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Vinylogous Systems. 4. Mass Spectra of Vinylogous Ureas and Ureides[1]

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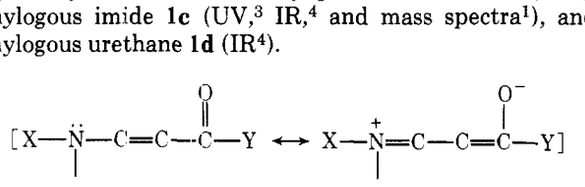
The mass spectra of 16 acyclic and isocyclic vinylogous ureas **1a** and 18 acyclic, isocyclic, and heterocyclic vinylogous ureides **1b** are reported and discussed. Preferred fragmentation pathways for both **1a** and **1b** are dominated by cleavage at the ends of the conjugated system, with the enaminone core (N—C=C—C=O) being retained within either a charged daughter ion or an ejected neutral fragment. Such decomposition usually furnishes the base peak in the mass spectrum, and is very often a primary step as well.

In continuation of our studies of elongated functional groups in which nitrogen is the electron donor and carbonyl the acceptor, we wish to report the syntheses and mass spectra of some vinylogous ureas **1a,** β-amino α,β-unsaturated amides, and vinylogous ureides **1b,** β-amido α,β-unsaturated amides. Our main goal was to provide a further evidence of the importance of resonance stabilization within the enaminone core of **1**. The competing cross conjugation which exists in **1a–d** is apparently minimal, as shown by spectral results for **1a** (UV[2]), vinylogous imide **1c** (UV,[3] IR,[4] and mass spectra[1]), and vinylogous urethane **1d** (IR[4]).



1a, X = R; Y = NR_2
b, X = RC(O); Y = NR_2
c, X = RC(O); Y = R
d, X = R; Y = OR
e, X = R; Y = R

Electron impact-induced fragmentations of vinylogous amides **1e**[5–7] and imides **1c**[1,8] have been reported, and distinct analogies between the behavior of **1a** and **1e,** and of **1b** and **1c** also, were to be expected. Thus, the formation of a relatively stable β-amino α,β-unsaturated acylium ion from **1a** would be reasonable, although we were unsure whether oxazolium and/or isoxazolium daughter ions would be as important for **1b** as they are in the fragmentation of **1c**. Compounds prepared for the present investigation are collected in Tables I and II.

Experimental Section

Melting and boiling points are uncorrected. Common reagents were freshly distilled (amines from BaO) under a dry atmosphere. Commercial samples of anhydrous alcohol, acrylic anhydride (Aldrich Chemical Co.), and reagent grade acetic anhydride were used. Propiolamide (Terro-Marine Bioresearch) was sublimed under vacuum. Reaction progress and product purity were monitored by thin-layer chromatography. Preparative chromatography was carried out on columns dry packed with Florisil. Solvents were evaporated under reduced pressure on a rotary evaporator with a bath of suitable temperature. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Mass spectra were obtained on either an A.E.I. MS-30 or MS-902 mass spectrometer using a direct-insertion probe under the following conditions: electron voltage 70 eV, ion source temperature 200–250 °C, probe temperature 75–230 °C.[9] Accurate mass measurements were also obtained for compounds **2e, 2h, 2k, 8a–c, 12a, 12n,** and **19a,** as well as for selected peaks of compounds **2d** and **19d.** Infrared spectra were recorded on a Beckman IR-8. Deuteration of compound **12f** was carried out in $CDCl_3$ by shaking with D_2O for 6 h, NMR measurements showing no evidence for exchange except at NH, where it was complete.

Preparation of Compounds. A number of the compounds were synthesized according to the literature, including **2a,**[10] **2b,**[11] **2c,**[12] **2h,**[13] **8d,**[14] **12a,**[15] **12h,**[15] **19a,**[16] and **19b.**[16] Such procedures were also used to prepare many of the new compounds reported in Tables I and II. The following experimental directions are illustrative.

β-Amino-*N,N*-pentamethylenecrotonamide (2d). A solution of piperidine (7.72 g, 0.0907 mol) in dry ether (30 mL) was added dropwise under a dry atomosphere to a stirred solution of diketene (7.63 g, 0.0907 mol) in dry ether (30 mL). The reaction solution was refluxed for 45 min, cooled to ice temperature, and then saturated with NH_3 for 4 h. Removal of the ether left a thick oil which did not solidify in the refrigerator overnight. Using Becker's[17] method, a catalytic amount of NH_4NO_3 was added to the thick liquid, and the mixture was saturated with NH_3 for 5 h at 80 °C. Cooling gave a crystalline mass, which upon recrystallization from ethyl acetate and chromatography (ether) of the mother liquor yielded 12.59 g (83%) of **2d,** mp 78–79 °C. Recrystallization from cyclohexane–ether and subsequent sublimation at 68 °C (0.1 mm) gave pure **2d,** mp 79–80 °C.

2-Aminocyclopentene-1-*N*-ethylcarboxamide (2e). A solution of 2-oxocyclopentane-1-*N*-ethylcarboxamide[18] [4.10 g, 0.0264 mol, bp 102–107 °C (0.5 mm), mp 83–84 °C, lit.[19] mp 84 °C] in absolute ethanol (50 mL) was saturated with NH_3 for 2 h on each of five suc-

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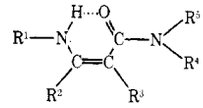
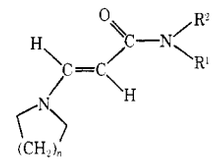
Table I. Vinylogous Ureas



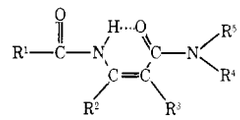
Compd[a]	Registry no.	R^1	R^2	R^3	R^4	R^5	Mp, °C	Yield, %	Recrystn solvent
2a	64163-94-6	H	Me	H	H	H	97-98[b]	82	$CHCl_3$
2b	64163-95-7	H	Me	H	H	Me_2CH	140-142[c]	62	MeCN
2c	59846-47-8	H	Me	H	H	Ph	143-144[d]	76	EtOAc
2d	64163-93-5	H	Me	H	$-(CH_2)_5-$		79-80	83	C_6H_{12}-Et_2O
2e	64163-92-4	H	$-(CH_2)_3-$		H	Et	125-126	70	EtOAc
2f	49786-30-3	H	$-(CH_2)_3-$		H	Ph	200-201 dec[e]	81	MeCN
2g	59846-79-6	H	$-(CH_2)_4-$		H	Ph	108.5-110	92	
2h	64163-96-8	Me_2CH	Me	H	H	Me_2CH	93-95[f]	82	C_6H_{12}
2i	64163-97-9	Me_2CH	$-(CH_2)_3-$		H	Et	111-112	80	C_6H_{12}
2j	64163-98-0	Me_2CH	$-(CH_2)_3-$		H	Ph	121-122	81	$CHCl_3$-Et_2O
2k	64163-99-1	Me_2CH	$-(CH_2)_4-$		H	Et	108-109	84	C_6H_{12}



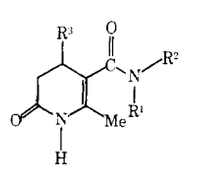
Compd[g]	Registry no.	n	R^1	R^2	Mp, °C	Yield, %	Recrystn solvent
8a	64164-00-7	2	H	H	202-204 dec	97	MeCN
8b	64164-01-8	3	H	H	147-148	97	EtOAc-95% EtOH
8c	64164-02-9	2	$-(CH_2)_4-$		69-72	98	Et_2O-C_6H_{14}
8d	64164-03-0	3	$-(CH_2)_5-$		99-100[h]	61	Et_2O

[a] Satisfactory elemental analysis were obtained for new compounds 2d-g and 2i-k. [b] Lit.[10] mp 98-100 °C. [c] Lit.[11] mp 144-145 °C. [d] Lit.[12] mp 145 °C. [e] Lit.[20] mp 203-205 °C. [f] Lit.[13] mp 90-93 °C. [g] Molecular weight values for new compounds8a-c from exact mass measurements were accurate to within 10 ppm. [h] Lit.[14] mp 99-100 °C.

Table II. Vinylogous Ureides



Compd[a]	Registry no.	R^1	R^2	R^3	R^4	R^5	Mp, °C	Yield, %	Recrystn solvent
12a	64164-04-1	Me	Me	H	H	H	180-181[b]	44	EtOAc
12b	64164-05-2	Me	Me	H	H	Me_2CH	116-118	73	EtOAc-C_6H_{12}
12c	64164-06-3	Me	Me	H	H	Ph	148-149	73	EtOH-H_2O
12d	64163-75-3	Me	$-(CH_2)_3-$		H	Et	110-111	73	H_2O-MeOH
12e	64163-76-4	Me	$-(CH_2)_3-$		H	Ph	101-105	88	MeOH
12f	64163-77-5	Me	$-(CH_2)_4-$		H	Et	103-105	63	EtOAc-C_6H_{12}
12g	64163-78-6	Me	$-(CH_2)_4-$		H	Ph	189-190	68	MeCN
12h	64163-79-7	Ph	Me	H	H	H	148-149[c]	38	MeCN
12i	64163-80-0	Ph	Me	H	H	Me_2CH	148-149	70	EtOAc
12j	64163-81-1	Ph	Me	H	Et	Et	81.5-82.5	51	MeOH
12k	64163-82-2	Ph	Me	H	$-(CH_2)_5-$		110-110.5	65	Et_2O
12l	64163-83-3	Ph	$-(CH_2)_3-$		H	Et	124-125	51	C_6H_{12}-EtOAc
12m	64163-84-4	Ph	$-(CH_2)_4-$		H	Et	143-144	68	EtOAc
12n	64163-85-5	Ph	$-(CH_2)_4-$		H	Ph	255-256 dec	64	$HCONMe_2$



Compd[a]	Registry no.	R^1	R^2	R^3	Mp, °C	Yield, %	Recrystn solvent
19a	63897-27-8	H	H	H	245-246 dec[d]	44	95% EtOH
19b	63897-29-0	H	H	Me	203-204[e]	60	95% EtOH
19c	64163-86-6	H	Me_2CH	H	193-194	35	95% EtOH-H_2O
19d	64163-87-7	$-(CH_2)_5-$		H	117-118.5	47	Me_2CO

[a] Satisfactory elemental analysis were obtained for all new compounds listed in the table. [b] Lit.[15] mp 176-177 °C. [c] Lit.[15] mp 147-148 °C. [d] Lit.[16] mp 241-242 °C dec. [e] Lit.[16] mp 199-200 °C dec.

cessive days. Removal of solvent left a white solid which was redissolved in fresh anhydrous ethanol (30 mL) prior to treatment with NH_3 as above for 2 more days. Freed of solvent, the crude product was recrystallized from ethyl acetate to give 2.86 g (70%) of **2e** as fine white needles, mp 123–126 °C. Vacuum sublimation at 115 °C (0.1 mm) gave the analytical sample, mp 125–126 °C.

2-Isopropylaminocyclopentene-1-*N*-ethylcarboxamide (2i). A mixture of 2-oxocyclopentane-1-*N*-ethylcarboxamide[18] (3.10 g, 0.0200 mol) and isopropylamine (1.77 g, 0.0300 mol) in anhydrous ether (80 mL) was refluxed under a dry nitrogen atmosphere until a light-yellow solution formed (2 days). Removal of solvent followed by recrystallization from cyclohexane yielded 3.12 g (80%) of white needles of **2i**, mp 109–111 °C. Vacuum sublimation at 100 °C (0.1 mm) provided an analytical sample, mp 111–112 °C.

β-Pyrrolidinoacrylamide (8a). A solution of pyrrolidine (1.14 g, 0.0160 mol) in anhydrous ether (15 mL) was added dropwise to a stirred solution of propiolamide (1.00 g, 0.0145 mol, mp 58–60 °C) in ether (15 mL) under dry nitrogen. When approximately one-third of the amine solution has been added, a fine white precipitate formed. After 4 days, 1.98 g (97%) of **8a** was collected as a cream-colored powder, mp 202–204 °C dec (preheated bath). Recrystallization from acetonitrile gave the analytical sample, mp 206–207 °C dec.

β-Acetylamino-*N*-isopropylcrotonamide (12b). A mixture of **2b** (5.68 g, 0.0400 mol) and acetic anhydride (24.5 g, 0.240 mol) was heated to boiling under a dry atmosphere and then allowed to stand at room temperature overnight. Acetic acid and excess anhydride were distilled off under reduced pressure (10 mm) to leave a crystalline residue. Recrystallization of the product from ethyl acetate–cyclohexane yielded white needles (5.35 g, 73%) of **12b**, mp 116–118 °C.

β-Benzoylamino-*N*-isopropylcrotonamide (12i). Benzoyl chloride (4.22 g, 0.0300 mol) was added dropwise to an ice-cold solution of **2b** (4.26 g, 0.0300 mol) in pyridine (20 mL). After standing at room temperature overnight, the reaction mixture was poured into ice water (150 mL). Faintly yellow **12i** (5.15 g, 70%) was collected and, when recrystallized from ethyl acetate, formed white needles, mp 148–149 °C.

6-Methyl-5-pentamethylenecarbamoyl-3,4-dihydro-2-pyridone (19d). A solution of acrylic anhydride (5.10 g, 0.0400 mol) and **2d** (6.73 g, 0.0400 mol) in $CHCl_3$ (100 mL) was refluxed for 1 h. Solvent removal followed by addition of water (100 mL) yielded an aqueous solution. Four extractions of the solution with 100-mL portions of ethyl acetate, followed by removal of organic solvent, provided a gummy residue which soon solidified. Crystallization from acetone led to 4.19 g (47%) of **19d** as white platelets, mp 117–118.5 °C.

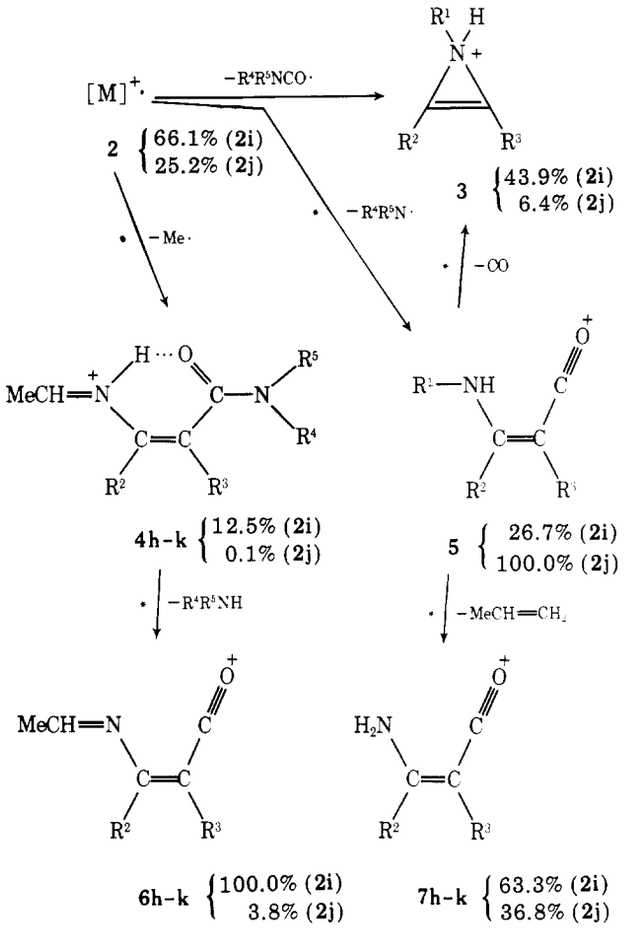
Results and Discussion

Structural assignments for all new compounds are based upon analogy to synthetic procedures and infrared data (1550–1750-cm^{-1} region) in the literature. Infrared assignments for compounds in our collection[21] compare favorably to published results for β-keto amides,[22] vinylogous ureas,[2,14,23] and vinylogous ureides.[16] Conformations and configurations of compounds as shown in the tables are tentative in many instances, and questions of relative stereochemical stabilities will be dealt with in future publications. Fragmentation pathways proposed in Schemes I–IV are supported by appropriate metastable peaks and by selective high-resolution mass measurements, although ion intensities are given for selected compounds only. (See paragraph on supplementary material at the end of the paper.)

Vinylogous Ureas. We turn first to an examination of principal ions in the mass spectra of compounds **2a–k** (Table I) for which the cis configuration is favored by chelation, if not indeed required by a cycloalkene unit. The fragmentation pattern of molecular ion **2** (Scheme I) is strongly influenced by bond cleavage at the carbonyl carbon (as is the case with vinylogous amides[5–7]), the groups (R^1, R^4, and R^5) attached to both nitrogens strongly influencing the relative abundances of the charged species produced upon electron impact.

Thus, the resonance-stabilized β-amino α,β-unsaturated acylium ion **5** shown in Scheme I is the base peak in most instances. Substituent effects are readily apparent, and the exceptional intensity of base peak **5j** (25% of total ion current for m/e >39) is attributed to both the electron-donating power of the isopropyl group (R^1) and to the stability of the neutral

Scheme I



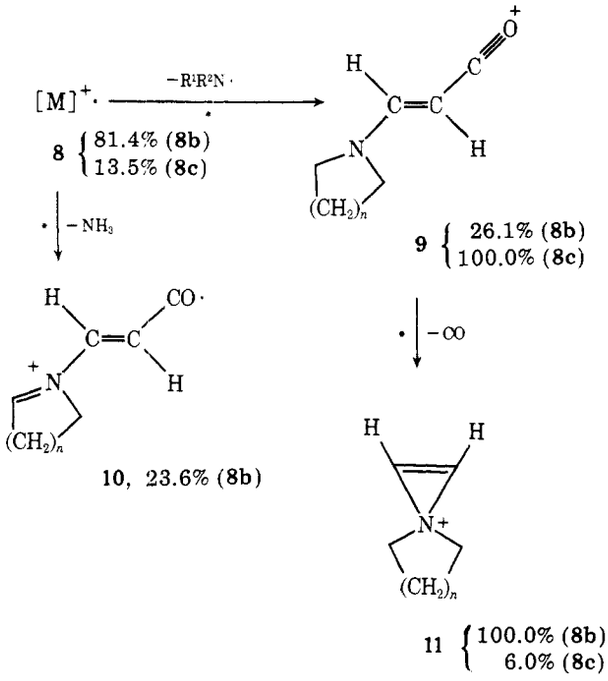
fragment (PhNH·) being expelled during **2j** → **5j**. Loss of propylene from cation **5** yields the abundant acylium ion **7**, whose structure and resonance stabilization is comparable to its progenitor. Another highly conjugated acylium ion, cation **6**, is formed by primary fission of a methyl radical (**2** → **4**), followed by ejection of an amine molecule. As expected, cation **6i** is particularly favored because the competing pathway, carbonyl carbon–nitrogen bond cleavage (**2i** → **5i**), produces the relatively unstable primary amine radical EtNH·.

The mass spectra of trans[24] vinylogous ureas **8a–d** (Table I) were examined next, and the basic fragmentation pattern (see Scheme II) is clearly related to that of Scheme I, as shown in the relative importance of acylium ion **9**. Primary fission adjacent to the enamino nitrogen atom also occurs, our formulation of radical cation **10** being supported by metastable peaks, accurate mass measurements for **8a** and **8b**, and fragmentation modes for vinylogous amides of comparable structures.[5–7] Whereas primary loss of a hydroxyl radical is very important in the mass spectra of appropriate vinylogous amides derived from piperidine,[5,7] we find that both **8a** and **8b** prefer to oust a neutral ammonia molecule.

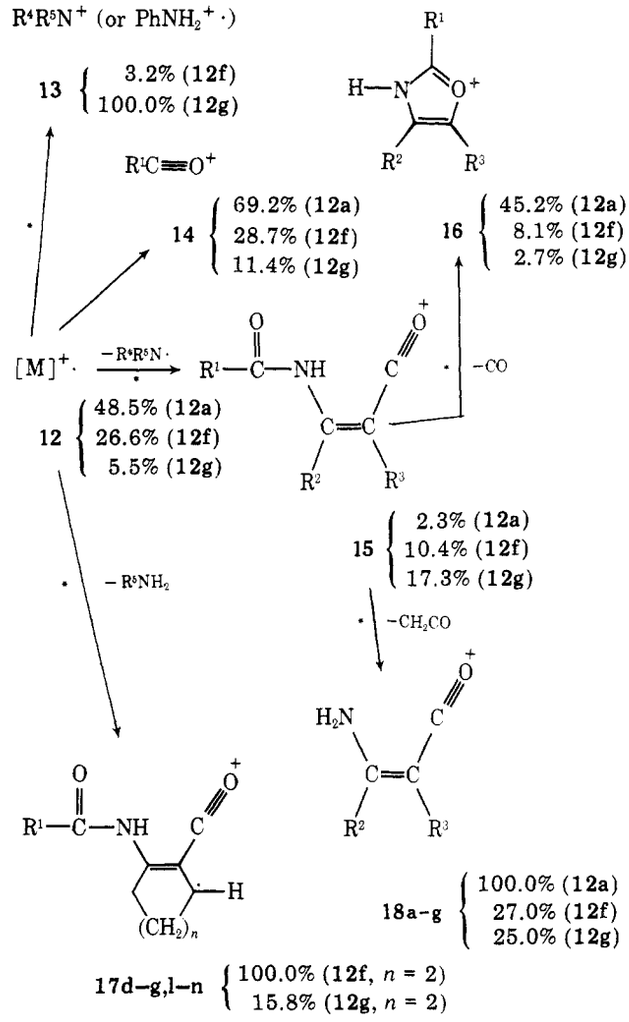
Vinylogous Ureides. Interpretation of mass spectral information for cis compounds **12a–n**[25] (Table II) is reasonably straightforward, and is outlined in Scheme III. The presence of the acyl group R^1CO evidently destabilizes fragment ion **15** (as compared to **5** in Scheme I), and the initial decomposition of vinylogous ureides **12a–n** produces a variety of important charged fragments. Thus, the base peak in the spectra of **12c**, **12e**, and **12g** is the aniline radical cation **13**; for compounds **12h–n** it is the benzoyl cation **14**. Oxazolinium ion **16** is of moderate importance, its abundance ranging from 45.2 (**12a**) to 0.3% (**12c**) of the appropriate base peak.

None of these pathways is particularly favored in the case

Scheme II



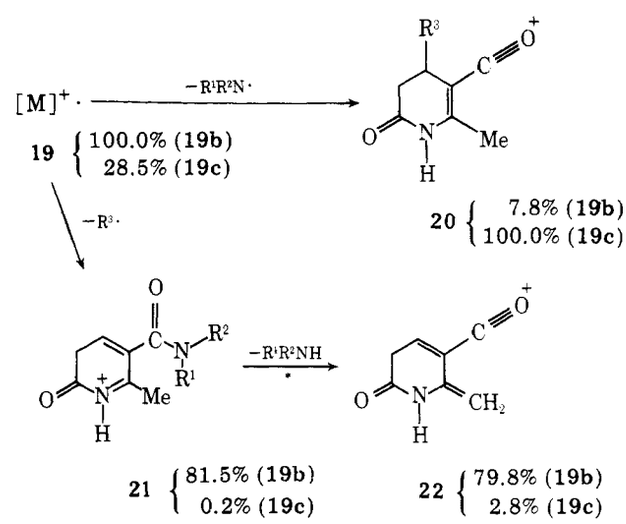
Scheme III



of **12d** and **12f**. In each instance, the molecular ion expels ethylamine, affording radical cation **17** as the base peak. Removal of an allylic hydrogen atom occurs twice as often at carbon than it does at nitrogen, and the dominant path is depicted in Scheme III. This was established when mass spectra of *N*-deuterated vinylogous ureide **12f**-d_2 and the unlabeled compound were compared.[26] Evidently chelation in **12f**[27] is not strong enough to direct attack exclusively at the ring methylene.

Finally, four heterocyclic trans compounds (Table II) were studied. The decomposition mechanism outlined in Scheme IV for **19a–d** parallels the results of an earlier investigation[8] of 5-acetyl-6-methyl-3,5-dihydro-2-pyridone and some substituted 3,4-dihydro-5-carbethoxy-2-pyridones. Loss of $Me_2CHNH\cdot$ rather than the poorer leaving group $NH_2\cdot$ accounts for the greater abundance of cation **20c** compared to **20b**. Allylic cleavage competes, particularly in **19b** → **21b**, where a methyl radical (rather than H·) is lost. Subsequent expulsion of ammonia generates even electron ion **22b**.

Scheme IV



Summary

The electron impact-induced fragmentations of both vinylogous ureas and ureides are dominated by cleavage at the ends of the conjugated system. The enaminone core (N—C=C—C=O), a structural unit which enjoys considerable resonance stabilization, is retained within either a charged daughter ion or an ejected neutral fragment. Such decomposition usually furnishes the base peak in the mass spectrum, and is very often a primary step as well.

Thus, a β-amino α,β-unsaturated acylium ion forms readily from vinylogous ureas, unless expulsion of the relatively unstable neutral fragments $NH_2\cdot$ and EtNH· (which prefer to leave as NH_3 and $EtNH_2$) is required. Vinylogous ureides behave much like vinylogous imides, loss of ketene from *N*-acetyl compounds and formation of $PhCO^+$ from *N*-benzoyl compounds being favorable fragmentation steps. Oxazolium ions are of lesser importance in the mass spectra of vinylogous ureides compared to the imides.

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Registry No.—piperidine, 110-89-4; diketene, 674-82-8; 2-oxocyclopentane-1-*N*-ethycarboxamide, 64163-88-8; isopropylamine, 75-31-0; pyrrolidine, 123-75-1; propiolamide, 7341-96-0; acetic an-

hydride, 108-24-7; benzoyl chloride, 98-88-4; acrylic anhydride, 2051-76-5; 2-oxocyclopentane-1-carboxanilide, 4874-65-1; 2-oxocyclohexane-1-carboxanilide, 51089-06-6; 2-oxocyclohexane-1-*N*-ethylcarboxanilide, 64163-89-9; 1-*N*-morpholinocyclohexene, 670-80-4; ethyl isocyanate, 109-90-0; 3-chloropropenoyl chloride, 3721-36-6; 2-aminocyclohexene-1-*N*-ethylcarboxamide, 64163-90-2; *N,N*-diethylacetoacetamide, 2235-46-3; β-amino-*N,N*-diethylcrotonamide, 64163-91-3.

Supplementary Material Available. Further synthetic details (7 pages) plus amplified mass spectral data and interpretation (16 pages). Ordering information is given on any current masthead page.

References and Notes

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(24) A trans–cis structure for all four compounds is supported by previous authors,[2,14] and is expected since the cis configuration would not be chelated and is sterically hindered as well.
(25) Acylation of the enamino nitrogen of a cis vinylogous urea should enhance existing chelation when possible in the vinylogous ureide product.
(26) Some reversion of the original deuteration of **12f** occurred in the mass spectrometer and could not be prevented even by deuterating the probe. Correcting for natural isotopic abundances, the actual molecular ion mass ratios for "dideuterio" **12f** were 0.08:0.52:1.00 for *m/e* values 210 (**12f**), 211 (**12f-d_1**), and 212 (**12f-d_2**), respectively. Observed mass ratios of 1.00:1.18:0.13 (corrected as above) for *m/e* values 165 (**17f**), 166 (**15f** and **17f-d_1**), and 167 (**15f-d_1**) respectively, agree quite well with those calculated, assuming the deuterium atoms in a sample of **12f-d_1** are divided equally between the two nitrogen atoms, and only a statistical preference exists between N–H and C–H cleavage when ethylamine is ejected by molecular ion **12f.**
(27) No irregularities are apparent in the 100-MHZ NMR spectrum of **12f** in $CDCl_3$, and it includes signals at δ 12.7 (s, 1 H, chelated) and 6.10 (t, J = 7 Hz, 1 H).

A New Reaction of Amino Acids: Conversion to Benzoxazoles

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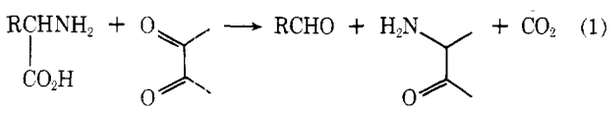
Reaction of α-amino acids with *o*-benzoquinones of type **3** is unique in that the expected Strecker degradation does not occur. We have observed that a decarboxylative condensation reaction takes place affording benzoxazoles. The new reaction appears to be general for α-amino acids and specific for quinones of type **3**.

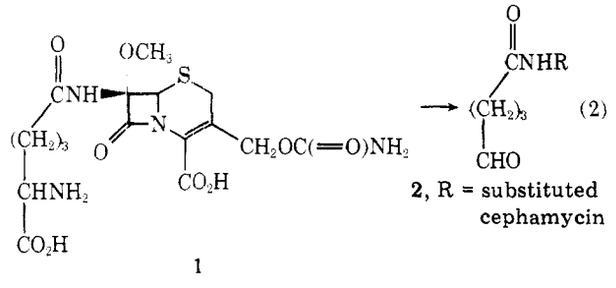
It has been reported that several diones (including *o*-quinones) oxidize α-amino acids to aldehydes while being reduced to α-amino carbonyls[1] (see eq 1). This reaction has been



(1)

termed[1] the "Strecker degradation" in honor of this discoverer.[2]

We were interested in oxidizing the antibiotic α-amino acid **1** to the corresponding aldehyde **2** (eq 2). The Strecker degradation appeared to be the most suitable method since the complexity and sensitivity of **1** warrants mild handling. Furthermore, the use of commercially available 3,5-di-*tert*-butylbzoquinone (**3**) appeared to be the most suitable dione since the steric bulk of the *tert*-butyl groups would prevent undesirable 1,4 addition of the amino acid, and the formation of an aromatic moiety (the reduced α-amino carbonyl now being an *o*-aminophenol) would provide a driving force for the oxidation–reduction process.



1 **2**, R = substituted cephamycin (2)

Results and Discussion

Amino acid **1** required 2 equiv of quinone **3** for complete reaction. However, instead of isolating the desired aldehyde **2** and the *o*-aminophenol, the benzoxazole **4** and catechol **5** were obtained (eq 3).

This oxidation reaction appears to be general for α-amino acids since alanine, α-aminoadipic acid, and phenylalanine all yielded the corresponding benzoxazoles[3] when treated with 2 equiv of **3**. The reaction with phenylalanine is complicated by a few minor side reactions; however, fair to good yields of pure products may be isolated by chromatography (see Experimental Section).

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