moles) in water (480 ml.) there was added dropwise epichlorohydrin (192 g., 2.08 moles), during a period of 1.5 hr. While this addition was being made, the temperature of the contents of the flask was kept at 0–5° using an acetone–Dry Ice bath. Very strong cooling was required to maintain this temperature and without it a highly exothermic and almost explosive reaction took place. Upon complete addition of the epichlorohydrin, the temperature was held between 10–20° for 5 hr. with stirring, and thereafter at room temperature overnight. Filtration of the dark red reaction mixture removed a small amount (4.5 g.) of a colorless crystalline solid, m.p. 165–167°. A specimen twice recrystallized from ethanol had m.p. 167° [lit.[3] m.p. 166–167° for 2,5-bis(cyanomethyl)-1,4-dioxane]. The aqueous filtrate then was continuously extracted with ethyl acetate for 75 hr. At the end of this time the extract was decanted from a considerable amount of crystalline material. Removal of the ethyl acetate under reduced pressure furnished a sludge of oil and crystalline matter. The latter was diluted with hot ethanol and after cooling the crystals were removed by filtration. These were combined with the crop which had separated out during the extraction procedure and were recrystallized from ethanol to afford lemon yellow crystals (31 g.), m.p. 154–156°. A sample recrystallized three times from acetone furnished the pure compound, m.p. 157°. Its ultraviolet absorption spectrum exhibited a maximum at 3300 Å. (ϵ 5700).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.1; N, 16.9; mol. wt., 166. Found: C, 57.8; H, 6.1; N, 16.7; mol. wt. (by mass spectral analysis), 166.

When double the quantity of sodium cyanide was used in this reaction, the yields of I were diminished considerably.

B.—A solution of 3-hydroxy-4-chlorobutyronitrile (13 g. 0.108 mole) in benzene (100 ml.) was placed in a three-necked 1-l. flask equipped with mechanical stirrer, a condenser with a drying tube, and an addition funnel with a nitrogen purge. After the atmosphere in the flask had been replaced with nitrogen, a solution of sodium methoxide (from 2.3 g.-atoms of sodium, 0.1 mole) in methanol (40 ml.) and benzene (20 ml.) was added during 4 hr. to the rapidly stirred solution of the nitrile. During the addition a colorless precipitate gradually appeared and the solution assumed a deep orange color. Stirring was continued overnight and the insoluble white precipitate was then removed by filtration and discarded. The filtrate was evaporated under reduced pressure to remove solvent and the gummy yellow residue was triturated with ethanol. The solid material (1.6 g.) thus obtained was recrystallized twice from ethanol and furnished lemon yellow crystals (0.8 g.) of the desired substance, m.p. 157°. A mixture melting point (156–157°) of this substance with a sample prepared as described under A showed no depression. Their infrared spectra were also identical.

***trans*-3,4-Dihydro-2-cyano-3-acetoxymethyl-4-acetoxyaniline** (II).—The dialcohol I (0.5 g.) was added to pyridine (2 ml.) and acetic anhydride (2 ml.) was added dropwise. The solution was allowed to stand overnight and the excess reagents were then removed under reduced pressure. The viscous residue was crystallized from petroleum ether (b.p. 30–60°)–ethyl acetate and afforded the highly crystalline diacetate, m.p. 126–128° (0.51 g.). Several recrystallizations from small amounts of ethanol yielded the analytical sample, m.p. 129–130°.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.6; H, 5.6; N, 11.2. Found: C, 57.8; H, 5.7; N, 11.4.

1-Amino-2-cyano-3-hydroxymethyl-4-hydroxycyclohexene (III).—A solution of the dialcohol I (3.0 g.) in methanol (50 ml.) was hydrogenated in the presence of a 10% palladium-on-charcoal catalyst (104 mg.) at room temperature and pressure. Absorption of hydrogen (1 equiv.) ceased after 34 min. and the solution was then filtered and evaporated to small bulk. The product then crystallized as colorless prisms, m.p. 175–176°. Three further crystallizations from the same solvent gave the analytically pure material (2.1 g.), m.p. 175–176°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.1; H, 7.2; N, 16.7. Found: C, 57.4; H, 6.8; N, 16.7.

1-Amino-2-cyano-3-acetoxymethyl-4-acetoxycyclohexene (IV). A.—A solution of the diacetate III (1.00 g.) in methanol (30 ml.) was stirred in an atmosphere of hydrogen with a 10% palladium-on-charcoal catalyst (102 mg.) for 36 min. at 25°. Absorption of hydrogen (1 equiv.) ceased at this point and the solution was filtered through diatomaceous earth and evaporated to dryness. The residue, m.p. 99–102°, obtained in almost quantitative yield, was essentially pure product. A specimen recrystallized twice from acetone–ether furnished the analytical specimen, m.p. 102–104°.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.1; H, 6.4; N, 11.1. Found: C, 56.9; H, 6.4; N, 11.1.

B.—A solution of III (0.5 g.) in pyridine (3 ml.) and acetic anhydride (3 ml.) was heated on the steam bath for 90 min. and the reaction mixture was then evaporated to dryness under reduced pressure. Crystallization of the residual yellow gum from acetone–ether afforded the title compound, m.p. 103–104°. This did not depress the melting point of a specimen prepared by method A, m.m.p. 102–104°.

3-Amino-2-cyanobenzyl Acetate.—The diacetate II (1.0 g.) in a 25-ml. flask fitted with a distillation apparatus was immersed in an oil bath at 195°. A vacuum of 160 mm. was maintained in the apparatus by means of a water pump, nitrogen being aspirated through the system. The temperature of the oil bath was raised to 215° and, during 25 min., acetic acid (0.87 g., theoretical yield) distilled out. The pot residue, dark brown in color, crystallized on cooling. This was taken up in methylene chloride (25 ml.) and percolated through a column of silica gel. (25 g.). Elution of the column with methylene chloride containing 20% ethyl acetate afforded a pale yellow product which crystallized from ether–petroleum ether (b.p. 30–60°) as yellow plates, m.p. 63–64° (2.6 g., 83%). Two further crystallizations from the same solvent mixture led to the pure compound, m.p. 66°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3; N, 14.7. Found: C, 63.2; H, 5.2; N, 14.7.

7-Aminophthalide.—3-Amino-2-cyanobenzyl acetate (0.25 g.) was dissolved in 6 *N* hydrochloric acid (10 ml.) and the solution was heated on a steam bath for 24 hr. The liquid was then evaporated to dryness under reduced pressure and the resulting solid was triturated with sodium hydrogen carbonate solution. Removal of the solid by filtration gave an almost white product (0.256 g.) which when recrystallized from ether led to 7-aminophthalide as small, white, diamond-shaped crystals, m.p. 122°. One further recrystallization from ether gave the analytical sample, m.p. 122.5–123°.

Anal. Calcd. for $C_8H_7NO_2$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.3; H, 4.8; N, 9.3.

7-Hydroxyphthalide.—7-Aminophthalide (0.2 g.) was dissolved in a mixture of sulfuric acid (3.04 g.) and water (20 ml.) and diazotized at −5° with a solution of sodium nitrite (95 mg.) in water (5 ml.) during 8 min. The mixture was then stirred below 0° for 1 hr. and excess nitrous acid was decomposed thereafter by the addition of a small amount of urea. The liquid was then heated on a steam bath for 1.5 hr. and filtered while hot to remove a trace of a bright red precipitate. The filtrate on cooling deposited a crop of fine, needle-shaped crystals (0.153 g.) which were removed, dissolved in methylene chloride (5 ml.), and percolated through a column of alumina (3 g.). Elution with methylene chloride (40 ml.) gave white material which when recrystallized from ether–petroleum ether (b.p. 30–60°) afforded pure 7-hydroxyphthalide as colorless prisms, m.p. 135–136°. A mixture melting point of this material with an authentic sample prepared according to Blair, *et al.*,[15] showed no depression, m.m.p. 135–136°. The infrared spectra of the two specimens were also identical.

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Mechanism of the Desulfurization of Episulfides with Methyl Iodide[1]

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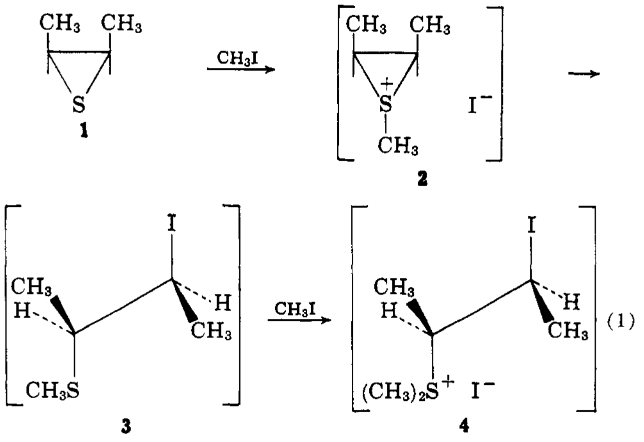
The principal route for the stereospecific desulfurization of 2-butene episulfides with methyl iodide involves the following sequence of intermediates: episulfonium salt, β-iodosulfide, β-iodosulfonium iodide. When methyl bromide was used as the alkylating agent, the sulfide and sulfonium bromide could be isolated. These were also converted to butene when treated with iodide ion or iodine under the original reaction conditions. All elimination reactions were highly stereospecific except that between iodide ion and the β-bromosulfonium bromides. The exceptional situation probably involves a bromide ion induced racemization *via* a vinylsulfonium intermediate or epimerization *via* nucleophilic displacement of the secondary bromide.

In an earlier report on the desulfurization of 2-butene episulfides, the mechanism was discussed in terms of the observed stereospecific formation of 2-butene corresponding to the starting episulfide.[3] The route proposed by Culvenor, Davies, and Heath[4] for olefin formation (eq. 1, 2, and 4) could be modified by substituting an alternate iodide-induced elimination (eq. 3).



Attempts to isolate any of the proposed intermediates **2**, **3**, and **4**, were unsuccessful, probably because of the high reactivity of iodide ion as a nucleophile and iodine-containing organic compounds as substrates. However, it seemed feasible to block the process and accumulate one or more of the intermediates by using methyl bromide in place of methyl iodide, for bromide ion should not be expected to be involved in an elimination reaction of the type shown in the last step of either mechanistic route. It would seem most likely that intermediate **4** should accumulate.

When *cis*-2-butene episulfide was allowed to react with methyl bromide in acetonitrile at room temperature (eq. 5), the threo-β-bromosulfonium bromide (**6**) slowly precipitated as large, white crystals. After a reaction time of 18 days the yield of solid was 47%. Evapora-

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[2] Abstracted in part from the Ph.D. Thesis of D. J. Pettitt, March, 1964.

[3] G. K. Helmkamp and D. J. Pettitt, *J. Org. Chem.*, **25**, 1754 (1960).

[4] C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 282 (1949).