

Proton Magnetic Resonance Studies of *cis-trans* Equilibria of Some *N*-(2,5-Dichlorophenyl)-3-aminocrotonamides

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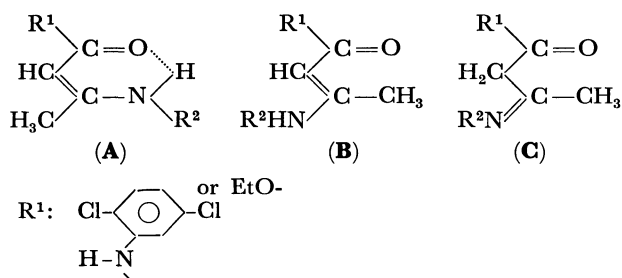
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The ^1H NMR spectra of 3-(alkylamino)crotonamides indicate that these substances exist in solution as a mixture of the geometric isomers, *cis* and *trans*, in which the chelated *cis* form is predominant. Unsubstituted 3-aminocrotonamide appears to exist in the *cis* form only, and *N,N*-disubstituted derivatives in the *trans* form. In the case of 3-(alkylamino)crotonamide it is found that the *cis-trans* equilibrium is solvent dependent and that the apparent rate of interconversion between the isomers is very slow in chloroform- d_3 , fast in dimethyl- d_6 sulfoxide, and intermediate in acetone- d_6 and methanol- d_4 . It seems that the *cis-trans* equilibrium is almost independent of both temperature and concentration, and that the replacement of the olefinic H by D proceeds through enamine $\rightleftharpoons$ imine tautomerization.

^1H NMR spectroscopy has proved to be a powerful method for studying structural problems such as tautomeric equilibrium and proton-deuteron exchange. The previous paper reported the ^1H NMR spectroscopic study of *N*-(2,5-dichlorophenyl)acetoacetamide (**7**), in which the *enol* form was found to be a minor component in any solvent used.¹⁾ The ^1H NMR spectral study of the title compounds, easily prepared from **7** and appropriate amines, will give further information about their conformations.

From the ^1H NMR spectral studies of 3-aminocrotonic esters it has been found that *N*-monosubstituted derivatives exist as mixtures of two geometric isomers, *cis* (**A**) and *trans* (**B**).^{2,3)} In the case of the title compounds there is another problem, the *cis-trans* isomerism about the amide bond, but its conformation can be confined to *trans* on the basis of the diagnostic acylation-desielding shifts of the ring proton-6.⁴⁾ Hereafter the terms *cis* and *trans* will refer to the conformation about the olefinic bond, $\text{C}_2\text{--C}_3$, unless otherwise noted.



Another point of interest is that the shift direction of the olefinic proton signals of the title compounds was opposite to that for ethyl 3-(alkylamino)crotonate when the solvent was changed from CDCl_3 to DMSO.

Experimental

Materials. To 2,5-dichloroacetoacetanilide (1/20 mol) suspended in ethanol (50 ml) was added an appropriate amine in slight excess. The reaction mixture was gently warmed to give a pale yellow solution and then concentrated to near dryness at room temperature. Repeated crystallizations of the precipitates from ethanol or aqueous ethanol gave the pure compounds, as proved by the satisfactory results of elemental analyses. This indicates that the condensation reaction occurred at either the acetyl-carbonyl or the amide-carbonyl group. However, the latter position may

be ruled out from the constancy of the chemical shifts of the ring protons of these six compounds. Therefore, it is concluded that the reaction products are 3-aminocrotonamides (**A** and **B**) or their imino-tautomer (**C**). The structure **C** can be ruled out on the basis of the absence of signals assignable to methylene protons.

	(2,5) $\text{Cl}_2\text{C}_6\text{H}_3\text{NHCCH}=\text{C}(\text{CH}_3)\text{X}$		
	1	2	3
X	NH_2	NHCH_3	NHCH_2CH_3
mp($^\circ\text{C}$)	130.5	72.5	85.0
	4	5	6
X	$\text{N}(\text{CH}_3)_2$	$\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$	$\text{N}(\text{CH}_3)\text{CH}_2\text{C}_6\text{H}_5$
mp($^\circ\text{C}$)	141(dec)	195.5	157

The ^1H NMR spectra were recorded on a Varian T-60A spectrometer. Sample concentrations were 20 mg/ml unless otherwise noted. The concentration dependence of the chemical shifts of **2** was examined in DMSO and found to be negligible. The temperature dependence of the spectra of **2** was tested in DMSO at higher temperatures, using a Varian A-60D spectrometer.

Results and Discussion

Signal Assignment. A single set of signals was observed for CDCl_3 solution of **2** and **3**, whereas two sets of signals were observed for DMSO solutions of **2** and **3**; one set of the two corresponded well to the signals observed for the CDCl_3 solution. The amino proton signals of **2** and **3** in CDCl_3 are located at δ 9.17 and 9.21 respectively, suggesting a molecular conformation containing an intramolecular hydrogen bond between the amino proton and the amide carbonyl, i.e., the *cis* conformation (**A**). The other set of signals of the DMSO solutions of **2** and **3** can be attributed to the *trans* conformation. The chemical shifts thus assigned to the *cis*- and *trans*- $\text{C}-\text{CH}_3$, $\text{N}-\text{CH}_3$, and $=\text{CH}$ protons of **2** in DMSO, for example, are in fair agreement with those reported for the corresponding protons of ethyl 3-(methylamino)crotonate (**8**) in DMSO.³⁾

Each of the ^1H NMR spectra of **1**, **4**, **5**, and **6** consists of only a single set of signals in both CDCl_3 and DMSO solutions. The chemical shifts of various kinds of protons of **1**, except for the amino protons, are close to those of **2** in the *cis* form, leading to the conclusion that the molecular conformation of **1** in the solutions is *cis*. A similar comparison of the chemical shifts of

TABLE 1. THE CHEMICAL SHIFTS OF VARIOUS KINDS OF PROTONS IN SOME *N*-(2,5-DICHLOROPHENYL)-3-(ALKYLAMINO)CROTONAMIDES IN CDCl₃ AND DMSO

Compd	Solvent		CCH ₃	NCH ₃	=CH	NH	NHCO	H-3	H-4	H-6
1	CDCl ₃	c ^{a)}	1.95	—	4.58	6.60	7.20	7.26	6.93	8.56
	DMSO	c	1.84	—	4.80	7.50	8.44	7.44	7.03	8.20
2	CDCl ₃	c	1.93	2.93	4.51	9.17	7.07	7.24	6.88	8.52
		t	(not detected)							
	DMSO	c	1.92	2.88	4.87	9.05	8.38	7.43	7.03	8.26
		t	2.26	2.65	4.95	6.60	8.26	7.42	7.01	8.34
3	CDCl ₃	c	1.95	b)	4.48	9.21	7.03	7.24	6.88	8.52
		t	(not detected)							
	DMSO	c	1.91	b)	4.83	9.07	8.43	7.44	7.03	8.18
		t	2.23	b)	4.97	6.53	8.30	7.41	7.00	8.26
4	CDCl ₃	t	2.53	2.98	4.56	—	7.23	7.25	6.88	8.61
	DMSO	t	2.42	2.93	5.02	—	8.43	7.43	7.01	8.25
5	CDCl ₃	t	2.49	c)	4.80	—	7.3	7.25	6.92	8.58
	DMSO	t	2.40	c)	5.36	—	8.64	7.45	7.07	8.23
6	CDCl ₃	t	2.61	2.96	4.71	—	d)	d)	6.89	8.58
	DMSO	t	2.50	2.93	5.20	—	8.50	7.41	7.02	8.23

a) c and t mean *cis* and *trans*, respectively. b) *N*-Ethyl signals are omitted. c) Signals of the morpholine moiety are omitted. d) Not identified because of overlapping of the benzyl signals.

TABLE 2. DMSO-INDUCED SHIFTS ($\delta_{\text{DMSO}} - \delta_{\text{CDCl}_3}$)

Compd	CCH ₃	NCH ₃	=CH	NH	NHCO	H-3	H-4	H-6
1 (<i>cis</i>)	-0.09	—	0.22	0.90	1.24	0.18	0.10	-0.36
2 (<i>cis</i>)	-0.01	0.05	0.36	-0.12	1.31	0.19	0.15	-0.26
3 (<i>cis</i>)	-0.04	—	0.35	-0.14	1.40	0.20	0.15	-0.34
4 (<i>trans</i>)	-0.09	-0.05	0.46	—	1.20	0.18	0.13	-0.36
5 (<i>trans</i>)	-0.09	—	0.56	—	1.34	0.20	0.15	-0.35
6 (<i>trans</i>)	-0.09	-0.03	0.49	—	—	—	0.13	-0.35

various kinds of protons of **4**, **5**, and **6**, with those of **2** leads to the conclusion that these three amides have *trans* conformation in the solutions.

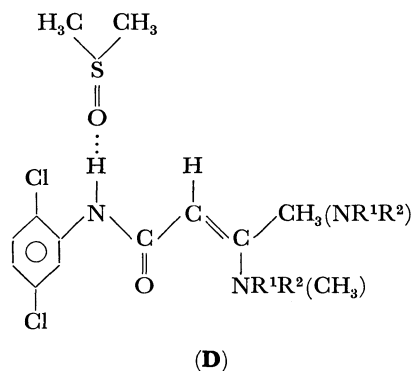
The chemical shifts thus determined are collected in Table 1.

DMSO-induced Shifts. The changes ($\delta_{\text{DMSO}} - \delta_{\text{CDCl}_3}$) in the chemical shifts of various protons are summarized in Table 2.

The chemical shifts of the ring protons show characteristic changes upon changing solvents from CDCl₃ to DMSO: proton 3 and 4 show downfield shifts of about 0.1–0.2 ppm and proton 6 an upfield shift of about 0.33 ppm. Similar observations were reported for a number of acetanilides having an electronegative ortho substituent capable of forming an intramolecular hydrogen bond with the amide proton.⁴⁾

The same solvent change caused slight upfield shifts of the C-CH₃ and N-CH₃ signals (<0.1 ppm), but remarkable downfield shifts of the olefinic proton (0.22–0.56 ppm) and the amide proton signals (1.20–1.40 ppm). This DMSO-induced downfield shift of the olefinic proton signal may be explained in terms of the deshielding effect⁵⁾ of a DMSO molecule intermolecularly hydrogen bonded with the amide proton (**D**), because DMSO is known as a powerful solvent for disrupting the intermolecular association among

amide molecules through forming intermolecular hydrogen bonds with the amide proton.⁶⁾ This kind of deshielding effect is not expected for *N,N*-dimethylamide or the ethyl ester of 3-aminocrotonic acid, because each of them can be supposed to have no specific interactions with DMSO molecules. In fact, the olefinic proton signals for these compounds remained at almost the same field for the solvent change described above.^{3,7)}



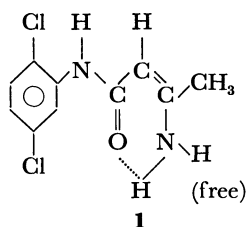
The fact that the *cis* form was observed for **1**, **2**, and **3** only is indicative of the important role of the intramolecular hydrogen bond between the amino proton and the carbonyl oxygen in stabilizing the *cis* form.

As for the amino protons of **1**, the DMSO-induced deshielding shift is 0.90 ppm. The deshielding shift for the amino proton not involved in the intramolecular hydrogen bond could be calculated as 1.92 ppm (see next section). This value is a little larger than the deshielding shift of about 1.3 ppm for the amide proton, probably reflecting stronger interactions with DMSO molecules.

Intramolecular Hydrogen Bonds. The amino protons of **2** and **3** in the *cis* form resonate at very low fields (δ 9.17 and 9.21, respectively) even in CDCl₃. The concentration dependence of these resonances was found to be negligible. This means that the *cis*-amino proton is involved in the intramolecular hydrogen bond with the carbonyl oxygen. With the change of solvents from CDCl₃ to DMSO, this amino-signal showed only a trivial upfield shift which may be a reflection of the persistence of the intramolecular hydrogen bond with almost the same strength even in DMSO. The UV absorption spectrum of **2** in DMSO is very similar to that in cyclohexane; this supports the above argument about the intramolecular hydrogen bond.

The amino protons of **1** resonate at δ 6.60 in CDCl₃ and at δ 7.50 in DMSO. These values are smaller by as much as about 2.59 and 1.56 ppm than those for the *cis*-amino protons of **2** and **3** in CDCl₃ and those in DMSO, respectively, mainly because of time averaging through a rapid internal exchange on the NMR time scale between the two amino protons (one is involved and the other is not involved in the intramolecular hydrogen bond) and partly because of the difference between NH₂ and NHR (R=CH₃ or C₂H₅).

It is reasonable to assume that the inductive effect due to the alkyl group is common and has the same magnitude for both the *cis* and *trans* amino protons. In this approximation, the hydrogen bonded and free amino protons of **1** in DMSO are expected to resonate at $\delta_{\text{h.b.}} = 9.06 - \Delta I$ and $\delta_{\text{free}} = 6.57 - \Delta I$, where ΔI stands for the inductive effect. From these two values and the observed chemical shift (δ 7.50), the inductive effect is evaluated as $\Delta I = 0.32$ ppm. Since the inductive effect can be assumed to be solvent independent, the hydrogen bonded amino proton of **1** dissolved in



CDCl₃ is expected to resonate at δ 8.87. Therefore, the free amino proton of **1** in CDCl₃ would resonate at δ 4.33. The free amino proton of ethyl 3-(methylamino)crotonate in CDCl₃ was reported to resonate at δ 5.18 at -30°C .⁸⁾ This difference could be ascribed to the difference in intermolecular interactions under different temperatures as well as the difference between the ester and the amide. The DMSO-induced shift for the free amino proton would be calculated as 1.92 ppm.

The splitting of about 5 Hz in the N-CH₃ signal of

2 and the N-CH₃ signal of **3** suggests that the intramolecular hydrogen bond is not the RH₂C=N $\cdots$ HO-C type but the RH₂CNH $\cdots$ O=C type. Dudek *et al.* discussed a similar problem for some ¹⁵N enriched anilides.⁹⁾

Population Equilibrium between the two Isomers and the H/D Exchange of the Olefinic Proton. In this section the isomeric equilibrium of **2** will be discussed in some detail. The equilibrium is solvent dependent; the percentage of the *trans* isomer is negligible in CDCl₃ even after two days, 7% in acetone, 22% in methanol-*d*₄, and 32% in DMSO at the sample concentration of 100 mg/ml at room temperature, respectively.

In a CDCl₃ solution of **2**, the ¹H NMR spectrum consists of only the *cis*-signal; the *trans*-signals were not observed even after two days. In the case of a methanol-*d*₄ solution of **2**, on the other hand, the ¹H NMR spectrum recorded just after dissolution consists of almost only the *cis*-signals and then the *trans*-signals for the C-CH₃ and the N-CH₃ grew gradually on repeated recording at the expense of the *cis*-signals until the *cis-trans* equilibrium was attained after about 30 min.

These observations can be explained by assuming the *cis* conformation of **2** in the crystalline state. During the *cis-trans* equilibration in the methanol solution of **2** described above, the *cis*-signal for the olefinic proton disappeared.

In acetone solution of **2** the *cis-trans* equilibrium is established in one and a half hours. An addition of D₂O of about 10% v/v to this acetone solution induced the disappearance of the olefinic proton signal without any change in the intensity ratio of *trans/cis*. Each of the doublet signals due to the N-CH₃ protons for both the *cis* and *trans* forms collapsed more rapidly because of the remarkable reduction in the spin-spin coupling constant by the deuteration of the amino proton. However, the C-CH₃ signals did not show any change in either their signal positions or their relative intensities.

Almost the same behavior was observed for a DMSO solution of **2**, with the addition of D₂O (5% v/v). The H/D replacement at the olefinic site attained equilibrium in about 40 min (Fig. 1).

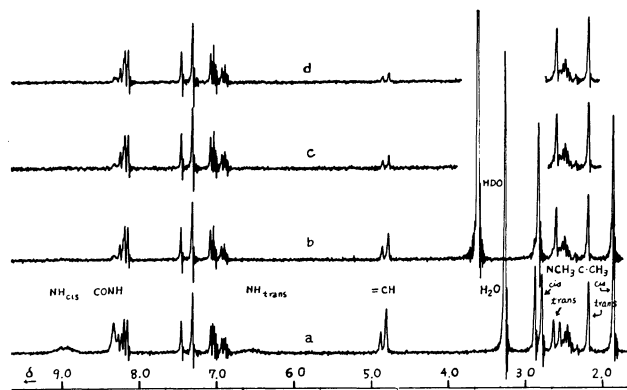
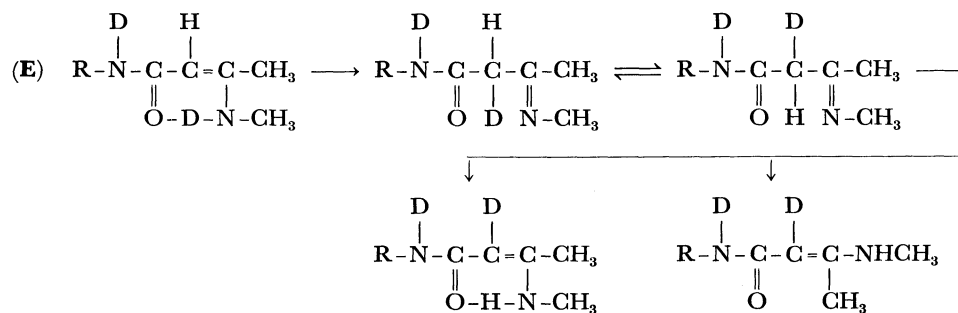


Fig. 1. The time dependent ¹H NMR spectrum of *N*-(2,5-dichlorophenyl)-3-(methylamino)crotonamide (**2**) in DMSO-D₂O (20:1) (*ca.* 80 mg/ml): a) no D₂O; b) just after the addition of D₂O; c) after 25 min; d) after 43 min.

From these observations, the H/D replacement at the olefinic site seems to proceed through a transient state which is also involved in the *cis*⇌*trans* isomerization process.

In order to clarify whether or not the *cis*-amino proton plays an important role in the H/D exchange, the ^1H NMR spectrum of **6** in DMSO- D_2O was recorded. The addition of D_2O of about 5% v/v to a DMSO solution of **6** induced a very slow reduction in the intensity of the olefinic proton signal and the amide one, without any changes in the other signals. The

plot of the log-value of the ratio, I/I_0 , of the intensity of the olefinic proton signal to the initial intensity *vs.* time yielded a straight line. This suggests that a unimolecular mechanism is operative in the H/D exchange at the olefinic site. The exchange rate is much slower for **6** than for **2**, suggesting that the olefinic proton exchange in **2** may occur mainly through enamine⇌imine tautomerization (*E*), but there must be some other mechanism concurrently contributing to the H/D exchange.



The deuteration of the vinyl proton of some enamino ketones was detected by means of the ^1H NMR spectroscopy; the imine tautomer has been proposed as an intermediate in the *cis-trans* isomerization.¹⁰⁾ The replacement of the olefinic proton by a deuterium was found to be rapid (<10 min) for *N,N*-dimethyl-3-(methylamino)crotonamide, but much slower for methyl 3-(1-pyrrolidinyl)crotonate, upon addition of D_2O to the DMSO solutions. These results are consistent with the above argument about the exchange mechanism.

The concentration dependence of the *cis-trans* equilibrium was tested for DMSO solutions of **2** and found to be negligible over the concentration range from 10 to 140 mg/ml, reflecting the relative importance of the intramolecular mechanism for the isomerization.

The temperature variation of the ^1H NMR spectrum of **2** in DMSO was found to be negligible for all protons except for the amide proton and the *trans* amino proton; their signals shifted upfield with raising the temperature, probably because of reduced intermolecular interactions both between the solute-solute and the solute-solvent molecules. The population ratio of the *trans* to the *cis* isomer seemed to be constant within the experimental accuracy over the temperature range from room temperature to about 90 °C. This fact may be ascribed to an occasional cancellation

between two counteracting factors: (i) increased thermal motions at the elevated temperatures would break the intramolecular hydrogen bond and shift the equilibrium to the *trans* preference, and (ii) weaker intermolecular interactions at elevated temperatures would destabilize the *trans* form.

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