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Geometrical Isomerism of Ethyl *N*-(Pyrimidinyl)aminomethylenecyanoacetates (I)

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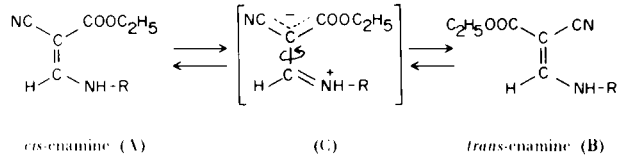
The geometrical isomers of ethyl *N*-(pyrimidinyl)aminomethylenecyanoacetates were isolated and their structures and interconversions are discussed.

N-Substituted aminomethylenecyanoacetates could exist in equilibrium between two geometrical isomeric forms with the amino and the carboalkoxy groups *cis* (A) (referred to hereafter as the *cis*-enamine) and *trans* (B) (*trans*-enamine). The interconversion between these enamines may occur through a transition intermediate (C) which implies reduction of the bond order of the formally located double bond in A or B resulting in rotation about the carbon-carbon double bond. Since the energy barriers to the rotation are exceptionally low (2-4) in such an extensive delocalized π-system as A or B and accordingly the isomers are readily interconverted in solution (5,6), the isolation of stable stereoisomers may be impossible or very difficult at room temperature. However, the introduction of an electron-withdrawing substituent onto the

Chart 1



cis-enamine (A) (C) *trans*-enamine (B)

amino group results in attraction of the unshared pair of electrons on the nitrogen of the amino group in the opposite direction thus raising the energy barriers for isomerization between A and B around the double bond. In this case it would be expected that the isolation of geometrical isomers, for example, by fractional crystallization, might be possible.

In the condensation reaction between 4-aminopyrimidines and ethyl ethoxymethylenecyanoacetate, we obtained unequivocally the geometrical isomeric condensation products, ethyl *N*-(pyrimidinyl)aminomethylenecyanoacetates, and have isolated the pure *cis*- and *trans*-isomers. Therefore, the pyrimidinyl group does behave as an electron-withdrawing substituent and its introduction onto the amino group raises the energy barrier for isomerization thus facilitating the isolation of stereoisomers. Preparation of the ethyl *N*-(pyrimidinyl)aminomethylenecyanoacetates was carried out by fusion of 4-amino-2-methylpyrimidines with ethyl ethoxymethylenecyanoacetate under the conditions described in Table I and, in general, stereoisomeric mixtures were obtained except when using 6-amino-4-anilino-2-methylpyrimidine as the starting material. The *trans*-form (*trans*-III) of *N*-(4-ethoxy-2-methyl-6-pyrimidinyl)aminomethylenecyanoacetate was obtained as a complex (*trans*-III*) consisting of *trans*-III and 6-amino-4-ethoxy-2-methylpyrimidine. This complex was easily decomposed with 10% hydrochloric acid giving the free *trans*-enamine (see Table I). Preparation of *N*-(4-anilino-2-methyl-6-pyrimidinyl)aminomethylenecyanoacetate gave exclusively the *trans*-enamine at low temperature and the *cis*-enamine at high temperature. The separation of the stereoisomeric mixtures obtained into the *cis*- and *trans*-enamines was usually effected by fractional crystallization from benzene.

Tables II and III give the spectral data for the *cis*- and *trans*-enamines obtained. Although the ultraviolet absorption maxima of the *cis*-enamines show small red shifts of 3.5-4.5 mμ compared with those of the *trans*-enamines, this is not sufficient to assign the structures of the isomers. It should be noted that the ultraviolet spectra of both *cis*- and *trans*-*N*-(2-methyl-6-pyridinyl)aminomethylenecyanoacetate show a maximum peak at the same wavelength (325 mμ), although the intensity of the *trans*-isomer (log ϵ 4.408) is slightly stronger than that of the *cis*-isomer (log ϵ 4.225) (7).

TABLE I

Reaction of 4-Aminopyrimidines with Ethyl Ethoxymethylenecyanoacetate

Starting Material	Reaction Time min.	Reaction Temp. °C	Approximate Ratio of *cis*- and *trans*-Enamine (a)	M.p. °C	Recrystallization Solvent
6-amino-2-methyl-pyrimidine	8	100-115	50:50	101 (*cis*-I) 138 (*trans*-I)	benzene benzene
6-amino-4-chloro-2-methylpyrimidine	10	160	68:32	157 (*cis*-II) 173 (*trans*-II)	benzene ethanol
6-amino-4-ethoxy-2-methylpyrimidine	5	110-120	35:65 (b)	114 (*cis*-III) 163 (*trans*-III) (c) 139 (*trans*-III*) (b)	benzene benzene benzene
6-amino-2-methyl-4-phenoxypyrimidine	10 30	135 150-155	50:50 45:55	174 (*cis*-IV) 185 (*trans*-IV)	benzene ethanol
6-amino-4-anilino-2-methylpyrimidine	8 10	130-140 200	0:100 100:0	187 (*cis*-V) 194 (*trans*-V)	benzene chloroform

(a) This number was measured by NMR spectroscopy and is probably accurate within ± 5. (b) A complex of *trans*-enamine and 6-amino-4-ethoxy-2-methylpyrimidine. (c) Prepared by decomposition of *trans*-III* with 10% hydrochloric acid (80°, 30 minutes).

TABLE II

Ultraviolet and Infrared Data for Ethyl *N*-(Pyrimidinyl)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	319.5	(4.323)	1699	*trans*-I	315	(4.400)	1727
cis-II	318	(4.578)	1678	*trans*-II	314	(4.512)	1730
cis-III	314	(4.445)	1680	*trans*-III	309.5	(4.450)	1719
cis-IV	315.5	(4.375)	1686	*trans*-IV	311	(4.489)	1719
cis-V	322.5	(4.505)	1686	*trans*-V	319	(4.453)	1710

(a) In chloroform. (b) In Nujol.

Infrared and NMR spectroscopy were, however, very useful in determining the stereochemical relationship of the *cis*- and *trans*-enamines. The carbonyl stretching bands of the *cis*-enamines always appear at lower frequency than those of the *trans*-enamines. The shifts into a lower frequency of the *cis*-enamines are attributed to an intramolecular hydrogen-bonding effect, thus suggesting a *cis*-relationship between the amino and the ester group. This was also supported by NMR spectroscopy. As can be seen from Table III, the NMR data in deuteriochloroform show that (a) in the *cis*-enamine the olefinic proton is at higher field than in the *trans*-enamine (difference about 0.3-0.6 ppm), (b) the presence of a hydrogen-bonded chelate ring in the *cis*-enamine is inferred from the downfield NH-signal (10.6-10.9 ppm) (6,8), which is consistent with the results of the infrared spectroscopy, (c) the NH-CH spin-spin coupling of 12-13 Hz in the *cis*-enamine is contrasted with the coupling constant (~ 4 Hz) in the *trans*-enamine (6,8). These observations suggest the structures D and E, respectively, for the *cis*- and *trans*-enamines.

TABLE III

NMR Data for Ethyl *N*-(Pyrimidinyl)aminomethylenecyanoacetates at 60 MHz (J in parentheses) (a)

No.	4-Substituent	Solvent	=CH		NH		C_5H		CH_3		C_2H_5	
			cis	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
I	H (b)	$CDCl_3$	8.81d (13)	9.40d (1)	10.86d (13)	9.48d (1)	6.66d (6)	6.88d (6)	2.68	2.67	1.40t, 4.35q (7)	1.38t, 4.35q (7)
II	Cl	$CDCl_3$	8.69d (12)	9.25d (4)	10.85d (12)	9.40d (4)	6.68	6.89	2.65	2.64	1.38t, 4.33q (7)	1.39t, 4.33q (7)
III	OC_2H_5	$CDCl_3$	8.72d (12)	9.14d (3)	10.72d (12)	9.02d (3)	5.96	6.17	2.54	2.54	1.39t, 4.32q (7)	1.40t, 4.39q (7)
IV	OC_6H_5	$CDCl_3$	8.75d (12)	9.04d (2)	10.78d (12)	8.92d (2)	5.95	6.16	2.55	2.49	1.36t, 4.31q (7)	1.35t, 4.29q (7)
		DMSO-d_6	8.97br	9.16br	11.28br	11.50br (c)	6.48	6.60	2.45	2.49	1.26t, 4.23q (7)	1.28t, 4.28q (7)
V	NHC_6H_5	$CDCl_3$ (d)	8.69d (13)	---	10.61d (13)	---	5.93	---	2.45	---	1.35t, 4.27q (7)	---
		DMSO-d_6 (e)	9.05d (13)	---	11.20d (13)	---	6.54	---	2.43	---	1.26t, 4.21q (7)	---

(a) Referred to internal tetramethylsilane. (b) Signals of C_4H *cis*: 8.53d (6), *trans*: 8.52d (6). (c) A strong hydrogen bonding to DMSO-d_6 may shift the NH resonance downfield. (d) The data of *trans*-V could not be obtained due to low solubility in deuteriochloroform. (e) The data of *trans*-V in DMSO-d_6 is not available because of its quick conversion into *cis*-V in this solvent.

TABLE IV

Interconversion Between *cis*- and *trans*-Enamines

Starting Material (4-substituent)		Reaction Condition: Time min.	Reaction Condition: Temp. °C	Solution	Results
cis-I	(H)	30	80-90	70% EtOH	*cis*-I and *trans*-I (50:50)
trans-I	(H)	30	250	Dowtherm A	no change
cis-II	(Cl)	30	80-90	70% EtOH	*trans*-II (100%)
trans-II	(Cl)	30	250	Dowtherm A	decomposition
cis-III	(OC_2H_5)	30	80-90	70% EtOH	*trans*-III (almost 100%)
trans-III	(OC_2H_5)	30	250	Dowtherm A	cyclization (b)
cis-IV	(OC_6H_5)	8	250	Dowtherm A	*trans*-IV (100%)
		10	80-90	EtOH	*trans*-IV (100%)
trans-IV	(OC_6H_5)	30	250	Dowtherm A	no change
cis-V	(NHC_6H_5)	10	80-90	EtOH	*cis*-V and *trans*-V (50:50)
		30	80-90	dil HCl in EtOH (a)	*cis*-V and *trans*-V (45:55)
		180	15-20	dil HCl in EtOH (a)	*trans*-V (almost 100%)
trans-V	(NHC_6H_5)	10	250	Dowtherm A	*cis*-V (100%)
		5	100	DMSO	*cis*-V (100%)

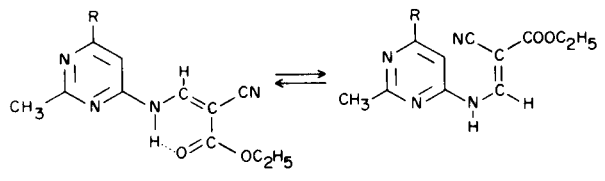
(a) Hydrochloric acid (0.2%) in 80% ethanol. (b) To 6-cyano-4-ethoxy-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine.

TABLE V

Analytical Data for *N*-(2-Methyl-4-substituted-6-pyrimidinyl)aminomethylenecyanoacetates

Product	Formula	Analysis (%): Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
cis-I	$C_{11}H_{12}N_4O_2$	56.89	5.21	24.13	57.03	5.42	24.08
trans-I					56.88	5.09	24.35
cis-II	$C_{11}H_{11}N_4O_2Cl$	49.54	4.16	21.01	49.60	4.09	20.98
trans-II					49.82	4.21	20.62
cis-III	$C_{13}H_{16}N_4O_3$	56.51	5.84	20.21	56.56	5.80	20.03
trans-III					56.63	5.63	19.89
trans-III*	$C_{20}H_{27}N_7O_4$	55.93	6.34	22.83	56.39	6.54	22.83
cis-IV	$C_{17}H_{16}N_4O_3$	62.95	4.97	17.28	62.73	4.96	17.53
trans-IV					62.80	4.91	17.29
cis-V	$C_{17}H_{17}N_5O_2$	63.14	5.30	21.66	63.13	5.11	21.63
trans-V					62.92	5.15	22.00

Chart 2



cis-enamine (D) *trans*-enamine (E)

Some aspects of the interconversion between the *cis*- and *trans*-enamines are summerized in Table IV. The equilibrium seems to favor the *trans*-enamines thermally except in the case of *N*-(4-anilino-2-methyl-6-pyrimidinyl)-aminomethylenecyanoacetate (V). The *trans*-form of *N*-(4-anilino-2-methyl-6-pyrimidinyl)aminomethylenecyanoacetate (*trans*-V) was converted completely into the *cis*-form (*cis*-V) on heating in Dowtherm A or DMSO.

The *cis*-V, on the other hand, was converted almost completely into *trans*-V by treatment with dilute hydrochloric acid in ethanol at room temperature. This offers an interesting precedent in the interconvertibility of the geometrical isomers.

Heating of *trans*-*N*-(4-ethoxy-2-methyl-6-pyrimidinyl)-aminomethylenecyanoacetate (*trans*-III) in Dowtherm A gave a cyclized product, 6-cyano-4-ethoxy-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine (9).

EXPERIMENTAL (10)

Preparation of Ethyl *N*-(2-Methyl-4-substituted-6-pyrimidinyl)-aminomethylenecyanoacetates. General Procedure.

A mixture of 6-amino-2-methyl-4-substituted-pyrimidine and an 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, higher melting, *trans*-enamine precipitated. Condensation of the filtrate gave the crude, lower melting, *cis*-enamine. The procedure was repeated several times and recrystallization from the appropriate solvents gave analytically pure samples (Table V).

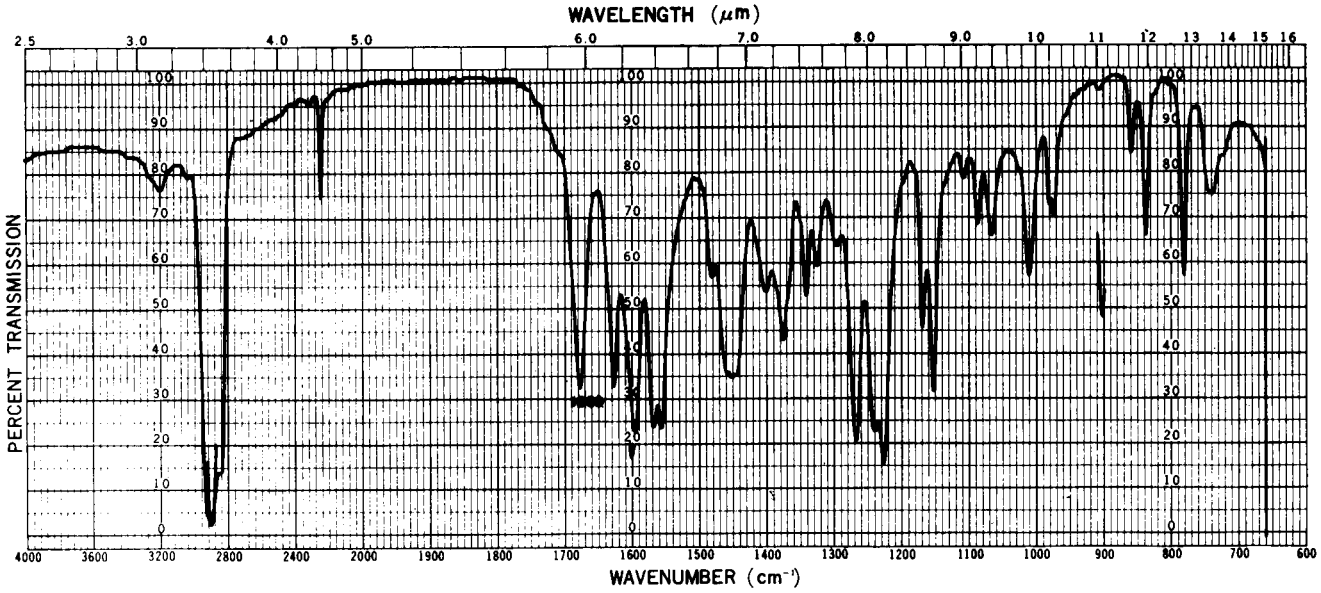


Fig. 1. *cis*-III

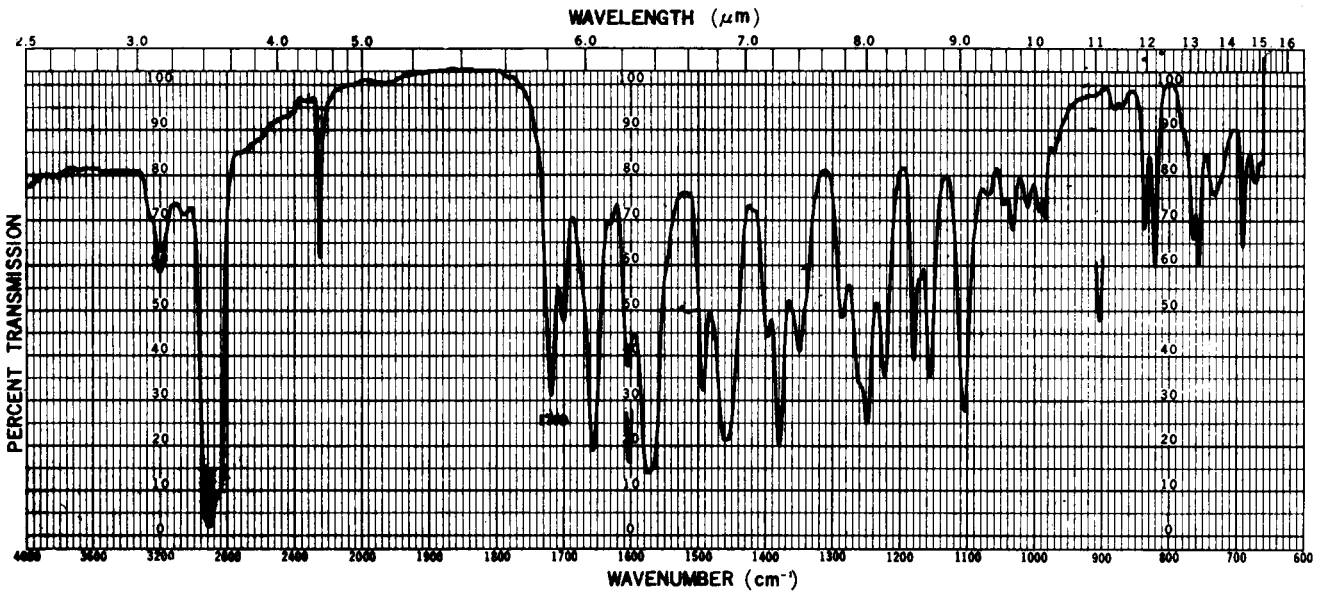


Fig. 2. *trans*-III

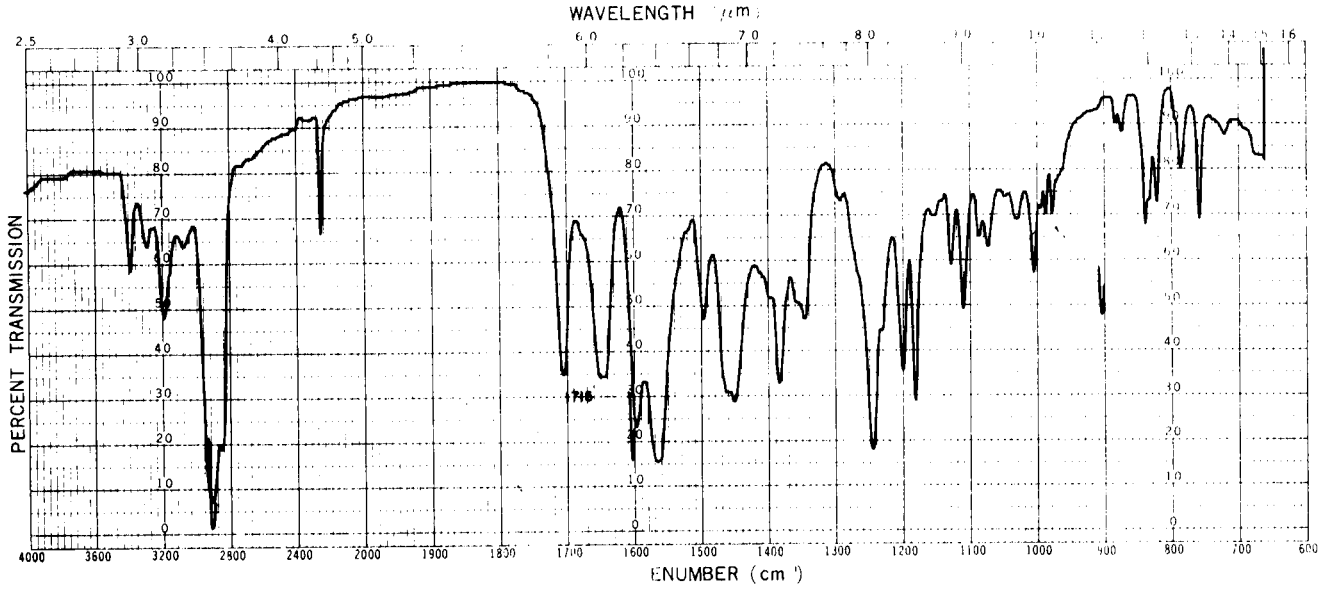


Fig. 3. *trans*-III*

Preparation of *trans*-III by Decomposition of *trans*-III*.

The complex *trans*-III* was warmed with 10% hydrochloric acid at 80° for 30 minutes. The reaction mixture was neutralized with aqueous ammonium hydroxide and the precipitate was collected by filtration and recrystallized from benzene to give *trans*-III as colorless needles.

Preparation of *trans*-III*.

A mixture of 6-amino-4-ethoxy-2-methylpyrimidine and an equimolar amount of *trans*-III was warmed in ethanol at 70° for 30 minutes. The reaction mixture was evaporated and recrystallized from benzene to give *trans*-III*.

Conversion of *cis*-V into *trans*-V.

The isomer *cis*-V was stirred into 0.2% hydrochloric acid in 80% ethanol at room temperature for 3 hours. The solvent was evaporated *in vacuo* at room temperature and neutralized with aqueous ammonium hydroxide to precipitate *trans*-V.

Conversion of *trans*-V into *cis*-V.

After refluxing *trans*-V in Dowtherm A, the reaction mixture was diluted with *n*-hexane or petroleum benzene to precipitate *cis*-V.

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