proper preparation and practice it was possible to begin rate measurements within a few seconds after mixing so that quite rapid rates of hydrolysis could be followed. However, it should be pointed out that in the fastest rates in Tables I-V ($k_r = 10^{-1}$ sec^{-1}) we were able to follow only the last 25-30% of the hydrolysis of II. Since all the reactions followed good first-order kinetics this did not really make any difference, however, particularly since by using a larger initial concentration of II we could still follow the hydrolysis over essentially the same over-all change in optical density.

The initial sulfinyl sulfone concentrations used in the kinetic runs were in the range 0.9–1.8 × 10^{-4} M, except for the very fast runs where initial concentrations of 1.8–3.5 × 10^{-4} M were used. The per cent dioxane in our solutions was calculated after the fashion of Bunton, *et al.*[12]

Acknowledgment. We acknowledge a most stimulating discussion of the problem with Professor C. A. Bunton.

Mechanism of the Pyridoin Condensation

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Contribution from the Department of Chemistry, University of Arizona, Tucson, Arizona. *Received February 17, 1967*

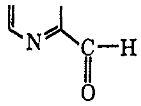
Abstract: When pyridine-2-aldehyde (**1**) is dissolved in acetic acid, 2,2′-pyridoin is formed. The reaction is second order in aldehyde and is catalyzed by acids and metal ions. At 70° an isotope effect ($k_{\mathrm{RCHO}}/k_{\mathrm{RCDO}}$) of 2.52 was measured which indicates that the aldehydic hydrogen bond is being broken in the rate-determining step. A mechanism which involves nucleophilic addition of **1** to the conjugate acid of **1** followed by a rate-determining removal of a proton, cyclization, and elimination is proposed.

From a classical viewpoint, the benzoin condensation is of importance since it represents one of the first organic reactions whose mechanism was defined using the now commonplace tools of physical organic chemistry.[1,2] For a number of years the reaction was thought to be specifically catalyzed by cyanide ion,[3] but recent work on the mechanism of thiamine action has shown that similar reactions in biological systems and in the laboratory can be accomplished through the catalytic action of thiazolium salts.[4–6] Less well known is the fact that in certain circumstances acid-catalyzed condensations leading to benzoins are also possible; this paper attempts to elucidate the mechanism of such a reaction.

Results and Discussion

The dimerization of pyridine-2-aldehyde (**1**) to 2,2′-pyridoin (**2**), hereafter referred to as the pyridoin condensation, was first reported in 1953 by Hensel.[7] He found that orange crystals of **2** precipitated when equal volumes of **1** and glacial acetic acid were stirred together for a few hours; it was also observed that the 3- and 4-aldehydes failed to undergo condensation under similar conditions. Also, Marvel and Stille[8] have noted that **2** was a by-product which they obtained during some boron trifluoride catalyzed condensation reactions of **1** with other substrates.

To define the scope of this reaction in greater detail, we studied the behavior of furfural, thiophene-2-aldehyde, pyrrole-2-aldehyde, imidazole-4(5)a-ldehyde, 8-acetoxyquinoline-2-aldehyde, and quinoline-2-aldehyde under similar conditions; of these compounds only quinoline-2-aldehyde underwent condensation. These observations suggest that the minimum structural factors which are required for reaction are



and that secondary factors, such as steric effects and basicity, play an important role in determining the ease with which condensation occurs.

A preliminary investigation of the ultraviolet spectrum of **2** showed that in the presence of acid the strong absorption maximum at 380 mμ (ε 18,000) quickly disappeared with the concurrent appearance of two maxima at 233 and 260 mμ (ε ~3000). Since **1** has two maxima in the ultraviolet at 233 and 260 mμ (ε 3460 and 2950, respectively) it appeared either (a) that the condensation was reversible and, under dilute conditions, **2** was reverting to **1**, (b) that a disproportionation reaction was taking place giving 2,2′-pyridil (**3**) and 2,2′-dihydropyridoin (**4**), or (c) that **2** was simply being oxidized to **3** by air. Compounds **3** and **1** should have similar spectral properties in the ultraviolet region of the spectrum.

Thin layer chromatography (tlc) using RSC silica gel G and developing with a 50:50 mixture of chloroform–ethyl acetate gave a clean separation of authentic individual and mixed samples of **1** (R_f 0.79), **2** (R_f 0.21), **3** (R_f 0.63), and **4** (R_f 0.10). Using a 1:9 mixture of concentrated ammonium hydroxide and ethanol, a good separation of **4** (R_f 0.58) and picolinic acid (**5**) (R_f 0.24) was obtained. Regardless of the reaction conditions used, only 2,2′-pyridoin and 2,2′-pyridil were observed as products.

Further product analysis was carried out by vapor phase chromatography (vpc) utilizing a 10 ft × 0.25

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(1) A. Lapworth, *J. Chem. Soc.*, **83**, 995 (1903).
(2) A. Lapworth, *ibid.*, **85**, 1206 (1904).
(3) For an excellent summary of the scope and a historical review, see W. S. Ide and J. S. Buck, *Org. Reactions*, **4**, 269 (1948).
(4) T. Ugai, S. Tanaka, and S. Dokawa, *J. Pharm. Soc. Japan*, **63**, 269 (1943).
(5) T. Ugai, S. Tanaka, and S. Dokawa, *ibid.*, **64**, 605 (1944).
(6) R. Breslow, *J. Am. Chem. Soc.*, **80**, 3719 (1958), and other papers in this series.
(7) H. Hensel, *Angew. Chem.*, **65**, 491 (1953).
(8) C. S. Marvel and J. K. Stille, *J. Org. Chem.*, **21**, 1313 (1956).

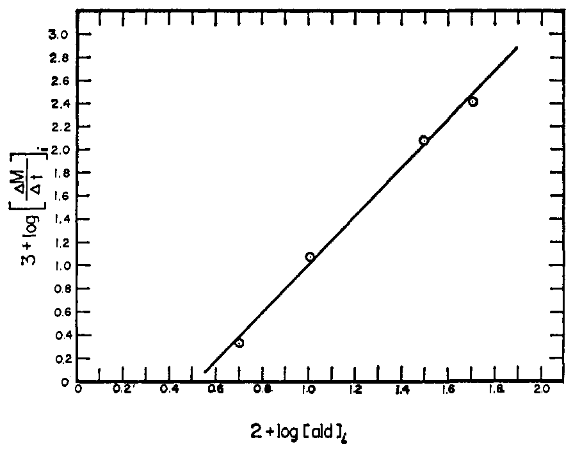


Figure 1. Initial rate of dimerization as a function of the initial aldehyde.

in. column packed with GE-SE silicone on firebrick and heated at 200°. Although **2** and **4** decomposed under these conditions, their acetates passed through the column without difficulty. Acetylation of the reaction mixture described above followed by vpc indicated the presence of only **2** and **3** again. In a similar experiment in which **1** was used rather than **2**, analysis of the reaction mixture showed that only **2**, **3**, and unreacted **1** were present.

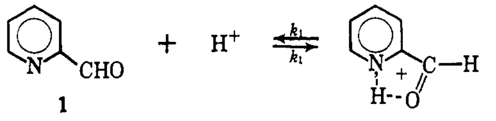
The tlc and vpc data both indicate that pyridoin in the presence of acid is converted to pyridil; however, neither analytical method gave any evidence for the reversal of the condensation or for the disproportionation of **2** to **3** and **4**. Since the production of **3** from **2** was markedly slowed when care was taken to exclude air from contact with the solutions of **2**, these data suggest that the condensation of **1** proceeds exclusively to **2** which may in turn be oxidized by air to **3**.

Kinetic studies were carried out in glacial acetic acid solvent, and the reaction rates were measured dilatometrically. Due to the gradual concurrent oxidation of **2** to **3**, we were forced to confine our observations to the initial portion of the dimerization. A plot of the initial rate of the reaction as a function of aldehyde concentration (Figure 1) clearly demonstrated that the reaction is second order with respect to pyridine-2-aldehyde in the concentration range which was studied (0.05–0.50 *M*).

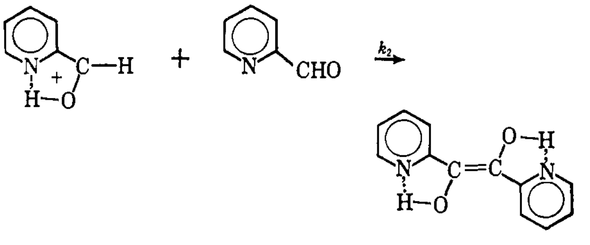
The influence of added strong acid was measured by observing the effect of added toluenesulfonic acid on the initial rate of reaction. At low concentrations of added acid, the reaction rate appears to be directly proportional to the concentration of *added* acid. However, we were unable to make measurements over a very wide range of acid concentrations since the heat of neutralization was sufficiently high to cause initial volume changes not attributable to the dimerization reaction.

These observations place severe limitations on the mechanistic interpretations which are possible and require that the following general scheme (eq 1 and 2) applies.

To obtain further details concerning step 2, we prepared and studied the reaction of the deuterioaldehyde; this was synthesized according to eq 3.

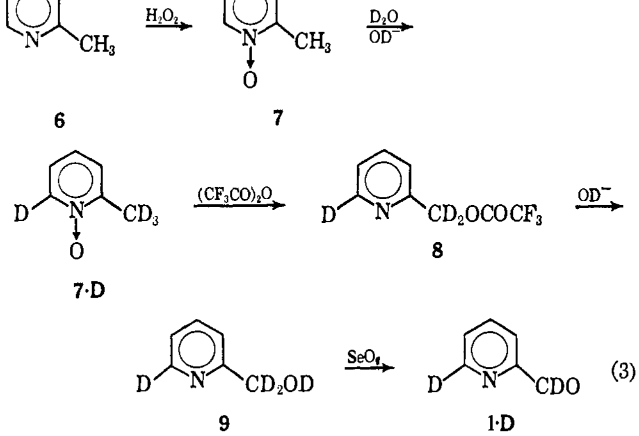


1 (1)



(2)

2



6 **7** **7-D** **8** **9** **1-D** (3)

Picoline was converted to its N-oxide (**7**) and heated at 80–90° in deuterium oxide to which a small piece of sodium metal had been added. Rapid exchange of the methyl protons occurred along with a slower exchange of the proton at C_5, as evidenced by the change in the nmr spectrum of the compound. After several successive equilibrations, an nmr spectrum and a deuterium analysis indicated that all four active hydrogens were exchanged. Rearrangement of the N-oxide to the trifluoroacetate **8** followed by hydrolysis and oxidation gave the desired deuterated aldehyde **1-D**.

The ratio of rate constants (k_H/k_D) at 70° was found to be 2.52 which indicates that the carbon–hydrogen bond of the aldehyde is being broken in the rate-determining step. Since this kinetic isotope effect is at the low end of the range usually observed for primary isotope effects, we considered the possibility that deuterium was being lost from our labeled aldehyde through exchange with the solvent. The results of the following two experiments suggest that this is not an important reaction.

When the condensation was carried out in an nmr tube with deuterated aldehyde in acetic acid solvent, repeated scanning of the region at τ 0 (the position of the aldehyde resonance) did not provide any evidence for the formation of unlabeled aldehyde during the course of the reaction. Since the possibility existed that this technique was not sufficiently sensitive to detect low concentrations of aldehyde, a series of kinetic experiments which would provide similar evidence was designed.

The rate of the pyridoin condensation was followed to about 80% completion with **1** and **1-D** in both acetic and deuterioacetic acid solvents. If isotopic exchange of the aldehyde hydrogen with the solvent was occurring, it would be expected that the rate of reaction of **1** in deuterioacetic acid would slow down at the latter stage of reaction, whereas that of 1-D in acetic acid would increase. It is apparent from an inspection of Figure 3, which summarizes these experiments, that isotopic exchange does not occur under the conditions of the pyridoin condensation. These data also show that no over-all kinetic solvent isotope effect exists; this, however, is not unusual in multistep reactions involving equilibria.

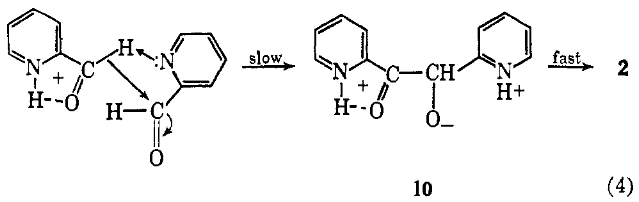
In a further study of catalytic effects, we have found that the condensation is also catalyzed by metal ions, although their catalytic influence is quite small when compared to the efficiency of comparable concentrations of strong acids. These results are summarized in Table I.

Table I. Effect of Catalysts on the Pyridoin Condensation[a]

Metal	Concn, *M*	Relative rates
Cu^{2+}	0.05365	2.32
Zn^{2+}	0.05365	2.14
Co^{2+}	0.05365	1.22
Ni^{2+}	0.05365	0.65
K^{2+}	0.1073	0.97
None	...	1.00
$p\text{-}CH_3C_6H_4SO_3H$	0.01073	6.68

[a] The concentration of pyridine-2-aldehyde in all runs was 0.1073 *M*. The solvent used was glacial acetic acid at 30°.

On the basis of these data, several sequences for the dimerization process can be written which are consistent with the experimental observations. The simplest of these, from a conceptual viewpoint, is illustrated in eq 4.

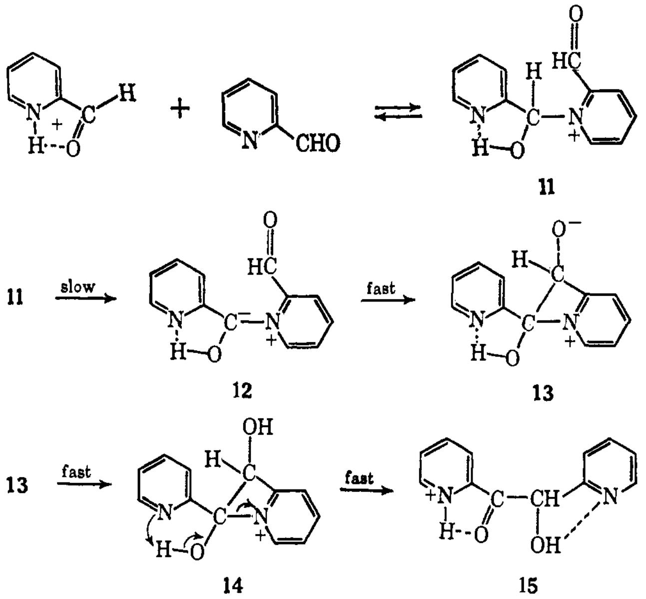


10 (4)

Protonation (or chelation) of **1** should result in a substantial enhancement of the acidity of the aldehydic proton. Attack on this proton by the nitrogen of a second molecule of **1** with a concerted reorganization of the electrons would result in the formation of **10** which, after a tautomeric shift, would produce **2**. Although we can offer no concrete evidence against this pathway, reactions in which an aldehydic proton is removed by a relatively weak base are without precedence and we regard it as unlikely.

An analogous sequence which involves the aldehyde hydrate can also be written; this modification of (4) has some merit since it has been demonstrated that pyridinium salt formation markedly increases the acidity of methylenic protons on carbon atoms in the 2 and 6 positions. Weighing against this possibility is our observation that when the pyridoin condensation was attempted with **1** in absolute alcohol containing toluenesulfonic acid, the diethyl acetal of **1** rapidly formed and did not undergo further reaction. This observation suggests that a process similar to reaction 4 but involving the hydrate is probably not involved in the dimerization reaction. An alternative mechanism which we favor is Scheme I.

Scheme I



Nucleophilic addition of **1** to a protonated (or chelated) second molecule would give **11**; loss of a proton from this ion to produce **12** should be favored by the fact that the betaine can be stabilized by resonance interactions with both pyridine rings. In view of the isotope effect studies, this step must be rate determining and irreversible.

Intramolecular cyclization of **12** would result in the formation of **13** which on protonation would give **14**; rearrangement of **14** as indicated would produce the observed product. Although numerous minor modifications of the latter stages of the sequence are possible, we prefer to avoid further speculation on these points in the absence of more definitive experimental data.

From rate constants measured over a 40° temperature range, an activation energy (E_a) was calculated from the Arrhenius equation and found to be 6.2 kcal/mole. From transition-state theory, the free energy of activation ($\Delta G^{\ddagger}$) was 25 kcal/mole and the entropy of activation ($\Delta S^{\ddagger}$) was -55 eu. These parameters require a highly ordered transition state and are typical of those observed for a number of ionic condensations in rather nonpolar solvents.

Experimental Section

Melting points were determined in capillary tubes and are corrected; boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer and calibrated with a polystyrene film. Ultraviolet spectra were recorded with a Cary 14 instrument; all nmr measurements were taken with the Varian A-60 spectrometer in deuterated chloroform using tetramethylsilane as an internal standard. Microanalyses were obtained by C. F. Geiger, Ontario, Calif., and deuterium analyses were performed by Josef Nemeth, Urbana, Ill.

2,2′-Pyridoin. The method of Hensel[7] was employed. To 10 ml of glacial acetic acid was added 10 ml (11.2 g, 0.105 mole) of pyridine-2-aldehyde, and the solution was stirred at room temperature. After 5 hr the crystalline product was collected by filtration and weighed 7.85 g (70%), mp 156–157° (lit.[7] mp 156°). For large-scale preparative runs the cyanide-catalyzed reaction described by Buckler[9] is more rapid and practical.

2,2′-Pyridil. Oxidation of 2,2′-pyridoin with nitric acid or by bubbling air through a solution of the compound in glacial acetic acid warmed to 60° gave the diketone in yields of 60–65% after

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[9] C. A. Buckler and J. O. Harris, *J. Am. Chem. Soc.*, 72, 5015 (1950).

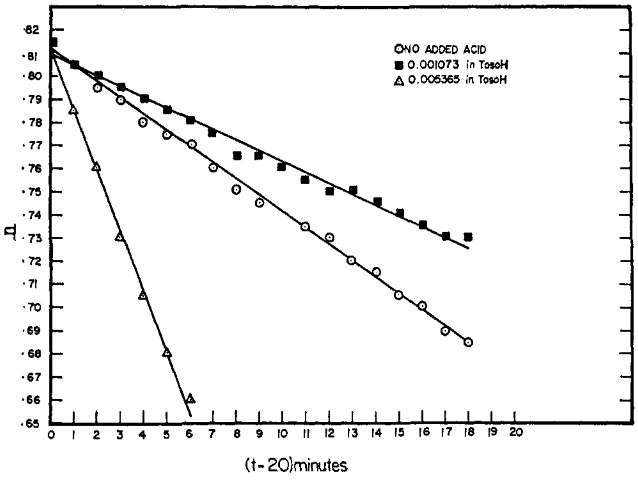

Figure 2. Acid catalysis studies.

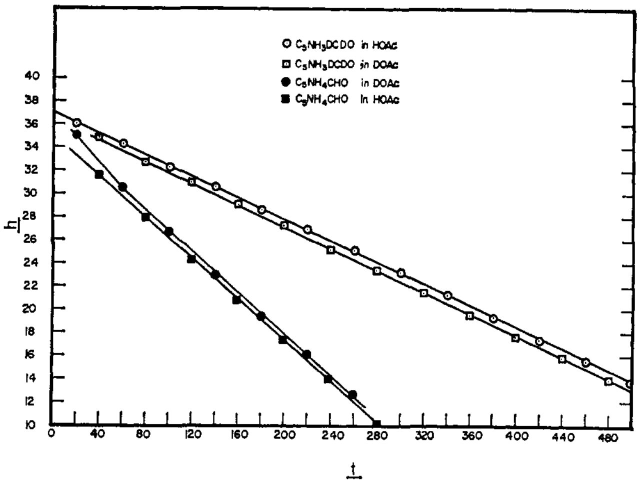

Figure 3. Isotope effects as a function of solvent.

recrystallization from ethanol. The product melted at 156–157° (lit.[10] mp 154–155°).

2,2′-Dihydropyridoin. Reduction of 2,2′-pyridoin with sodium borohydride in ethanol and dilution of the reaction mixture with water followed by continuous extraction with chloroform gave the title compound in 70% yield after recrystallization from ethanol, mp 158–159° (lit.[11] mp 154°).

2,2′-Pyridoin Monoacetate. This compound was prepared by the method described by Cramer in a yield of 51%, mp 116.5–118° (lit.[11] mp 119°).

2,2′-Dihydropyridoin Diacetate. 2,2′-Dihydropyridoin (0.30 g, 0.014 mole) was stirred with 15 ml of pyridine and 7.15 g (0.0701 mole) of acetic anhydride for 1.5 days and then poured onto 100 g of ice. The product was recrystallized from methanol and was obtained in 70% yield, mp 139–140°.

Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.37; H, 5.38; N, 8.60.

2,2′-Quinaldoin. To 10.0 g (0.0637 mole) of quinoline-2-aldehyde was added 10 ml of glacial acetic acid, and the solution was stirred overnight at 40°. The acetic acid was removed under reduced pressure, and the product (7.5 g, 75%) was recrystallized from dioxane, mp 235–240° (lit.[9] mp 232–233°). Using similar conditions, we were unable to obtain analogous condensations or crossed condensations with furfural, thiophene-2-aldehyde, pyrrole-2-aldehyde, imidazole-4(5)-aldehyde, or 8-acetoxyquinoline-2-aldehyde.

Pyridine-2-aldehyde-d_2. Picoline N-oxide was heated at 80–90° in deuterium oxide to which a small piece of sodium had been added until equilibration had occurred as evidenced by no further change in the nmr spectrum. The water was then distilled under reduced pressure and the process repeated until the nmr spectrum indicated that complete exchange of the methyl protons and the α hydrogen of the pyridine ring occurred.

Anal. Calcd for $C_6H_3D_4NO$: atom % excess D, 57.14. Found: atom % excess D, 57.05.

To 36.0 g (0.315 mole) of the above was added 140.0 g (0.670 mole) of trifluoroacetic anhydride; care was taken to keep the solution cooled to 0° in an ice bath. After the addition was complete, the solution was kept at 0° for an additional 3 hr and then stirred at room temperature overnight. The solution was distilled to yield 94.5 g (94%) of 2-trifluoroacetatomethylpyridinium trifluoroacetate-d_4, bp 84–86° (2 mm).

To 94.3 g (0.296 mole) of this salt was added 51 g (0.75 mole) of sodium ethoxide in 51 ml of deuterium oxide, and the solution was warmed at 60° for 18 hr. Distillation gave 19.0 g (57.2%) of 2-pyridylmethanol-d_4, bp 80–85° (2.2 mm).

To 165 ml of dry dioxane was added 18.5 g (0.163 mole) of the above 2-pyridylmethanol-d_4 and 9.00 g (0.018 mole) of selenium dioxide, and the mixture was heated at 80° for 4 hr. After removal of the precipitated selenium (60 g, 94%) the filtrate was distilled to give 14.9 g (83.3%) of the deuterated aldehyde, bp 83–84°.

Anal. Calcd for $C_6H_3D_2NO$: atom % excess D, 40.00. Found: atom % excess D, 39.95.

Pyridine-2-aldehyde Diethyl Acetal. Pyridine-2-aldehyde was dissolved in absolute ethanol containing a trace of toluenesulfonic acid. After several hours, distillation of the reaction mixture gave an oil, bp 127–128°, which was shown to be the diethyl acetal of pyridine-2-aldehyde by a comparison of the infrared and nmr spectra with those of an authentic sample.[12]

Kinetics. Reaction rates were followed using standard dilatometric techniques. At the start of a kinetic run, 50 ml of purified and degassed glacial acetic acid was placed in the dilatometer and allowed to stand until thermal equilibrium with the constant-temperature bath was achieved. The appropriate weight of aldehyde was then added to obtain the desired concentration and, after allowing 15 to 20 min for thermal equilibration, the rate of reaction was followed by measuring the decrease in volume of solution as a function of time. A cathetometer was used to measure the height of the solutions in the capillary tube to the nearest 0.005 cm, and the constant-temperature bath varied less than 0.001° during a kinetic run. The dilatometer constant was determined by making high-precision density measurements on the initial and final solutions to determine the total volume change which occurred. Pertinent data are summarized in Tables I and II and Figures 1–3.

Table II. Initial Rates as a Function of Concentration

Run	[Aldehyde], M	$\Delta M/\Delta t$	2 + log [aldehyde]	3 + log [$\Delta M/\Delta t$]
1	0.3078	0.1190	1.488	2.076
2	0.3078	0.1204	1.488	2.081
3	0.1046	0.0118	1.020	1.073
4	0.1046	0.0122	1.020	1.087
5	0.5033	0.2533	1.702	2.404
6	0.05049	0.0021	0.703	0.325

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[10] G. H. Lenart, *Ann.*, **410**, 109 (1915).

[11] F. Cramer and W. Krum, *Ber.*, **86**, 1586 (1953).

[12] W. Mathes, W. Souermilck, and T. Klein, *ibid.*, **87**, 1870 (1954).