Reactions of 3-Carboxyacryloylhydrazines III. (1,2) Correlation of Acid Dehydration Products with NMR Spectra

Michael Parnarouskis

Office of Research and Development, U.S. Coast Guard

and

*Harry Rubinstein**

Department of Chemistry, Lowell Technological Institute, Lowell, Massachusetts 01854

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The dehydration of 3-carboxyacryloylhydrazines in acid media has been shown to give either aminomaleimides or pyridazinones. Criteria, using nmr techniques, are presented for correlating the nmr spectra with product formation.

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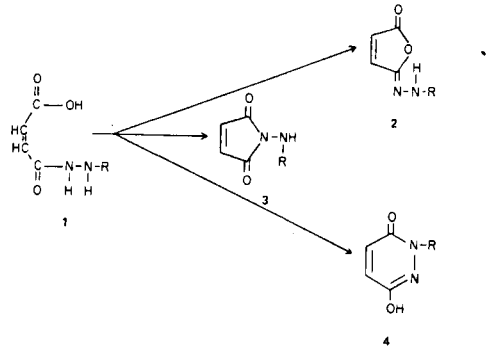
The use of ir and nmr analysis (1) has established that the dehydration of 3-carboxyacryloylhydrazines (**1**) with acetic anhydride or thionyl chloride produces the corresponding aminoisomaleimide (**2**) whereas treatment with acetic acid produces either the aminomaleimide (**3**) or the pyridazinone (**4**), with electron-withdrawing substituents (R) favoring maleimide formation and electron-donating groups favoring pyridazinone formation (1-19).

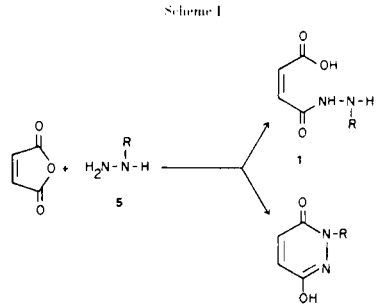


Examination of the nmr data of the 3-carboxyacryloylhydrazines (1,2) disclosed that the vinyl protons appear either as a singlet or an AB pair of doublets. Subsequent ring closure reactions of 1 appeared to give an interesting correlation in that the hydrazine 1 exhibiting singlets led to the formation of aminomaleimides (**3**), whereas the hydrazines exhibiting a pair of doublets generally gave pyridazinones (**4**). These initial structure reactivity correlations led us to believe that a method for predicting product formation based on nmr spectra could be developed.

Results

The reaction of hydrazines with maleic anhydride (Scheme I) gives the pyridazinone directly in those cases where R is a relatively strong electron-donating group (**5a-c**). With neutral or electron-withdrawing groups (**5d-l**) the corresponding 3-carboxyacryloylhydrazines (**1d-l**) are formed. The reactions of **1d-l** with acetic acid are summarized in Scheme II. The spectral properties of the 3-carboxyacryloylhydrazines and their derivatives are summarized in Table I.

Scheme I



a. R = CH_3
b. R = C_2H_5
c. R = o-$CH_3OC_6H_4$
d. R = CH_3CO
e. R = $C_6H_5SO_2$
f. R = 2,4-$(NO_2)_2C_6H_3$
g. R = 2-$NO_2C_6H_4$
h. R = 4-$NO_2C_6H_4$
i. R = 4-$MeOC_6H_4$
j. R = 3-$NO_2C_6H_4$
k. R = 4-t-butylC_6H_4
l. R = C_6H_5

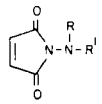
Discussion

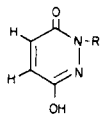
In addition to affecting product formation in the dehydration of 3-carboxyacryloylhydrazines (**1**), the substituents affect the nmr spectrum of the vinyl protons of the

Table I

Spectral Properties of 3-Carboxyacryloylhydrazines and Their Derivatives

R	R′	Ir (a) cm^{-1} CO Stretch	Nmr (b-e) Olefinic Proton	J Hz	Inner/Outer Intensities
		3-Carboxyacryloylhydrazines	$HOCCH = CHC-NH-N-R'$ (O, O, R)		
H	CH_3CO	1688	6.34 s		
H	$C_6H_5SO_2$	1694	6.31 s		
H	2,4-$(NO_2)_2C_6H_3$	1706	6.55 d, 6.41 d	13	12.7
H	2-$NO_2C_6H_4$	1705	6.52 d, 6.38 d	12	11.7
H	4-$NO_2C_6H_4$	1694	6.31 d, 6.17 d (f)	12	11.4
H	4-$CH_3OC_6H_4$	1710	6.43 d, 6.27 d	13	10.5
H	3-$NO_2C_6H_4$	1703	6.46 d, 6.30 d (f)	13	9.4
H	4-$(CH_3)_3CC_6H_4$	1695	6.49 d, 6.37 d	10	9.0
H	C_6H_5	1695	6.43 d, 6.27 d	12	8.9
CH_3	CH_3	1700	6.79 d, 6.09 d	10	1.7

R	R′	Ir cm^{-1} (a) CO Stretch	Nmr (b-e) Olefinic Protons	J Hz
		Aminomaleimides 		
CH_3	CH_3	1700	6.63 s	
H	CH_3CO	1725	7.17 s	
H	$C_6H_5SO_2$	1715	7.08 s	
H	2,4-$(NO_2)_2C_6H_3$	1715	7.30 s	
H	2-$NO_2C_6H_4$	1730, 1715	7.19 s	
H	4-$NO_2C_6H_4$	1707	7.19 s	

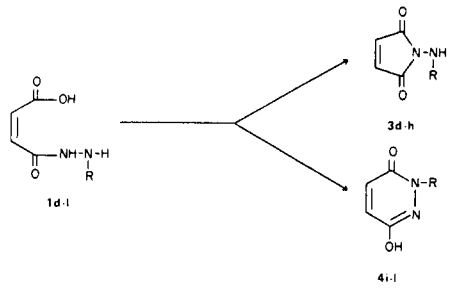
R	R′	Ir cm^{-1} (a) CO Stretch	Nmr (b-e) Olefinic Protons	J Hz
		Pyridazinones 		
H	4-$CH_3OC_6H_4$	1660	7.16 d, 6.97 d	11
H	3-$NO_2C_6H_4$	1662	7.28 d, 7.06 d	10.5
H	4-$(CH_3)_3CC_6H_4$	1662	7.24 d, 7.01 d	9
H	C_6H_5	1660	7.15 d, 6.95 d	9
H	2-$CH_3OC_6H_4$	1665	7.19 d, 6.93 d (g)	10
H	CH_3	1660	7.20 d, 7.04 d	10
H	C_2H_5	1655	7.20 d, 6.96 d	9

(a) Run as a nujol mull. (b) Parts per million. (c) All spectra were run in DMSO-d_6. (d) d = doublet, s = singlet. (e) All spectra run on P.E. R-24 unless indicated otherwise. (f) Run using P.E. R-20. (g) Run using Varian A-60.

open chain compound (1,2).

In the analysis of the proton nmr data of **1** we have found that we are able to predict *a priori* the correct reaction product by analysis of the absorptions of the vinyl protons. As shown in Table I strongly electron-withdrawing substituents give rise to singlets in the absorptions of the vinyl protons. In every case where the vinyl protons are singlets, the five membered ring product is formed. With less strongly electron-withdrawing substituents, pairs of doublets are seen in the vinyl protons. In this case either five or six membered ring products are formed. However, by analyzing the ratio of the line intensities of these doublets we can again predict the correct reaction product.

Scheme II



In this analysis we consider a singlet to be a limiting doublet (A_2) case in which the ratio of intensities of the inner line is infinitely greater than that of the outer line. The classical doublet (AX) case occurs when the intensities of the inner and outer lines are equal. Between these two extremes is the AB case, in which the inner and outer lines have unequal intensities (20-22). It is this AB case that is present in the nmr spectrum of the vinyl protons of **1**. According to Jackman, the ratio of the line intensities may be determined if the chemical shift of each of the peaks is known by using the following equation: (where 1 represents the chemical shift of the peak furthest downfield 2,

$$\frac{\text{intensity of inner line}}{\text{intensity of outer lines}} = \frac{1\text{-}4}{2\text{-}3}$$

the chemical shift of the next peak in the upfield direction, and so on).

Table I indicates the ratio of inner to outer line intensities of various substituted 3-carboxyacryloyl hydrazines. If a singlet or a doublet with ratio of greater than 11 is seen in the vinyl proton region, then the five membered ring is formed. If the ratio of the line intensities is less than 11, then the six membered ring is formed.

From such strictly empirical analysis, we are able to predict the correct reaction product for the dehydration of **1** if the nmr spectrum is known. The cause of the formation of singlets or pairs of doublets in the vinyl protons remains obscure at this time. One possibility is that the nature of the substituent group is transmitted through the bonds and affects the vinyl protons. Yet this would be a rather long range interaction. Another possibility is that the substituent group causes certain preferred orientations to be taken by the molecule. These conformations may orient the substituent group in such a manner that it now can affect the vinyl protons by a through-space mechanism. Since the substituent group alone determines the final product, its possible orienting effect on the molecule's conformation may be a major factor in the determination of the reaction product instead of the thermodynamics of the final products. While such interpretations remain highly speculative, we do nonetheless have a highly effective empirical procedure for determining the final reaction product of this particular reaction. Presently more detailed studies on this reaction system are being conducted with ^{13}C nmr in order to elucidate the molecular basis for these empirical observations. It is hoped that this kind of relationship is general and that it can be extended to other systems.

EXPERIMENTAL

All infrared spectra were obtained on Beckman IR-10 and Perkin-Elmer 727 instruments using sodium chloride cells and Nujol mulls. The nmr spectra were obtained on Perkin-Elmer R-20, R-24 and Varian A-60 spectrometers. Mass spectra were recorded with a DuPont 21-491 mass spectrometer. Melting points were obtained using a Thomas-Hoover melting point apparatus and are corrected.

Hydrazines.

All hydrazines were purchased commercially or prepared by previously described procedures (1,2,23).

'*p*-*t*-Butylphenylhydrazine.

This hydrazine was prepared by the general method reported by Hunsberger (23). Recrystallization of the yellow solid gave 1.99 g. of the hydrazine, m.p. 74.5-75.5°.

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.14; H, 9.82; N, 17.06. Found: C, 73.14; H, 9.85; N, 17.06.

3-Carboxyacryloylhydrazines (**1**).

The 3-carboxyacryloylhydrazines were prepared by the methods reported in the literature: 1,1-dimethyl-2-(3-carboxyacryloyl)-hydrazine (24), 1-acetyl-2-(3-carboxyacryloyl)hydrazine (3), 1-benzenesulfonyl-2-(3-carboxyacryloyl)hydrazine (3), 1-(2,4-dinitrophenyl)-2-(3-carboxyacryloyl)hydrazine (4), 1-(2-nitrophenyl)-2-(3-carboxyacryloyl)hydrazine (10), 1-(4-nitrophenyl)-2-(3-carboxyacryloyl)hydrazine (10), 1-(3-nitrophenyl)-2-(3-carboxyacryloyl)-hydrazine (10), 1-phenyl-2-(3-carboxyacryloyl)hydrazine (25), 1,2-bis-(3-carboxyacryloyl)hydrazine (3).

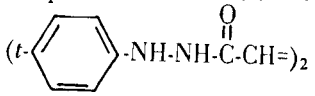
1-(4-Methoxyphenyl)-2-(3-carboxyacryloyl)hydrazine (**1i**).

Glacial acetic acid (25 ml.) and maleic anhydride (0.71 g.) were mixed and 1.00 g. of *p*-methoxyphenylhydrazine was added to the mixture. After stirring at room temperature, for 80 minutes, the solvent was removed *in vacuo* leaving a dark orange oil. Cooling to 0°, filtration of the resulting solid and recrystallization from ethanol gave 0.30 g. of **1-i**, m.p. 104.0-105.5°.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 55.92; H, 5.12; N, 11.86. Found: C, 56.16; H, 5.07; N, 11.70.

1-(4-*t*-Butylphenyl)-2-(3-carboxyacryloyl)hydrazine (**1-k**).

Glacial acetic acid (25 ml.) and maleic anhydride (0.65 g.) were mixed and 1.09 g. of 4-*t*-butylphenylhydrazine was added to the mixture. After stirring at room temperature for 3 hours, the solvent was removed *in vacuo* giving a red oil. The solid formed upon cooling was recrystallized from benzene to give 1.43 g. of **1-l**, m.p. 111.5-113.0°; mass spectrum m/e (relative intensity): 149 (37), 164 (12), 229 (100), 224 (31), 262 (M^+, 1) and minor peaks at 393 and 408. The mass spectrum indicates that this sample was contaminated with a small amount of the dimer



Aminomaleimides (**3**).

The aminomaleimides were prepared by methods reported in the literature: *N,N*-dimethylaminomaleimide (1), *N*-acetylaminomaleimide (1,3,6), *N*-benzenesulfonylaminomaleimide (2,4), *N*-(2,4-dinitrophenyl)aminomaleimide (1,4), *N*-(2-nitrophenyl)aminomaleimide (2), and *N*-(4-nitrophenyl)aminomaleimide (2).

Pyridazinones (**4**).

The pyridazinones were prepared by methods reported in the literature: 2-(3-nitrophenyl)-6-hydroxy-3(2*H*)pyridazinone (2), 2-phenyl-6-hydroxy-3(2*H*)pyridazinone (1), 2-methyl-6-hydroxy-3-(2*H*)pyridazinone (1) and 2-ethyl-6-hydroxy-3(2*H*)pyridazinone (1).

2-(4-Methoxyphenyl)-6-hydroxy-3(2*H*)pyridazinone (**4j**).

Glacial acetic acid (25 ml.) and maleic anhydride (0.71 g.) were mixed and 1.00 g. of *p*-methoxyphenylhydrazine was added to the mixture. Stirring at room temperature for 80 minutes followed by solvent removal *in vacuo* produced a dark orange oil. The solid obtained upon cooling was recrystallized from ethanol to give 0.20 of **4i**, m.p. 241.5-243.0°.

This pyridazinone was also obtained by treating a 0.50 g. portion of the crude solid with 15 ml. of refluxing acetic acid. Upon cooling a light beige solid formed, was filtered and recrystallized from ethanol to give 0.30 g. of **4j**, m.p. 241.5-242.0°.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.35; H, 4.55; N, 12.62.

2-(4-*t*-Butylphenyl)-6-hydroxy-3(2*H*)pyridazinone (**4k**).

Glacial acetic acid (12 ml.) and 0.32 g. of 1-(4-*t*-butylphenyl)-2-(3-carboxyacryloyl)hydrazine were mixed and heated at reflux for 4 hours. Removal of the solvent *in vacuo* produced a yellow solid. Several washings with benzene removed the yellow coloration and gave 0.26 g. of cream colored **4l**, m.p. 285-286°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.85; H, 6.56; N, 11.48. Found: C, 68.91; H, 6.79; N, 11.43.

2-(2-Methoxyphenyl)-6-hydroxy-3(2*H*)pyridazinone.

Glacial acetic acid (25 ml.) and 0.71 g. of maleic anhydride were mixed and 1.00 g. of *o*-methoxyphenylhydrazine was added to the mixture. After stirring at room temperature for 3.5 hours the solvent was removed to give a red-brown oil. Washing with ethanol produced a yellow solid which upon recrystallization from ethanol gave 1.47 g. of the desired product, m.p. 230.0-231.0°.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.43; H, 4.68; N, 12.85.

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