Carbon-13 NMR Characterisation of Carboxyl Derivatives of 1-Ureidopyrroles (1)

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1-Ureido-5-methyl-2,3-dicarbethoxypyrrole under acidic conditions afforded different partially hydrolyzed or decarboxylated products. It has been possible to characterize two isomeric monoethyl esters of dicarboxylic acids of 1-ureidopyrroles by proton gated decoupled carbon-13 nmr spectra on the basis of multiplicities of the carbonyl carbons resonances.

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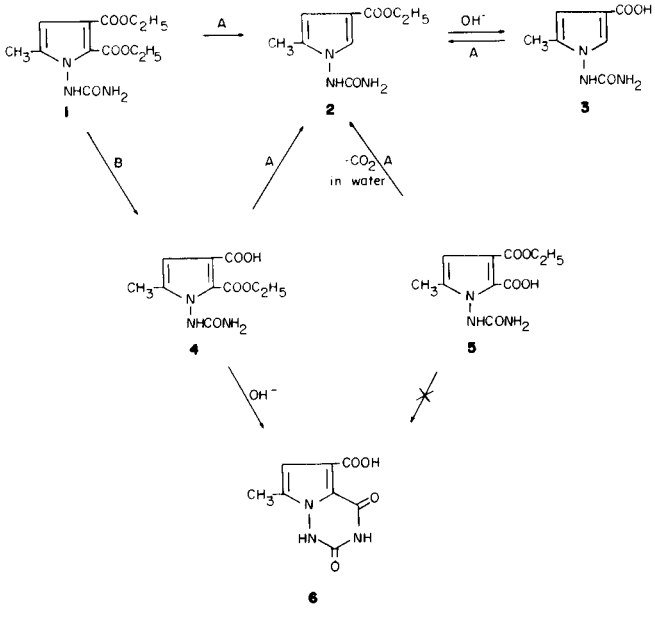
Recently (2), we have described the cyclization in alkaline conditions of carboxyl derivatives of 1-ureidopyrroles giving pyrrolo[2,1-*f*]-1,2,4-triazine derivatives. In this paper we report the chemical behaviour of the same 1-ureidopyrroles under acidic conditions. According to the concentration of the acid solutions employed (hydrochloric acid in ethanol), the 1-ureido-5-methyl-2,3-dicarbethoxypyrrole (**1**) affords different partially hydrolyzed or decarboxylated products. Cyclized compounds are not obtained, according to the reduced nucleophilic character of the terminal nitrogen of the ureido group.

In ethanolic solution saturated with hydrochloric acid, the compound **1** (Scheme I) undergoes hydrolysis and decarboxylation of the -COOEt group at C-2, as evidenced by the proton nmr spectrum of the resulting ethyl 1-ureido-5-methylpyrrole 3-carboxylate (**2**). In fact, it shows a doublet at δ 7.20 with J = 2.0 Hz, characteristic of the coupling constant of the hydrogens at C-2 and C-4 of the pyrrole ring (Table 1). By alkaline hydrolysis, the compound **2** gives the corresponding 3-carboxylic acid (**3**), which in turn converts back to **2** by ethanol saturated with hydrochloric acid.

Scheme I

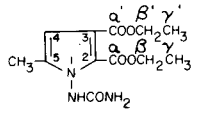


In contrast, in a diluted solution of hydrochloric acid in aqueous ethanol, **1** undergoes hydrolysis at only one -COOEt group affording **4**. This compound is an isomer of another esterified monoethyl 2,3-dicarboxylic derivative **5**, formed in the course of the preparation of **1** (2), separated in low yields from the mixture of reaction products and not described in our preceding paper. In a concentrated solution of hydrochloric acid in ethanol, both **4** and **5** give **2**. Furthermore, **5** gives **2** by evolution of carbon dioxide in aqueous solution.

It is not possible to individually characterize the two isomeric monoethyl esters by proton nmr spectra, because no reliable differences of the shifts are seen in their spectra. Evidence for their identification is derived from carbon-13 nmr chemical shift measurements (Table 2 and Table 3). On the basis of characteristic chemical shifts, multiplicities, and $^1J_{CH}$ values, it is possible to assign the resonances due to the methyl and methylene carbons. The signals of the four ring carbons are assigned by considering either the deshielding effect of the pyrrole nitrogen and the reduced nuclear Overhauser enhancement for quarternary centers. The remaining resonances at the lowest field (in the range *ca.* 157-165 ppm) in the spectra in DMSO-d_6 solution are for the carbonyl carbon atoms. The more upfield (*ca.* 157 ppm) carbonyl carbon shift must be assigned to the amide carbonyl resonance. In fact, in the proton gated decoupled spectra of all compounds, this signal appears as a doublet with *ca.* J = 5.0 Hz, which collapses to a singlet after exchange with deuterium oxide. Assignment of the more downfield peaks is made by intercompound correlation (the substitution at C-2 in **1**, **4**, and **5**), which allows the assignment of the signal at *ca.* 160 ppm to the carbonyl carbon at C-2 and that at *ca.* 165 ppm

Table 1

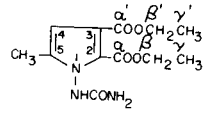
Proton NMR Parameters (a)
ppm (b) Integration, Multiplicity (c), Coupling Constant (d)



	(1)	(2)	(3)	(4)	(5)
CH_3 (γ)	1.20 (6H, t, 7.1)			1.22 (3H, t, 7.1)	
CH_3 (γ')		1.22 (3H, t, 7.0)			1.26 (3H, t, 7.0)
CH_3	2.03 (3H, d, <1.0)	2.01 (3H, d, <1.0)	2.02 (3H, d, <1.0)	2.04 (3H, d, <1.0)	2.08 (3H, d, <1.0)
CH_2 (β)	4.13 (2H, q, 7.1) 4.15 (2H, q, 7.1)			4.20 (2H, q, 7.1)	
CH_2 (β')		4.15 (2H, q, 7.0)			4.25 (2H, q, 7.0)
C_4-H, NH_2	6.15 (3H, sb) (e)	6.15 (3H, m) (f)	6.13 (3H, m) (f)	6.22 (3H, sb) (e)	6.27 (3H, sb) (e)
C_2-H		7.20 (1H, d, 2.0)	(7.16 (1H, d, 2.0)		
NH	9.10 (1H, s) (g)	9.31 (1H, s) (g)	9.27 (1H, s) (g)	9.10 (1H, s) (g)	9.20 (1H, s) (g)
COOH			11.65 (1H, s) (g)		

(a) Solvent is DMSO-d_6. (b) downfield from internal TMS. (c) s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; b = broad. (d) in Hz. (e) after exchange with deuterium oxide: 1H, q, 0.8. (f) after exchange with deuterium oxide: 1H, m. (g) exchangeable with deuterium oxide.

Table 2
Carbon-13 NMR Chemical Shifts
(ppm downfield from TMS) (a)



	(1)	(2)	(3)	(4)	(5)
$C_{\alpha'}$	163.54	163.54	165.12	164.30	165.51
C_{α}	159.48			160.35	159.53
HN-CO	156.90	157.19	157.37	156.99	157.13
C_5	134.46	130.94	130.79	134.88	135.54
C_2	124.40	126.66	126.73	123.67	124.58
C_3	116.60	112.04	112.81	118.35	115.67
C_4	105.55	105.08	105.46	106.64	106.12
$C_{\beta'}$	60.30 59.72	58.75			60.77
C_{β}				60.70	
$C_{\gamma'}$	13.94 13.72	14.22			13.81
C_{γ}				13.66	
CH_3	10.41	10.17	10.37	10.53	10.54

(a) Chemical shifts were measured from the central solvent peak (DMSO-d_6) and converted to the TMS scale by using the difference of 39.6 ppm between DMSO-d_6 and TMS.

to the carbonyl carbon at C-3 (respectively, C-α and C-α' in Table 2). However, a chemical shift comparison of the compounds **2** and **3** does not show a reliable difference of the shift of the carbonyl carbon when it carries an ester or an acid function.

Shieldings of ester and acid carbonyl carbons separated by about 4-7 ppm have been reported in carbon-13 nmr spectra in deuteriochloroform solution (3), whereas near equality of the shieldings have been found in acetone (4). Comparison between the carbon-13 parameters of the di-ester derivative **1** and those of the two isomeric monoethyl esters **4** and **5** shows that the chemical shifts of the carbonyl carbons are only slightly influenced by the replacement of an ester by an acid function on the solutions used (DMSO-d_6). On these grounds, the possibility of characterisation of the two isomers exclusively from their chemical shifts is ruled out.

However, an examination of the proton gated decoupled spectra (Figure 1) reveals that the signal at *ca.* 165 ppm appears as a slightly broadened singlet in the monoacid **3**, whilst the same signal shows a non-resolved three bond coupling to the methylene hydrogens of the ethoxy group in the corresponding monoester **2**. Thus, it is possible to characterize the two isomers **4** and **5** on the basis of multiplicities of the carbonyl carbons resonances.

In the compound **4**, the signal of C-α at *ca.* 160 ppm shows a non-resolved coupling with the methylene hydrogens of the ester function, whilst the signal corresponding to C-α' at lowest field is a doublet with J = 1.4 Hz due to a

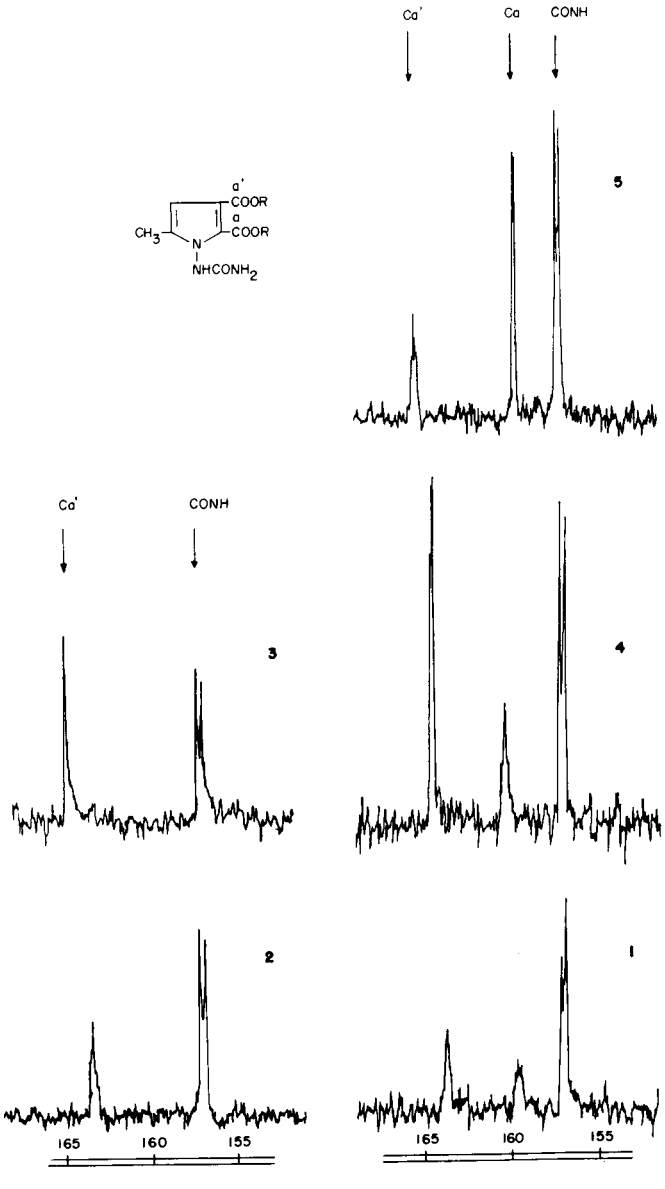
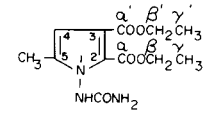


Figure 1. A part of the proton undecoupled carbon-13 nmr spectra of the 1-ureidopyrroles acquired under gated decoupling conditions in order to retain nuclear Overhauser enhancements. Carbonyl carbons signals of all derivatives are reported, namely, the 2,3-dicarbethoxy (**1**), the 3-carbethoxy (**2**), the 3-carboxylic acid (**3**), the 2-carbethoxy-3-carboxylic acid (**4**) and the 3-carbethoxy-2-carboxylic acid (**5**). Solvent is DMSO-d_6 and chemical shifts are referred to the TMS scale.

three bond coupling with the hydrogen at C-4. In fact, the signal of C-α' remains a doublet after exchange with deuterium oxide. Thus, this compound has the ester function at C-2 and the acid function at C-3. Similarly, showing

Table 3

Coupling constants C,H (in Hz) (a)



	1	2	3	4	5
$^1J_{C_2,H_2}$		192.0	191.5		
$^1J_{C_4,H_4}$	176.3	175.0	174.5	176.2	177.1
$^1J_{C_\beta,H_\beta}$	147.8 147.4			148.1	
$^1J_{C_{\beta''},H_{\beta'}}$		146.9			148.1
$^1J_{C_\gamma,H_\gamma}$	126.7 127.0			127.0	
$^1J_{C_{\gamma''},H_{\gamma'}}$		126.7			126.9
$^1J_{CH_3,H}$	128.9	128.4	128.0	129.0	129.4
$^2J_{C_3,H_2}$		6.1	6.0		
$^2J_{C_3,H_4}$	2.6	2.1	2.5	2.3	2.2
$^2J_{C_5,H_4}$	6.9	(b)	(b)	6.9	7.0
$^2J_{C_5,CH_3}$	6.9	(b)	(b)	6.9	7.0
$^2J_{HN,CO}$(d)	5.0	5.5	5.4	5.1	4.4
$^2J_{C_\beta,H_\gamma}$	4.5 4.4			4.5	
$^2J_{C_{\beta''},H_{\gamma'}}$		4.4			4.4
$^2J_{C_\gamma,H_\beta}$	2.4 2.6			2.6	
$^2J_{C_{\gamma''},H_{\beta'}}$		2.5			2.5
$^3J_{C_2,H_4}$	5.1	4.5	4.6	4.8	5.0
$^3J_{C_4,H_2}$		(c)	(c)		
$^3J_{C_4,CH_3}$	3.8	(c)	(c)	3.8	4.0
$^3J_{C_5,H_2}$		(b)	(b)		
$^3J_{C_\alpha,H_\beta}$	(c)			(c)	
$^3J_{C_{\alpha''},H_{\beta'}}$	(c)	(c)			(c)
$^3J_{C_{\alpha''},H_4}$	(c)	(c)	< 1.0 (e)	1.4 (e)	(c)
$^3J_{CH_3,H_4}$	1.4	< 1.0	< 1.0	< 1.0	1.7
$^4J_{C_\alpha,H_4}$	(c)			(c)	1.1 (e)

(a) Taken from proton undecoupled spectra in gated decoupling mode; (b) overlapped by C_2; (c) non-resolved multiplet; (d) this coupling disappears after exchange with deuterium oxide; (e) this coupling remains after exchange with deuterium oxide.

a non-resolved multiplet for the signal at lowest field and a doublet with J = 1.1 Hz (due to a four bond coupling with the hydrogen at C-4) for the signal at *ca.* 160 ppm, the compound **5** must have the ester function at C-3 and the acid function at C-2. Evidently, the diester **1** shows two non-resolved multiplets for both carbonyl carbons at 160 and 165 ppm.

In addition, the structure of **4** was confirmed by chemical proof, as, under alkaline conditions (Scheme I), it undergoes cyclization to pyrrolo[2,1-*f*]-1,2,4-triazine (**6**) described above (2), whereas it does not occur for **5**.

EXPERIMENTAL

Melting points were determined on a Buchi-Tottoli capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord 137 spectrophotometer as nujol mulls. Proton and carbon-13 nmr spectra at natural abundance were obtained on a Varian FT-80A pulsed Fourier transform spectrometer. Samples were studied in DMSO-d_6 solutions. For the protons spectra, the solutions were contained in 5 mm tubes and TMS was used as the internal standard. For the carbon-13 spectra, 10 mm tubes were used and the chemical shifts were measured from the central solvent peak and converted to the TMS scale by using the difference of 39.6 ppm between DMSO-d_6 and TMS. The magnitude of all J_{CH} values have been taken from proton gated decoupled spectra in gated decoupling mode in order to retain nuclear Overhauser enhancements. A 90° pulse of 17 μs used to collect 16K data points. Both the number of transients and the pulse delay were varied to obtain spectra with suitable signal-to-noise ratio in a minimum amount of time and a sensitivity factor of -0.8 seconds was used. Mass spectra were measured with a Jeol-OISG-2 double focusing mass spectrometer at 75 eV (100 μA). The samples were directly introduced and heated at about 200°.

1-Ureido-5-methyl-3-carbethoxypyrrole (**2**).

Compound **1** (2 mmoles), prepared by the general method previously described (2), was refluxed in ethanol saturated with hydrochloric acid (10 ml) for 3 hours. The reaction solution was evaporated to a small volume under reduced pressure and allowed to stand at room temperature for a few hours. The reaction product, precipitated by cooling, was recrystallized as white crystals, mp 255° (ethanol) (yield 70%); ir: 3400, 3280 (NH, NH_2) 1710 and 1690 cm^{-1} (CO); ms: 211 (M^+).

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.17; H, 6.20; N, 19.90. Found: C, 51.53; H, 5.83; N, 19.86.

The action of ethanol saturated with hydrochloric acid on compound **4** under the same experimental conditions gave a product identical (mp, ir, nmr, and mass spectra) with the carbethoxypyrrole **2** described above. By the same method, compound **2** was obtained from compound **3** and from compound **5** also.

1-Ureido-5-methylpyrrole-3-carboxylic Acid (**3**).

Compound **2** (3 mmoles) was refluxed in 70 ml of 2% of sodium hydroxide solution [water-ethanol (1:1)] for 5 hours, then allowed to stand at room temperature overnight. After evaporation of the solvent to a small volume, the cooled solution was acidified with concentrated hydrochloric acid. A solid precipitated and was collected and recrystallized as white needles, mp 280° (ethanol) (yield 50%); ir: 3400, 3300, 3200 (NH, NH_2) 1680 cm^{-1} (CO); ms: 183 (M^+).

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 46.04; H, 5.09; N, 22.96.

1-Ureido-5-methyl-2-carbethoxypyrrole-3-carboxylic Acid (**4**).

To a solution of **1** (2.5 mmoles) in ethanol (60 ml), concentrated hydrochloric acid (1 ml) was added and refluxed for 2 hours. After cooling, a solid which precipitated was collected and recrystallized as white needles, mp 280° (ethanol) (yield 60%); ir: 3400, 3250 (NH, NH_2) 1700 cm^{-1} (CO); ms: 255 (M^+).

Anal. Calcd. for $C_{10}H_{13}N_3O_5$: C, 47.06; H, 5.13; N, 16.47. Found: C, 46.98; H, 5.30; N, 16.61.

1-Ureido-5-methyl-3-carbethoxypyrrole-2-carboxylic Acid (**5**).

To a stirred suspension of the sodium salt of diethyl oxalacetate obtained from 0.01 g-atom of sodium, 100 ml of absolute ethanol and 0.01 mole of diethyl oxalacetate, chloroacetone semicarbazone (0.01 mole) was added in small portions over a period of 15 minutes. After the addition, the mixture was stirred at room temperature for 3 additional hours and then stored in the refrigerator overnight. The reaction solution was evaporated to a small volume and filtered. After evaporation of the resultant solution under reduced pressure, a residue was collected and treated with 100 ml of a saturated solution of sodium bicarbonate. The suspension was stirred for a few hours, then filtered and the resultant solution acidified. After a few hours, a solid which precipitated was collected and recrystallized as white needles, mp 255° (ethanol) (yield 10%); ir: 3450, 3280 (NH, NH_2) 1730 and 1690 cm^{-1} (CO); ms: 255 (M^+).

Anal. Calcd. for $C_{10}H_{13}N_3O_5$: C, 47.06; H, 5.13; N, 16.47. Found: C, 47.19; H, 5.40; N, 16.40.

The Ebullition in Water of Compound **5**.

Compound **5** (1 mmole) was refluxed in water (5 ml) for 7 hours to give a white product which was identical (mp, ir, nmr, and mass spectra) with compound **2** described above.

Action of Sodium Hydroxide in Ethanol on Compound **4**.

Compound **4** (1 mmole) was refluxed in 70 ml of 2% sodium hydroxide solution [water-ethanol (1:1)] for 2 hours to give a solid precipitate which was collected, washed with acidified water and recrystallized from a large excess of ethanol (yield 60%). This product was identical (mp, ir, nmr and mass spectra) with the 7-methylpyrrolo[2,1-*f*]-1,2,4-triazine-2,4-(1*H*,3*H*)-dione-5-carboxylic acid (**6**) described in our preceding paper (2).

REFERENCES AND NOTES

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