

COMPETITIVE FORMATION OF PYRROLE AND PYRIDAZINE RING: STABLE  
TETRAHYDROPYRIDAZINE CARBINOLAMINE AS COMMON PRECURSOR

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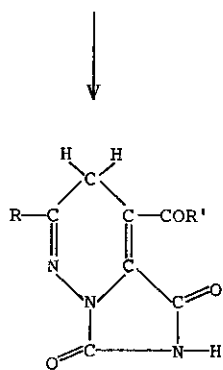
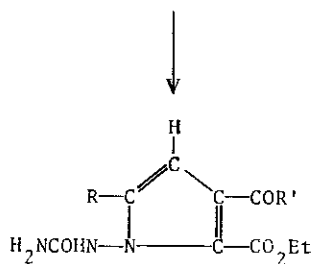
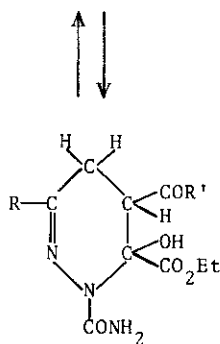
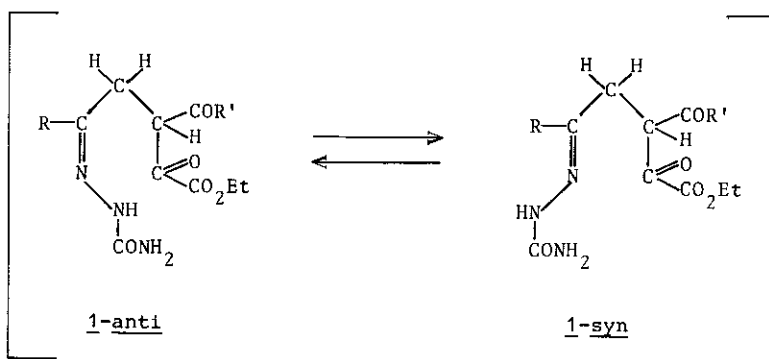
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Abstract - It is demonstrated, by <sup>13</sup>C-nmr analysis, that the precursors of both imidazo [1,5-b]pyridazines 3a-c and 1-ureidopyrroles 4d-f have the tetrahydropyridazine structure 2a-f, rather than the previously reported semicarbazone one 1a-f.

As hydantoins are known to possess sedative, hypnotic and anticonvulsivant properties<sup>1</sup>, we became interested in polycondensed nitrogen heterocyclic compounds having the hydantoin moiety in their molecule. Particularly, in the course of the synthesis of imidazo [1,5-b]pyridazines we observed as, in acid conditions, semicarbazones 1a-f<sup>2</sup> follow different reaction routes in dependence on the substituent R: namely, they afford imidazo [1,5-b]pyridazines 3a-c when R = Ph<sup>3</sup> and 1-ureidopyrroles 4f-d when R = Me<sup>4</sup> (Scheme). This different behaviour could have been well rationalized by the prevalence of anti-form (R respect to NHCONH<sub>2</sub>), suitable for pyridazine ring formation, in the phenyl derivatives 1a-c and syn-form, suitable for pyrrole ring formation, in the methyl derivatives 1d-f. As the nmr data are often helpful in order to distinguish anti- and syn-isomers<sup>5-10</sup>, it seemed useful to examine the <sup>1</sup>H- and <sup>13</sup>C-nmr spectra of these semicarbazones. Their <sup>13</sup>C-nmr spectra in DMSO-d<sub>6</sub> solutions (Table) revealed that these compounds have the 1,4,5,6-tetrahydropyridazine structure 2a-f and therefore neither 1-anti nor 1-syn structures were present. In fact, they show a resonance without one-bond C-H interaction at 79 ppm ca., which is consistent with a quaternary sp<sup>3</sup> carbon deshielded by two bonded



	a	b	c	d	e	f
R	Ph	Ph	Ph	Me	Me	Me
R'	Ph	Me	OEt	Ph	Me	OEt

heteroatoms. Besides the signals of the substituents (R, COR', CO<sub>2</sub>Et, CONH<sub>2</sub>), the <sup>13</sup>C-nmr spectra show the resonances due to the C=N, methine and methylene ring carbons.

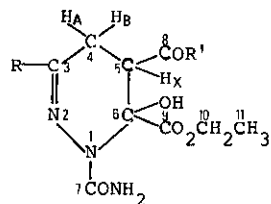
Their <sup>1</sup>H-nmr spectra evidenced equatorially oriented COR' group; in fact, the analysis of the ABX system originating from the CH<sub>2</sub>-CH group of 2a and 2d<sup>11</sup> (carried out in pyridine-d<sub>5</sub> solutions, where there is a larger relative shift between A and B) provides vicinal coupling constants values due to ax,ax (J = 12.75 Hz) and eq,ax (J = 5.25 Hz) interactions.

Moreover, we have no specific proof for configuration of CO<sub>2</sub>Et group and, even if the kinetically favoured isomer should have CO<sub>2</sub>Et and COR' groups trans to each other (arising from the less sterically hindered transition state), there is no reason to assume, a priori, that this is also the thermodynamically preferred one<sup>12</sup>.

Finally, the presence of these unusual stable carbinolamines led us to verify that a cyclic form was present also in the solvent used for their preparation and, as a matter of fact, the <sup>13</sup>C-nmr spectra in ethanol-d<sub>6</sub> solutions resulted practically identical with those in DMSO-d<sub>6</sub> solutions.

It can be concluded that, while the formation of the imidazo[1,5-b]pyridazines 3a-c from the 'anti-blocked' form 2a-c does not require further comments, the evolution of compounds 2d-f (under the same hydrochloric acid treatment) to 1-ureido pyrroles 4d-f should involve a ring opening reaction 2 → 1-anti followed by 1-anti → 1-syn isomerization. In fact, it is reasonable that the ring opening reaction affords, almost exclusively, 1a-c anti-forms when R = Ph (due to steric and n-π repulsive interactions<sup>13</sup>) and 1d-f syn-forms when R = Me<sup>5,13</sup> (these latter can now evolve to compounds 4d-f since the poor nucleophile of the sp<sup>2</sup> nitrogen is balanced by the enhanced reactivity of the carbonyl group in these acid media). If this is true, the absence of the 3-methylimidazo[1,5-b]pyridazine derivatives 3d-f means that 2 → 1-anti → 1-syn reactions should be faster than 2 → 3 ones.

TABLE -  $^1\text{H}$ - and  $^{13}\text{C}$ -nmr chemical shifts of compounds 2a-f, with  $\delta_{\text{H}}$  in parentheses<sup>a</sup>.



	<u>2a</u> (R=R'=Ph)	<u>2b</u> (R=Ph, R'=Me)	<u>2c</u> (R=Ph, R'=OEt)	<u>2d</u> (R=Me, R'=Ph)	<u>2e</u> (R=R'=Me)	<u>2f</u> (R=Me, R'=OEt)
C-3	144.46	143.85	143.71	146.93	146.35	146.58
C-4	21.58 (2.90-3.50) <sup>b</sup>	21.10 (2.80-3.10) <sup>b</sup>	20.80 (2.85-3.35) <sup>b</sup>	25.12 (2.00-3.00) <sup>b</sup>	24.47 (2.00-2.40) <sup>b</sup>	24.24 (2.10-2.40) <sup>b</sup>
C-5	43.62 (4.20) <sup>c</sup>	50.14 (3.35) <sup>c</sup>	43.49 (3.70) <sup>c</sup>	43.42 (4.00) <sup>c</sup>	50.13 (2.80) <sup>c</sup>	43.41 (2.80) <sup>c</sup>
C-6	79.33 (6.50) <sup>d</sup>	79.17 (6.70) <sup>d</sup>	79.15 (6.70) <sup>d</sup>	78.79 (6.10) <sup>d</sup>	78.62 (6.45) <sup>d</sup>	78.64 (6.45) <sup>d</sup>
C-7	155.60 (6.85) <sup>e</sup>	155.51 (6.85) <sup>e</sup>	155.54 (6.80) <sup>e</sup>	155.67 (6.55) <sup>e</sup>	155.58 (6.52) <sup>e</sup>	155.73 (6.52) <sup>e</sup>
C-8	197.46	204.96	168.88	197.66	204.94	168.97
C-9	169.45	169.51	169.15	169.12	169.69	169.43
C-10	60.60 (3.50) <sup>f</sup>	61.05 (4.15) <sup>f</sup>	61.00 (4.15) <sup>f</sup>	60.62 (3.48) <sup>f</sup>	60.95 (4.10) <sup>f</sup>	61.02 (4.10) <sup>f</sup>
C-11	13.40 (1.00) <sup>g</sup>	13.91 (1.25) <sup>g</sup>	13.94 (1.25) <sup>g</sup>	13.42 (0.95) <sup>g</sup>	13.88 (1.20) <sup>g</sup>	13.89 (1.21) <sup>g</sup>

TABLE (contd.)

	<u>2a</u>	<u>2b</u>	<u>2c</u>	<u>2d</u>	<u>2e</u>	<u>2f</u>
R : C-1'	136.54	136.38	136.39			
C-2', 6'	125.66	125.65	125.62			
C-3', 5'	128.33	128.34	128.44			
C-4'	129.04	129.07	129.14			
	(7.35-8.00) <sup>h</sup>	(7.35-8.00) <sup>h</sup>	(7.35-8.00) <sup>h</sup>			
CH <sub>3</sub>				23.28 (2.00) <sup>i</sup>	23.23 (1.96) <sup>i</sup>	23.32 (1.95) <sup>i</sup>
R' : C-1'	137.53			137.48		
C-2', 3', 5', 6'	128.33			128.26		
C-4'	133.03			133.05		
	(7.35-8.00) <sup>h</sup>			(7.45-7.85) <sup>h</sup>		
CH <sub>3</sub>		29.40 (2.20) <sup>i</sup>			29.28 (2.07) <sup>i</sup>	
OCH <sub>2</sub> CH <sub>3</sub>			60.75 (4.08) <sup>f</sup>			60.72 (4.00) <sup>f</sup>
OCH <sub>2</sub> CH <sub>3</sub>			13.82 (1.20) <sup>g</sup>			13.89 (1.14) <sup>g</sup>

<sup>a</sup>Nmr spectra were recorded on a Varian FT-80A pulsed Fourier transform spectrometer in DMSO-d<sub>6</sub> solutions and chemical shifts are given in ppm downfield from TMS. In the <sup>1</sup>H-nmr spectra TMS was used as internal standard; the multiplicity of the signals is indicated by the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet; the coupling constants values are given in Hz. In the <sup>13</sup>C-nmr spectra at natural abundance the chemical shifts were measured from the central solvent peak and converted to the TMS scale by using the difference of 39.60 ppm between DMSO-d<sub>6</sub> and TMS; all assignments were confirmed by off-resonance experiments. <sup>b</sup>2H, m. <sup>c</sup>1H, m. <sup>d</sup>1H, s, OH, exchangeable with D<sub>2</sub>O. <sup>e</sup>2H, s, NH<sub>2</sub>, exchangeable with D<sub>2</sub>O. <sup>f</sup>2H, q, J=7. <sup>g</sup>3H, q, J=7. <sup>h</sup>5H, m. <sup>i</sup>3H, s.

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11. Owing to superimposed signals, it was not possible to perform analogous analysis in the  $^1\text{H}$ -nmr spectra of the other compounds.
12. It must be noticed that the  $^{13}\text{C}$ -nmr spectra show, nearly to the reported resonances in Table, signals which can be attributable to small amounts ( $\leq 10\%$ ) of the other isomer.
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