[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF TENNESSEE EASTMAN CO., DIVISION OF EASTMAN KODAK CO.]

Cyclization of 2-Aminopyridine Derivatives. III. Reaction of Some 2-Aminopyridines with Alkyl Acrylates and Alkyl 3-Halopropionates

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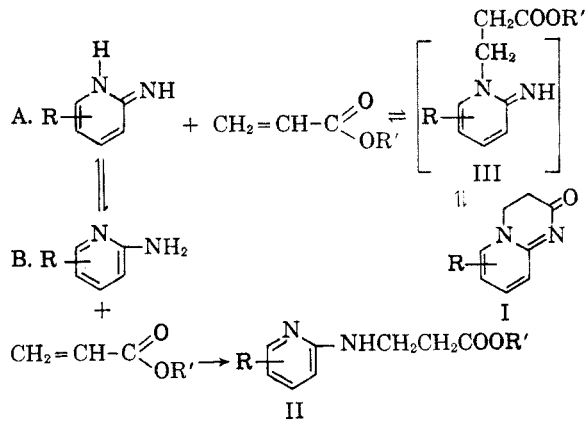
The reaction of 2-aminopyridine with alkyl acrylates gave not only the previously reported 3,4-dihydro-2*H*-pyrido[1,2-*a*]-pyrimidin-2-one but also a noncyclic product, an alkyl ester of *N*-(2 pyridyl)-*β*-alanine. The cyclic product was converted to the noncyclic adduct by alcoholysis. 4-Methyl-2-aminopyridine and 5-methyl-2-aminopyridine reacted with methyl acrylate in a similar manner. 6-Methyl-2-aminopyridine gave only the noncyclic product. 3-Methyl-2-aminopyridine gave only the cyclic product. Alkyl 3-halopropionates reacted with 2-aminopyridine and all of the methyl-2-aminopyridines, except 6-methyl-2-aminopyridine, to give not only the previously reported 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one hydrohalide but also the aminopyridine hydrohalide and alkyl acrylate. Only dehydrohalogenation occurred when 6-methyl-2-aminopyridine reacted with alkyl 3-halopropionates.

The reaction of 2-aminopyridine with ethyl acrylate has been reported to give a 53% yield of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (I, R = H), the product of the attack at the ring nitrogen of the imino form of 2-aminopyridine.[1] In the course of the synthesis of certain pyridopyrimidines this reaction was studied in detail and was found to follow a more complex course than that proposed by the original investigators.

When the reaction of ethyl acrylate with 2-aminopyridine was carried out as described by Adams and Pachter, that is, by heating the mixture on the steam bath for 12 hr., 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (I, R = H) was obtained, although the conversion was lower than these authors reported. Distillation of the liquid portion of the reaction mixture gave, in an almost equal amount, a second, low-melting, product as well as some unreacted 2-aminopyridine. This low-melting product gave the correct analysis for a noncyclic adduct of ethyl acrylate and 2-aminopyridine. Hydrolysis of this product gave an acid, $C_8H_{10}N_2O_2$, (m.p. 144–145° without decomposition) isomeric with, but different from, 2-imino-1(2*H*)-pyridinepropionic acid (m.p. 178° with decomposition), reported by Adams and Pachter[1] as being formed by hydrolysis of I (R = H) or by addition of acrylic acid to 2-aminopyridine. This new acid must then be *N*-(2-pyridyl)-*β*-alanine and the noncyclic adduct is, therefore, the ethyl ester of *N*-(2-pyridyl)-*β*-alanine (II, R = H, R′ = C_2H_5) rather than ethyl 2-imino-1-(2*H*)-pyridinepropionate (III R = H, R′ = C_2H_5). This appears to be the first reported example of a single reaction of 2-aminopyridine giving derivatives of the imino and amino forms. Similar results were obtained with methyl acrylate except that the over-all conversion was higher. For this reason, the further investigation of the reaction was made with this ester.

It was found that a shorter heating time, 6 hr., gave a ratio of cyclic to noncyclic product of about



8, although the total conversion was decreased. A longer heating time, 100 hr., gave almost no cyclic product but a 74% yield of the methyl ester of *N*-(2-pyridyl)-*β*-alanine. Thus it was evident that the effect of long heating was to convert I to II; that is, reaction A must be reversible under these conditions, whereas reaction B is not. This conclusion was confirmed when the methyl ester of *N*-(2-pyridyl)-*β*-alanine together with some 2-aminopyridine was obtained by heating 3,4-dihydro-2*H*-pyrido[1,2-*a*]-pyrimidin-2-one with a small excess of methanol. Further confirmation was obtained from the results of adding methanol to the reaction mixture after 4 hr. and then heating for an additional 16 hr. The yield of I, as compared to a similar experiment in which no methanol was added, was decreased from 45% to 12%, while the yield of II was increased from 42% to 71%.

Although an effort was made to obtain evidence for the formation of the other noncyclic adduct, methyl 2-imino-1(2*H*)pyridinepropionate (III, R = H, R′ = CH_3—), none was found. It is interesting to note that 2-aminopyridine has been found to give products derived directly from the imino form only in those amine reactions which give either a cyclic derivative such as I in which the bonds are constrained in the imino structure or a salt which can be written also as a quarternary salt in which the aromaticity of the pyridine ring is preserved. In all

(1) R. Adams and I. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).

cases in which neither of these types of product can be formed, 2-aminopyridine gives derivatives of the amino form.

The 4- and 5 methyl-2-aminopyridines reacted with methyl acrylate to give both methyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one and the methyl ester of *N*-(*X*-methyl-2-pyridyl)-β-alanine. The relative proportion of the cyclic product was again found to decrease with an increase in time and at a somewhat faster rate than in the case of 2-aminopyridine.

Only methyl ester of *N*-(6-methyl-1-pyridyl)-β-alanine was formed in the reaction with 6-methyl-2-aminopyridine. The failure of 6-substituted-2-aminopyridines to form cyclic derivatives by reaction at the ring nitrogen has been observed previously[2,3] and has been attributed to steric hindrance.

In the reaction of 3-methyl-2-aminopyridine with methyl acrylate, a high yield of cyclic product was obtained but no β-alanine derivative could be isolated. Whether the failure to give a noncyclic product was due to steric hindrance or to stabilization of the imino form in some manner is not known.

The results obtained in these reactions with methyl-2-aminopyridines are summarized in Table I.

TABLE I

REACTION OF AMINOPYRIDINES WITH METHYL ACRYLATE

Substituent in 2-Amino-Pyridine	Reaction Time, Hr.	Amino-pyridine Recovered, %	Yield Type I, %	Yield Type II, %
H	6	25	72	9
H	20	17	45	42
H	20[a]	15	12	71
H	100	12	ca. 2	75
6-CH_3—	2[b]	—	0	—
	8[b]	—	0	—
	24[b]	—	0	—
	48	39	0	87
5-CH_3—	2	44	67	10
	18	20	14	73
4-CH_3—	3[c]	30	82	10
	48	20	0	70
3-CH_3—	8	60	21	0
	60	5	83	0

[a] Twenty g. (0.62 mole) methanol added after 4 hr. [b] Small samples withdrawn, diluted with benzene, and chilled. [c] No solid separated from the reaction mixture before addition of benzene.

The reaction of 2-aminopyridine with ethyl 3-chloropropionate has also been reported to give a high yield of the hydrochloride of I (R = H).[4] This result was confirmed. However, it was also found that a small amount of ethyl acrylate was present in the volatile product from the reaction. When this reaction was applied to the various methyl-2-aminopyridines, the extent of the dehydrohalogenation increased. Only dehydrohalogenation occurred when 6-methyl-2-aminopyridine reacted with alkyl 3-halopropionate; no cyclic product was formed. The results of this investigation are summarized in Table II. It may be seen that the extent of dehydrohalogenation increases with the expected order of increasing basicity of the aminopyridine.

TABLE II

REACTION OF AMINOPYRIDINES WITH ALKYL 3-HALOPROPIONATES

Amino-pyridine Substituent	Alkyl 3-Halopropionate Alkyl	Halogen	Mole Fraction[a] Cycliz-ation	Dehydro-halogenation
None	C_2H_5	Cl	0.90	0.10
None	CH_3	Br	0.85	0.15
6-CH_3—	C_2H_5	Cl	0.00	1.00[b]
6-CH_3—	CH_3	Br	0.00	1.00[b]
5-CH_3—	CH_3	Br	0.80	0.20
4-CH_3—	C_2H_5	Cl	0.55	0.45
4-CH_3—	CH_3	Br	0.40	0.60
3-CH_3—	CH_3	Br	0.45	0.55

[a] Average of value obtained by infrared analysis of liquid product and the value obtained by elemental analysis of the solid product. [b] No methanol detected. Solid product was analytically pure 6-methyl-2-aminopyridine hydrohalide.

EXPERIMENTAL

Reaction of 2-aminopyridine with ethyl acrylate. The reaction of 47 g. (0.50 mole) of 2-aminopyridine with 55 g. (0.55 mole) of ethyl acrylate was carried out under the conditions described by Adams and Pachter[1] (heating the mixture for 12 hr. on the steam bath). The reaction mixture was diluted with 500 ml. of ether, chilled, and filtered to give 22 g. (30% conversion, 56% yield) of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one, m.p. 185–187° (reported 187–188°). The ether was removed from the filtrate, and the residue was distilled under vacuum through a 6-in. Vigreux column to give 22 g. of recovered 2-aminopyridine, b.p. 80–85° (0.5 mm.) and 19 g. (21% conversion, 36% yield) of ethyl ester of *N*-(2-pyridyl)-β-alanine, b.p. 122–125° (0.2 mm.), m.p. after recrystallization from benzene-hexane mixture, 45–46°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.85; H, 7.22; N, 14.43. Found: C, 61.93; H, 7.18; N, 14.55.

Reaction of aminopyridines with methyl acrylate. A mixture of 0.50 mole of the selected aminopyridine, 0.55 mole of methyl acrylate, and 0.5 g. of 2,5-di-*tert*-butylhydroquinone (to prevent polymerization of the acrylate) was refluxed on the steam bath for the desired length of time. The mixture was then diluted with 500 ml. of benzene and chilled at 10° for about 6 hr. The 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine was removed by filtration and purified by crystallization from chloroform-hexane mixture. The benzene was removed from the filtrate under reduced pressure, and the residue was distilled through a 6-in. Vigreux at 0.5 mm. pressure to give the recovered aminopyridine and the methyl ester of *N*-pyridyl-β-alanine.

Methyl ester of N-(2-pyridyl)-β-alanine. Boiling point 122–125° at 0.5 mm., m.p. 50–51° after recrystallization from benzene-hexane mixture.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.9; H, 6.67; N, 15.57. Found: C, 60.0; H, 6.72; N, 15.68.

Methyl ester of N-(6-methyl-2-pyridyl)-β-alanine. Boiling point 128–132° at 0.5 mm.

(2) G. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).

(3) G. Lappin, Q. B. Petersen, and C. Wheeler, *J. Org. Chem.*, **15**, 377 (1950).

(4) R. Adams and I. Pachter, *J. Am. Chem. Soc.*, **74**, 4906 (1952).

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.7; H, 7.22; N, 14.45. Found: C, 61.8; H, 7.18; N, 14.53.

Methyl ester of N-(5-methyl-2-pyridyl)-β-alanine. Boiling point 130–135° at 0.5 mm., m.p. 34–35° after recrystallization from benzene-hexane mixture.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.7; H, 7.22; N, 14.45. Found: C, 61.6; H, 7.28; N, 14.61.

Methyl ester of N-(4-methyl-2-pyridyl)-β-alanine. Boiling point 140–145° (0.5 mm.), m.p. 43–44° after recrystallization from benzene-hexane mixture.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.7; H, 7.22; N, 14.45. Found: C, 61.7; H, 7.26; N, 14.40.

6-Methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one. Melting point 195–196° after recrystallization from chloroform-hexane mixture.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.8; H, 6.17; N, 17.28. Found: C, 66.7; H, 6.13; N, 17.36.

7-Methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one. Melting point 167–169° after recrystallizztion from chloroform-hexane mixture.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.8; H, 6.17; N, 17.28. Found: C, 66.5; H, 6.23; N, 17.33.

8-Methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one. Melting point 230–232° after recrystallization from chloroform-hexane mixture.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.8; H, 6.17; N, 17.28. Found: C, 66.8; H, 6.10; N, 17.39.

Methanolysis of 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one. Fifty g. (0.338 mole) of I (R = H) and 16 g. (0.50 mole) of absolute methanol was heated on the steam bath for 20 hr. The excess methanol was removed under vacuum. The residue was diluted with 150 ml. of benzene and chilled at 10° for 6 hr. Filtration gave 7.0 g. of recovered pyrimidinone, m.p. 184–187°. The filtrate was distilled under vacuum through a 6-in. Vigreux column to give 6.5 g. (23% yield) of 2-aminopyridine, b.p. 80–85° (0.5 mm.), m.p. 55–56°, and 34 g. (63% yield) of methyl ester of N-(2-pyridyl)-β-alanine, b.p. 120–125° (0.4 mm.), m.p. 49–50°, m.p. of mixture with authentic sample 50–51°.

N-(2-pyridyl)-β-alanines. The methyl ester of *N*-(2-pyridyl)-β-alanine (5.0 g.) was refluxed with 50 ml. of water for 16–20 hr. The water was then removed by evaporation on the steam bath and the residue was recrystallized from ethyl alcohol. The amino acid was obtained in nearly quantitative yield. The following new compounds were prepared in this manner.

N-(2-pyridyl)-β-alanine. Melting point 144–145°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.03; N, 16.86. Found: C, 57.8, H, 5.94; N, 16.89.

N-(6-methyl-2-pyridyl)-β-alanine. Melting point 155–156°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.67; N, 15.56. Found: C, 59.9: H, 6.72; N, 15.61.

N-(5-methyl-2-pyridyl)-β-alanine. Meling point 198–200°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.67; N, 15.56. Found: C, 59.8; H, 6.80; N, 15.42.

N-(4-methyl-2-pyridyl)-β-alanine. Meling point 134–136°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.67; N, 15.56. Found: C, 59.8, H, 6.77; N, 15.46.

Reaction of aminopyridines with alkyl 3-halopropionates. A mixture of 0.25 mole of the aminopyridine and 0.25 mole of the alkyl 3-halopropionate was heated on the steam bath in a flask fitted with a short Vigreux column topped by a Dry Ice-cooled trap to collect the volatile products. In every case a vigorous reaction occurred within a few minutes, and the reaction mixture solidified. Heating was continued for 4 hr. The solid residue was then pulverized and heated at 100° and 0.5 mm. pressure for 4 hr. The volatile material removed during this heating was collected in a Dry Ice–cooled trap and was added to the volatile products collected during the reaction. The relative proportion of methanol and alkyl acrylate in this liquid product was determined by infrared analysis. The ratio of pyrido[1,2-*a*]pyrimidin-2-one hydrohalide to aminopyridine hydrohalide in the solid product was calculated from its elemental analysis. In all cases the ratios given by the two methods were in good agreement.

Repeated crystallization of the crude solid product from ethyl alcohol gave relatively pure 3,4-dihydro-2*H*-pyrido-[1,2-*a*]pyrimidin-2-one hydrohalides in 50–80% recovery of the amount calculated from elemental analysis to be in the crude product. These hydrohalides were all white, crystalline solids that decomposed above 300°. These salts were converted to the free bases in 70–80% yield by dissolving them in excess cold, saturated, aqueous potassium carbonate solution, then extracting the mixture with chloroform. The dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones were shown by mixture melting point to be identical with the cyclic products obtained by the reaction of the aminopyridine with methyl acrylate.

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Basic Ethers Derived from β-Hydroxyphenethylamines

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A series of basic ethers represented by the general formula I has been prepared. Several of these compounds, which are derivatives of *N,N*-disubstituted β-hydroxyphenethylamines, have local anesthetic activity.

Derivatives of β-hydroxyphenethylamine have long been known to possess marked physiological activity, the nature of this activity being dependent on the type and number of substituents present. Many of the sympathomimetic amines contain this fundamental structure; other derivatives are central nervous system stimulants or local anesthetics.[2]

Some years ago we began the investigation of some compounds derived from β-hydroxyphenethylamine, and selected a series of aryl and aralkyl ethers of *N,N*-disubstituted β-hydroxyphenethylamines as a starting point. This series had at that

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(2) W. H. Hartung, *Ind. Eng. Chem.*, **37**, 126 (1945).