An ^1H and ^{13}C NMR Spectroscopic Study of Ethyl 3-(2-Pyrimidylamino)crotonate, Ethyl 3-(5-Bromo-3-pyridylamino)crotonate, *N*-(2-Pyrimidyl)-3-(methylamino)crotonamide, and *N*-(4-Methyl-2-pyridyl)-3-(methylamino)crotonamide

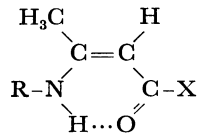
Michio KONDO

Central Research Laboratories, Sankyo Co., Ltd., Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140

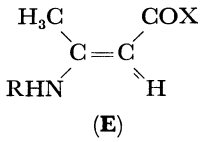
(Received January 10, 1978)

It has been found, from the ^1H NMR spectra that two esters exist in an intramolecularly hydrogen bonded form (**Z**) in $CDCl_3$ and DMSO solutions. Two amides, on the other hand, have been found to exist as a mixture of the **Z** and **E** isomers in DMSO solutions. H/D exchange at the olefinic site has been found to occur by the addition of D_2O to the DMSO solutions of the amides, but not in the cases of the esters. The amide configurations are discussed. An interpretation of the ^{13}C NMR spectra of these compounds is also given.

It was found that esters[1,2] and amides[3] of 3-(alkylamino)crotonic acid exist as mixtures of the **Z** and **E** isomers, with the **Z** form preferred in various solvents. The **Z**-**E** equilibrium was found to be solvent-dependent.[3] It was also found that the H/D exchange at the olefinic site of these compounds is closely related to the **Z**-**E** tautomerism, which was assumed to proceed through enamine⇌imine tautomerization. These properties of enamine derivatives are expected to depend upon the double-bond character of the olefinic linkage, which is determined by the combination of electron-donating and electron-withdrawing substituents on the opposite ends of the olefinic bond.



(**Z**)



(**E**)

1: R=2-Pyrimidyl, X=OEt, mp 76.2 °C
2: R=5-bromo-2-pyridyl, X=OEt, mp 90.0 °C
3: R=CH_3, X=2-pyrimidylamino, mp 178.5 °C
4: R=CH_3, X=4-methyl-2-pyridylamino, mp 165 °C.

This paper will be concerned with the ^1H and ^{13}C NMR spectroscopic study of the four title compounds in $CDCl_3$ and DMSO solutions.

Experimental

Compound **1** was prepared by heating an equimolar mixture of ethyl acetoacetate and 2-aminopyrimidine at about 130 °C for 5 h. The volatile components were removed under reduced pressure, and the residue was extracted with hot cyclohexane. The concentration of the extract gave crude **1**, which was then purified by recrystallization from cyclohexane.

Compound **2** was prepared in a similar way.

Compounds **3** and **4** were prepared by the condensation of methylamine with the corresponding crotonamides; 2-acetoacetamidopyrimidine was commercially available, and 2-acetoacetamido-4-methylpyridine was derived from 2-amino-4-methylpyridine and ethyl acetoacetate.[4]

All four compounds gave satisfactory results of elemental analyses.

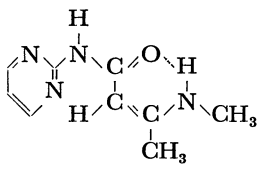
The ^1H NMR spectra were recorded on a Varian XL-100A-15 spectrometer at the CW mode at room temperature (*ca.* 28 °C), using TMS as the internal standard. The sample concentration was 50 mg/ml unless otherwise noted. The ^{13}C NMR spectra were taken under the FT mode under these conditions: spectrometer frequency, 25.16 MHz; spectral width, 5,500 Hz; aquisition time, 2 s; pulse width, 20 μs; pulse delay, 1.6—5.2 s; number of transients, 1000—10000; with or without proton-noise decoupling (10 W of rf power).

Results and Discussion

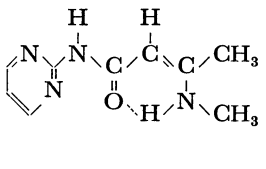
Assignment of NMR Spectra. In each of the ^1H NMR spectra of these four compounds in $CDCl_3$, there was a broad signal which was concentration-insensitive. This implies the amino structure (**Z**), including the intramolecular hydrogen bond, NH···OC.

In DMSO, the ^1H NMR spectra of **1** and **2** can be well explained in terms of one molecular species (**Z** form), whereas those of **3** and **4** can be explained by assuming two molecular species (**Z** and **E**) coexisting in the solution. A similar DMSO-induced isomerization has been reported for enamino ketones[5] and 1-carbamoyl-5-fluorouracil.[6] The ^1H chemical shifts are summarized in Table 1.

Amide Configurations. It is noteworthy that the olefinic proton of **3** resonates at a field lower by as great as 1.15 ppm than that of **4** in $CDCl_3$, and that the former signal shows an upfield shift, whereas the latter shows a downfield shift, with the solvent change from $CDCl_3$ to DMSO. This solvent change induced a great downfield shift of the amide signals of both the compounds. These observations can be well explained by assuming that **3** exists predominantly in a *s-cis* form in $CDCl_3$ and in a *s-trans* form in DMSO, because a similar phenomenon was observed for 2-acetamidopyrimidine[7] and 2-acetoacetamidopyrimidine.[8] On the other hand, it seems that the amide configuration of **4** is *s-trans* and solvent-independent.



s-cis



s-trans

TABLE 1. ^1H CHEMICAL SHIFTS OF VARIOUS KINDS OF PROTONS OF **1**, **2**, **3**, AND **4** IN $CDCl_3$ AND DMSO-d_6

	Solv.	CH_3	CH_2	$=CCH_3$	NCH_3	=CH	H-3′	H-4′	H-5′	H-6′	NHCO	NH	p[a]
1	$CDCl_3$	1.29	4.17	2.50	—	4.85	—	8.42	6.77	8.42	—	11.25	
	DMSO	1.23	4.11	2.48	—	4.89	—	8.55	7.01	8.55	—	11.17	
2	$CDCl_3$	1.30	4.16	2.43	—	4.80	6.67	7.61	—	8.27	—	11.02	
	DMSO	1.23	4.10	2.37	—	4.82	7.01	7.86	—	8.33	—	10.90	
3	$CDCl_3$	—	—	2.01	2.95	5.62	—	8.55	6.84	8.55	8.44	9.74	
	DMSO[b]	—	—	1.93	2.89	5.41	—	8.53	6.98	8.53	9.48	9.42	82
		—	—	2.24	2.62	5.22	—	c)	c)	c)		6.66	18
4	$CDCl_3$	—	—	1.91	2.91	4.47	8.01	(2.32)[d]	6.71	8.04	7.78	9.16	
	DMSO[b]	—	—	1.88	2.87	4.76	7.97	(2.28)[d]	6.73	8.04	9.38	9.06	70
		—	—	2.24	2.60	4.86	c)	c)	c)	c)	9.34	6.38	30

a) Population (±5%). b) The figures in the upper row correspond to the *Z* isomer, and those in the lower, to the *E* isomer. c) Not identified because of the overlap with the *Z*-signals. d) Methyl substituent at the 4′-position.

Hydrogen-deuterium Exchange at the Olefinic Site. The addition of about 5% v/v D_2O to the DMSO solutions of **3** and **4** caused a gradual disappearance of the olefinic proton signal as well as of the amino and amide proton signals, whereas the addition of D_2O to the DMSO solutions of **1** and **2** induced the disappearance of the amino proton signal only. This means that the coexistence of the **Z** and **E** isomers in the DMSO solutions of **3** and **4** is essential to the H/D exchange at the olefinic site.

^{13}C NMR Spectra. The signal assignment was rather simple when the relative intensity and multiplicity in the proton-coupled ^{13}C spectra were taken into account (Table 2). The ring carbon, 2′, in these compounds can be identified by its rather large spin-coupling constant of about 12 Hz with the ring proton, 6′.[9]

Paired signals corresponding to the **Z** and **E** isomers were observed for **3** and **4** dissolved in DMSO; this is consistent with the results obtained from the ^1H NMR spectroscopic study.

The chemical-shift difference between the two isomers (**Z** and **E**) is appreciable for the carbonyl and the olefinic C-3 only. These two carbons are more deshielded in the **Z** form than in the **E** form, probably because of the enhanced polarization of the carbonyl group by the

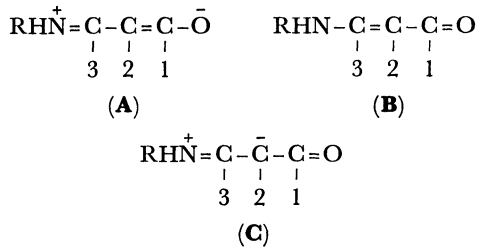
TABLE 2. ^{13}C CHEMICAL SHIFTS OF VARIOUS CARBONS OF **1**, **2**, **3**, AND **4**

Compd	**1**		**2**		**3**		**4**	
Solv.	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO
C=O	169.3	168.8	170.1	168.9	168.8	167.8 (165.7)	169.1	168.9 (167.1)
C-2′	159.4	158.6	152.3	151.7	158.6	158.3 (158.7)	153.3	153.5 (153.9)
C-3′	—	—	114.9	115.5	—	—	113.9	113.0 (113.0)
C-4′	157.9	158.4	140.2	140.6	158.1	157.9 (157.9)	149.2	147.8 (147.8)
C-5′	114.4	115.2	112.6	112.5	114.3	114.6 (114.6)	119.1	118.4 (118.3)
C-6′	157.9	158.4	148.6	148.2	158.1	157.9 (157.9)	147.2	147.2 (147.8)
=C(3)N	156.0	156.1	157.2	156.6	164.2	162.9 (160.0)	161.9	161.1 (158.7)
=C(2)H	93.1	92.2	91.2	90.5	85.0	84.9 (84.6)	85.2	85.0 (84.8)
CH_2O	59.3	59.0	59.2	58.7	—	—	—	—
CH_3N	—	—	—	—	29.6	29.1 (29.3)	29.5	29.0 (29.3)
$CH_3C=$	22.9	22.4	22.4	21.7	19.6	19.2 (19.3)	21.4	20.9 (20.9)
CH_3(C-4′)	—	—	—	—	—	—	19.3	19.0 (18.9)
CH_3CH_2	14.5	14.3	14.5	14.6	—	—	—	—
Population					**Z** (**E**)	79±2 (21±2)		73±2 (27±2)

C-2′ means the ring carbon-2, for example. The values in parentheses correspond to the **E** isomer.

intramolecular hydrogen bonding. Another olefinic carbon, C-2, resonates at almost the same field in the either form of **Z** and **E**.

As has been mentioned before, it is very likely that the double-bond character of the C_2=C_3 linkage plays an important role in the isomerization and in the H/D exchange. An enhanced contribution of the canonical forms, **A** and **C**, to the ground state can be expected to reduce the double-bond character of the olefinic linkage and, as a consequence, to make the **Z-E** tautomerization as well as the H/D exchange easy.



(**A**) (**B**)

(**C**)

It is noteworthy that the ^{13}C chemical shifts of the C-2 and C-3 of **1** and **2** are systematically different from those of **3** and **4**; C-3 is more shielded in **1** and **2** than in **3** and **4**, but C-2 is, on the contrary, more shielded in **3** and **4**. Since there is no appreciable difference among the chemical shifts of the carbonyl carbons of the four compounds, the above systematic difference is probably to be ascribed to the different substituents at the 3-position, which influence both C-2 and C-3 mainly by a mesomeric mechanism. Therefore, the more shielded nature of the C-2 in **3** and **4** implies a higher contribution of the polar canonical form **C** than in **1** and **2**. This in turn means an easier formation of the transient imino form and an easier occurrence of H/D exchange.

The carbon-proton spin-spin coupling constants, $^{1}J_{CH}$'s, are given in Table 3. The $^{1}J_{CH}(2)$ values for **1** and **2** are slightly but definitely greater than those for **3** and **4**, reflecting a smaller *s* character of the C-2 hybrid orbital in **3** and **4**. This is consistent with the above argument that the contribution of the canonical form **C** is to be considered larger in **3** and **4** than in **1** and **2**.

Table 3. $^{1}J_{CH}$ values for **1**, **2**, **3**, and **4** in $CDCl_3$

	1	**2**	**3**	**4**
CH(2)	166.1	166.1	163.5	160.2
CH_3(4)	126.8	126.9	128.1	127.4
NCH_3	—	—	137.7	136.5
CH(3′)	—	162.9	—	167.9
CH_3(C4′)	—	—	—	123.3
CH(4′)	179.1	166.3	180.3	—
CH(5′)	169.5	—	169.6	162.7
CH(6′)	179.1	186.6	180.3	175.9
OCH_2CH_3	146.8	146.5	—	—
OCH_2CH_3	129.8	129.9	—	—

References

1) G. O. Dudek and G. P. Volpp, *J. Am. Chem. Soc.*, **85**, 2697 (1963).
2) A. G. Sanchez, M. T. Aldave, and U. Scheideggar, *J. Chem. Soc., C*, **1968**, 2570.
3) M. Kondo, *Bull. Chem. Soc. Jpn.*, **50**, 2961 (1977).
4) M. Shur and S. S. Israelstam, *J. Org. Chem.*, **33**, 3015 (1968).
5) M. L. Filleux-Blanchard, H. Durand, M. T. Bergeon, F. Clesse, H. Quiniou, and G. J. Martin, *J. Mol. Struct.*, **3**, 351 (1969).
6) S. Ozaki, Y. Ike, H. Mizuno, K. Ishikawa, and H. Mori, *Bull. Chem. Soc. Jpn.*, **50**, 2406 (1977).
7) M. Kondo, *Bull. Chem. Soc. Jpn.*, **49**, 1443 (1976).
8) M. Kondo, *Bull. Chem. Soc. Jpn.*, **51**, 1905 (1978).
9) M. Hansen and H. J. Jacobsen, *J. Magn. Reson.* **10**, 74 (1973).