Geometrical Isomerism of Ethyl *N*-(2-Pyridinyl)aminomethylenecyanoacetates

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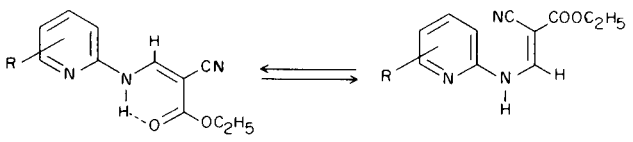
The pure *cis*- and *trans*-isomers of ethyl *N*-(2-pyridinyl)aminomethylenecyanoacetates were obtained and their structure and their interconvertibility is discussed. 4*H*-Pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylic acids were synthesized by treatment of both *cis*- and *trans*-isomers with hydrochloric acid.

In the previous paper (2), it was shown that the introduction of an electron-withdrawing substituent onto the amino group of aminomethylenecyanoacetate raises the energy barriers for its geometrical isomerization facilitating the isolation of stereoisomers and the pure *cis*- and *trans*-isomers of a series of ethyl *N*-(pyrimidinyl)aminomethylenecyanoacetates where the pyrimidinyl groups behaved as electron-withdrawing substituents were obtained. This paper presents information on the preparation of geometrical isomeric ethyl *N*-(2-pyridinyl)aminomethylenecyanoacetates, isolation of the stereoisomers and their interconvertibility, and also their cyclization into 4*H*-pyrido[1,2-*a*]-pyrimidin-4-one-3-carboxylic acids. The condensation reaction of ethyl ethoxymethylenecyanoacetate with 2-aminopyridines to give the corresponding ethyl *N*-(2-pyridinyl)aminomethylenecyanoacetates has been reported earlier by Antaki (3), however the question of their geometrical configurations remained unexplained.

Preparation of ethyl *N*-(2-pyridinyl)aminomethylenecyanoacetates was carried out by fusion of 2-aminopyridines with ethyl ethoxymethylenecyanoacetate at 100-120° and stereoisomeric mixtures were obtained (see Table I). Recrystallization of the reaction mixtures from benzene separated the less soluble *trans*-enamines (B) (the isomers with the amino and the alkoxycarbonyl groups *trans*). Dilution of the filtrate with petroleum ether gave the *cis*-

SCHEME I



cis-Enamine (A) *trans*-Enamine (B)

TABLE I

Reaction of 2-Aminopyridines with Ethyl Ethoxymethylenecyanoacetate

Starting Material	Reaction Time min	Reaction Temp °C	Approximate Ratio of *cis*- and *trans*-Enamine (a)	M.p. °C	Recrystn Solvent
2-Aminopyridine	15	100	34:66	91-93 (*cis*-I)	Benzene + Petroleum ether
				125 (*trans*-I)	Benzene
	120	150	0:100		
	120	180	0:100		
2-Amino-4-methyl-pyridine	15	100	45:55	85-87 (*cis*-II)	Benzene + Petroleum ether
				155-157 (*trans*-II)	Benzene
	120	150	0:100		
	120	180	0:100		
2-Amino-6-methyl-pyridine	10	110	46:54	113-114 (*cis*-III)	Benzene + Petroleum ether
				135-137 (*trans*-III)	Benzene
	30	115	46:54		

(a) This number was measured by nuclear magnetic resonance spectrocopy and is probably accurate within ±5.

enamines (A) (the isomers with the amino and the alkoxycarbonyl groups *cis*). When the reaction was carried out at above 150° for 2 hours, the exclusive formation of *trans*-enamines was observed. The structures of the *cis*- and *trans*-enamines were apparent by the similarity of the infrared spectra of these products with ethyl *N*-(pyrimidinyl)aminomethylenecyanoacetates (2). Namely, the carbonyl stretching bands of the *cis*-enamines appear at lower frequency than those of the *trans*-enamines (Table II). The ultraviolet spectra of both *cis*- and *trans*-enamines are very similar which is consistent with the data of ethyl *N*-(pyrimidinyl)aminomethylenecyanoacetates (2). The nuclear magnetic resonance data in deuteriochloroform are also consistent with the results of the infrared spectroscopy: (a) The olefinic proton of the *cis*-enamine is at higher field than that of the *trans*-enamine. (b) The presence of a hydrogen-bonded chelate ring in the *cis*-enamine is inferred from the down field NH-signal. (c) The NH-CH spin-spin coupling of 12-13 Hz in the *cis*-enamine is contrasted with the coupling of 1-2 Hz in the *trans*-enamine (Table III). Antaki (3) recorded in the condensation of 2-amino-4-methylpyridine with ethyl ethoxymethylenecyanoacetate the formation of ethyl 4-imino-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (C) and ethyl *N*-(2-imino-4-methyl-1,2-dihydropyridinyl)methylenecyanoacetate (D), whose structures were assigned without definite proof. Our reinvestigation according to the procedure of Antaki showed that both structures C and D are identical to the *trans*-form of ethyl *N*-(4-methyl-2-pyridinyl)-aminomethylenecyanoacetate (*trans*-II).

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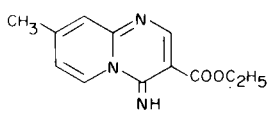
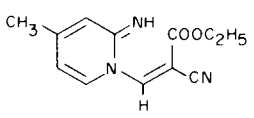


(C)



(D)

The interconversions between *cis*- and *trans*-enamines are summarized in Table IV. As can be seen, the equilibrium leans to *cis*-enamines under fusion. Especially *trans*-II is converted completely into *cis*-II. On the other hand, *cis*-II is converted almost completely into *trans*-II on heating in Dowtherm A.

Refluxing *cis*-I (or *trans*-I) in a mixture of concentrated hydrochloric acid and water (1:1) gave 4*H*-pyrido[1,2-*a*]-pyrimidin-4-one-3-carboxylic acid (IV). Similarly, *cis*-II (or *trans*-II) was converted to 8-methyl-4*H*-pyrido[1,2-*a*]-

TABLE II

Ultraviolet and Infrared Data for Ethyl *N*-(2-Pyridinyl)aminomethylenecyanoacetates

No	λ max mμ (log ε) (a)		C=O Absorption (cm^{-1}) (b)	No	λ max mμ (log ε) (a)		C=O Absorption (cm^{-1}) (b)
cis-I	327 (4.456)	277 (3.925)	1690	*trans*-I	320 (4.518)	275 (4.083)	1710
cis-II	326 (4.500)	276 (3.901)	1670	*trans*-II	320 (4.394)	275 (3.875)	1710
cis-III	325 (4.225)	275 (3.829)	1690	*trans*-III	325 (4.408)	275 (4.079)	1710

(a) in Chloroform. (b) in Nujol.

TABLE III

Nuclear Magnetic Resonance Data for Ethyl *N*-(2-Pyridinyl)aminomethylenecyanoacetates at 60 MHz (J in parentheses) (a)

No	Solvent	=CH-		-NH-	
		cis	*trans*	*cis*	*trans*
I	Deuteriochloroform	8.71d (13)	9.20d (1)	10.89d (13)	9.20d (1)
II	Deuteriochloroform	8.68d (12)	9.22d (1)	10.80d (12)	9.22d (1)
III	Deuteriochloroform	8.73d (13)	9.16d (2)	10.83d (13)	9.09d (2)

(a) Referred to internal tetramethylsilane.

TABLE IV

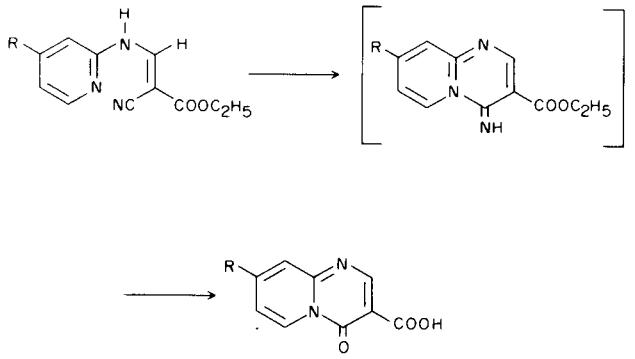
Interconversions between *cis*- and *trans*-Enamines

Starting Material	Reaction Condition	Results	
cis-I	A (a)	*cis*-I and *trans*-I	(45:55)
	Reflux for 1 hour in ethanol	*cis*-I and *trans*-I	(50:50)
	B (a)	*cis*-I and *trans*-I	(50:50)
	C (a)	*cis*-I and *trans*-I	(62:38)
trans-I	A	*cis*-I and *trans*-I	(34:66)
	Reflux for 1 hour in ethanol	*cis*-I and *trans*-I	(50:50)
	B	unchanged	
	C	*cis*-I and *trans*-I	(67:33)
cis-II	A	unchanged	
	B	*cis*-II and *trans*-II	(3:97)
	C	unchanged	
trans-II	A	*cis*-II and *trans*-II	(54:46)
	Reflux for 1 hour in ethanol	*cis*-II and *trans*-II	(54:46)
	B	unchanged	
	C	*cis*-II and *trans*-II	(100:0)
cis-III	A	*cis*-III and *trans*-III	(90:10)
	B	*cis*-III and *trans*-III	(59:41)
	C	*cis*-III and *trans*-III	(62:38)
	Reflux for 30 minutes in a mixture of conc. hydrochloric acid and water (1:1)	*cis*-III and *trans*-III	(0:100)
trans-III	A	*cis*-III and *trans*-III	(45:55)
	B	*cis*-III and *trans*-III	(76:24)
	C	*cis*-III and *trans*-III	(90:10)
	Reflux for 30 minutes in a mixture of conc. hydrochloric acid and water (1:1)	*cis*-III and *trans*-III	(86:14)

(a) see EXPERIMENTAL

pyrimidin-4-one-3-carboxylic acid (V), which was further esterified to give ethyl 4*H*-pyrido[1,2-*a*]-pyrimidin-4-one-3-carboxylate (VI). The structures of these cyclized products were ascertained by elemental analysis, molecular weight determination by mass spectrometry, and the similarity of their ultraviolet spectra (see Fig. I) to those of

SCHEME III



(IV) R = H
(V) R = CH_3

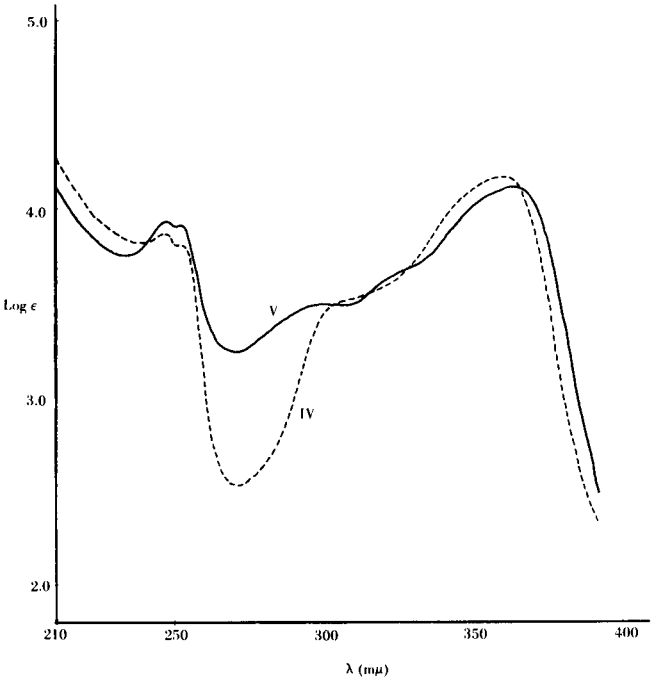


Figure 1. Ultraviolet spectra of IV and V in ethanol.

the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives (4). It is known that the 2*H*-pyrido[1,2-*a*]pyrimidin-2-one system has different patterns in ultraviolet spectra (3,4). Additional evidence for these structures was obtained by alkaline hydrolysis which yielded the corresponding 2-aminopyridines. It is interesting to note that *cis*-III (or *trans*-III) did not give the cyclized product on treatment with hydrochloric acid, but only isomerization took place (see Table IV), this is a behavior ascribed to steric hindrance by the 6-methyl group.

EXPERIMENTAL (6)

Preparation of Ethyl *N*-(2-Pyridinyl)aminomethylenecyanoacetates. General Procedure.

A mixture of 2-aminopyrimidine and equimolar amount of ethyl ethoxymethylenecyanoacetate was fused under the conditions described in Table I. After cooling, the reaction mixture was recrystallized from benzene and the less soluble, high melting, *trans*-enamine precipitated. Dilution of the filtrate with petroleum ether gave the crude *cis*-enamine having low melting point. These procedures were repeated several times and recrystallization from the appropriate solvents gave analytically pure samples.

Interconversion between *cis*- and *trans*-Enamines.

Each isomer was treated under following conditions to yield the reaction products.

(A) After refluxing of *cis*- (or *trans*-) enamine in ethanol for 30 minutes, the solvent was evaporated *in vacuo*.

(B) After refluxing of *cis*- (or *trans*-) enamine in a small amount of Dowtherm A for 10 minutes, the reaction mixture was diluted with benzene.

(C) *cis*- (or *trans*-) Enamine was fused at 180° for 20 minutes.

4*H*-Pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylic Acid (IV).

A solution of 0.2 g. of *cis*-I (or *trans*-I) in 0.5 ml. of a mixture of concentrated hydrochloric acid and water (1:1) was refluxed for 20 minutes. After cooling, the reaction mixture was neutralized with aqueous ammonia and the precipitates were collected by filtration. Recrystallization from methanol gave 0.1 g. (57%) of colorless crystals, m.p. 278° (lit (4), m.p. 265°).

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 56.81; H, 3.04; N, 14.64.

8-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylic Acid (V).

A solution of 0.1 g. of *cis*-II (or *trans*-II) in 0.5 ml. of a mixture of concentrated hydrochloric acid and water (1:1) was treated under the same conditions described above to yield 0.1 g. (54%) of colorless crystals, m.p. 223° (from methanol).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 59.19; H, 3.94; N, 13.52.

Ethyl 8-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylate (VI).

A solution of 0.6 g. of V in 80 ml. of anhydrous ethanol was introduced with dried hydrogen chloride for 5 hours under warming at 70°. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was neutralized with concentrated ammonia to yield pale brown crystals, which were recrystallized from benzene to give 0.18 g. (26%) of pale yellow leaflets, m.p. 156-158°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.89; H, 5.07; N, 11.76.

Hydrolysis of V.

A solution of V in 10% ethanolic sodium hydroxide was refluxed for 1 hour. After evaporation of the solvent, the residue was extracted with chloroform and dried over anhydrous sodium sulfate. Evaporation of the chloroform gave 2-amino-4-methylpyridine.

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(5) Idem., *ibid.*, **74**, 4906 (1952).

(6) All melting points were determined on a Yanagimoto Micro-Melting Point Apparatus and are uncorrected.