

tions from ether-petroleum ether mixture, the acid melted at 146° (cor.) and was identical with β -longineic acid, obtained by direct hydrolysis of β -longilobine. The basic portion was isolated in the usual way and proved to be retronecanol identified conveniently as the picrate, m. p. 211°.

Summary

1. The alkaloid from *Senecio longilobus*, first isolated by Manske, has been shown to be a mixture of two components designated as α - and β -longilobine, whose empirical formulas are $C_{18}H_{23}O_5N$ and $C_{18}H_{25}O_6N$, respectively. The separation was achieved by an empirical chromatographic procedure, combining the liquid chromatogram method and examination of the column. The course of the chromatogram was followed by determining the specific rotations of the different fractions and the two main components were rechromatographed until a constant specific rotation was attained.

2. On hydrolysis α -longilobine gives one molecule of retronecine and one molecule of a crystalline dibasic acid $C_{10}H_{14}O_5$, designated as α -longineic acid.

3. Similarly β -longilobine gives one molecule of retronecine and one molecule of a crystalline dibasic acid $C_{10}H_{16}O_6$, designated as β -longineic acid.

4. On reduction with hydrogen and Raney nickel, α -longilobine absorbs two moles of hydrogen to form tetrahydro- α -longilobine which has the properties of an amino acid and on hydrolysis yields retronecanol and α -longineic acid. With platinum oxide as catalyst four moles of hydrogen are absorbed, yielding an amorphous product which gives on saponification retronecanol and an oily acid which was not purified.

5. β -Longilobine absorbs only two moles of hydrogen in the presence of platinum oxide as catalyst, yielding an amorphous product which gives on hydrolysis retronecanol and β -longineic acid.

6. Both α - and β -longilobine are shown to be cyclic diesters, from one mole of retronecine and one mole of a dibasic acid, each of the two hydroxyls in retronecine being utilized.

URBANA, ILLINOIS

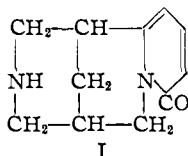
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Condensation Reactions of N-Substituted Pyridones¹

BY ROGER ADAMS AND ANTHONY W. SCHRECKER

A consideration of possible methods for the synthesis of cytosine² (I) leads to the necessity of further knowledge of the activity of a 6-methyl



group in N-substituted 2-pyridones. This communication is devoted primarily to the description of the reactivity of the ring-substituted methyl group in 1,6-dimethyl-2-pyridone. It includes also the results of a similar study of 1,4-dimethyl-2-pyridone. 6-Methyl-2-pyridone-1- β -proprionitrile and ethyl 6-methyl-2-pyridone-1-acetate were synthesized and preliminary experiments on pyridocoline formation were attempted. The activity of the methyl group in 2-acetamido-6 (and 4)-methylpyridine is also described.

The ability of such compounds as 2-picoline to undergo condensation reactions with carbonyl compounds has been attributed to the double bond linking the nitrogen with the carbon atom carrying the methyl group.³ A molecule carrying such a

structural unit can undergo an electromeric shift permitting formation of a carbanion and subsequent condensation with a carbonyl group.⁴ No such double bond appears in the formula of a compound such as 1,6-dimethyl-2-pyridone (IIa). If N-alkylpyridones are, however, resonance hybrids of an uncharged and a betaine (IIb) structure, as postulated by Arndt and Kalischek,⁵ and the carbanion (III) is stabilized by resonance, then the requirement for base-catalyzed condensation reactions should be fulfilled. Replacement of the 6-methyl group by a carboethoxymethyl group would render the compound somewhat similar in its behavior to a β -keto ester and replacement by a cyanomethyl group similar to a β -carbonylated nitrile, such as ethyl cyanoacetate. Such compounds should form sodium enolates which react with alkyl and acyl halides. These predictions have been realized experimentally.

The predictions were supported by the experiments of Kaslow and Cook⁶ who demonstrated the reactivity of the 4-methyl group in 1,4-dimethyl-carbostyryl toward ethyl oxalate. The condensation product was readily transformed into 1-methyl-4-carbostyrylacetonitrile, which underwent condensation with benzaldehyde.

The starting materials, 1,6-dimethyl-2-pyridone

(1) From a thesis presented by Anthony W. Schrecker to the Graduate College of the University of Illinois, August, 1948, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

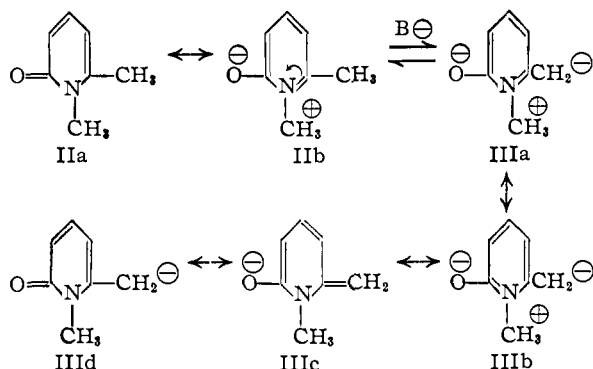
(2) Späth and Galinovsky, *Ber.*, **66**, 1338 (1933).

(3) Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

(4) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 130.

(5) Arndt and Kalischek, *Ber.*, **63**, 587 (1930).

(6) Kaslow and Cook, *THIS JOURNAL*, **67**, 1969 (1945).



(II) and 1,4-dimethyl-2-pyridone, were prepared from the sodium salts of 6-methyl-2-pyridone and 4-methyl-2-pyridone by alkylation with dimethyl sulfate. They were low-melting, water-soluble compounds, which was to be expected from a consideration of the physical properties of the previously characterized 1-methyl-2-pyridone⁷ and 1,4,6-trimethyl-2-pyridone.⁸ Mumm⁹ has described a product reputed to be 1,6-dimethyl-2-pyridone. He obtained it in a series of reactions starting with diethyl 2,6-dimethylpyridine-3,5-dicarboxylate and reported it to melt at 352° and to be difficultly soluble in water. The physical properties and chemical reactions of the compound, m. p. 56.5–58°, described in the present paper, prove conclusively that this substance is actually 1,6-dimethyl-2-pyridone.

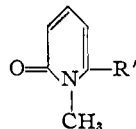
1,6-Dimethyl-2-pyridone underwent condensation with ethyl oxalate in the presence of potassium or sodium ethoxide to form the yellow potassium or sodium salt of ethyl 1-methyl-2-pyridone-6-pyruvate in 95% yield, from which the free ester (IV) was obtained by acidification. The same reaction proceeded at a somewhat lower rate with 1,4-dimethyl-2-pyridone to give the potassium salt (84% yield) and from it ethyl 1-methyl-2-pyridone-4-pyruvate. Hydrolysis of the esters gave 1-methyl-2-pyridone-6-pyruvic acid (V) and 1-methyl-2-pyridone-4-pyruvic acid.

The pyruvic acids underwent oxidative decarboxylation when treated with aqueous sodium hydroxide and hydrogen peroxide to give respectively 1-methyl-2-pyridone-6-acetic acid (VI) (84–87% yield) and 1-methyl-2-pyridone-4-acetic acid (46–59% yield). The former was also obtained when the pyruvic ester instead of the acid was treated with hydrogen peroxide in aqueous sodium hydroxide, though in lower yield. The oxidation took a different course when the potassium salt of ethyl 1-methyl-2-pyridone-6-pyruvate was treated with hydrogen peroxide, and one mole of dilute sodium hydroxide was added only after some time. None of the 6-acetic acid was obtained, but 1-methyl-2-pyridone-6-carboxylic acid¹⁰ (VII) was formed in a 58% yield. 1-Methyl-2-pyridone-6-

acetic acid (VI), m. p. 188°, and 1-methyl-2-pyridone-6-carboxylic acid (VII), m. p. 260°, decompose at their melting points with loss of carbon dioxide to give, respectively, 1,6-dimethyl-2-pyridone and 1-methyl-2-pyridone. Consideration of the betaine structure of pyridones (IIb) shows that the former acid is somewhat analogous to a β -keto acid, the latter to an α -keto acid.

By treatment of 1-methyl-2-pyridone-6-pyruvic acid (V) with hydroxylamine or by alkaline hydrolysis of the oximino ester prepared similarly from the pyruvic ester (IV), 1-methyl-2-pyridone-6-(α -oximino)-propionic acid (VIII) was readily formed and this was converted in 93% yield to 1-methyl-2-pyridone-6-acetonitrile (IX) by pyrolysis. By alkaline hydrolysis of the nitrile the 6-acetic acid (VI) results. Ethyl 1-methyl-2-pyridone-6-acetate (X), formed by esterification of the corresponding acid (VI), and 1-methyl-2-pyridone-6-acetonitrile (IX) condensed with benzyl chloride in the presence of ethanolic sodium ethoxide, the former to give ethyl 1-methyl-2-pyridone-6-(α -benzyl)-acetate (XI, R = C₆H₅CH₂-) in 61% yield and the latter to give the corresponding nitrile in 42% yield. On hydrolysis, the ethyl 1-methyl-2-pyridone-6-(α -benzyl)-acetate as well as the nitrile gave the corresponding acid (XII, R = C₆H₅CH₂-) which melted at 155° with evolution of carbon dioxide and formation of 1-methyl-6-phenethyl-2-pyridone (XIII, R = C₆H₅CH₂-). An analogous condensation of ethyl 1-methyl-2-pyridone-6-acetate with *n*-butyl bromide or better *n*-butyl iodide gave the α -*n*-butyl derivative (XI, R = C₄H₉-) which was hydrolyzed and decarboxylated to 6-*n*-amyl-1-methyl-2-pyridone (XIII, R = C₄H₉-).

The sodium derivative of ethyl 1-methyl-2-pyridone-6-acetate also reacted with acetyl chloride to give in 38% yield a β -keto ester (XI, R = CH₃CO-) which was an oil. It was not purified, but hydrolyzed and decarboxylated directly with formation of 6-acetyl-1-methyl-2-pyridone (XIII, R = CH₃CO-).



R' =	R' =
IV, CH ₂ COCOOEt	IX, CH ₂ CN
V, CH ₂ COCOOH	X, CH ₂ COCOOEt
VI, CH ₂ COOH	XI, CHR'COOEt
VII, COOH	XII, CHR'COOH
VIII, CH ₂ C(=NOH)COOH	XIII, CH ₂ R

Condensation of 1,6-dimethyl-2-pyridone with *m*-nitrobenzaldehyde in the presence of acetic anhydride gave only about 1% yield of 1-methyl-6-(*m*-nitrostyryl)-2-pyridone, in contrast to a 90% yield obtained in the reaction of *m*-nitrobenzaldehyde with 2-picoline.¹¹ In view of the unsatisfactory result of the attempts to prepare condensation products of pyridone homologs with alde-

(7) Binz and R ath, *Ann.*, **489**, 107 (1931).

(8) Hantzsch, *Ber.*, **17**, 2903 (1884).

(9) Mumm, *Ann.*, **443**, 272 (1925).

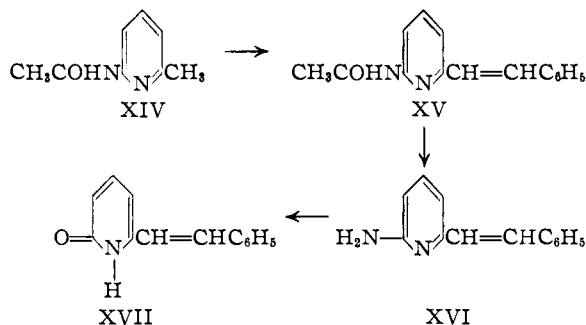
(10) Sp ath and Koller, *Ber.*, **56**, 880 (1923).

(11) Shaw and Wagstaff, *J. Chem. Soc.*, 77 (1933).

hydes, the possibility of obtaining such compounds by an indirect route was investigated.

2-Acetamido-6-methylpyridine (XIV) was condensed with benzaldehyde in the presence of acetic anhydride to give 6-acetamido-2-stilbazole (XV) in 12% yield. A yield of 87% is reported in the condensation of benzaldehyde with 2-picoline.¹¹ The acetamidostilbazole was hydrolyzed in hydrochloric acid and the 6-amino-2-stilbazole (XVI) purified by taking advantage of the low solubility of its hydrochloride in cold 20% hydrochloric acid. Diazotization of the amino compound gave a 48% yield of 6-hydroxy-2-stilbazole (6-styryl-2-pyridone) (XVII). When the same series of reactions was carried out with 2-acetamido-4-methylpyridine, a 14% yield of 2-amino-4-stilbazole resulted. In this case the intermediary acetamido compound was not isolated but the reaction mixture hydrolyzed directly by boiling with hydrochloric acid. Diazotization of the aminostilbazole gave a 36% yield of 2-hydroxy-4-stilbazole (4-styryl-2-pyridone). In the formation of 2-amino-4-stilbazole there was isolated from the condensation a yellow crystalline by-product, m. p. 234–235°, the structure of which was not determined.

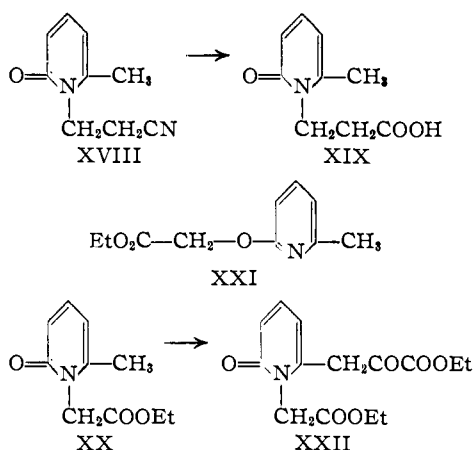
6-Methyl-2-pyridone condenses in the same manner as 2-pyridone¹² in presence of alkaline



catalysts with acrylonitrile to form 6-methyl-2-pyridone-1- β -propionitrile (XVIII). This product was hydrolyzed to the corresponding acid (XIX). Esterification of the acid by the usual methods failed to give a pure product. On distillation the oily esters were unstable and decomposed into 6-methyl-2-pyridone and acrylic esters. The nitrile (XVIII), which can be readily purified since it is a crystalline solid, also decomposes on distillation. All attempts to cause a ring closure between the carbalkoxy group and the 6-methyl group in the esters of XIX in order to obtain a bicyclic molecule more closely resembling cytisine were unsuccessful.

The stable ethyl 6-methyl-2-pyridone-1-acetate (XX) was prepared by the reaction of 6-methyl-2-pyridone sodium with ethyl bromoacetate. A 70% yield resulted, with 5% of the corresponding 2-pyridyl ether (XXI) as a by-product. Ethyl oxalate condensed with ethyl 6-methyl-2-pyri-

done-1-acetate (XX) to form probably ethyl 1-carbethoxymethyl-2-pyridone-6-pyruvate (XII), but no bicyclic product which might result from the elimination of two moles of ethanol.



Attempts to introduce halogen into the 6-methyl group of 6-methyl-2-pyridone failed. Bromination invariably resulted in ring substitution.

Experimental

6-Methyl-2-pyridone.—A solution of 108 g. of 2-amino-6-methylpyridine (b. p. 209–210°) in a cold mixture of 111 ml. of concd. sulfuric acid and 830 ml. of water was placed in an ice-salt-bath. With mechanical stirring a solution of 73 g. of 97% sodium nitrite in 140 ml. of water was introduced through a dropping funnel, the orifice of which reached nearly to the bottom of the beaker, at such a rate that the temperature of the reaction mixture did not rise above 5°. To complete the reaction, it was stirred for an additional hour below 10° and finally heated on a steam-bath until the temperature reached 90°.

The yellow solution was made alkaline by adding 205 g. of anhydrous potassium carbonate and evaporated to dryness on the steam-bath. The residue was powdered in a mortar and then extracted exhaustively with boiling benzene. The extract was clarified with Norit, filtered hot, concentrated to a volume of about 500 ml. and allowed to cool in an icebox. The yellow crystals were collected on a Büchner funnel and, after drying, weighed 95.3 g. By working up the mother liquor, an impure product was obtained which after recrystallization from benzene weighed 5.9 g. The over-all yield was thus 101.2 g. (92.8%). The material as initially obtained and after crystallization from benzene melted at 158–159° (cor.). By recrystallization from acetone or by distillation, b. p. 282° (760 mm.), colorless prismatic needles of the same melting point resulted.

This compound was first described by Errera¹³ who obtained it by decarboxylation of 6-methyl-2-pyridone-3,5-dicarboxylic acid. He reported a melting point of 159°. A somewhat similar procedure was described by Seide,¹⁴ who also reported the same melting point.

6-Methyl-2-pyridone Sodium.—The diazotized solution of 108 g. of 2-amino-6-methylpyridine was heated to boiling and neutralized by the addition of 568 g. of barium hydroxide octahydrate dissolved in 1500 ml. of boiling water. Barium sulfate was removed by filtration on a Büchner funnel and extracted several times with boiling water. The combined filtrate and washings, after addition of 50 ml. of 25% aqueous sodium hydroxide, were evaporated to dryness and the residue extracted exhaus-

(12) Adams and Jones, *THIS JOURNAL*, **69**, 1803 (1947).

(13) Errera, *Ber.*, **33**, 2969 (1900).

(14) Seide, *J. Russ. Phys.-Chem. Soc.*, **50**, 534 (1918).

tively with hot 95% ethanol. Cooling of the extract caused the separation of yellowish leaflets. Recrystallization from 95% ethanol served for purification. The product formed colorless glittering leaflets. The yield was 115.5 g. (88%), after drying *in vacuo* at 100°; m. p. 290°.

The sodium salt is very soluble in water, moderately soluble in ethanol, difficultly soluble in acetone and insoluble in ether.

Anal. Calcd. for C_6H_5ONNa : Na, 17.54. Found: Na, 17.48.

1,6-Dimethyl-2-pyridone (II).—This product was prepared in a manner similar to that used for the preparation of 1-methyl-2-pyridone from 2-pyridone potassium.⁷

In a 2-l. round-bottomed flask fitted with reflux condenser and dropping funnel, 98.7 g. of 6-methyl-2-pyridone was dissolved in a warm, freshly prepared solution of 21.0 g. of sodium in 250 ml. of methanol. After cooling to room temperature, 130 g. of dimethyl sulfate was added with shaking during a period of fifteen minutes. After refluxing on a water-bath for two hours, the solution was made strongly alkaline by adding 220 g. of 25% aqueous sodium hydroxide and steam-distilled until the odor of the by-product, 2-methoxy-6-methylpyridine, had disappeared from a sample of the distillate. After cooling to room temperature, sodium sulfate was removed from the steam-distillation residue by filtration on a Büchner funnel and the filter-cake washed with two 75-ml. portions, then with four 50-ml. portions of chloroform. The successive chloroform washings were used to extract the filtrate. After drying over potassium carbonate, the solvent was removed under reduced pressure and the product distilled, b. p. 110° (2 mm.). The yield was 82 g. (74%). The distillate solidified to a colorless crystalline mass which was recrystallized from dry ether; deliquescent plates, m. p. 56.5–58°.

The compound is very soluble in water, ethanol, chloroform and benzene, moderately soluble in ether, insoluble in petroleum ether. Its aqueous solutions are neutral.

Anal. Calcd. for C_7H_9ON : C, 68.27; H, 7.37; N, 11.37. Found: C, 68.40; H, 7.33; N, 11.36.

Attempts to prepare this compound by alkaline hydrolysis of the product from methyl iodide and 2-amino-6-methylpyridine according to the procedure of Chichibabin and Konvalova¹⁵ gave only a 23% yield. The use of dimethyl sulfate on α -picoline followed by the action of alkaline ferricyanide¹⁶ failed to give any product.

1,6-Dimethyl-2-pyridone Hydrochloride.—This hydrochloride was prepared in absolute ether with dry hydrogen chloride. After several recrystallizations from absolute ethanol, it formed colorless prismatic needles, m. p. 202–203° (cor.). The compound had to be dried at room temperature, as it sublimes readily at 75° (3 mm.).

Anal. Calcd. for $C_7H_{10}ONCl$: C, 52.67; H, 6.32; N, 8.78; Cl, 22.21. Found: C, 52.75; H, 6.30; N, 8.92; Cl, 22.31.

1,6-Dimethyl-2-pyridone Picrate.—The picrate was obtained by the usual procedure. It was purified by crystallization from 95% ethanol and formed long yellow needles, m. p. 134–136° (cor.).

Anal. Calcd. for $C_{13}H_{12}O_8N_4$: C, 44.32; H, 3.43; N, 15.91. Found: C, 44.53; H, 3.58; N, 15.84.

4-Methyl-2-pyridone.—This product was synthesized in a manner similar to that described for converting 2-amino-6-methylpyridine to 6-methyl-2-pyridone. Two runs of 54 g. of 2-amino-4-methylpyridine were diazotized, combined and then made alkaline by adding 210 g. of anhydrous potassium carbonate. After evaporation on a steam-bath, the nearly dry residue was extracted several times with a total of 1 l. of boiling ethanol. The brown extract was freed from ethanol under reduced pressure and the residue distilled. The 4-methyl-2-pyridone boiled at 186–187° (12 mm.) and solidified in the receiver to a colorless crystalline mass which was recrystallized from benzene

and washed with petroleum ether (b. p. 30–60°). The yield was 85.1 g. (78%) of large colorless prisms, m. p. 130° (cor.).

Seide¹⁷ reported a melting point of 130° and a boiling point of 307–309° (atm. press.).

1,4-Dimethyl-2-pyridone.—This compound was prepared in a manner analogous to the preparation of 1,6-dimethyl-2-pyridone from 6-methyl-2-pyridone. The crude reaction product, obtained from 85.1 g. of 4-methyl-2-pyridone by methylation, addition of base, steam-distillation and extraction of the residue with chloroform, was distilled *in vacuo*, b. p. 110° (1 mm.). The yield was 73.6 g. (77%). The product solidified in the receiver to a colorless mass, which after crystallization from dry ether formed colorless needles, m. p. 59°. It is somewhat deliquescent, though less so than 1,6-dimethyl-2-pyridone.

Anal. Calcd. for C_7H_9ON : C, 68.27; H, 7.37. Found: C, 68.05; H, 7.52.

1,4-Dimethyl-2-pyridone Hydrochloride.—This compound was prepared by saturating a solution of the base in a little absolute ethanol with dry hydrogen chloride, while cooling in ice water, and then adding dry ether. Recrystallization was accomplished from ethanol-ether; small colorless needles, m. p. 173–174° (cor.).

Anal. Calcd. for $C_7H_{10}ONCl$: Cl, 22.21. Found: Cl, 22.22.

1,4-Dimethyl-2-pyridone Picrate.—The picrate crystallized from 95% ethanol as yellow needles, m. p. 168–169° (cor.).

Anal. Calcd. for $C_{13}H_{12}O_8N_4$: N, 15.91. Found: N, 15.84.

Ethyl 1-Methyl-2-pyridone-6-pyruvate (IV).—A procedure was employed somewhat similar to one described for quinaldine.¹⁸

(a) **Potassium Ethoxide.**—A solution of potassium ethoxide was prepared by adding cautiously through a dropping funnel 69 ml. of absolute ethanol to 10.55 g. of potassium previously covered with 60 ml. of absolute ether and finally refluxing the mixture until the potassium had completely dissolved. After cooling to room temperature a solution of 39.5 g. of anhydrous ethyl oxalate in 250 ml. of absolute ether was added and the slightly yellow solution allowed to stand at room temperature for ten minutes. Then 30.75 g. of 1,6-dimethyl-2-pyridone was introduced and the flask stoppered securely and shaken until the dimethylpyridone had dissolved. The potassium salt of the keto ester started to separate immediately as a dense yellow powder. The mixture was allowed to stand at room temperature for three days, after which the potassium salt was collected on a Büchner funnel, washed with a liberal amount of absolute ether and dried in a vacuum desiccator over phosphorus pentoxide. The yield was 61.8 g. (94.7%).

Recrystallization from absolute ethanol gave yellow microcrystals, m. p. 310–320°, with decomposition.

Anal. Calcd. for $C_{11}H_{12}O_4NK$: C, 50.56; H, 4.63; N, 5.36; K, 14.96. Found: C, 51.19; H, 4.90; N, 5.55; K, 14.76.

Conversion to the free ester was accomplished by adding 61.8 g. of the crude potassium salt gradually to a well-stirred ice-cold solution of 27 g. of concd. sulfuric acid in 450 ml. of water. The yellow microcrystalline precipitate was collected on a Büchner funnel, washed with cold water, suspended in 300 ml. of cold water, refiltered, washed again and dried. The yield of ester was 42.8 g. (81.1% based on potassium salt, 76.8% based on dimethylpyridone). After recrystallization from 95% ethanol it formed small yellow needles; m. p. 175–176° (cor.). The product is very difficultly soluble in water; soluble in ten parts of boiling ethanol.

Anal. Calcd. for $C_{11}H_{12}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.39; H, 5.79; N, 6.23.

(15) Chichibabin and Konvalova, *Ber.*, **54**, 814 (1921).

(16) Prill and McElvain, *Org. Syntheses*, Coll. Vol. II, p. 419.

(17) Seide, *Ber.*, **57**, 791 (1924).

(18) Wislicenus and Kleisinger, *ibid.*, **42**, 1140 (1909).

(b) **Sodium Ethoxide.**—By use of sodium ethoxide prepared from sodium hydride in absolute ether and absolute ethanol, following the procedure just described, a 95% yield of sodium salt and from it a yield of 85% of ester (based on sodium salt) was obtained.

When the same procedure was applied to condensations of ethyl oxalate with 2-picoline, 6-methyl-2-pyridone or 2-acetamido-6-methylpyridine, no pyruvic esters could be obtained.

Ethyl 1-Methyl-2-pyridone-4-pyruvate.—The procedure described for making ethyl 1-methyl-2-pyridone-6-pyruvate was used. The potassium salt of the keto ester separated only very gradually as a dense yellow powder. It was collected on a Büchner funnel after standing for four and one-half days at room temperature, washed with absolute ether and dried over phosphorus pentoxide in a vacuum desiccator. The yield was 84%.

Conversion to the free ester was carried out by adding 12.0 g. of the potassium salt to a mixture of 5.25 g. of concd. sulfuric acid in 55 ml. of water, 30 g. of chopped ice and 100 ml. of chloroform, which was agitated by an efficient mechanical stirrer. The chloroform layer was decanted and the aqueous phase extracted with 50 ml. of chloroform. It was then made nearly neutral by adding with stirring 3.5 ml. of 28% aqueous ammonia in 30 ml. of water and again extracted with 50 ml. of chloroform. The combined chloroform solutions were washed twice with a small amount of water, filtered and concentrated to a volume of 49 ml., then diluted with 200 ml. of petroleum ether (b. p. 30–60°). The ester separated as small yellow crystals, which were filtered and washed with petroleum ether (b. p. 30–60°) after standing for three hours in the icebox. The yield was 8.1 g. (79% based on potassium salt, 67% based on dimethylpyridone). The ester crystallized from acetone or from ethanol–benzene as small colorless needles, m. p. 157–158° (cor.). The product is very soluble in ethanol and chloroform, moderately soluble in acetone, sparingly soluble in benzene, insoluble in water and petroleum ether.

Anal. Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87. Found: C, 59.14; H, 5.89.

When the potassium salt was converted into the free ester by the method described under the preparation of ethyl 1-methyl-2-pyridone-6-pyruvate, the yield based on the potassium salt was only 56%.

The condensation was also effected by the use of sodium ethoxide in a similar manner. The over-all yield was 65%.

1-Methyl-2-pyridone-6-pyruvic Acid (V).—A mixture of 22.3 g. of 6% sulfuric acid and 2.23 g. of ethyl 1-methyl-2-pyridone-6-pyruvate was boiled under reflux for one-half hour with mechanical stirring. At first the ester dissolved, then after several minutes the acid started to separate. The mixture was allowed to stand in the icebox for several hours, the acid collected on a filter, washed with cold water and dried. There was obtained 1.78 g. (91%) of yellowish-white fine small needles. After recrystallization from water the acid melted at 239–240° (cor.) with effervescence.

Anal. Calcd. for $C_9H_9O_3N$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.06; H, 4.78; N, 7.21.

1-Methyl-2-pyridone-4-pyruvic Acid.—The hydrolysis of the ester was carried out as described for the analogous 6-pyruvic ester. The product was obtained in 55% yield. It was purified by recrystallization from 50% acetic acid; small pale yellow needles, m. p. 246° (cor.) with effervescence.

Anal. Calcd. for $C_9H_9O_4N$: C, 55.38; H, 4.65. Found: C, 55.31; H, 4.88.

1-Methyl-2-pyridone-6-acetic Acid (VI)

(a) **From 1-Methyl-2-pyridone-6-pyruvic Acid.**—A solution of 1.95 g. of the keto acid in 18 ml. of ice-cold 10% aqueous sodium hydroxide was cooled in an ice-salt-bath and shaken vigorously, while 3.3 ml. of 30% hydrogen peroxide diluted with 5 ml. of water was added at such a rate that the temperature did not rise above 0°. The solution, which at first was yellow but became colorless after some

time, was kept in the icebox for forty-eight hours. A little powdered manganese dioxide was then added to cause decomposition to excess hydrogen peroxide and the mixture left in the icebox for another hour. Manganese dioxide was removed by filtration and washed with a little water and the combined filtrate and washings were acidified to congo red by the cautious addition of concd. hydrochloric acid. Crystals separated from the blue solution which, when heated, turned red, then yellowish. After boiling for several minutes, the mixture was cooled and allowed to stand in the icebox to complete crystallization. The pinkish crystals were collected on a filter and washed with ice-cold water; 1.46 g. (87%). By recrystallization from water the acid formed colorless crystals, m. p. 188° (cor.) with effervescence.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.54; H, 5.33; N, 8.25.

When 0.3 g. of the acid was heated at its melting point, it formed 1,6-dimethyl-2-pyridone with evolution of carbon dioxide. The dimethylpyridone was identified as the picrate; yellow needles from ethanol; m. p. 134–136°.

(b) **From Ethyl 1-Methyl-2-pyridone-6-pyruvate.**—To 0.446 g. of the keto ester was added a mixture of 3.6 ml. of 10% aqueous sodium hydroxide, 0.7 ml. of 30% hydrogen peroxide and 2 g. of ice. After standing for fourteen hours in the icebox, 0.3 ml. of 30% hydrogen peroxide was added to the still slightly yellow solution, which then was allowed to stand in the icebox for another twenty-four hours. A little powdered manganese dioxide was added to the now colorless solution, which was filtered after several minutes and acidified to congo red with concd. hydrochloric acid. When heated, the blue solution turned tan-colored. Cooling caused crystals to separate which were washed with ice-cold water after standing for some time in an ice-bath. The yield was 0.18 g. (54%) of colorless crystals, m. p. 186.5° (cor.) with effervescence.

1-Methyl-2-pyridone-4-acetic Acid.—This acid was prepared in a manner similar to the 6-acetic acid analog. From 3.9 g. of 1-methyl-2-pyridone-4-pyruvic acid 1.98 g. (59%) of product resulted. It was purified by crystallization from water; colorless needles, m. p. 184° (cor.) with effervescence.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; neut. equiv., 167.2. Found: C, 57.50; H, 5.57; neut. equiv., 167.7.

1-Methyl-2-pyridone-6-carboxylic Acid (VII).—To 10.4 g. of the potassium salt of ethyl 1-methyl-2-pyridone-6-pyruvate was added 92 g. of ice, followed by 14 ml. of 30% hydrogen peroxide and the solution kept in the icebox for one and one-half hours. An ice-cold solution of 1.8 g. of sodium hydroxide in 10 ml. of water was added and, after forty-two hours in the ice-box, excess hydrogen peroxide was decomposed by adding a little manganese dioxide. The mixture was allowed to stand in the ice-box for another hour, filtered and acidified with 7.5 ml. of concd. hydrochloric acid, which caused the blue solution to turn brown. Tan crystals separated immediately; they were filtered after standing for two hours in the icebox, 3.55 g. (58%). The acid was purified by dissolving it in dilute aqueous sodium carbonate, boiling the solution with Darco, then filtering and acidifying with dilute hydrochloric acid and recrystallizing the precipitate twice from glacial acetic acid. It formed colorless needles, m. p. 260° (cor.) with effervescence. Späth and Koller¹⁰ reported m. p. 247–248° for the compound as prepared by methylation of 6-hydroxypyridine-2-carboxylic acid.

Anal. Calcd. for $C_7H_7O_3N$: C, 54.90; H, 4.61. Found: C, 54.87; H, 4.79.

A small quantity of the acid was melted in a small tube and the liquid distilled. The distillate was dissolved in ether and an ethereal solution of mercuric chloride added. The colorless needles of the mercuric chloride double salt of 1-methyl-2-pyridone, m. p. 127°, as reported by Späth and Koller, resulted.

Methyl 1-Methyl-2-pyridone-6-acetate.—A mixture of 0.55 g. of 1-methyl-2-pyridone-6-acetic acid, 14 ml. of

methanol and 0.5 ml. of concd. sulfuric acid was boiled under reflux for two hours, cooled, poured into an excess of aqueous potassium carbonate and the resulting solution extracted several times with chloroform. Addition of petroleum ether (b. p. 30–60°) to the chloroform solution which had been concentrated to a small volume caused the separation of 0.46 g. (77%) of crystals. Recrystallization from ether–petroleum ether (b. p. 30–60°) yielded small colorless needles, m. p. 102°.

Anal. Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.90; H, 6.01; N, 8.06.

Ethyl 1-Methyl-2-pyridone-6-acetate (X).—A mixture of 17.6 g. of 1-methyl-2-pyridone-6-acetic acid, 500 ml. of absolute ethanol and 6 ml. of concd. sulfuric acid was boiled under reflux for two hours. After addition of 50 ml. of benzene, the solution was distilled slowly for one hour on the steam-bath until about half volume was reached and then concentrated under reduced pressure to a volume of about 110 ml. Upon adding carefully 20 g. of anhydrous potassium carbonate, then 50 g. of chopped ice, followed by 200 ml. of water, and extracting of the solution with eight 25-ml. portions of chloroform, a chloroform solution was obtained. This was dried, concentrated to about 30 ml. and diluted with 100 ml. of petroleum ether (b. p. 30–60°) which caused the deposition of 17.8 g. of colorless needles, m. p. 100–101° (cor.). Another 0.5 g. of less pure product was obtained from the filtrate, giving a total yield of 18.3 g. (89%). Recrystallization of the first crop from dry ether did not cause modification of the melting point.

The ester was very soluble in water, benzene and chloroform, moderately soluble in ether, sparingly soluble in petroleum ether.

Anal. Calcd. for $C_{11}H_{13}O_4N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.59; H, 6.61; N, 7.12.

The ester failed to undergo condensation with aromatic aldehydes in the presence of piperidine or with ethyl oxalate in the presence of potassium ethoxide.

Ethyl 1-Methyl-2-pyridone-6-(α -oximino)-propionate.—A solution of 15.0 g. of ethyl 1-methyl-2-pyridone-6-pyruvate and 15 g. of hydroxylamine hydrochloride in 75 ml. of pyridine and 75 ml. of absolute ethanol was refluxed for four hours on the steam-bath. The hot solution was filtered to remove a small amount of impurity and the filtrate freed from solvents by distillation under reduced pressure. The yellowish gelatinous residue was triturated with 75 ml. of cold water. White crystals separated which were collected on a filter, washed with water and dried. The yield was 13.8 g. (86%). The ester was purified by crystallization from 95% ethanol; colorless needles, m. p. 198° (cor.).

Anal. Calcd. for $C_{11}H_{14}O_4N_2$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.49; H, 6.15; N, 11.86.

1-Methyl-2-pyridone-6-(α -oximino)-propionic Acid (VIII)

(a) **By Hydrolysis of the Oximino Ester.**—A solution of 8.91 g. of the oximino ester in 45 ml. of 2 *N* aqueous sodium hydroxide was boiled under reflux for one hour and twenty minutes. A small amount of impurity was removed by filtration, 10 ml. of water being used for washing flask and filter. The combined yellow filtrate and washings were cooled in an ice-bath and acidified with 9 ml. of concd. hydrochloric acid. Small colorless needles separated; 7.49 g. (95%), m. p. 182° (cor.) with decomposition. Purification by crystallization from 50% acetic acid did not change the melting point.

Anal. Calcd. for $C_9H_{10}O_4N_2$: C, 51.43; H, 4.80. Found: C, 51.31; H, 4.87.

(b) **By Action of Hydroxylamine on 1-Methyl-2-pyridone-6-pyruvic Acid.**—To 19.5 g. of the keto acid was added an ice-cold solution of 14.75 g. of 95% sodium hydroxide in 60 ml. of water, followed by an ice-cold solution of 10.42 g. of hydroxylamine hydrochloride in 20 ml. of water. The mixture was shaken to dissolve the acid, then allowed to stand at 30° for forty-three hours. A small amount of impurity was removed by filtration and the

yellow filtrate, which was cooled in an ice-bath to 5°, acidified by the addition of 33 ml. of concd. hydrochloric acid. Small colorless needles separated, which were filtered after standing for several hours in the icebox, washed with ice-cold water and, when dried, melted at 182° (cor.) with decomposition. The yield was 19.15 g. (91%).

1-Methyl-2-pyridone-6-acetonitrile (IX).—A distilling flask containing 19.1 g. of 1-methyl-2-pyridone-6-(α -oximino)-propionic acid was heated cautiously with a free flame. The solid melted with copious evolution of carbon dioxide and water. The residue was then distilled under reduced pressure, b. p. 168° (1 mm.), as a yellow oil which solidified in the receiver. The yield was 12.5 g. (93%). After recrystallization from benzene–ether and a second vacuum-distillation the product formed colorless needles, m. p. 95.5–96.5°, very soluble in water, ethanol and acetone, moderately soluble in benzene, sparingly soluble in ether.

Anal. Calcd. for $C_8H_8ON_2$: C, 64.85; H, 5.44. Found: C, 64.78; H, 5.33.

The nitrile failed to condense with ethyl carbonate. With benzaldehyde in the presence of pyridine and piperidine, a yellow condensation product, m. p. 260–262° (cor.), formed in a high yield, but could not be obtained in analytically pure form.

The nitrile was readily hydrolyzed by boiling with dilute ethanolic sodium hydroxide for three hours. After acidification 1-methyl-2-pyridone-6-acetic acid, m. p. 187° (cor.) with effervescence, resulted in 86% yield.

Ethyl 1-Methyl-2-pyridone-6-(α -benzyl)-acetate (XI, R = $C_6H_5CH_2$).—To a solution of 0.084 g. of sodium in 2 ml. of absolute ethanol was added 0.69 g. of ethyl 1-methyl-2-pyridone-6-acetate, followed by 0.45 ml. of benzyl chloride. The mixture was refluxed on the steam-bath for twenty-one hours with exclusion of moisture. Another 0.2 ml. of benzyl chloride was added and refluxing continued for three hours until the reaction mixture was neutral. After steam-distillation to remove excess benzyl chloride, the oil which had separated from the residue was dissolved in ether. The ether solution was washed twice with dilute aqueous sodium carbonate, dried over potassium carbonate and concentrated to a volume of about 3 ml., which caused colorless crystals to separate. Crystallization was completed by adding 30 ml. of petroleum ether (b. p. 30–60°) and chilling in an ice-bath for one hour. The solid weighed 0.62 g. (61%). After two recrystallizations from 35% ethanol it formed small colorless needles, m. p. 104–105° (cor.), very soluble in benzene and ethanol, moderately soluble in ether, insoluble in water.

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.74; H, 6.96; N, 4.80.

1-Methyl-2-pyridone-6-(α -benzyl)-acetic Acid (XII, R = $C_6H_5CH_2$).—To 1.0 g. of sodium hydroxide dissolved in 2 ml. of water and 5 ml. of ethanol was added 0.74 g. of the ester and the solution refluxed for two hours. After cooling and acidification to congo red with dilute hydrochloric acid, colorless crystals separated. The yield of material was 0.59 g. (88%). It was purified by dissolving in dilute aqueous ammonia, filtering (Darco) and reprecipitating it with dilute hydrochloric acid; small colorless needles, m. p. 155° (cor.) with effervescence.

Anal. Calcd. for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88. Found: C, 70.15; H, 5.88.

1-Methyl-6-phenethyl-2-pyridone (XIII, R = $C_6H_5-CH_2-$).—In a vacuum-sublimation apparatus 0.1 g. of 1-methyl-2-pyridone-6-(α -benzyl)-acetic acid was heated carefully in an oil-bath. At approximately 150° the crystals melted with evolution of carbon dioxide. When gas evolution had ceased, the temperature was raised slowly to 180°, maintained there for five minutes and again decreased to 150°. When the pressure was reduced to 2 mm., the material distilled and solidified on the cold finger. Redistillation at 2 mm. gave small colorless needles, m. p. 95.5–96.5°, soluble in ether, difficultly soluble in water.

Anal. Calcd. for $C_{14}H_{15}ON$: C, 78.84; H, 7.09. Found: C, 79.05; H, 6.99.

1-Methyl-2-pyridone-6-(α -benzyl)-acetonitrile.—To a solution of 0.23 g. of sodium in 4 ml. of absolute ethanol was added dropwise with mechanical stirring and exclusion of moisture a solution of 1.48 g. of 1-methyl-2-pyridone-6-acetonitrile in 5 ml. of absolute ethanol and 5 ml. of dry benzene, followed by 1.3 ml. of benzyl chloride in 5 ml. of dry benzene. The dark mixture was stirred at room temperature for fifteen minutes, then at the refluxing temperature for fifteen hours. Water was added and the brown benzene layer extracted several times with water, dried over potassium carbonate and boiled with Darco. The yellow filtrate was heated, diluted with petroleum ether (b. p. 30–60°) until it became cloudy, and filtered rapidly. Cooling and scratching with a glass rod caused separation of light tan-colored crystals. The yield was 1.0 g. (42%). After recrystallization from dilute ethanol, then from benzene-ether, the nitrile formed small colorless leaflets, m. p. 132° (cor.).

Anal. Calcd. for $C_{15}H_{14}ON_2$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.71; H, 5.66; N, 11.11.

The nitrile was hydrolyzed by 62% sulfuric acid or preferably by dilute ethanolic potassium hydroxide to form the corresponding acid, m. p. 155°, previously described.

Ethyl 1-Methyl-2-pyridone-6-(α -*n*-butyl)-acetate (XI, R = C_4H_9).—To a solution of 0.51 g. of sodium in 10 ml. of absolute ethanol was added 4.30 g. of ethyl 1-methyl-2-pyridone-6-acetate, followed by 3.5 ml. of *n*-butyl iodide. The orange-colored solution was refluxed with exclusion of moisture on the steam-bath for twenty hours, after which time it was no longer alkaline. Solvent and unreacted butyl iodide were evaporated on the steam-bath under reduced pressure; then 20 ml. of water was added to dissolve sodium iodide. The oil was dissolved in ether and the solution washed twice with aqueous sodium bicarbonate, then thrice with water and dried. Removal of the solvent and fractionation under reduced pressure gave 3.6 g. (65%), b. p. 159–160° (2 mm.). After another distillation the product was a pale yellow oil, n_D^{20} 1.5180. It solidified to colorless crystals on cooling in Dry Ice-acetone.

Anal. Calcd. for $C_{14}H_{21}O_3N$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.87; H, 8.58; N, 5.81.

The reaction was carried out also with *n*-butyl bromide, but somewhat less satisfactory results were obtained.

Hydrolysis and Decarboxylation of Ethyl 1-Methyl-2-pyridone-6-(α -*n*-butyl)-acetate.—A mixture of 0.59 g. of the ester and 0.93 g. of 33% aqueous sodium hydroxide was heated on the hot-plate until a homogeneous solution resulted, then on the steam-bath for one hour. The solution was diluted with 1 ml. of water, cooled in an ice-bath and acidified by the addition of 0.7 ml. of concd. hydrochloric acid. The 1-methyl-2-pyridone-6-(α -*n*-butyl)-acetic acid separated as a viscous oil which could not be induced to solidify. This oil was dissolved in chloroform, the solution washed with water, then concentrated to a small volume and placed in the terminal bulb of a three-bulb microdistillation tube. Chloroform was removed and the residue heated in an oil-bath. The acid decomposed at 150° with evolution of carbon dioxide. The temperature was slowly raised to 185° and maintained there for five minutes. The residue was then distilled into the other bulbs in a vacuum (below 1 mm.) by placing the tube partly in an air-bath heated at 90°. The 6-*n*-amyl-1-methyl-2-pyridone (XIII, R = C_4H_9) was obtained as a colorless oil; n_D^{20} 1.5250 (after redistillation).

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.26; H, 10.06; N, 8.41.

6-Acetyl-1-methyl-2-pyridone (XIII, R = CH_3CO).—To 0.31 g. of sodium hydride and 10 ml. of absolute ether in a 50-ml. round-bottomed flask provided with a mechanical stirrer and a reflux condenser fitted with a calcium chloride tube, was added 0.77 ml. of absolute ethanol diluted with 10 ml. of absolute ether. As soon as

the sodium hydride had been transformed completely into sodium ethoxide, 2.52 g. of ethyl 1-methyl-2-pyridone-6-acetate was added and the mixture refluxed with stirring for fifteen minutes. After cooling in an ice-bath, 0.97 ml. of acetyl chloride, diluted with 10 ml. of absolute ether, was added in one lot. The yellow suspension turned colorless and sodium chloride separated. Stirring was continued for five minutes while keeping the flask in the ice-bath, then for two hours at the boiling point of ether. The slightly acid reaction mixture was extracted with aqueous sodium bicarbonate, then with water. The ethereal solution, after drying, was treated with petroleum ether (b. p. 30–60°) to cause the separation of an oil which partly solidified at 6°, but became liquid again at room temperature. The ether and petroleum ether were evaporated and the residual oil freed from traces of solvent in a vacuum desiccator. The yield of β -keto ester, which was not further purified, was 1.16 g. (38%).

A mixture of 0.97 g. of the crude keto ester and 15 ml. of concd. hydrochloric acid was boiled under reflux on the steam-bath for twenty-two hours. The solution was concentrated under reduced pressure to a small volume, made alkaline by the addition of a large excess of saturated aqueous sodium carbonate and extracted twice with chloroform. The extract was boiled with Darco and the yellow filtrate evaporated on the steam-bath. When petroleum ether (b. p. 30–60°) was added, the oil solidified to pale yellow crystals. The yield was 0.18 g. (27% based on the crude keto ester, 10% based on starting material). The ketone crystallized from benzene as almost white needles, m. p. 135.5–136.5° (cor.). After distillation in a vacuum-sublimation apparatus (bath 150°, 5 mm.) it formed colorless oblong leaflets, m. p. 136.5–137.5° (cor.), very soluble in water and acetone.

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71. Found: C, 65.62; H, 6.83.

6-Acetyl-1-methyl-2-pyridone *p*-Nitrophenylhydrazine.—A solution of 55 mg. of the ketone and of 60 mg. of *p*-nitrophenylhydrazine in 2 ml. of glacial acetic acid was boiled under reflux for thirty minutes. After dilution with water, 79 mg. (79%) of small yellow needles separated. After two recrystallizations from 95% ethanol, the product melted at 209–210° (cor.) with blackening.

Anal. Calcd. for $C_{16}H_{16}O_3N_4$: C, 59.99; H, 5.37. Found: C, 60.14; H, 5.42.

1-Methyl-6-*m*-nitrostyryl-2-pyridone.—A mixture of 2.1 g. of 1,6-dimethyl-2-pyridone, 2.58 g. of *m*-nitrobenzaldehyde and 1.77 g. of acetic anhydride was heated in an oil-bath at 175–180° for twenty hours. The black oil was dissolved in 30 ml. of methanol, the solution boiled with 0.2 g. of Norit for five minutes and filtered, diluted with 3 ml. of concd. hydrochloric acid and 20 ml. of water and boiled on the hot plate to remove methanol. The yellow solution, in which a black-brown oil was suspended, was cooled to room temperature and extracted with benzene to remove tar and unreacted aldehyde. The benzene phase was extracted twice with dilute hydrochloric acid. The combined light yellow acid solutions were boiled for two minutes and made alkaline with 25% aqueous sodium carbonate. A yellow microcrystalline precipitate separated; 0.05 g. (1.1%). It was purified by dissolving in 2 ml. of boiling ethanol, filtering from a black impurity and diluting with 30 ml. of water. The solid was recrystallized from benzene-petroleum ether, then from 95% ethanol, and formed small yellow crystals, m. p. 216–218° (cor.).

Anal. Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.56; H, 4.77; N, 11.04.

6-Acetamido-2-stilbazole (XV).—A mixture of 15.0 g. of 2-acetamido-6-methylpyridine,¹⁴ 10.6 g. of benzaldehyde and 5.1 g. of acetic anhydride was boiled under reflux for thirty hours. The reaction mixture was steam-distilled to remove unreacted benzaldehyde, of which 50% was recovered as the semicarbazone. The residue from the steam-distillation was diluted with water to 250 ml., acidified with hydrochloric acid, treated with Norit and Celite to remove a tarry impurity and filtered through a

Büchner funnel. The yellow filtrate was rendered alkaline by adding aqueous ammonia. A yellow oil separated which was dissolved in ether. After drying and removal of the ether, the residue was dissolved in a small amount of chloroform and the solution diluted with petroleum ether. A solid separated which was dissolved in dilute hydrochloric acid, filtered from a tarry impurity; then ice was added to the solution, followed by an excess of aqueous ammonia. A yellow flocculent mass separated which was filtered and washed with ice-cold water. It was then dissolved in 95% ethanol, the solution boiled with Norit, filtered hot and diluted with hot water until a precipitate started to form. When cooled slowly, a yellow solid separated weighing 2.94 g. (12.3%). After one recrystallization from benzene-petroleum ether (b. p. 90–110°) and one recrystallization from 70% ethanol, the compound formed colorless needles, m. p. 149–150° (cor.).

Anal. Calcd. for $C_{16}H_{14}ON_2$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.85; H, 6.15; N, 11.86.

6-Amino-2-stilbazole Hydrochloride.—A solution of 4.2 g. of 6-acetamido-2-stilbazole in 70 ml. of concd. hydrochloric acid and 70 ml. of water was boiled under reflux for three hours, then cooled and allowed to stand in the icebox overnight. The hydrochloride was collected on a filter, washed with ice-cold 20% hydrochloric acid, then with ether and dried; yield 3.98 g. (97%), m. p. 249–252° (cor.). It was recrystallized from ethanol to form yellow needles of the same melting point.

Anal. Calcd. for $C_{13}H_{13}N_2Cl$: C, 67.09; H, 5.63; N, 12.04; Cl, 15.24. Found: C, 67.02; H, 5.72; N, 12.12; Cl, 15.37.

6-Amino-2-stilbazole (XVI).—A solution of 0.67 g. of the hydrochloride in a small amount of water was made alkaline with aqueous ammonia. A pale yellow oil separated which solidified rapidly on standing; yield 0.54 g. (96%). It was purified by crystallization from benzene-petroleum ether (b. p. 90–110°); small colorless prismatic needles, m. p. 110°.

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.74; H, 6.09; N, 14.46.

6-Hydroxy-2-stilbazole (6-Styryl-2-pyridone) (XVII).—To a warm solution of 0.165 g. of 6-amino-2-stilbazole in 0.1 ml. of concd. sulfuric acid and 3 ml. of water was added 0.07 g. of powdered sodium nitrite. A brown flocculent mass separated. After boiling the mixture for five minutes, an excess of aqueous ammonia was added and boiling continued for two minutes. The red-brown powder was removed by filtration and treated with hot dilute aqueous potassium hydroxide. A black tarry impurity was removed by filtration and the yellow filtrate buffered with Dry Ice. The hydroxystilbazole separated as a yellow oil which rapidly solidified. The yield was 0.08 (48%). Two recrystallizations from 95% ethanol (Norit) yielded small yellow needles, m. p. 210–211° (cor.).

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.67; H, 5.77; N, 7.52.

2-Amino-4-stilbazole.—A mixture of 8.0 g. of 2-acetamido-4-methylpyridine,¹⁷ 6.3 g. of benzaldehyde and 2.7 g. of acetic anhydride was refluxed under nitrogen for forty-six hours. The dark oil, to which 15 ml. of concd. hydrochloric acid had been added, was steam-distilled to remove unreacted benzaldehyde. To the residue, consisting of a dark sticky mass and about 50 ml. of an aqueous solution, was added 50 ml. of concd. hydrochloric acid. The mixture was heated to boiling and filtered from a brown solid, which was then boiled with 50 ml. of concd. hydrochloric acid and refiltered.

The combined filtrates were boiled with Norit and filtered. The clear dark yellow solution was boiled under reflux for three hours, diluted with 50 ml. of water and refluxed for an additional four hours. When cooled, a yellow flocculent precipitate separated. It was collected on a filter, dissolved in boiling ethanol, the solution made alkaline with aqueous ammonia and diluted with water. The tan flocculent precipitate was dissolved in 50 ml. of concd. hydrochloric acid, the solution boiled with Norit,

filtered hot and diluted with 50 ml. of boiling water. After standing for three hours in the icebox, the material which had separated was isolated by filtration, washed with cold water and dissolved in 50 ml. of hot ethanol; to the boiling solution was added 4 ml. of 28% aqueous ammonia in 10 ml. of ethanol, then water, until crystallization started, and the mixture allowed to stand in the icebox. The tan-colored leaflets of the aminostilbazole weighed 1.52 g. (14.5%). After two recrystallizations from 95% ethanol it formed pale yellow glittering leaflets, m. p. 216–217° (cor.).

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.76; H, 6.09; N, 14.23.

The solid, which proved to be insoluble when the original reaction mixture was extracted with hydrochloric acid, was digested with ice-cold acetone, then with boiling concd. hydrochloric acid and refiltered. It was then dissolved in 70 ml. of boiling ethanol, the solution filtered and heated with 40 ml. of concd. hydrochloric acid. Upon slow dilution with 100 ml. of boiling water a yellow flocculent solid separated. After dissolving in ethanol and adding aqueous ammonia to the boiling solution, yellow microcrystals formed. The product (0.29 g.) was recrystallized from ethanol-methyl ethyl ketone; small yellow needles, m. p. 234–235° (cor.).

Analysis did not serve to identify the product.

Anal. Found: C, 84.26; H, 5.59; N, 6.87.

2-Hydroxy-4-stilbazole (4-Styryl-2-pyridone).—A solution of 2.4 g. of 2-amino-4-stilbazole in 1.5 ml. of concd. sulfuric acid and 10 ml. of glacial acetic acid was stirred and cooled in an ice-salt-bath, which caused separation of the sulfate. It was diazotized by the gradual addition of 1.0 g. of sodium nitrite in 2 ml. of water. The mixture was then allowed to come to room temperature and treated with small portions of solid sodium nitrite until it gave a positive reaction with starch-iodide paper (ten minutes). Addition of 100 ml. of water caused separation of a tan-colored flocculent solid. The suspension was heated to 90° and made alkaline with aqueous ammonia. The solid was removed by filtration, dissolved in 100 ml. of boiling ethanol, a tan-colored impurity removed by filtration and the filtrate allowed to stand in the icebox. The greyish-brown crystals were collected and weighed 0.86 g. (36%). By repeated recrystallizations from 95% ethanol (Darco), yellowish prismatic needles, m. p. 238–239° (cor.), resulted.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.04; H, 5.71; N, 7.45.

6-Methyl-2-pyridone-1- β -propionitrile (XVIII).—An intimate mixture of 42.5 g. of 6-methyl-2-pyridone and 1.3 g. of 6-methyl-2-pyridone sodium was heated under reflux on a steam-bath with 22.8 g. of acrylonitrile. The mixture was shaken frequently until it had liquefied, which took about ten minutes, then heated for twenty more minutes. After addition of 1 ml. of glacial acetic acid in 110 ml. of boiling benzene, the solution was filtered hot from sodium acetate and allowed to cool in the icebox. Tan crystals separated, which were collected on a filter and washed with a small amount of ice-cold benzene. The yield was 52.5 (81% based on total methylpyridone, 83% based on free methylpyridone). It was recrystallized from methyl ethyl ketone to give colorless prisms, m. p. 109–110° (cor.), very soluble in water, moderately soluble in benzene, acetone and methyl ethyl ketone, insoluble in petroleum ether.

Anal. Calcd. for $C_9H_{10}ON_2$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.88; H, 6.20; N, 17.13.

Other catalysts, such as 50% aqueous potassium hydroxide, powdered sodium hydroxide, Triton B (with addition of dioxane) gave satisfactory results, although the yield of product was slightly less.

Pyrolysis of the nitrile in a small distilling flask gave acrylonitrile and 6-methyl-2-pyridone, showing the reversibility of this reaction.

6-Methyl-2-pyridone-1- β -propionic Acid (XIX).—A solution of 18.4 g. of the propionitrile in 92 ml. of water

and 6 ml. of concd. sulfuric acid was refluxed for three hours. When cooled in the icebox, colorless crystals separated; the yield was 18.9 g. (92%). After recrystallization from water, then from acetone, the acid formed colorless plates or prisms, m. p. 165–166° (cor.).

Anal. Calcd. for $C_8H_{11}O_2N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.73; H, 6.24; N, 7.82.

Many experiments were performed to prepare the esters of this acid. None gave satisfactory results. An oil which could not be distilled without decomposition into acrylic ester and 6-methyl-2-pyridone always resulted. The methods employed were alcoholysis of the corresponding nitrile, condensation of 6-methyl-2-pyridone sodium with ethyl β -bromopropionate, esterification of the acid with hydrogen chloride and ethanol, reaction of the silver salt of the acid with methyl or ethyl iodide, attempted condensation of 6-methyl-2-pyridone with ethyl acrylate, the action of diazomethane on the acid.

The crude oil obtained in many of these experiments was treated with reagents such as potassium, potassium ethoxide, and sodium hydride in an attempt to eliminate ethanol or methanol from the ester grouping and 6-methyl group in order to obtain a pyridocoline ring. All experiments failed.

Ethyl 6-Methyl-2-pyridone-1-acetate (XX) and 2-Carboethoxymethoxy-6-methylpyridine (XXI).—To a solution of 2.3 g. of sodium in 50 ml. of absolute ethanol and 20 ml. of dry benzene was added 10.9 g. of 6-methyl-2-pyridone, followed by 18 g. of ethyl bromoacetate. The mixture was refluxed in a boiling water-bath for two hours; then ethanol, benzene and most of the unreacted ethyl bromoacetate were removed on the steam-bath under reduced pressure. After addition of 100 ml. of hot water, the mixture was steam-distilled. The steam-distillate from which a heavy oil had separated was extracted with chloroform and the extract dried over potassium carbonate. Chloroform was removed under reduced pressure and the residual oil distilled *in vacuo*. The 2-carboethoxymethoxy-6-methylpyridine boiled at 132° (15 mm.), n_D^{20} 1.4909. The yield was 1 g. (5%).

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71. Found: C, 61.56; H, 6.88.

The residue of the steam-distillation was made alkaline by the addition of 2 g. of potassium carbonate and extracted with chloroform in a continuous extractor. The extract was dried over potassium carbonate and freed completely from chloroform by heating on the steam-bath under reduced pressure. The ethyl 6-methyl-2-pyridone-1-acetate remained as a brown liquid which on cooling solidified to a tan-colored solid. The yield was 13.7 g. (70%). It was dissolved in hot benzene, the solution boiled with Norit, filtered and diluted with petroleum ether (b. p. 30–60°) until incipient cloudiness. When cooled in the ice-box, 11.7 g. (60%) of crystals separated. They were dissolved in cold acetone, a colorless impurity removed by filtration and the filtrate diluted with petroleum ether (b. p. 30–60°). Repeated recrystallizations gave colorless needles, m. p. 81–82°. The ester was purified for analysis by vacuum-sublimation.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.41; H, 6.44; N, 7.04.

6-Methyl-2-pyridone-1-acetic Acid.—A mixture of 1.24 g. of the ester (XX) and 7.4 ml. of 35% aqueous potassium hydroxide was boiled under reflux for thirty minutes. The solution was filtered, diluted with 10 ml. of water and acidified by the addition of 5.7 ml. of concd. hydrochloric acid. The colorless prisms were collected on a filter after standing in an ice-box overnight; yield 0.68 g. (64%). The acid was purified from ethanol; m. p. 229° (cor.) with effervescence.

Anal. Calcd. for $C_8H_9O_3N$: N, 8.38. Found: N, 8.77.

The same compound was made as follows. To a solution of 2.18 g. of 6-methyl-2-pyridone in 4.62 g. of hot 50% aqueous potassium hydroxide was added 1.98 g. of chloroacetic acid and the mixture boiled on the hot plate for two minutes. The solid which formed was dissolved

by adding 2 ml. of water and boiling was continued for three more minutes. When cooled, the mixture solidified to a crystalline mass. It was dissolved in 7 ml. of hot water and acidified by the addition of 1.8 ml. of concd. hydrochloric acid. Cooling to room temperature and scratching the wall of the container with a glass rod caused separation of colorless crystals; yield 0.4 g. (12%). After washing with a little acetone, the remaining 0.3 g. was recrystallized from boiling water, then ethanol; m. p. 229° (cor.) with effervescence.

Ethyl 1-Carboethoxymethyl-2-pyridone-6-pyruvate (XXII).—To a solution of 0.76 g. of potassium in 4.3 ml. of absolute ethanol and 9 ml. of absolute ether was added at 0° 2.84 g. of ethyl oxalate, then after ten minutes 3.48 g. of ethyl 6-methyl-2-pyridone-1-acetate, followed by 15 ml. of dry benzene and 26 ml. of absolute ether. The flask was flushed with nitrogen, tightly stoppered and allowed to stand at room temperature for nineteen hours. In a short time the potassium salt started to separate as a yellow powder and the solution turned at first bright yellow, then orange, finally dark red-brown. The potassium salt of the condensation product was collected on a Büchner funnel, washed with absolute ether and weighed 2.42 g. (41%).

The potassium salt was stirred into a mixture of 0.5 ml. of concd. sulfuric acid and 20 g. of ice. A yellow oil separated which rapidly solidified. The ester was collected on a filter, washed with water and dried. It weighed 1.61 g. (30.6%). It was purified by crystallization from 95% ethanol (Norit); small lemon-yellow leaflets, m. p. 137–138°.

Anal. Calcd. for $C_{14}H_{17}O_6N$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.90; H, 5.73; N, 4.84.

Reaction of 6-Methyl-2-pyridone with N-Bromosuccinimide.—A mixture of 2.18 g. of 6-methyl-2-pyridone, 7.12 g. of N-bromosuccinimide and 0.25 g. of benzoyl peroxide in 60 ml. of carbon tetrachloride was boiled under reflux for thirty minutes. Succinimide was removed by filtering the hot mixture and washing with boiling carbon tetrachloride. The combined filtrate and washings were evaporated to dryness and the residue recrystallized from 95% ethanol. The product consisted of 1.2 g. of colorless needles, which after recrystallization melted at 254–255° (cor.). Admixture of an authentic sample of 3,5-dibromo-6-methyl-2-pyridone did not depress the melting point.

2-Amino-5-bromo-6-methylpyridine.—A solution of 10.8 g. of 2-amino-6-methylpyridine in 47 g. of 20% sulfuric acid was cooled in ice water and 18.7 g. of bromine was added dropwise over fifteen minutes with continuous swirling. It was then shaken at room temperature until a colorless solution resulted (about fifteen minutes). cooled again in ice water and made alkaline by adding 80 g. of ice-cold aqueous 20% sodium hydroxide. A partly crystalline, partly oily white mass separated which solidified completely after standing for several hours in the ice-box. The crude product weighed 14.6 g. (78%). Recrystallization from petroleum ether (b. p. 90–110°) in which the contaminants are very soluble, gave 9.3 g. (50%) of long silky colorless needles, m. p. 83–84°. The analytical sample was prepared by vacuum-sublimation.

Anal. Calcd. for $C_8H_7N_2Br$: N, 14.98; Br, 42.73. Found: N, 15.00; Br, 42.76.

2-Amino-3,5-dibromo-6-methylpyridine.—To a solution of 10.8 g. of 2-amino-6-methylpyridine in 47 g. of 20% sulfuric acid was added with continuous swirling 32 g. of bromine. The temperature was maintained below 35° by occasional immersion in ice water. The mixture was heated on the steam-bath for two hours, then allowed to stand in the icebox overnight. The white crystalline sulfate was collected on a filter and washed with ice-cold 20% sulfuric acid, then with acetone. The yield was 24.6 g. (78%).

The sulfate was added in small portions with stirring to 50 g. of ice-cold 10% aqueous sodium hydroxide and the mixture allowed to stand in the icebox for several hours. The colorless crystals weighed 17.15 g. (82.5% based on sulfate). After recrystallization from 95% ethanol, the

base formed short colorless prismatic needles, m. p. 144° (cor.).

Anal. Calcd. for $C_6H_6N_2Br_2$: C, 27.09; H, 2.27; N, 10.53; Br, 60.10. Found: C, 27.31; H, 2.33; N, 10.63; Br, 59.93.

5-Bromo-6-methyl-2-pyridone.—A solution of 8.4 g. of 2-amino-5-bromo-6-methylpyridine in 40 g. of ice-cold 20% sulfuric acid was diazotized below 10° by adding dropwise a solution of 3.3 g. of sodium nitrite in 7 ml. of water. The sulfate of the pyridone separated during the reaction. The paste was diluted with 30 ml. of water and the suspension heated on the steam-bath for five minutes. A solution of 9 g. of potassium carbonate in 15 ml. of water was added with stirring and the yellow suspension heated to boiling, then allowed to stand in the icebox. The yield of tan needles was 6.9 g. (82%). The compound was recrystallized from 95% ethanol, then from benzene to form colorless needles, m. p. 204° (cor.). The analytical sample was prepared by vacuum-sublimation.

Anal. Calcd. for C_6H_6ONBr : N, 7.45; Br, 42.50. Found: N, 7.28; Br, 42.50.

3,5-Dibromo-6-methyl-2-pyridone.—A warm solution of 13.3 g. of 2-amino-3,5-dibromo-6-methylpyridine in 54 g. of 20% sulfuric acid was cooled rapidly in an ice-salt bath with efficient stirring to cause separation of very small crystals, then diazotized by adding dropwise a solution of 3.7 g. of sodium nitrite in 10 ml. of water. The mixture became pasty as the sulfate of the pyridone separated. The suspension obtained by adding 300 ml. of water was heated to boiling and made alkaline by adding slowly with stirring a solution of 13 g. of potassium carbonate in 50 ml. of water. The yield of colorless crystals was 12.9 g. (97%). After recrystallization from ethanol-benzene and then from 95% ethanol, colorless needles, m. p. 254–255° (cor.), resulted. Errera¹³ reported m. p. 238–239°.

Summary

1. In order to devise methods by which cytosine might be synthesized, a further knowledge of the activity of a 6-methyl group in 1-substituted 2-pyridones was required. It has been shown that the 6-methyl group in 1,6-dimethyl-2-pyridone condenses readily with ethyl oxalate in presence of potassium or sodium ethoxide to give the corresponding pyruvate. The same is true of the 4-methyl group in 1,4-dimethyl-2-pyridone.

2. These pyruvic esters were saponified to the corresponding acids and these by means of alkali and hydrogen peroxide degraded to the corresponding 1-methyl-2-pyridone-6(or 4)-acetic acids. The 6-pyruvic ester was converted directly in one step to the 6-acetic acid with alkali and hydrogen peroxide. Its potassium salt, however, by treatment with hydrogen peroxide, gave 1-methyl-2-pyridone-6-carboxylic acid.

3. Pyrolysis of 1-methyl-2-pyridone-6-(α -oximino)-propionic acid, obtained by reaction of the 6-pyruvic acid and hydroxylamine or by hydrolysis of the oximino ester, gave the 6-acetonitrile which could be alkylated with alkyl halides in the presence of sodium ethoxide. In the same way the 6-acetic ester, obtained from the acid, was alkylated with benzyl chloride and *n*-butyl iodide and acylated with acetyl chloride, the resulting products saponified and the corresponding acids decarboxylated by pyrolysis. 1-Methyl-6-phenethyl-2-pyridone, 6-*n*-amyl-1-methyl-2-pyridone and 6-acetonyl-1-methyl-2-pyridone were thus obtained.

4. 1,6-Dimethyl-2-pyridone condensed with *m*-nitrobenzaldehyde in presence of acetic anhydride to give a very low yield of 1-methyl-6-*m*-nitrostyryl-2-pyridone.

5. 2-Acetamido-6(or 4)-methylpyridine condensed with benzaldehyde to give 2-acetamido-6(or 4)-stilbazole, from which by saponification of the acetyl group and diazotization, 6- or 4-styryl-2-pyridone resulted.

6. 6-Methyl-2-pyridone condensed with acrylonitrile in presence of alkaline catalysts to give 6-methyl-2-pyridone-1- β -propionitrile, which was hydrolyzed to the corresponding acid. 6-Methyl-2-pyridone sodium condensed with bromoacetic ester to give ethyl 6-methyl-2-pyridone-1-acetate which in turn condensed with ethyl oxalate to form a pyruvate.

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[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

Hyperconjugation. III. Relative Rates of Bromination of Twelve Monoalkylbenzenes

BY ERNST BERLINER AND FRANCES BERLINER

The relative rates of bromination of toluene, ethylbenzene, *i*-propylbenzene and *t*-butylbenzene in aqueous acetic acid at 25° are 100, 76, 44 and 23, respectively.¹ A competitive bromination study of toluene and *t*-butylbenzene has confirmed the order for the latter two compounds.² These results have been explained by hyperconjugation involving the hydrogen atoms on the carbon atom alpha to the benzene ring.^{1,2,3} In the work pre-

sented here the above order of reactivity is confirmed and investigation of the relative rates of bromination of monoalkylbenzenes is extended to include both propylbenzenes, all four butylbenzenes, and four of the eight amylbenzenes. The results are considered in the light of hyperconjugation.

Method. The procedure adopted for measuring the relative rates of bromination was similar to that used by De la Mare and Robertson.¹ The relative rates were calculated by comparing the times necessary for ten per cent. reaction of bro-

(1) De la Mare and Robertson, *J. Chem. Soc.*, 279 (1943).
 (2) Berliner and Bondhus, *THIS JOURNAL*, 68, 2355 (1946).
 (3) Baker and Nathan, *J. Chem. Soc.*, 1844 (1935).