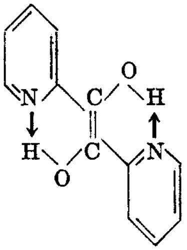
[Contribution No. 147, Department of Chemistry, University of Tennessee]

THE INFLUENCE OF CHELATION ON THE STABILITY OF ENEDIOLS. I. 2-PYRIDOIN, 1-PHENYL-2-(2-PYRIDYL)-1,2-ETHENEDIOL, AND 1-PHENYL-2-(4-PYRIDYL)-1,2-ETHENEDIOL

C. A. BUEHLER, JOHN W. ADDLEBURG, and DAN M. GLENN

Received May 25, 1955

It has been shown that the 2-aldehydes of pyridine and quinoline form remarkably stable enediols. This fact has been accounted for (1, 2c) on the basis of a *trans* chelated formula which in the case of pyridine would be represented as I:

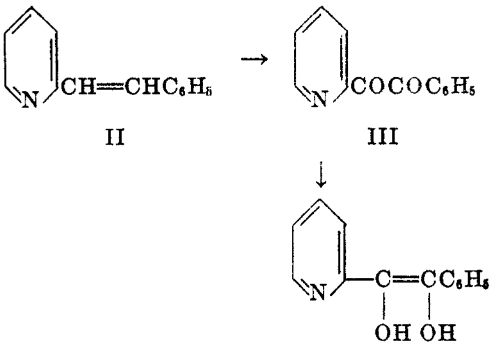


I

In the present article the effects of partially and completely inhibiting the chelation on the stability of the enediol are discussed.

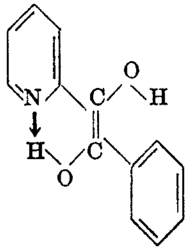
The reference compound selected is known as 2-pyridoin but is, in fact, the isomeric enediol. It has been studied by various investigators (2), the most convincing evidence for the enediol structure having been advanced by Hensel (2c) and Cramer and Krum (2d). The enediol can be prepared from pyridine 2-aldehyde by treatment with potassium cyanide or glacial acetic acid, by low pressure catalytic reduction of 2-pyridil, or sometimes the compound forms as the aldehyde is heated. The preparation by the benzoin condensation differs from that of quinaldehyde and 6-methylquinaldehyde (1) in that no glycol and acid are formed. The enediol can be kept indefinitely in the dry form, gives the characteristic tests with sodium 2,6-dichlorobenzeneoneindophenol and Tollens' reagent, and in solution is readily oxidized to the pyridil. Further evidence for the enediol structure is the fact that the compound forms a dibenzoate. Acetylation led not to the diacetate, but to the monoacetate of the isomeric pyridoin. Hydrolysis of the latter under varying conditions of acidity and alkalinity produced invariably the enediol. All attempts at methylation of the enediol failed. Cleavage resulted in the attempts with sodium and methyl iodide in liquid ammonia (3) and with dimethyl sulfate and potassium hydroxide by a special procedure (4). In the former case picolinamide was produced and in the latter, methyl picolinate. Further evidence for the stability of the enediol is the fact that it cannot be converted into the isomeric benzoin with alcoholic hydrogen chloride nor can it be reduced to the glycol by low pressure hydrogenation in the presence of Adams platinum catalyst.

1-Phenyl-2-(2-pyridyl)-1,2-ethenediol (IV) was prepared from α-stilbazole (II) by the reactions shown below.


II III IV

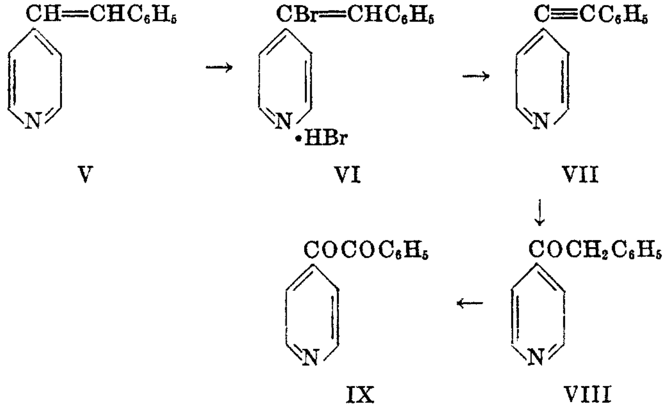
Reduction of a methanolic solution of III with hydrogen in the presence of Adams platinum catalyst gave the enediol IV, m.p. 61°. The isolation required operation at low temperatures in an atmosphere of nitrogen in order to prevent the formation of an oil. The enediol responds to the usual tests with sodium 2,6-dichlorobenzeneoneindophenol and Tollens' reagent and is so easily reduced to the glycol that it was necessary for isolation to terminate the hydrogenation when one mole of hydrogen had been absorbed.

The mixed enediol is best represented by IVa:


IVa

Thus it possesses partial chelation, an effect which permits isolation but which gives a type considerably less stable than the completely chelated 2-pyridoin. Fuson (5a) in his study of *o*-substituted 1,2-diphenyl-1,2-ethenediols found that *o*-substituted groups such as isopropyl offer sufficient steric hindrance to permit the isolation of the enediol. It was not possible, however, to obtain the enediol with a mixed type such as 1-phenyl-2-(2,4,6-triisopropylphenyl)-1,2-ethenediol (5b). Thus it appears that chelation, made possible by the nitrogen atom of the pyridine ring, makes a greater contribution toward stability than the steric hindrance offered by the two *o*-isopropyl groups in the substituted phenyl group.

Several courses were investigated in the attempts to synthesize 1-phenyl-2-(4-pyridyl)-1,2-ethenediol. The oxidation of γ-stilbazole gave 2-(4-pyridyl)-selenonaphthene (6) as the sole recoverable product. An approach through the corresponding benzoin was ruled out when it was discovered that the benzoin condensation of benzaldehyde and pyridine-4-aldehyde gave ordinary benzoin, 1,2-di-4-pyridyl-1,2-ethanediol and pyridine-4-carboxylic acid as products. Finally the reactions (7) below led to the proper benzil.



γ-Stilbazole (V) was treated with bromine and acetic acid to give 4-(α- (or β) bromostyryl)pyridine hydrobromide (VI) which when treated with alcoholic potassium hydroxide produced 1-(4-pyridyl)-2-phenylethyne (VII). The latter was hydrated by the use of 65% sulfuric acid and concentrated ammonium hydroxide to give the desoxybenzoin VIII which upon oxidation with selenium dioxide gave 1-phenyl-2-(4-pyridyl)-1,2-ethanedione (IX), 28%, and an unidentified product, $C_{13}H_9NO$, 19%, of m.p. 249°. Reduction of IX with equimolar quantities of hydrogen at low pressure using Adams platinum catalyst led to approximately equal quantities of 1-phenyl-2-(4-pyridyl)-1,2-ethanediol and the unchanged dione. Thus the intermediate enediol in which no chelation is possible cannot be prepared by the method which is satisfactory for the completely chelated 2-pyridoin (I) and the partially chelated 1-(2-pyridyl)-2-phenyl-1,2-ethenediol (IVa). It is so unstable, in fact, that it exhibits preferential reduction over the corresponding dione.

EXPERIMENTAL[1]

2-Pyridoin. A solution of 30 g. of freshly distilled pyridine-2-aldehyde in 50 ml. of pyridine and 200 ml. of water was heated on a steam-bath and 2 g. of potassium cyanide in 10 ml. of water was added with stirring. The reaction mixture, which turned dark with the formation of a precipitate, was heated on a steam-cone for 30 minutes. After cooling in an ice-bath, the precipitate was removed by filtration and washed with about 15 ml. of cold ethanol. Crystallization from pyridine gave 28.5 g. (95%) of yellow to orange needles of 2-pyridoin, m.p. 156° [Harries and Lenart (2a) give 156°; Mathes, Sauermilch, and Klein (2b), 156°].

(*A*) *The dibenzoate* was prepared by the method of Buehler and Harris (1); m.p. 198° [Cramer and Krum (2d) give 190°].

Anal. Calc'd for $C_{26}H_{18}N_2O_4$: C, 73.93; H, 4.27.
Found: C, 73.65; H, 4.49.

(*B*) *2-Pyridoin acetate* was prepared from 2-pyridoin, acetic anhydride, and *p*-toluene-

---

[1] All melting points are uncorrected and were determined on an aluminum block.

sulfonic acid at room temperature. Crystallization of the crude product from ethyl acetate by adding petroleum ether gave a 66% yield of a white product, m.p. 117° [Cramer and Krum (2d) give 119°]. The infrared absorption curve of the acetate gives absorption bands[2] at 1707 and 1745 $cm.^{-1}$ corresponding to the ketone and ester carbonyl groups respectively.

The p-nitrophenylhydrazone of (*B*) was prepared in the usual manner, m.p. 173.5° (dec.).

Anal. Calc'd for $C_{20}H_{17}N_5O_4$: C, 61.37; H, 4.38.

Found: C, 61.12; H, 4.60.

Hydrolysis of 2-pyridoin acetate p-nitrophenylhydrazone with 20% sulfuric acid gave the p-nitrophenylhydrazone, m.p. 143.5°.

Anal. Calc'd for $C_{18}H_{15}N_5O_3$: N, 20.04. Found: N, 19.93.

(*C*) *Attempts to prepare 1,2-di-2-pyridyl-1,2-dimethoxyethene.* Methylation of the enediol by the conventional methods using dimethyl sulfate, diazomethane (8), methyl *p*-toluenesulfonate, or methyl iodide and silver oxide was unsuccessful. The action of the Grignard reagent on the dione (9) also failed. Two methods as indicated below gave cleavage products. Modified Hendricks and Rundles' method (3): To 0.5 g. of sodium in 100 ml. of liquid ammonia in a Dewar flask was added 3 g. of the enediol. The original blue color disappeared after 30 minutes and 0.5 g. more of the metallic sodium in 50 ml. of liquid ammonia was added. After standing for one hour, the blue color was retained and 5 ml. of methyl iodide was added dropwise with stirring. Upon evaporation the residue was treated with 2 *N* hydrochloric acid and steam was passed through the mixture for one hour. The filtrate was saturated with sodium sulfate and extracted four times with 100-ml. portions of chloroform. The combined extracts were dried with sodium sulfate, the chloroform was removed, and the residue consisting of crystals in a syrup was distilled to give 0.9 g. of a product boiling at 150–155° at 10 mm. pressure. The solid formed on cooling, m.p. 102°, proved to be picolinamide since it gave, with nitrous acid, pyridine-2-carboxylic acid, m.p. 133°, which showed no depression when mixed with an authentic sample of this acid. Modified Gomm and Nierenstein's method (4): The enediol, 4 g., in 50 ml. of methanol and 15 ml. of dimethyl sulfate in an ice-bath was kept slightly basic for one day by the addition of small amounts of a 10% methanolic potassium hydroxide solution. After removing the solvent under diminished pressure, the residue was extracted with 200 ml. of chloroform and the solution was washed with 50 ml. of 5% sodium carbonate solution and dried over sodium sulfate. Removal of the solvent gave a brown liquid which when distilled gave a product, 0.08 g., boiling at 96° at 16 mm. pressure. By combining the products from several trials it was shown that this liquid, which solidified at 12°, was methyl picolinate since its acidic hydrolysis gave an acid which showed no depression in melting point when mixed with an authentic sample of pyridine-2-carboxylic acid.

(*D*) *Reduction of 2-pyridoin.* Reduction was not possible by low pressure hydrogenation in the presence of Adams catalyst. A successful procedure follows: A solution of 4 g. of the enediol in 180 ml. of methanol and 20 ml. of 1% aqueous sodium hydroxide solution was heated on a steam-cone and 2 g. of finely powdered sodium borohydride was added at intervals. After the yellow color of the enediol had disappeared, the solution was evaporated to approximately 50 ml., 3 g. of sodium fluoride in 200 ml. of water was added to break up the complex formed, and the mixture was boiled for 30 minutes. Extraction of the cooled solution with four 100-ml. portions of chloroform and evaporation gave 3.2 g. of crude 1,2-di-2-pyridyl-1,2-ethanediol, m.p. 151–153°. Crystallization from acetone and ethyl acetate elevated the m.p. to 153° [Mathes, Sauermilch, and Klein (2b) give 153.5–154.0°].

1-Phenyl-2-(2-pyridyl)-1,2-ethanedione (III) was prepared by the method of Buehler, Harris, and Arendale (6).

1-Phenyl-2-(2-pyridyl)-1,2-ethenediol (IV). The dione, 2.1 g. (0.01 mole) was dissolved in 10 ml. of methanol and hydrogenated under three atmospheres of hydrogen with Adams platinum catalyst until 0.01 mole of hydrogen was absorbed. The mixture was immediately

---

[2] We are indebted to Dr. K. B. Whetsel of Tennessee Eastman Company, Kingsport, Tennessee, for determination and interpretation of the infrared spectra.

placed under an atmosphere of nitrogen, and taken to a cold room at 4 to 5° where the platinum was removed and the filtrate was evaporated by passing nitrogen over the solution until crystals formed. The yellow solid was taken up twice in absolute alcohol and recovered as before. An analytical sample dried for an hour in a vacuum desiccator containing aluminum sulfate melted at 61°.

Anal. Calc'd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20.
Found: C, 73.01; H, 5.29.

The enediol decolorizes a solution of sodium 2,6-dichlorobenzeneoneindophenol and reduces Tollens' reagent. In the air it turns to a dark oil in several minutes.

1-Phenyl-2-(4-pyridyl)ethanone-2 (VIII) was prepared by the method of Smith, Stewart, Roth, and Northey (7) from γ-stilbazole (V).

(*A*) *The oxime* prepared in the usual manner was a white solid, m.p. 135°.

Anal. Calc'd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70.
Found: C, 73.54; H, 5.65.

1-Phenyl-2-(4-pyridyl)-1,2-ethanedione (IX). The ethanone, 50 g., held at 190–200° by means of a paraffin bath heated to 190 to 230°, was treated with 25 g. of C.P. selenium dioxide added in small portions during stirring. This temperature was maintained until the evolution of water ceased, after which the mixture was cooled and diluted with 150 ml. of methanol. Filtration removed the selenium and the filtrate was diluted with water, neutralized with sodium carbonate, and extracted with ether. The ethereal solution was treated with Norit A and evaporated to yield 14 g. (28%) of crude product. Distillation gave a fraction boiling at 202–207° (17 mm.) which, when crystallized several times from pyridine and once from ethanol, produced yellow crystals, m.p. 77°.

Anal. Calc'd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29.
Found: C, 74.17; H, 4.30.

(*A*) *The quinoxaline* prepared in the usual manner melted at 149°.

Anal. Calc'd for $C_{19}H_{13}N_3$: C, 80.54; H, 4.63.
Found: C, 80.54; H, 4.77.

(*B*) *The monoxime* prepared in the usual manner melted at 159°.

Anal. Calc'd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46.
Found: C, 68.76; H, 4.55.

Unknown compound of formula $C_{13}H_9NO$. The methanol-water layer, which remained after the ether extraction above, contained 9.5 g. (19%) of an insoluble product which when crystallized three times from pyridine, using Norit A, was white and melted at 249°.

Anal. Calc'd for $C_{13}H_9NO$: C, 79.97; H, 4.65, N. 7.19; Mol. wt., 195.1.
Found: C, 79.44; H, 4.65; N, 7.40; Mol. wt., 198.5, 189.9.

Attempted preparation of 1-phenyl-2-(4-pyridyl)-1,2-ethenediol. The dione, 2.1 g. (0.01 mole) in 10 ml. of methanol was hydrogenated using two atmospheres of hydrogen and 20 mg. of Goldsmiths' platinum catalyst. When 0.01 mole of hydrogen was absorbed, the catalyst was removed by filtration and the filtrate was diluted with twice its volume of water. An ether extraction followed by evaporation gave 0.80 g. of the ethanediol which when crystallized from ethanol and pyridine melted at 166°.

Anal. Calc'd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09.
Found: C, 72.76; H, 5.99.

The same compound was obtained as the sole product when one mole of the dione was hydrogenated with two moles of hydrogen.

From the methanol-water solution there was recovered by evaporation unreacted dione, which when crystallized from pyridine weighed 0.70 g. No enediol was isolated.

SUMMARY

Chelation is an important factor in increasing stability since, of the three enediols studied, the order of decreasing stability is: 2-pyridoin (two chelate rings) > 1-phenyl-2-(2-pyridyl)-1,2-ethenediol (one chelate ring) > 1-phenyl-2-

(4-pyridyl)-1,2-ethenediol (no chelate ring). The first of these enediols can be isolated with ease, the second with difficulty, and the third not at all. A simple method for determining stability in these cases is low pressure reduction of the proper dione. Under these conditions 2-pyridil cannot be reduced beyond the enediol, 1-phenyl-2-(2-pyridyl)-1,2-ethanedione yields the enediol with equimolecular amounts of hydrogen and the diol with twice this amount, while 1-phenyl-2-(4-pyridyl)-1,2-ethanedione produces no enediol, but mixtures of the dione and diol or the diol alone.

KNOXVILLE 16, TENNESSEE

REFERENCES

(1) BUEHLER AND HARRIS, *J. Am. Chem. Soc.*, **72**, 5015 (1950); BUEHLER AND EDWARDS, *J. Am. Chem. Soc.*, **74**, 977 (1952).

(2) (a) HARRIES AND LENART, *Ann.*, **410**, 95 (1915); (b) MATHES, SAUERMILCH, AND KLEIN, *Ber.*, **84**, 452 (1951); (c) HENSEL, *Angew. Chem.*, **65**, 491 (1953); (d) CRAMER AND KRUM, *Ber.*, **86**, 1586 (1953).

(3) HENDRICKS AND RUNDLES, *J. Am. Chem. Soc.*, **60**, 2563 (1938).

(4) GOMM AND NIERENSTEIN, *J. Am. Chem. Soc.*, **53**, 4408 (1941).

(5) (a) FUSON, *J. Am. Chem. Soc.*, **62**, 2962 (1940); (b) FUSON, *J. Am. Chem. Soc.*, **65**, 915 (1943).

(6) BUEHLER, HARRIS, AND ARENDALE, *J. Am. Chem. Soc.*, **72**, 4953 (1950).

(7) SMITH, STEWART, ROTH, AND NORTHEY, *J. Am. Chem. Soc.*, **70**, 3997 (1948).

(8) SCHONBERG AND MUSTAFA, *J. Chem. Soc.*, 746 (1946).

(9) FUSON AND HORNING, *J. Am. Chem. Soc.*, **62**, 2962 (1940).

NOTICE TO AUTHORS

On and after September 1, 1955, the Journal will accept *Notes*; the Journal will accept *Communications to the Editor* received on or after November 1, 1955 for publication in Volume 21. See revised Notice to Authors for details.

Effective with Volume 21, the Journal will use a double column format with a page size approximately 6½″ by 9″. Authors should consider this in connection with graph sizes, and table compositions.