tered, neutralized, washed and dried; the yield was 5.1 g. (95%). Over-all yield for the above three steps was approximately 70%. The product was not crystallizable; from ethyl acetate the non-crystalline material gave a m.p. 245–246°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 61.27; H, 5.76.

4,4'-Bis-(γ-carboxypropoxy)-benzalazine (IV).—When 4.2 g. (0.02 mole) of III was treated with 1.8 g. (0.014 mole) of hydrazine sulfate, 3.7 g. (90%) of a yellow precipitate was obtained which could not be obtained in crystalline form; from ethyl acetate, m.p. 240–241°; neut. equiv. calcd. 206, found 208 (average of three).

Anal. Calcd. for $C_{22}H_{24}O_6N_2$: C, 64.06; H, 5.87. Found: C, 64.70; H, 6.44.

4,4'-Bis-(δ-keto-ε-chloropentoxy)-benzalazine (V).—To an iced mixture of 1.55 g. (0.0037 mole) of IV and 30 ml. of anhydrous benzene was added dropwise 3.38 g. (2.13 ml., 0.028 mole) of highly purified thionyl chloride. The mixture was gently refluxed until the evolution of sulfur dioxide and hydrogen chloride ceased, and excess thionyl chloride removed. Anhydrous benzene was added and the solution distilled to remove all traces of thionyl chloride. Approximately 150 ml. of dried dioxane was added to the solution and the mixture was added dropwise to freshly prepared cold, dried, ethereal diazomethane (4.3 g., 0.02 mole, of N-methyl-N-nitroso-*p*-toluenesulfonamide was used). After the solution remained chilled for 10 hours, the excess diazomethane and ether were removed under reduced pressure. To the solution of this diazomethylketone partially dissolved in dioxane was added an ether–chloroform mixture until a solution was achieved. Hydrogen chloride was added, the color of the solution lightened, and a small amount of semi-crystalline material separated; more of the material was obtained as the solvent was removed under reduced pressure. Recrystallization from a benzene–acetone mixture gave 0.5 g. of light brown needles, m.p. 179–180°.

Anal. Calcd. for $C_{24}H_{26}N_2O_4Cl_2$: Cl, 14.85. Found: Cl, 14.99.

***p*-Bromo-α-iodoacetophenone.**—On refluxing 8.34 g. (0.03 mole) of *p*,α-dibromoacetophenone with 4.50 g. (0.03 mole) of sodium iodide in 150 ml. of anhydrous acetone, sodium bromide precipitated. Addition of excess water caused the product to precipitate and it was removed by filtration. The product was washed with water, dried, and recrystallized from ethanol giving white needles, m.p. 95°, yield 8.2 g. (86%); it formed a 2,4-dinitrophenylhydrazone, red needles, m.p. 194–195°.

Anal. Calcd. for C_8H_6OBrI: C, 29.57; H, 1.86. Found: C, 29.85; H, 1.92.

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CLEVELAND, OHIO

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

A Synthesis of 6-Hydroxy-4-quinolizones

BY ROGER ADAMS AND WALTER REIFSCHNEIDER

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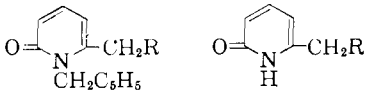
Ethyl 2-pyridone-6-acetate (IIa) and ethyl 2-ethoxy-6-pyridylacetate (IVe) were prepared from 1-benzyl-6-methyl-2-pyridone and 2-ethoxy-6-methylpyridine 1-oxide, respectively. Ethyl 2-pyridone-6-acetate but not ethyl 2-ethoxy-6-pyridylacetate condenses with diethyl ethoxymethylenemalonate to form 1,3-dicarbethoxy-6-hydroxy-4-quinolizone (VIa).

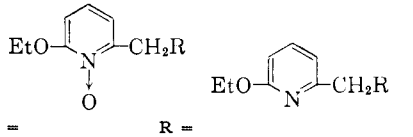
The possibility of building the condensed ring system found in cytisine[1] from either ethyl 2-pyridone-6-acetate (IIa) or ethyl 2-ethoxy-6-pyridylacetate (IVe) as the starting material stimulated a study of the syntheses and some of the reactions of these two compounds. The results are described in this Communication. Compound IIa has been synthesized by the following steps: (1) 1-benzyl-6-methyl-2-pyridone (Ia) with ethyl oxalate to ethyl 1-benzyl-2-pyridone-6-pyruvate (Ib); (2) hydrolysis of compound Ib to the corresponding acid Ic; (3) alkaline peroxide oxidation of compound Ic to 1-benzyl-2-pyridone-6-acetic acid (Id); esterification of compound Id to the ethyl ester Ie. This is a more satisfactory procedure than the one previously described[2] which combined steps 2 and 3 into one operation. An alternative procedure for synthesis of compound Ie consisted in pyrolysis of the 1-benzyl-2-pyridone-6-pyruvic acid oxime (If) to 1-benzyl-2-pyridone-6-acetonitrile (Ig). With ethanol and hydrogen chloride, the nitrile was converted to the ester Ie. Debenzylation of compound Ie was effected with sodium and liquid ammonia to give ethyl 2-pyridone-6-acetate (IIa).



R =
Ia, H
b, $COCO_2Et$
c, $COCO_2H$
d, CO_2H
e, CO_2Et
f, $-CCO_2H$ ‖ NOH
g, CN
h, $CONH_2$

R =
IIa, CO_2Et
b, $CONH_2$
c, $CH{=}CHCO_2H$

Ethyl 2-ethoxy-6-pyridylacetate (IVe) was derived from 2-ethoxy-6-methylpyridine 1-oxide (IIIa), formed either by the action of sodium ethoxide in ethanol on 2-bromo-6-methylpyridine 1-oxide or



R =
IIIa, H
b, $COCO_2R$

R =
IVa, $COCO_2Et$
b, CCO_2Et ‖ NOH
c, CCO_2H ‖ NOH
d, CN
e, CO_2Et

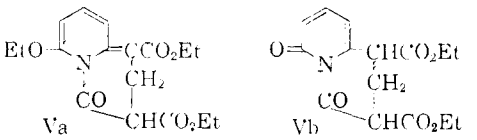
by the action of peracetic acid upon 2-ethoxy-6-methylpyridine. Condensation of the compound IIIa with ethyl oxalate gave ethyl 2-ethoxy-6-pyridylpyruvate 1-oxide (IIIb). Attempts to hydrolyze compound IIIb to the corresponding acid

(1) E. Späth and F. Galinovsky, *Ber.*, **66**, 1338 (1938).
(2) R. Adams and S. Miyano, THIS JOURNAL, **76**, 3168 (1954).

without concomitant hydrolysis of the ethoxy group on the nucleus failed. The N-oxide function was therefore removed by treatment with phosphorus trichloride in chloroform; ethyl 2-ethoxy-6-pyridylpyruvate (IVa) resulted in about 30% yield.[3]

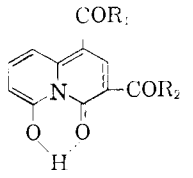
The oxime IVb of compound IVa was hydrolyzed to the acid IVc, and the latter pyrolyzed to 2-ethoxy-6-pyridylacetonitrile (IVd). Ethanol and hydrogen chloride converted IVd to ethyl 2-ethoxy-6-pyridylacetate (IVe).

Attempts to condense either compound IIa or IVe with diethyl methylenemalonate to the ring structures shown in Va or Vb, respectively, was unsuccessful.



Va Vb

On the other hand, diethyl ethoxymethylenemalonate reacted readily with ethyl 2-pyridone-6-acetate (IIa) to form 1,3-dicarbethoxy-6-hydroxy-4-quinolizone (VIa). Unexpectedly 2-pyridone-6-acetamide and diethyl methylenemalonate condensed to give the same quinolizone VIb that formed when diethyl ethoxymethylenemalonate was used; an oxidation apparently occurred concomitantly or during the isolation of the product.



	R =	R =
VIa,	OEt	OEt
b,	NH_2	OEt
c,	OEt	OH

These 6-hydroxy-4-quinolizones (VIa and VIb) could not be reduced successfully to the dimethylol analogs with lithium aluminum hydride. An orange-red solid formed immediately when the quinolizone solution in ether contacted the hydride solution. These products, metal complexes insoluble in ether, were treated continuously with 6% sulfuric acid without removal of the metal. No convenient method of purification was found. Whether any reduction of one or both of the carbethoxy groups occurred concomitantly is doubtful. Very stable lithium salts of a somewhat similar character have been reported in the literature.[4]

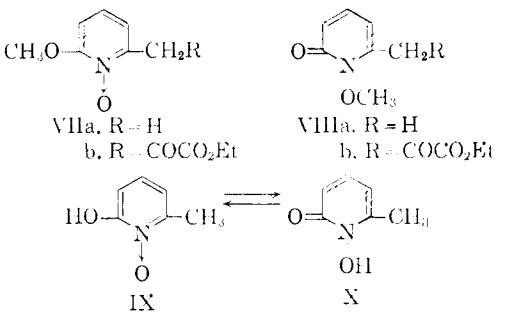
1,3-Dicarbethoxy-6-hydroxy-4-quinolizone (VIa) was hydrolyzed under various conditions. With concentrated hydrochloric acid or with aqueous sodium hydroxide, 2-pyridone-6-crotonic acid (IIc) resulted; with aqueous barium hydroxide, however, 1-carbethoxy-3-carboxy-6-hydroxy-4-quinolizone (VIc) was obtained.

(3) This yield might have been increased if triethyl phosphite or triphenyl phosphite [M. Hamana, *J. Pharm. Soc. Japan*, **75**, 139 (1955)], had been used in place of phosphorus trichloride. This reagent was not reported until after this work had been completed.

(4) G. A. Guter and G. S. Hammond, THIS JOURNAL, **78**, 5166 (1956).

Ethyl 2-ethoxy-6-pyridylpyruvate (IVe) or ethyl 2-ethoxy-6-pyridylacetonitrile (IVd) in contrast to ethyl 2-pyridone-6-acetate did not condense under similar conditions either with diethyl ethoxymethylenemalonate or diethyl methylenemalonate.

Oxidation of 2-methoxy-6-methylpyridine with fresh peracetic acid gave exclusively 2-methoxy-6-methylpyridine 1-oxide (VIIa); but oxidation with peracetic acid that had been opened and had stood for at least a year led to a mixture of two compounds, the expected 2-methoxy-6-methylpyridine 1-oxide (VIIa) and 1-methoxy-6-methyl-2-pyridone (VIIIa).



VIIa, R = H
b, R = $COCO_2Et$

VIIIa, R = H
b, R = $COCO_2Et$

IX X

	R =	R =		
VIIa,	H	VIIIa, R = H	IX	X
b,	$COCO_2Et$	b, $COCO_2Et$		

Both compounds VIIa and VIIIa were synthesized by unequivocal methods. The first, compound VIIa, was obtained by the action of sodium methoxide on 2-bromo-6-methylpyridine 1-oxide; the second, compound VIIIa, was formed in two steps. Hydrolysis of 2-bromo-6-methylpyridine 1-oxide gave 2-hydroxy-6-methylpyridine-1-oxide (IX) which is in equilibrium with 1-hydroxy-6-methyl-2-pyridone (X). The sodium salt of this product reacts with methyl iodide entirely as structure X to give compound VIIIa.

The corresponding pyruvates VIIb and VIIIb may be synthesized by the action of ethyl oxalate on compounds VIIa and VIIIa. The 1-oxide VIIb is water soluble but its isomer VIIIb is essentially water insoluble.

Acknowledgment.—The authors are indebted to Mr. J. Nemeth, Mrs. M. Stingl and Miss C. Higham for the micro-analyses and Mr. J. Brader for the determination of the infrared spectra.

Experimental

1-Benzyl-2-pyridone-6-pyruvic Acid (Ic). A suspension of 20.0 g. of ethyl 1-benzyl-2-pyridone-6-pyruvate[5] in 200 ml. of 6% sulfuric acid was heated under reflux and mechanically stirred. The yellow ester dissolved and the white acid precipitated gradually. After the hydrolysis was complete, the mixture was cooled and the acid was collected by filtration, washed with water and recrystallized from ethanol. Fine white crystals, m.p. 211°, were obtained. The yield was 18.1 g. (99.5%).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.17. Found: C, 66.79; H, 5.07; N, 5.14.

1-Benzyl-2-pyridone-6-(α-oximino)-propionic Acid (If).—To a mixture of 5.7 g. of 1-benzyl-2-pyridone-6-pyruvic acid and 3.1 g. of sodium hydroxide in 12 ml. of water cooled to 0° was added an ice-cold solution of 2.2 g. of hydroxylamine hydrochloride in 5 ml. of water. After standing for 36 hours the reaction mixture was filtered to remove a small amount of undissolved material, and after cooling in an ice-

(5) N. J. Leonard and J. E. Boyer, *ibid.*, **72**, 2980 (1950).

bath, was acidified with concd. hydrochloric acid. The product precipitated, and was recrystallized from glacial acetic acid to which water was added at the boiling temperature until turbidity appeared. Fine colorless needles were obtained, m.p. 191°. The yield was 5.5 g. (91.4%).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.10; H, 4.76; N, 9.60.

1-Benzyl-2-pyridone-6-acetonitrile (Ig).—A large test-tube containing 7.5 g. of 1-benzyl-2-pyridone-6-(α-oximino)-propionic acid was heated cautiously with a free flame. The oximino acid melted with evolution of water and carbon dioxide. After the gas evolution had stopped, the nitrile was dissolved in a small amount of ethanol and ether was added. Fine white crystals separated which were recrystallized from ethanol–ether; m.p. 92°. The yield was 5.2 g. (88.5%).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.40; N, 12.49. Found: C, 74.44; H, 5.18; N, 12.65.

1-Benzyl-2-pyridone-6-acetic Acid (Id).[2]—A solution of 8.1 g. of 1-benzyl-2-pyridone-6-pyruvic acid in 55 ml. of ice-cold 10% aqueous sodium hydroxide was placed in an ice–salt-bath and a mixture of 10 ml. of 30% hydrogen peroxide and 15 ml. of water was added very slowly with good agitation, so that the temperature did not rise above 0°. The yellow solution, which decolorized gradually, was kept at 0° for about 40 hours. Then manganese dioxide was added to destroy the excess hydrogen peroxide. After one hour standing at 0° the solution was filtered and cautiously acidified with concd. hydrochloric acid. White crystals precipitated which were recrystallized from water, m.p. 169° (with effervescence). The yield was 6.5 g. (89.5%).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.07; H, 5.48; N, 6.05.

Ethyl 1-Benzyl-2-pyridone-6-acetate (Ie). (A) From 1-Benzyl-2-pyridone-6-acetic Acid.—The esterification procedure described by Adams and Miyano[2] was used. The ester, after purification by recrystallization from petroleum ether (b.p. 30–60°), formed white crystals, m.p. 79°.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 70.68; H, 6.36.

(B) From 1-Benzyl-2-pyridone-6-acetonitrile.—A solution of 4.2 g. of 1-benzyl-2-pyridone-6-acetonitrile in 100 ml. of 95% ethanol was saturated with hydrogen chloride at 0°. The mixture was kept at room temperature for 12 hours and then was heated under reflux for 2 hours. The solvent was evaporated in vacuum and the residue was made alkaline by adding aqueous 10% potassium carbonate. The solid ester was purified as described in A and melted at the same point. The yield was 5.0 g. (98.5%).

1-Benzyl-2-pyridone-6-acetamide (Ih).—A mixture of 20 g. of ethyl 1-benzyl-2-pyridone-6-acetate and 150 ml. of concd. aqueous ammonia was stirred at room temperature for 12 hours. The solid, after recrystallization from dimethylformamide, formed white crystals, m.p. 250–252°. The yield was 17.0 g. (95%).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.46; H, 6.13; N, 11.40.

Ethyl 2-Pyridone-6-acetate (IIa).—Into a three-neck flask fitted with a mechanical stirrer and a Dry Ice condenser was placed about 80 ml. of liquid ammonia, and 5 g. of ethyl 1-benzyl-2-pyridone-6-acetate was added. To the resulting suspension sodium was added in small portions with stirring until the blue color remained (0.9 g. of sodium was necessary). The stirring was continued for 15 minutes and then 5.0 g. of ammonium chloride was added. The Dry Ice condenser was then replaced with a water condenser and the ammonia was evaporated by external heating (about one hour). The dry residue was taken up in water and the solid collected by filtration. The filtrate was extracted twice with chloroform and the chloroform solution was evaporated to dryness. The residue together with the solid obtained by filtration was recrystallized from benzene. Colorless needles were obtained, m.p. 170°. The yield was 2.4 g. (71.8%).

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.79; H, 5.84; N, 7.96.

2-Pyridone-6-acetamide (IIb).—If the evaporation of the ammonia in the previous preparation was postponed for 24 hours, 2-pyridone-6-acetamide was obtained instead of ethyl 2-pyridone-6-acetate. The dry residue was taken up in water, the solid was collected by filtration and the filtrate extracted with chloroform. The residue after evaporating the chloroform was combined with the solid collected by filtration and was extracted with hot benzene. The substance insoluble in benzene was then recrystallized from ethanol. Fine colorless needles were obtained, m.p. 254° dec. The yield was 1.8 g. (64.2%).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.42. Found: C, 55.51; H, 5.08; N, 18.36.

A small amount of ethyl 2-pyridone-6-acetate crystallized from the benzene solution.

2-Pyridone-6-acetamide was also prepared from ethyl 2-pyridone-6-acetate and concd. aqueous ammonia by stirring a suspension for 24 hours.

Methylation of Ethyl 2-Pyridone-6-acetate with Diazomethane; Ethyl 1-Methyl-2-pyridone-6-acetate.[6]—To a cold solution of 3.0 g. of ethyl 2-pyridone-6-acetate in 50 ml. of ethanol was added an excess of an ethereal diazomethane solution and the mixture was allowed to stand overnight. The solution was filtered and the solvents evaporated in vacuum. The residue was recrystallized from ether, yielding 2.25 g. (69.6%) of a substance, m.p. 100–101°. The compound was identical with an authentic sample of ethyl 1-methyl-2-pyridone-6-acetate.[6]

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71. Found: C, 61.72; H, 6.57.

Condensation of Ethyl 2-Pyridone-6-acetate with Diethyl Ethoxymethylenemalonate: 1,3-Dicarbethoxy-6-hydroxy-4-quinolizone (VIa).—To a mixture of 9.05 g. of ethyl 2-pyridone-6-acetate and a solution of 1.3 g. of sodium in 250 ml. of ethanol was added 11.0 g. of diethyl ethoxymethylenemalonate.[7] A yellow condensation product precipitated immediately. After heating on the water-bath for 5 minutes the mixture was cooled and the solid collected by filtration. It was then allowed to stand for 30 minutes with 180 ml. of 6% sulfuric acid after which it was collected by filtration and recrystallized from ethanol. Yellow crystals formed, m.p. 150–151°. The yield was 11.0 g. (72.1%).

Anal. Calcd. for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.04; H, 4.95; N, 4.48.

No condensation of ethyl 2-pyridone-6-acetate with diethyl methylenemalonate could be effected under similar conditions.

Condensation of 2-Pyridone-6-acetamide with Diethyl Ethoxymethylenemalonate: 1-Carboxamido-3-carbethoxy-6-hydroxy-4-quinolizone (VIb).—To a sodium ethoxide solution, prepared by dissolving 0.23 g. of sodium in 15 ml. of ethanol, was added 1.5 g. of 2-pyridone-6-acetamide, followed by 2.3 g. of diethyl ethoxymethylenemalonate. A yellow precipitate was formed immediately. The mixture was heated on the steam-bath for 30 minutes, cooled, and the solid was collected by filtration. After solution in hot water, it was acidified with 2 *N* sulfuric acid. The product was recrystallized from dimethylformamide and formed yellow crystals, m.p. 258° dec. (darkening at 245°). The yield was 2.2 g. (80.8%).

Anal. Calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.50; H, 4.31; N, 10.13.

Condensation of 2-Pyridone-6-acetamide with Diethyl Methylenemalonate; 1-Carboxamido-3-carbethoxy-6-hydroxy-4-quinolizone (VIb).—To a mixture of 1.75 g. of 2-pyridone-6-acetamide and a solution of sodium ethoxide prepared from 0.8 g. of sodium and 23 ml. of ethanol was added 2.1 g. of diethyl methylenemalonate.[8] After the mixture was heated on the steam-bath for 12 hours, a yellow condensation product gradually separated. This product was collected by filtration and dissolved in the necessary amount of boiling water, then acidified with dilute sulfuric acid. The yellow compound that precipitated was collected by filtration and recrystallized from dimethylformamide, m.p. 256° dec. (darkening at 245°). This compound, identified by analysis and infrared spectrum, was also prepared from 2-pyridone-6-acetamide and diethyl ethoxymethylenemalonate.

(6) R. Adams and A. W. Schrecker, THIS JOURNAL, **71**, 1191 (1949).

(7) W. E. Parham and L. J. Reed, *Org. Syntheses*, **28**, 60 (1948).

(8) G. B. Bachman and H. A. Tanner, *J. Org. Chem.*, **4**, 493 (1939). The diethyl methylenemalonate was twice distilled, a small amount of hydroquinone was added and the product preserved at Dry Ice temperature. It was used within two days after it was prepared.

Anal. Calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.72; H, 4.40; N, 9.95.

Hydrolysis of 1,3-Dicarbethoxy-6-hydroxy-4-quinolizone (VIa). (A) 2-Pyridone-6-crotonic Acid (IIc).—A mixture of 1.0 g. of 1,3-dicarbethoxy-6-hydroxy-4-quinolizone and 25 ml. of concd. hydrochloric acid was boiled under reflux for one hour. The solution was made alkaline, extracted with chloroform, and was then acidified again and extracted with chloroform. This chloroform solution was dried and the chloroform was evaporated. The residue was recrystallized from benzene, forming yellowish crystals, m.p. 199°. The yield was 0.27 g. (44.9%).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.16; H, 4.99; N, 7.85.

(B) 2-Pyridone-6-crotonic Acid (IIc).—A mixture of 1.0 g. of 1,3-dicarbethoxy-6-hydroxy-4-quinolizone, 0.4 g. of sodium hydroxide and 30 ml. of water was boiled under reflux for 2 hours. The solution was then acidified with hydrochloric acid and extracted with chloroform. The product after solvent evaporation was recrystallized from ethanol to form small yellowish needles, m.p. 199–200°. The yield was 2.9 g. (49.3%).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.13; H, 5.24; N, 7.60.

(C) 1-Carbethoxy-3-carboxy-6-hydroxy-4-quinolizone (VIc).—A mixture of 0.9 g. of 1,3-dicarbethoxy-6-hydroxy-4-quinolizone, 4.5 g. of barium hydroxide octahydrate and 125 ml. of water was heated under reflux for 15 hours. After cooling, the yellow precipitate was collected by filtration and added to boiling aqueous potassium carbonate. The hot mixture was filtered and the filtrate was acidified with dilute sulfuric acid. The yellow product was recrystallized from ethanol, m.p. 186° with effervescence. The yield was 0.6 g. (67.2%). The sample solidified after the decarboxylation was complete and melted again at 233–236°.

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.52; H, 4.35; N, 4.98.

2-Ethoxy-6-methylpyridine 1-Oxide (IIIa). (A) From 2-Ethoxy-6-methylpyridine.—To a solution of 30 g. of 2-ethoxy-6-methylpyridine in 35 ml. of glacial acetic acid was added 50 ml. of cold 40% peracetic acid. The mixture was first carefully heated to 60° and kept at this temperature for 5 hours and then heated to 80° for 2 more hours. After removal of acetic acid under reduced pressure, the residual oil was poured on ice and made alkaline with potassium carbonate. The mixture was then extracted with chloroform. After removal of solvent, the oily residue remaining crystallized and was recrystallized from ethanol–ether; white crystals, m.p. 108–109°. The yield was 25.3 g. (75.7%).

(B) From 2-Bromo-6-methylpyridine 1-Oxide.[9]—A solution of 72 g. of 2-bromo-6-methylpyridine 1-oxide in 100 ml. of ethanol was added drop by drop to a stirred solution of 20 g. of sodium in 200 ml. of ethanol. A vigorous reaction took place. After the addition the mixture was stirred and heated under reflux for one hour. The precipitated sodium bromide was removed by filtration and washed with ethanol. The ethanol solution was then concentrated in vacuum, the residue taken up in ice-water and the mixture was exhaustively extracted with chloroform. The chloroform extract was dried over potassium carbonate and was treated with Norit. The chloroform was then evaporated in vacuum, leaving 43.0 g. (73.3%) of the crude compound. Recrystallization from ethanol–ether gave white crystals, m.p. 108–109°.

Anal. Calcd. for $C_8H_4NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.75; H, 7.18; N, 9.29.

Ethyl 2-Ethoxy-6-pyridylpyruvate 1-Oxide (IIIb).—A potassium ethoxide solution was prepared by adding 48 ml. of absolute ethanol to 8.0 g. of potassium previously covered with 20 ml. of ether, and heating the mixture under reflux until the potassium was completely dissolved. After cooling to room temperature a solution of 15.2 g. of diethyl oxalate in 90 ml. of ether was slowly added, followed by a solution of 14.0 g. of 2-ethoxy-6-methylpyridine 1-oxide in 50 ml. of ethanol. The yellow potassium salt of the pyruvate precipitated and, after standing overnight at room temperature, was collected by filtration. The potassium salt was then dissolved in a mixture, prepared from about 500 g. of ice and 20 ml. of concd. sulfuric acid, and the solution was extracted with chloroform. After evaporation of the solvent, the residue crystallized. The product was recrystallized from ethanol–ether; yellow crystals, m.p. 116°. The yield was 17.5 g. (75.6%).

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.63; H, 6.02; N, 5.54.

Ethyl 2-Ethoxy-6-pyridylpyruvate (IVa).—To an ice-cold solution of 60 g. of ethyl 2-ethoxy-6-pyridylpyruvate 1-oxide in 300 ml. of chloroform, 60 ml. of phosphorus trichloride was added drop by drop. After the addition was complete, the mixture was heated on the steam-bath for 30 minutes. Then the chloroform was evaporated in vacuum and the residue taken up in ice-water and made alkaline with sodium hydroxide. The product was extracted with chloroform and after removal of the solvent was recrystallized from ethanol–water; colorless needles, m.p. 99.5°. The yield was 16.7 g. (29.7%).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.53; H, 6.33; N, 6.04.

Ethyl 2-Ethoxy-6-pyridyl-(α-oximino)-propionate (IVb).—A solution of 15 g. of ethyl 2-ethoxy-6-pyridylpyruvate and 15 g. of hydroxylamine hydrochloride in 75 ml. of pyridine and 75 ml. of ethanol was heated on a steam-bath for 3 hours. After filtering hot, the filtrate was concentrated in vacuum and the residue extracted with chloroform. Evaporation of the solvent yielded a product which was dissolved in ethanol and precipitated by addition of water. It was recrystallized from ethanol–water; colorless needles, m.p. 73°. The yield was 14.7 g. (92.4%).

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.34; H, 6.48; N, 10.87.

2-Ethoxy-6-pyridyl-(α-oximino)-propionic Acid (IVc).—A mixture of 14.5 g. of ethyl 2-ethoxy-6-pyridyl-(α-oximino)-propionate and 100 ml. of 2 *N* aqueous sodium hydroxide was boiled under reflux for 90 minutes. The solution was filtered and was then cautiously acidified with concd. hydrochloric acid. After standing for one hour the substance was collected by filtration and was recrystallized from ethanol–ether; white crystals, m.p. 129° (with effervescence). The yield was 12.0 g. (93.8%).

2-Ethoxy-6-pyridylacetonitrile (IVd).—A large test-tube containing 12 g. of the crude 2-ethoxy-6-pyridyl-(α-oximino)-propionic acid was heated cautiously with a free flame. The solid melted with evolution of carbon dioxide and water. After the gas evolution had stopped, the compound was distilled in a Kugelrohr. The substance boiled at 95° (0.05 mm.) (air-bath) and crystallized, m.p. 54°. The yield was 7 g. (80.6%), of colorless crystals.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.28. Found: C, 66.64; H, 6.24; N, 17.12.

Ethyl 2-Ethoxy-6-pyridylacetate (IVe).—A solution of 7 g. of 2-ethoxy-6-pyridylacetonitrile in 150 ml. of 95% ethanol was cooled to 0° and saturated with hydrogen chloride. The mixture was allowed to stand for 15 hours and was then heated under reflux for 30 minutes. After cooling, the precipitated ammonium chloride was removed by filtration and the filtrate was evaporated in vacuum. The residue was taken up in water and made alkaline with potassium carbonate. The mixture was then extracted with chloroform. After removal of the solvent the residual oil was distilled in vacuum using a Kugelrohr, b.p. 80° (0.3 mm.) (air-bath). The yield was 6.0 g. (66.3%).

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.43; H, 6.98; N, 7.11.

Oxidation of 2-Methoxy-6-methylpyridine with Peracetic Acid.—The character of the product varied with the quality of the peracetic acid used. Fresh peracetic acid resulted in 2-methoxy-6-methylpyridine 1-oxide exclusively. When peracetic acid that was over a year old was utilized, a mixture of 2-methoxy-6-methylpyridine 1-oxide and 1-methoxy-6-methyl-2-pyridone resulted.

To a solution of 30 g. of 2-methoxy-6-methylpyridine in 35 ml. of glacial acetic acid was added 50 ml. of cold year-old peracetic acid. The mixture was then cautiously heated until the reaction started (about 45°), and was then kept first by outside cooling and later by heating at 60° for 5 hours and then at 80° for 3 hours. The solution was then concentrated in vacuum to less than half of the original volume and was poured into ice and made alkaline by addi-

(9) R. Adams and W. Reifschneider, THIS JOURNAL, **79**, 2236 (1957).

tion of concentrated aqueous potassium carbonate. The mixture was then extracted with chloroform. After removal of solvent, the residual oil was distilled in vacuum, b.p. 107–110° (0.5 mm.). The yield of colorless oil was 21.2 g. (62.5%). Infrared analyses indicated the presence of a mixture of isomers.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.41; H, 6.52; N, 10.07. Found: C, 59.90; H, 6.30; N, 10.02.

The product was dissolved in ether and cooled to a low temperature; white crystals, m.p. 62°, separated which proved to be 2-methoxy-6-methylpyridine 1-oxide (VIIa) identical with a product prepared from 2-bromo-6-methylpyridine 1-oxide as described later. The remainder of the reaction mixture was 1-methoxy-6-methyl-2-pyridone (VIIIa), identical with the product obtained by methylation of 1-hydroxy-6-methyl-2-pyridone which is described later. Pure, fresh peracetic acid gave by a similar procedure just 2-methoxy-6-methylpyridine 1-oxide.

2-Methoxy-6-methylpyridine 1-Oxide (VIIa).—A solution of 28.6 g. of 2-bromo-6-methylpyridine 1-oxide in 50 ml. of absolute methanol was added slowly to a mechanically stirred solution of 10 g. of sodium in 100 ml. of methanol. A vigorous reaction took place. After the addition was completed, the mixture was stirred and heated under reflux for two hours. The precipitated sodium bromide was removed by filtration and was washed with methanol. The filtrate was then acidified with dilute hydrochloric acid and the methanol distilled off in vacuum. The remaining aqueous solution was made alkaline by adding potassium carbonate and was extracted with chloroform. The chloroform extract was dried, the chloroform evaporated and the residue was distilled in vacuum, b.p. 109–110° (0.5 mm.). The colorless distillate solidified and was recrystallized from methanol–ether, m.p. 62°. The yield was 14.0 g. (66.2%).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.41; H, 6.52. Found: C, 60.32; H, 6.64.

1-Hydroxy-6-methyl-2-pyridone (X).—To 160 ml. of 5% aqueous sodium hydroxide was added 18.8 g. of 2-bromo-6-methylpyridine 1-oxide and the mixture was heated on the steam-bath for 30 minutes. After cooling to room temperature, the clear solution was acidified with concd. hydrochloric acid and was extracted with chloroform. After evaporation of the solvent the solid residue was recrystallized from ethyl acetate and was then sublimed in vacuum at 80° (0.5 mm.); colorless crystals, m.p. 144–145° (lit.[2] 141–142°). The yield was 9.6 g. (76.7%).

Anal. Calcd. for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.69; H, 5.48; N, 11.11.

1-Methoxy-6-methyl-2-pyridone (VIIIa).—To a solution of 0.4 g. of sodium in 25 ml. of absolute methanol was added 1.8 g. of 1-hydroxy-6-methyl-2-pyridone, followed by 3 g. of methyl iodide. The mixture was then boiled under reflux for 2 hours. The solvent was distilled off in vacuum and the residue was taken up in chloroform. After removal of the chloroform 1.8 g. (89.9%) of a yellowish oil remained. The oil was dissolved in a small amount of ether and the solution was cooled to −70°. The substance crystallized and was recrystallized from ether; large colorless crystals, m.p. 33–34°.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.41; H, 6.52; N, 10.07. Found: C, 60.07; H, 6.78; N, 9.92.

Reaction of the Mixture of 2-Methoxy-6-methylpyridine 1-Oxide and 1-Methoxy-6-methyl-2-pyridone with Diethyl Oxalate: Ethyl 2-methoxy-6-pyridylpyruvate 1-Oxide (VIIb) and Ethyl 1-Methoxy-2-pyridone-6-pyruvate (VIIIb).—A potassium ethoxide solution was prepared by adding 20 ml. of ethanol to 4.0 g. of potassium covered with 25 ml. of ether. To this solution was added 7.5 g. of diethyl oxalate dissolved in 50 ml. of ether, followed by a solution of 7.0 g. of the mixture of 2-methoxy-6-methylpyridine 1-oxide and 1-methoxy-6-methyl-2-pyridone in 30 ml. of ethanol. The reaction mixture turned yellow, and the potassium salt of the pyruvate precipitated. After standing overnight, the yellow precipitate was collected by filtration and was added to a mixture of 100 g. of ice and 6 ml. of concd. sulfuric acid. After standing for one hour, 2.4 g. of fine crystals had separated. The compound was recrystallized from benzene–petroleum ether (b.p. 30-60°); yellow needles, m.p. 153°. This compound was ethyl 1-methoxy-2-pyridone-6-pyruvate (VIIIb) as shown by comparison with an authentic sample obtained by condensation of pure 1-methoxy-6-methyl-2-pyridone with diethyl oxalate.

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.22; H, 5.48. Found: C, 55.44; H, 5.53.

The acidic solution remaining after filtration of the compound VIIIb was extracted with chloroform, the chloroform extract was dried and the chloroform evaporated. The residue was recrystallized from benzene–petroleum ether (b.p. 30–60°); yellow plates, m.p. 132°. The yield was 5.0 g. The compound was 2-methoxy-6-pyridylpyruvate 1-oxide (VIIb) as shown by comparison with an authentic sample prepared from pure 2-methoxy-6-methylpyridine 1-oxide.

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.22; H, 5.48. Found: C, 55.34; H, 5.48.

URBANA, ILL.

[CONTRIBUTION FROM THE STAMFORD LABORATORIES, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

The Preparation and Reactions of 1-Cyanoformamide

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Conditions have been found for the rapid hydration of cyanogen to 1-cyanoformamide by excess water in high yield. Several carboxylic acids and phosphorus acids can perform the dual role of catalyzing the reaction and stabilizing the product, but other mineral acids are unable to do both. Chemically, 1-cyanoformamide was found to be very reactive with water, alcohols, hydrogen sulfide and amines, with reaction occurring at the nitrile C–N bond or the C–C bond depending on the conditions. Physical and toxicological properties of 1-cyanoformamide are also presented.

Chemical studies of cyanogen, both in these laboratories and elsewhere, have shown it to be one of the most active nitriles. For example, at room temperature it is quickly hydrated to oxamide in high yield by concentrated hydrochloric acid,[1] sulfhydrated to dithioöxamide quantitatively with a trace of aqueous base as a catalyst,[2] and transformed to N,N′-disubstituted oxamidines by the addition of amines.[3] Most nitriles require more vigorous conditions for these reactions. In view of the rapid transformation of both nitrile groups of cyanogen, it is not surprising that products formed by the reaction of only one cyano group with these reagents—derivatives of 1-cyanoformic acid and 1-cyanoformimidic acid—have not been obtained easily.[4–6]

(1) J. E. Bucher (to Nitrogen Products Co.) U. S. Patent 1,194,354 (1916).

(2) D. W. Kaiser and R. P. Welcher (to American Cyanamid Co.) U. S. Patent 2,806,879 (1957).

(3) H. M. Woodburn, B. A. Morehead and W. H. Bonner, *J. Org. Chem.*, **14**, 555 (1949); also papers II-X, *ibid.*, 1950 to date.

(4) R. Anschütz, *Ann.*, **254**, 262 (1889).

(5) J. Nef, *ibid.*, **287**, 265 (1895).

(6) N. Beketoff, *Chem. Ber.*, **3**, 872 (1870).