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THE REACTION OF PYRIDONES WITH CHLOROACETIC ACID

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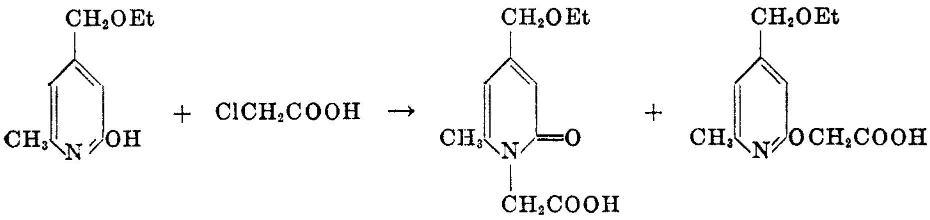
Various investigators have considered the reaction of 2- and 4-pyridones with chloroacetic acid especially in connection with the preparation of X-ray contrast media of the type of Diodrast (1), the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid, and Rayopake (2), a preparation containing 2-methyl-4,6-dioxo-5-iodotetrahydropyridine-N-acetic acid. To our knowledge only one product has been reported from this type of reaction, namely, that resulting from substitution on the nitrogen atom, although it was recognized that substitution on the oxygen was also possible. In this laboratory we have succeeded in obtaining from the reaction of 4-ethoxymethyl-6-methyl-2-pyridone (I) with chloroacetic acid, two products, which are undoubtedly the N-acetic acid II and the O-acetic acid III. However, we were confronted with the problem of determining which of these two products was to be assigned structure II and which was to be given structure III.

EQUATION A

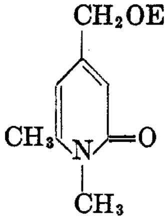


I II III

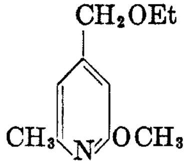
The two products were separated by distillation of their methyl esters. One of the methyl esters came over at a considerably lower temperature. When warmed with hydrochloric acid, the ester group was hydrolyzed to the carboxyl, but nevertheless the resulting compound was sufficiently basic to form a hydrochloride, which could be crystallized from a variety of solvents but not from water.

When the higher-boiling ester was warmed with hydrochloric acid, the ester group was again hydrolyzed, and apparently a hydrochloride was also obtained. However, crystallization from water was sufficient to cause dissociation, so that only the free acid was isolated. When this acid was heated over 200° *in vacuo*, decarboxylation occurred. The analysis indicated that the decarboxylated product could have either structure IV or V, depending on whether the parent acid had structure II or III respectively.

As a logical approach to the problem of assigning correct structures to the above reaction products, an unambiguous synthesis of IV was undertaken. It was early recognized that 1-methyl-3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (VII) might be a suitable starting material for the preparation of IV.



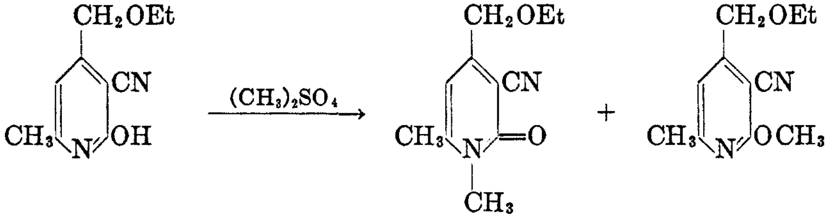
IV



V

Accordingly the methylation of the readily available 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (VI) was investigated. Treatment with methyl sulfate and alkali gave two compounds, resulting from methylation on the nitrogen atom and on the oxygen atom.

EQUATION B

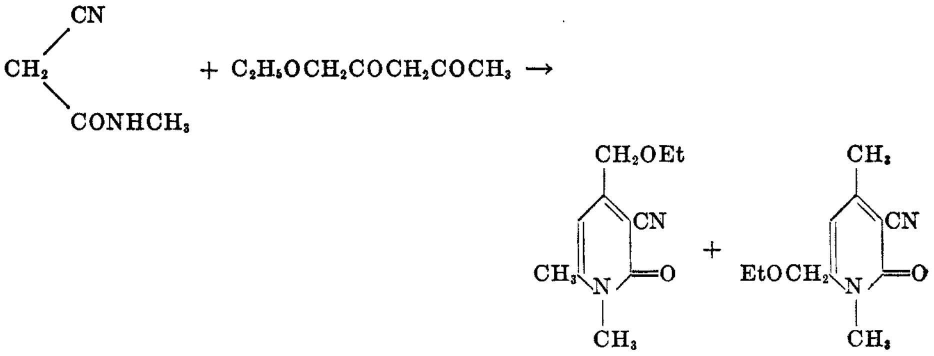


VI VII VIII

Again we were confronted with the problem of ascertaining which of these two compounds was to be assigned the structure VII and which was to be assigned structure VIII.

Fortunately, this latter problem was solved by a consideration of the reaction of cyanoacetmethylamide with ethoxyacetylacetone in the presence of piperidine. As pointed out by Bardhan (3) and investigated by us (4, 5) this type of reaction can occur by two different routes to give two different products. In agreement with this proposition two different compounds were actually isolated. To one of these products must be assigned the structure VII and to the other structure IX.

EQUATION C

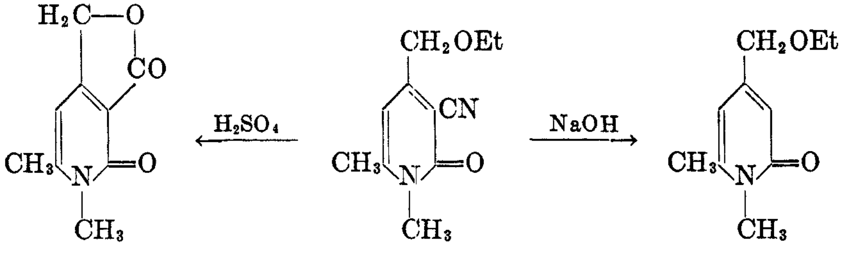


VII IX

An examination of the methylation reaction depicted in Equation B and the condensation reaction depicted in Equation C will show that of all the products only the one with structure VII can be formed in both reactions. A product was found which was common to both reactions and this obviously must possess structure VII. However, because the product VII obtained from the condensation reaction according to Equation C was difficult to purify and hence also difficult to identify positively by a mixed melting point determination, it was converted into the lactone X by refluxing with sulfuric acid. The identical lactone was also obtained from the product VII obtained from the methylation reaction according to Equation B. These findings leave no doubt about the structure of compound VII. It must be 1,6-dimethyl-3-cyano-4-ethoxymethyl-2-pyridone.

Having thus identified the compound VII, the next step was to convert it into compound IV. This conversion was readily accomplished by heating with dilute alkali at 170°, a procedure already described by us (4, 5). The resulting product is neutral but forms a well-crystallized picrate.

EQUATION D



X VII IV

The same compound IV, identified through its picrate, was obtained as a result of the decarboxylation of one of the products from the reaction of chloroacetic acid with 4-ethoxymethyl-6-methyl-2-pyridone (I). This product must thus have the N-acetic acid structure II.

Having thereby established the structure of one of the compounds definitely as the N-acetic acid, there remains no doubt that the isomeric compound found in the reaction must be the O-acetic acid.

Acknowledgment. Our thanks are due to Dr. A. Steyermark for microanalyses and to Mr. A. Motchane for absorption spectra.

EXPERIMENTAL

Part I. Reaction of 4-ethoxymethyl-6-methyl-2-pyridone with chloroacetic acid

A mixture of 235 g. of 4-ethoxymethyl-6-methyl-2-pyridone (4, 5) and 450 cc. of water was surrounded with a bath at 94° and treated at 5-minute intervals with 20 cc. of sodium hydroxide solution and 20 cc. of chloroacetic acid solution in water. The total volume of each solution used was 700 cc. containing respectively 226 g. of sodium hydroxide and 400 g. of chloroacetic acid. At the conclusion of the addition (about 3 hours) the mixture was stirred for an additional hour at 94° and then cooled in an ice-bath. Powdered sodium bicarbonate was added to bring the *p*H to about 7, and the whole was extracted 4 times with 300 cc. of chloroform to remove starting material. To the aqueous layer was added 450 cc. of concentrated hydrochloric acid and the acid solution was distilled to dryness *in vacuo.*

The residue was digested with 400 cc. of hot chloroform and filtered hot. The insoluble precipitate was digested twice more with 200 cc. of hot chloroform. The combined chloroform liquors from the digestion were distilled to dryness *in vacuo*, the residue was dissolved in 1100 cc. of methanol, and 160 g. of hydrogen chloride was passed into the mixture with cooling in an ice-bath. The mixture was refluxed for 8 hours and allowed to stand 3 weeks, when again the solvent was removed *in vacuo* below 60°.

To the residue, now containing the methyl esters, was added 100 g. cracked ice, and with further cooling in an ice-bath 50% (by weight) potassium carbonate solution to bring the *p*H to 7.5–8.0. The mixture was extracted 4 times with 300 cc. of ether and the ether extracts were dried with sodium sulfate, and distilled. A fraction, weighing 26.6 g. was obtained at 125–140° at 0.3 mm., and another fraction, weighing 21.2 g. at 170–175° at 0.3 mm.

A. 4-Ethoxymethyl-6-methyl-2-pyridyloxyacetic acid (III). The fraction boiling at 125–140°/0.3 mm. and 100 cc. of concentrated hydrochloric acid were heated on the steam-bath for 2 hours in an evaporating dish of 500 cc. capacity. After standing for some time crystals formed. These were filtered through a sintered glass funnel and dried in a desiccator over potassium hydroxide. The crystals weighed 20.3 g. and melted at 109–112°. They can be crystallized from alcohol-ether, acetone, or dilute hydrochloric acid. The purified product melted at 114–117°. The product was dried over P_2O_5 at room temperature at the oil-pump. The analysis indicates that the product is the hydrochloride of 4-ethoxymethyl-6-methyl-2-pyridyloxyacetic acid.

Anal. Calc'd for $C_{11}H_{15}NO_4 \cdot HCl$: C, 50.47; H, 6.16; N, 5.35.
Found: C, 49.36; H, 6.30; N, 5.63.

Drying at a higher temperature gave analyses which indicated that hydrogen chloride was being driven off. On the other hand drying in a vacuum desiccator over potassium hydroxide, previously evacuated at the water-pump, gave a product whose neutral equivalent indicated it contained a molecule of water.

Anal. Calc'd for $C_{11}H_{15}NO_4 \cdot HCl \cdot H_2O$: Neut. equiv., 140. Found: Neut. equiv., 138.

Thus, it is seen that incomplete drying leads to a low carbon analysis due to incomplete removal of water. To ensure a satisfactory analysis the benzylthiuronium salt was then prepared by adding 0.36 g. benzylthiuronium chloride to a solution of 0.50 g. of the hydrochloride and 3.6 cc. of *N* sodium hydroxide. The compound melted at 146–147° after crystallization from acetone.

Anal. Calc'd for $C_{19}H_{25}N_3O_4S$: C, 58.29; H, 6.44.
Found: C, 58.47; H, 6.43.

B. 4-Ethoxymethyl-6-methyl-2-pyridone-N-acetic acid. The fraction boiling at 170–175°/0.3 mm. and 100 cc. of concentrated hydrochloric acid were heated on the steam-bath for 2.5 hours in an evaporating dish of 500 cc. capacity. After adding 40 cc. of water, the mixture was scratched to induce crystallization. On drying the crystals weighed 12 g. and melted at 90–95°. These crystals represented a mixture of 4-ethoxymethyl-6-methyl-2-pyridone-N-acetic acid and its hydrochloride. Crystallization from water yielded 7.6 g. of the free N-acetic acid. Recrystallization from acetone or water gave the pure product, melting at 143–144°.

Anal. Calc'd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71.
Found: C, 58.93; H, 6.73.

Part II. Methylation of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (VI)

A. 2-Methoxy-3-cyano-4-ethoxymethyl-6-methylpyridine (VIII). A mixture of 460 g. of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone, 900 cc. of water, and 720 cc. of 16.7% (by weight) sodium hydroxide in water was warmed and stirred on the steam-bath, while 285 cc. of dimethyl sulfate was added during about an hour. The mixture was warmed and stirred for about 30 minutes longer, when an additional 60 cc. of dimethyl sulfate was added during 20 minutes. After 15 minutes this was followed by 120 cc. of 16.7% alkali. The treatment with 60 cc. of dimethyl sulfate and 120 cc. of alkali was repeated three times more. At the conclusion, 30 cc. of additional alkali was added, and the mixture was cooled to 5° and kept there for 17 hours. The resulting crystals were filtered and while still moist they were recrystallized from one liter of 50% methanol and again from 300 cc. of methanol. Thus a somewhat impure 2-methoxy-3-cyano-4-ethoxymethyl-6-methylpyridine was obtained. A further amount could be obtained by adding 200 cc. of water to the methanol filtrate and allowing the mixture to crystallize. The product was purified by crystallization from methanol containing a few drops of water. In this manner 23.5 g. of pure 2-methoxy-3-cyano-4-ethoxymethyl-6-methylpyridine, m.p. 80–81° was obtained.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59.
Found: C, 64.36; H, 6.68; N, 13.30.

B. 1,6-Dimethyl-3-cyano-4-ethoxymethyl-2-pyridone (VII). All the methanolic filtrates from A were combined and distilled to dryness *in vacuo*. The residue was extracted repeatedly by stirring a few minutes with 500-cc. portions of boiling water and decanting. An almost pure 1,6-dimethyl-3-cyano-4-ethoxymethyl-2-pyridone (VII) was obtained in the form of plates when the aqueous extracts were allowed to cool slowly with occasional stirring. The pure product melts also at 80–81°, after crystallization from carbon tetrachloride. It gave a depression in melting point, when mixed with 2-methoxy-3-cyano-4-ethoxymethyl-6-methylpyridine from Part IIA; yield 196 g.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84.
Found: C, 63.82; H, 6.65.

C. Lactone of 1,6-dimethyl-3-carboxy-4-hydroxymethyl-2-pyridone (X). A mixture of 5.5 g. of the product from Part B above and 28 cc. of 50% (by weight) sulfuric acid was refluxed for 3 hours and then poured into 75 cc. of water. In this manner 4.3 g. of almost pure lactone was obtained. The pure product, obtained by crystallization from water, melts at about 270° with decomposition. The melting point varies with the rate of heating.

Anal. Calc'd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82.
Found: C, 60.18; H, 5.27; N, 7.67.

Part III. Reaction of cyanoacetmethylamide with ethoxyacetylacetone

A. Isolation of 1,6-dimethyl-3-cyano-4-ethoxymethyl-2-pyridone (VII). A solution of 9.8 g. of cyanoacetmethylamide, 14.4 g. of ethoxyacetylacetone, one cc. of piperidine and 70 cc. of ethanol was refluxed during 2 hours and 45 minutes. The ethanol was removed on the steam-bath and the residue was triturated with petroleum ether. In this manner 20.5 g. of solid product was obtained. When 5 g. of this product was crystallized twice from water only 0.85 g. of impure crystals, m.p. 68–78° was obtained. These crystals were recrystallized from carbon tetrachloride to give a product melting at 73–77°. A mixed melting point with the product from Part II B showed no depression. Further crystallization from carbon tetrachloride did not raise the melting point. In line with the argument presented in the theoretical part of this paper, this product must also be 1,6-dimethyl-3-cyano 4-ethoxymethyl-2-pyridone (VII). Further proof is presented below.

B. Conversion to lactone of 1,6-dimethyl-3-carboxy-4-hydroxymethyl-2-pyridone (X). In an experiment carried out as described in Part III A, the residue remaining after trituration with petroleum ether was refluxed with 100 cc. of 50% (by weight) sulfuric acid for one hour and 20 minutes. The mixture was poured into 200 cc. of H_2O and allowed to crystallize. In this manner 5.38 g. of almost pure lactone was obtained. After crystallization from water it melted at 270° with decomposition. The ultraviolet absorption spectrum is identical with that of the product from Part II C with maxima at 236 and 325 mμ and minima at 230 and 264 mμ.

Anal. Calc'd for $C_9H_9NO_3$: C, 60.33; H, 5.06.
Found: C, 60.36; H, 5.38.

C. Isolation of 1,4-dimethyl-3-cyano-6-ethoxymethyl-2-pyridone (IX). The sulfuric acid filtrate after crystallization of the lactone X in Part III B was extracted twice with 100 cc. of chloroform and the chloroform was distilled off. The residue was dissolved in hot water and to the hot solution was added 20 cc. of 10% sodium hydroxide. On cooling 2 g. of 1,4-dimethyl-3-cyano-6-ethoxymethyl-2-pyridone was obtained. After crystallization from water it melted at 127–128°.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.86; N, 13.59.
Found: C, 63.60; H, 6.66; N, 13.12.

Part IV. 1,6-Dimethyl-4-ethoxymethyl-2-pyridone (IV)

A mixture of 20 g. of 1,6-dimethyl-3-cyano-4-ethoxymethyl-2-pyridone (VII), obtained from Part II B, 94 cc. of 10% sodium hydroxide and 106 cc. of water was heated in an autoclave at 170° for 24 hours with occasional shaking. After cooling it was extracted four times with 50 cc. of chloroform. The chloroform extracts were dried with sodium sulfate and distilled. At 130–135° and 0.2 mm., 13.4 g. of 1,6-dimethyl-4-ethoxymethyl-2-pyridone distilled over; d^{25}_{25} 1.084; n^{27}_{D} 1.5379.

To a solution of one gram of this material in ether was added a saturated solution of picric acid in ether until no further precipitate was obtained. In this manner 2.04 g. of almost pure picrate was obtained. After crystallization from about 8 cc. of ethanol, it weighed 1.71 g. and melted at 108–110°.

Anal. Calc'd for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42.
Found: C, 46.85; H, 4.54.

Part V. Decarboxylation of 4-ethoxymethyl-6-methyl-2-pyridone-N-acetic acid (II)

One pellet of sodium hydroxide was powdered and added to 0.50 g. of 4-ethoxymethyl-6-methyl-2-pyridone-N-acetic acid, m.p. 143–144°, from Part I. The mixture was heated in an air-bath at 210–230° under a pressure of 0.2 mm. in a short distilling flask until no further distillate was obtained. The distillate was dissolved in ether and treated with a saturated solution of picric acid in ether. On standing 0.16 g. of picrate, m.p. 102–107° was obtained. After recrystallization from ethyl alcohol it melted at 106–108°. It gave no depression in melting point when mixed with the picrate of 1,6-dimethyl-4-ethoxymethyl-2-pyridone from Part IV. The ultraviolet absorption spectra were identical with maxima at 314 and 365 mμ and minima at 273 and 328 mμ.

Anal. Calc'd for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42.
Found: C, 47.10; H, 4.38.

NUTLEY 10, N. J.

SUMMARY

The reaction of a pyridone with chloroacetic acid has been found in one particular instance to yield besides the N-acetic acid derivative an O-acetic acid derivative. The structure of the former was established by unambiguous methods.

REFERENCES

(1) REITMANN, U. S. Patent 1,993,039 (March 5, 1935), assigned to Winthrop Chemical Co.
(2) SCHNIDER, U. S. Patent 2,212,187 (August 20, 1941), assigned to Hoffmann-La Roche, Inc.
(3) BARDHAN, *J. Chem. Soc.*, 2233 (1929).
(4) WENNER AND PLATI, *J. Org. Chem.*, **11**, 751 (1946).
(5) WENNER AND PLATI, U. S. Patent 2,414,783 (Jan. 21, 1947), assigned to Hoffmann-La Roche, Inc.