TABLE II

COMPARISON OF SYNTHETIC AND NATURAL *dl-cis*-CINEROLONE AND THEIR DERIVATIVES

Source	n^tD	t, °C.	Boiling point °C.	Mm.	Semicarbazone m.p., °C. (dec.)	Acetate semicarbazone m.p., °C.	3,5-Dinitrobenzoate
Synthetic[a]	1.5168	25	113–114	0.1	205–206	150–151	124–125
Natural[a]	1.5190	25	118–122	.4	201–202	150.5–151.5	121–123.5
Synthetic[6]	1.5100	25	102–105	.05	197–199	147–148	.....
Synthetic[9]	1.513	20	116–130	.2	199–201	.....	.....
Natural[24]	1.5240	28	.....	..	199–200	151–152	.....
Natural[a] + synthetic[a]	....	..	.....	..	203–204	150–151	122.5–124.5

[a] This article.

The synthetic *cis*-cinerolone was further characterized by the preparation of the acetate, which boiled at 102–107° (0.3 mm.), n^{25}D 1.4937, and this was converted to the **acetate semicarbazone**, m.p. 150–151° (from methanol–ethyl acetate).

Anal.[20] Calcd. for $C_{13}H_{19}O_3N_3$: N, 15.84. Found: N, 15.22.

Natural *dl*-cinerolone.—This compound and a number of its derivatives were prepared again for purposes of comparison.

Four grams of natural *dl*-cinerolone semicarbazone,[26] m.p. 201–202° (dec.), was hydrolyzed as described above for the synthetic *cis*-cinerolone and the free cyclopentenolone was found to boil at 118–122° (0.4 mm.), n^{25}D 1.5190, yield 2.3 g.

The **3,5-dinitrobenzoate**, after two recrystallizations from methanol, melted at 121–123.5°.[2]

The **acetate semicarbazone** was prepared and found to melt at 150.5–151.5°.

A comparison of synthetic and natural *dl-cis*-cinerolone and their derivatives is given in Table II. Mixture melting points of corresponding derivatives of the synthetic and natural products gave no depressions.

BELTSVILLE, MARYLAND

(26) F. B. La Forge and W. F. Barthel, *J. Org. Chem.*, **10**, 106, 114 (1945).

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

Structure of the 2-Pyridone and α-Bromoacrylic Acid Adduct and its Derivatives

BY ROGER ADAMS AND IRWIN J. PACHTER

RECEIVED APRIL 30, 1952

Evidence is presented which requires reinterpretation of the structure and reactions previously attributed to the reaction product of 2-pyridone and α-bromoacrylic acid.[1] The product proved to be 2-carboxy-2,3-dihydroöxazolo[2,3-a]pyridinium bromide. New syntheses and reactions of 2-H-pyrido[1,2-a]pyrimidin-2-ones (2-keto-1,4a-diazonaphthalenes) are described.

The structure and reactions of the compound obtained when 2-pyridone and α-bromoacrylic acid are heated together were discussed previously.[1] Largely on the basis of infrared spectra, structures were assigned. It was later pointed out to one of us by Dr. Robert W. Holley of the New York State Agricultural Experiment Station that the structure of one of the compounds suggested as a β-lactam was almost certainly incorrect because its reactions did not coincide with those of previously known compounds of this type. As a consequence, the structures of many of the other compounds reported were probably erroneous. A restudy of these substances has now been made and evidence is presented in this paper which requires the following complete reinterpretation of the reactions and structures of the molecules involved.

When 2-pyridone reacted with α-bromoacrylic acid, the expected product[1] (I) was not obtained. Instead, cyclization occurred and 2-carboxy-2,3-dihydroöxazolo[2,3-a]pyridinium bromide (II) was formed. Reduction of II with hydrogen and platinum oxide yielded 1-piperidinelactic acid hydrobromide (III), the structure of which was proved by synthesis from 1-piperidineacetaldehyde cyanohydrin (IV).

When II was heated with dilute sodium hydroxide, the oxazolinium ring was cleaved and the salt of 2-oxo-1(2H)-pyridinelactic acid (V) resulted. The same compound (V) was also formed when 2-pyridone reacted with glycidic acid.

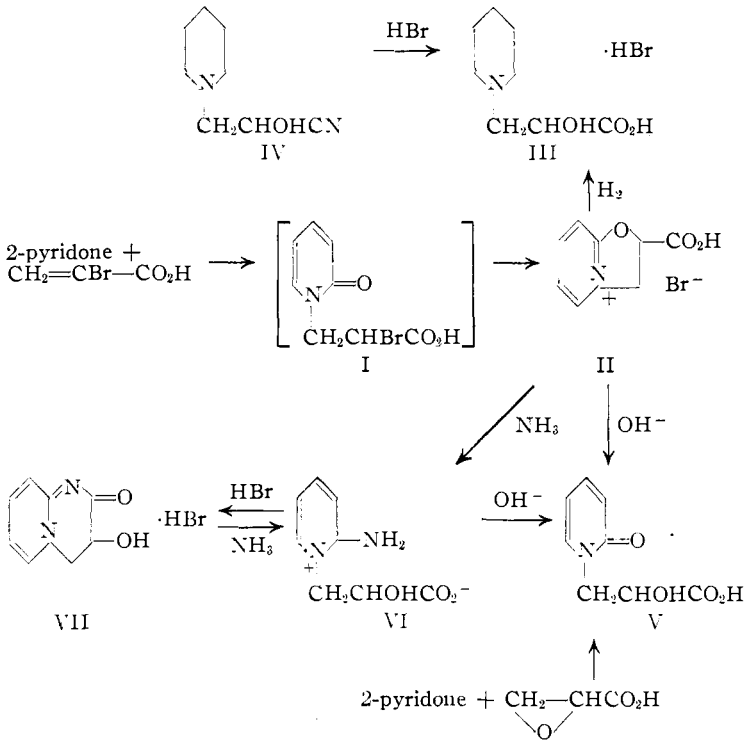
In quite analogous fashion, treatment of II with aqueous ammonia gave 2-imino-1(2H)-pyridinelactic acid (VI). Compound VI liberated ammonia when heated with dilute alkali and V was obtained.

When VI was treated with ethanolic or aqueous hydrogen bromide at room temperature, a remarkably facile ring-closure reaction occurred and 3,4-dihydro-3-hydroxy-2H-pyrido[1,2-a]pyrimidin-2-one hydrobromide (VII) was obtained. When aqueous ammonia was added to an aqueous solution of VII and the resulting solution was evaporated to dryness under reduced pressure on a water-bath, an equally remarkable ring-opening reaction occurred and VI was reformed.

When the present work was begun, structures other than that given were considered possible for the compound now designated as VII. However, the discussion in this paper will be confined to VII since the experimental facts have established it as correct. With the structure of compound VII proved, the structures assigned to compounds II, V and VI become unequivocal and those previously suggested become untenable.[1]

It is pertinent first to point out that in compound

(1) R. Adams and V. V. Jones, THIS JOURNAL, **71**, 3826 (1949).



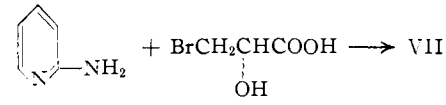
VI it has been established that the ring nitrogen atom is attached β to the carboxyl group because II, the precursor of VI, was reduced to 1-piperidinelactic acid hydrobromide (III). The fact that treatment of VI with alkali caused elimination of ammonia with formation of a 2-pyridone derivative provided further confirmation that it is the pyridine ring nitrogen and not the amino nitrogen of VI which is β to the carboxyl group. It follows, therefore, that if VII is a pyridopyrimidone, it must be a pyridopyrimidin-2-one and not a pyridopyrimidin-4-one.

The infrared absorption spectrum of VII showed bands at 3370 and 1108 cm.$^{-1}$, indicative of a hydroxyl group. Upon treatment with acetic anhydride, VII yielded a monoacetyl derivative, the infrared spectrum of which no longer had bands characteristic of a hydroxyl group.

When VII was heated with phosphorus pentoxide and then neutralized with alkali, a dehydrated product, 2H-pyrido[1,2-a]pyrimidin-2-one (VIII) was isolated. This same product may also be prepared from 2-aminopyridine and α-bromoacrylic acid, a reaction which will be discussed in more detail in a later communication. The structure of compound VIII was proved by its reduction with hydrogen and platinum oxide to octahydro-2H-pyrido[1,2-a]-pyrimidin-2-one (IX), which was identical with the product formed upon reduction of 3,4-dihydro-2H-pyrido-[1,2-a]pyrimidin-2-one (XI), the base of the corresponding hydrochloride (X).

Compound X was synthesized in the present study from either ethyl β-chloropropionate or β-chloropropionic acid and 2-aminopyridine. Assumption that this reaction would give a pyridopyrimidin-2-one and not a pyridopyrimidin-4-one is based upon the well-known fact that primary alkyl halides react preferentially with the ring nitrogen of 2-aminopyridine.[2] The work of Magidson and Elina[3] who synthesized X by a different procedure leaves little doubt as to its structure.

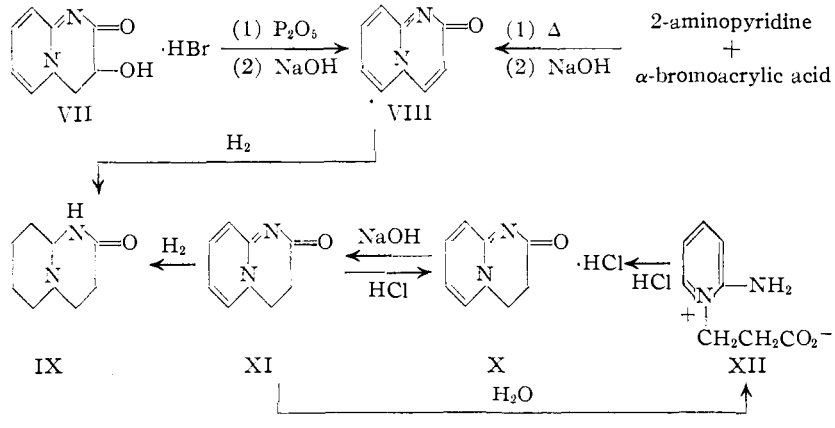
Compound VII was also synthesized from 2-aminopyridine and β-bromolactic acid. This synthesis proved that both VI and VII are 2-aminopyridine derivatives and therefore removes any question as to how the oxazolinium ring of II was opened by ammonia. Under



the same reaction conditions, 2-aminopyridine and β-bromopropionic acid gave the hydrobromide of XI identical with that prepared by treatment of an ethereal solution of XI with hydrogen bromide.

Further indication that compound VII and the hydrobromide of XI have the same basic structure was provided by a comparison of their ultraviolet spectra (Fig. 1). In view of the foregoing discussion, the similarity of the curves is, in itself, strong evidence that the compounds are both pyridopyrimidin-2-ones.

When a solution of X was neutralized with exactly one molar equivalent of sodium hydroxide and the resulting solution was evaporated to dryness on a water-bath, a mixture of XI and 2-oxo-1(2H)-pyridinepropionic acid (XII) was obtained. The two compounds were easily separated since XI was readily soluble in chloroform while XII was soluble only in more polar solvents. When a pure sample of XI was heated with water



(2) (a) A. E. Chichibabin, R. A. Konovalova and A. A. Konovalova, *Ber.*, **54**, 814 (1921); (b) A. Kirpal and B. Wojnar, *ibid.*, **71**, 1261 (1938); (c) T. M. Sharp, *J. Chem. Soc.*, 1855 (1939).

(3) O. Y. Magidson and A. S. Elina, *J. Gen. Chem.* (*U.S.S.R.*), **16**, 1933 (1946) [*C. A.*, **41**, 6219 (1947)].

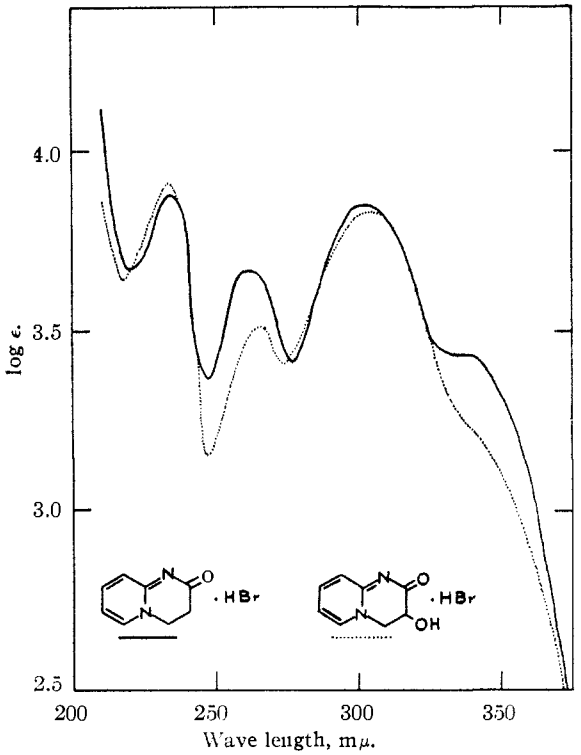


Fig. 1.—Ultraviolet spectra in 95% ethanol.

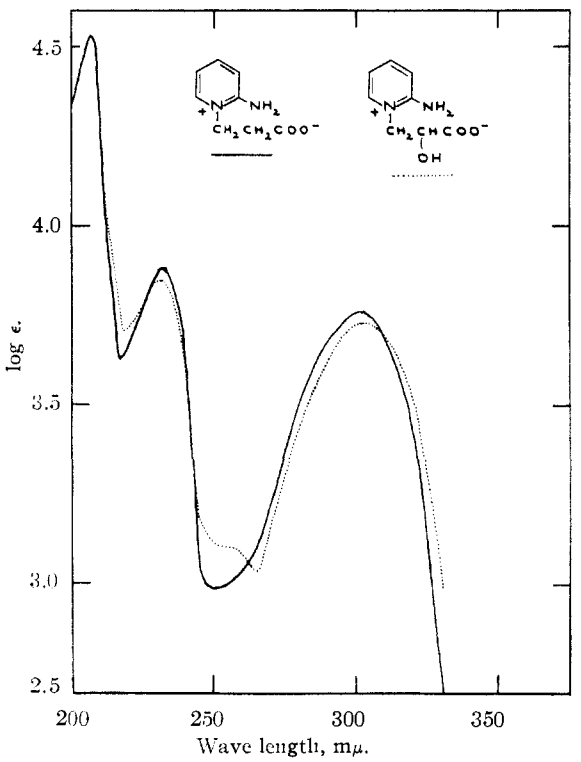


Fig. 2.—Ultraviolet spectra in 0.001 sodium hydroxide.

alone, it was hydrolyzed to XII. An ethereal solution of XI yielded X upon treatment with hydrogen chloride. Compound XII also yielded X when heated with hydrochloric acid. It is apparent that the ring-opening and ring-closing reactions of X or XI and XII closely parallel those of VI and VII.

Figure 2 shows the spectra of VI and XII. It is interesting to note that even in dilute alkali the compounds seem to exist in the zwitterionic form.[4]

Compound XII was previously synthesized by Kirpal and Wojnar.[2b] These workers heated a mixture of 2-aminopyridine and β-chloropropionic acid on a water-bath and believed that the product which they obtained was the hydrochloride of XII. They treated an aqueous solution of this hydrochloride with silver oxide, removed the silver salts, evaporated the solution to dryness on a water-bath and obtained XII. The work has been repeated in this Laboratory and it was found that their initial hydrochloride was actually X rather than the hydrochloride of XII. In their experiment with silver oxide, the evaporation on the water-bath apparently caused more or less complete hydrolysis of the intermediate compound XI, and XII was the only product which they isolated.

Compound XI was obtained from X in high yield by treatment of X with cold concentrated aqueous potassium carbonate and extraction of the resulting mixture with chloroform. The cyclic base of VII could not be obtained by the same procedure.

Although VI yielded ammonia and a 2-pyridone when treated with alkali, the related compound XII gave predominantly 2-aminopyridine and acrylic acid. Apparently due to the effect of a hydroxyl group in the α-position with respect to the carboxyl group, compound VI does not react with alkali in a manner frequently characteristic of β-aminocarbonyl compounds.

In summation, compound VII, $C_8H_9BrN_2O_2$, is a derivative of 2-aminopyridine. The ring nitrogen atom of VII is in the β-position with respect to the carbonyl group. Its infrared spectrum shows the presence of a hydroxyl group and its ultraviolet spectrum shows it to be a dihydropyrido[1,2-a]-pyrimidone. Upon dehydration it yielded a compound shown to be 2H-pyrido[1,2-a]pyrimidin-2-one. Compound VII must therefore be 3,4-dihydro-3-hydroxy-2H-pyrido[1,2-a]pyrimidin-2-one hydrobromide and compounds II, V and VI must consequently have the structures now assigned them.

Acknowledgment.—The authors are indebted to Miss Emily Davis, Mrs. Esther Fett and Mrs. Katherine Pih for the microanalyses, to Miss Helen Miklas for the infrared spectra determinations and to Mr. H. J. Birch for the ultraviolet spectra determinations.

Experimental[5]

The corrected names of several compounds mentioned in this paper are very different from those assigned formerly.[1] As a consequence, the following table is included to facilitate reference to the previous work.

Corrected name and number	Name and number found in previous paper[1]
2-Carboxy-2,3-dihydro-oxazolo[2,3-a]pyridinium bromide (II)	2-Pyridone α-bromoacrylic acid adduct (VIII)
2-Oxo-1(2H)-pyridinelactic acid (V)	α-(N-2-Pyridone)-β-hydroxypropionic acid (V)

(4) Compare L. C. Anderson and N. V. Seeger, THIS JOURNAL, **71**, 340 (1949).

(5) All melting points are corrected.

Corrected name and number	Name and number found in previous paper[1]
2-Imino-1(2H)-pyridinelactic acid (VI)	α-(N-2-Pyridone)-β-aminopropionic acid(III)
3,4-Dihydro-3-hydroxy-2H-pyrido[1,2-a]pyrimidin-2-one hydrobromide (VII)	α-(N-2-Pyridone)-β-aminopropiolactam hydrobromide (IV)

2H-Pyrido[1,2-a]pyrimidin-2-one (VIII).—A mixture of 0.40 g. of VII and 0.8 g. of phosphorus pentoxide was kept at 200–210° for 2 hours. It was then cooled, dissolved in water, made just basic to litmus with aqueous sodium hydroxide and evaporated to dryness. Sublimation of the residue at 230° (1 mm.) and recrystallization of the sublimate from chloroform–carbon tetrachloride yielded 12 mg. of VIII, m.p. 246–248° without decomposition. The same compound (VIII), m.p. 248–250°, was prepared *via* the reaction between 2-aminopyridine and α-bromoacrylic acid as will be described in a later communication.

Anal. Calcd. for $C_8H_6N_2O$: C, 65.74; H, 4.14. Found: C, 65.59; H, 4.05.

3,4-Dihydro-2H-pyrido[1,2-a]pyrimidin-2-one Hydrochloride (X) (a).—A mixture of 8.86 g. of ethyl β-chloropropionate and 6.1 g. of 2-aminopyridine was heated on a steam-bath for one hour. The solid mass was recrystallized from ethanol to give 7.4 g. (62%) of colorless prisms of X.

(b).—A repetition of the experiment of Kirpal and Wojnar[2] yielded 7.5 g. (78%) of X. The temperature of the water-bath employed in the present study was 75–80°.

(c).—An ethereal solution of XI (prepared as described below) yielded X on treatment with hydrogen chloride.

(d).—A solution of 0.30 g. of the amino acid XII (prepared as described below) in 3 ml. of concentrated hydrochloric acid was heated under reflux for 30 minutes and evaporated to dryness. The residue proved to be pure X. It is probable that the cyclization of XII would have proceeded under milder conditions than were actually employed.

Anal. Calcd. for $C_8H_9ClN_2O$: C, 52.04; H, 4.91. Found: C, 52.03; H, 4.86.

The compound obtained by each method melted when pure at 295–296° (dec.). The melting points of the substances obtained by methods (b), (c) and (d) were not depressed upon admixture with the compound prepared by method (a). The same picrate, m.p. 224–226°, was prepared from each of the four samples. The picrate was previously reported by Magidson and Elina.[3]

3,4-Dihydro-2H-pyrido[1,2-a]pyrimidin-2-one (XI) and 2-Imino-1(2H)-pyridinepropionic Acid (XII).—A solution of 5 g. of X in 20 ml. of water was exactly neutralized to phenolphthalein with 10% aqueous sodium hydroxide. Evaporation of the resulting solution to dryness on a steam-bath under a stream of air, and extraction of the residue with chloroform yielded 1.2 g. of XI, m.p. 191–192°. A final recrystallization from ethanol–acetone gave needles and prisms, m.p. 191–192.5°.

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44. Found: C, 64.88; H, 5.30.

The residual solid was extracted with 95% ethanol. Evaporation of the solvent and recrystallization from absolute ethanol yielded 1.65 g. of hygroscopic prisms of XII, m.p. 177.5–178.5° (dec.).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.57; H, 6.08; H, 16.99.

Kirpal and Wojnar[2b] reported both a hydrated form of XII, m.p. 156° (uncor.), and an anhydrous form for which no m.p. was given. The hydrated compound, m.p. 161–163°, was also prepared in the present study.

3-Acetoxy-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one Hydrobromide.—A mixture of 0.2 g. of VII, 10 ml. of acetic acid and 1 ml. of acetic anhydride was refluxed for 30 minutes. Evaporation to dryness and recrystallization of the residue from absolute ethanol yielded the acetyl derivative, m.p. 233–235° (dec.).

Anal. Calcd. for $C_{10}H_{11}BrN_2O_3$: C, 41.83; H, 3.86. Found: C, 41.79; H, 3.99.

Reaction of 3,4-Dihydro-2H-pyrido[1,2-a]pyrimidin-2-one Hydrochloride (X) with Potassium Carbonate.—To a saturated aqueous solution of potassium carbonate prepared from 25 ml. of water, was added 5.0 g. of X. The mixture was extracted with chloroform and the chloroform solution was dried over potassium carbonate, concentrated until crystallization commenced, diluted with 30 ml. of petroleum ether (b.p. 30–60°), cooled and filtered to give 3.5 g. (87%) of almost pure free base (XI), m.p. 188–190°.

Hydrolysis of 3,4-Dihydro-2H-pyrido[1,2-a]pyrimidin-2-one (XI).—A solution of 0.30 g. of XI in 10 ml. of water was heated under reflux for 3 hours. The solution was evaporated to dryness and the residue was recrystallized from absolute ethanol to give 0.26 g. of the amino acid XII, identical with a sample prepared as previously described.

Reaction of 2-Imino-1(2H)-pyridinepropionic Acid (XII) with Alkali.—A solution of 1.0 g. of XII in 15 ml. of 5% aqueous sodium hydroxide was heated under reflux for 2 hours. Although some ammonia was liberated during the reaction, the alkaline solution, upon extraction with ether, yielded 0.48 g. (85%) of 2-aminopyridine which was identified by comparison with an authentic sample.

Octahydro-2H-pyrido[1,2-a]pyrimidin-2-one (IX). (a) From the Dihydro Compound XI.—A solution of 0.200 g. of XI in 10 ml. of absolute ethanol was hydrogenated at 1 atm. using 20 mg. of platinum oxide catalyst. After 2 hours, a little over 3 molar equivalents of hydrogen had been taken up. The platinum was filtered off and the filtrate was evaporated at room temperature under a stream of air. The solid residue, on recrystallization from ligroin, gave 0.174 g. of needles, m.p. 140–142°. The compound sublimes at 100° (1 mm.).

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.30; H, 9.15. Found: C, 62.18; H, 8.96.

A picrate, m.p. 149–150°, crystallized from absolute ethanol.

Anal. Calcd. for $C_8H_{14}N_2O \cdot C_6H_3N_3O_7$: C, 43.86; H, 4.47. Found: C, 44.12; H, 4.64.

(b) From Compound VIII.—When 0.200 g. of VIII was treated in the same manner, four molar equivalents of hydrogen were absorbed in 3 hours and 0.177 g. of pure IX, identical with the product described in (a) was obtained. The same picrate was also formed.

The melting points of the products described in (a) were not depressed upon admixture with the products prepared as described in (b).

3,4-Dihydro-3-hydroxy-2H-pyrido[1,2-a]pyrimidin-2-one Hydrobromide (VII) (a).—To 0.50 g. of 2-imino-1(2H)-pyridinelactic acid (VI) in 2 ml. of water was added 2 ml. of 48% hydrobromic acid. The solution was evaporated to dryness at room temperature under a stream of air. The dry crystalline residue weighed 0.67 g. (100%); m.p. and m.p. on admixture with a sample prepared as previously described[1] was 301–303° (dec.).

(b).—A solution of 0.50 g. of β-bromolactic acid[6] and 0.30 g. of 2-aminopyridine in 25 ml. of chloroform was heated under reflux for 48 hours. The solid which separated was recrystallized from ethanol to give 0.097 g. (12.5%) of VII, m.p. 301° (dec.). The m.p. was not depressed on admixture with a sample prepared as described previously.[1]

Anal. Calcd. for $C_8H_9BrN_2O_2$: C, 39.20; H, 3.72. Found: C, 39.36; H, 3.78.

The product was converted to VI when treated with aqueous ammonia.[1]

3,4-Dihydro-2H-pyrido[1,2-a]pyrimidin-2-one Hydrobromide (a).—A solution of 3.1 g. of β-bromopropionic acid and 1.9 g. of 2-aminopyridine in 30 ml. of chloroform was heated under reflux with stirring for 24 hours. The product was filtered and recrystallized from ethanol to give 3.4 g. (75%) of the hydrobromide of XI, m.p. 303–305° (dec.).

(b).—An ethereal solution of XI yielded the hydrobromide on treatment with hydrogen bromide.

Samples prepared by methods (a) and (b) were identical with a sample prepared as described by Magidson and Elina[3] who reported m.p. 293–294°. The three samples yielded the same picrate, m.p. 224–226°.

URBANA, ILLINOIS

(6) K. Freudenberg, *Ber.*, **47**, 2027 (1914).