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

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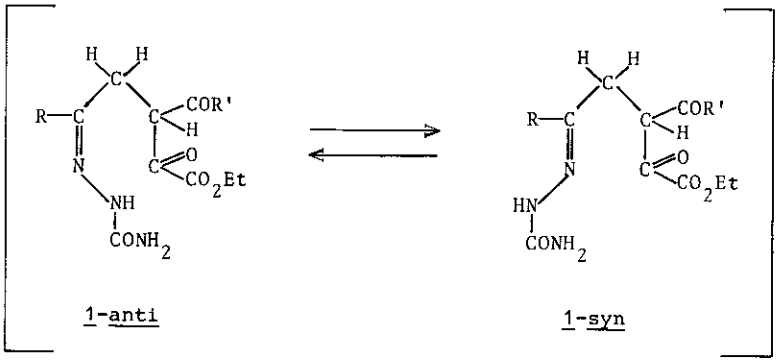
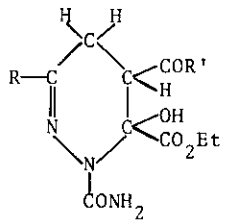
Abstract - It is demonstrated, by ^{13}C-nmr analysis, that the precursors of both imidazo[1,5-b]pyridazines 3a-c and 1-ureidopyrroles 4d-f have the tetrahydropyridazine structure 2a-f, rather than the previously reported semicarbazone one 1a-f.

As hydantoins are known to possess sedative, hypnotic and anticonvulsivant properties[1], 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[2] follow different reaction routes in dependence on the substituent R: namely, they afford imidazo[1,5-b]pyridazines 3a-c when R = Ph[3] and 1-ureidopyrroles 4f-d when R = Me[4] (Scheme). This different behaviour could have been well rationalized by the prevalence of anti-form (R respect to $NHCONH_2$), 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[5-10], it seemed useful to examine the ^{1}H- and ^{13}C-nmr spectra of these semicarbazones. Their ^{13}C-nmr spectra in DMSO-d_6 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^3 carbon deshielded by two bonded

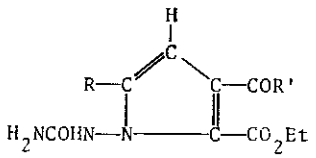


1-anti

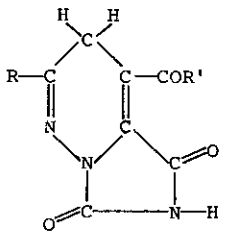
1-syn



2a-f



4d-f



3a-c

	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_2Et , $CONH_2$), the ^{13}C-nmr spectra show the resonances due to the C=N , methine and methylene ring carbons.

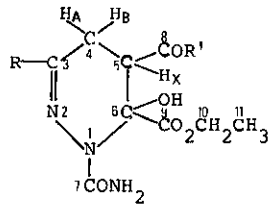
Their ^1H-nmr spectra evidenced equatorially oriented COR' group; in fact, the analysis of the ABX system originating from the CH_2-CH group of 2a and 2d[11] (carried out in pyridine-d_5 solutions, where there is a larger relative shift between A and B) provides vicinal coupling constants values due 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_2Et group and, even if the kinetically favoured isomer should have CO_2Et 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[12].

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 ^{13}C-nmr spectra in ethanol-d_6 solutions resulted practically identical with those in DMSO-d_6 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[13]) and 1d-f syn-forms when R = Me[5,13] (these latter can now evolve to compounds 4d-f since the poor nucleophile of the sp^2 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}H- and ^{13}C-nmr chemical shifts of compounds 2a-f, with δ_H in parentheses[a].



	2a (R=R'=Ph)	2b (R=Ph, R'=Me)	2c (R=Ph, R'=OEt)	2d (R=Me, R'=Ph)	2e (R=R'=Me)	2f (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)[b]	21.10 (2.80-3.10)[b]	20.80 (2.85-3.35)[b]	25.12 (2.00-3.00)[b]	24.47 (2.00-2.40)[b]	24.24 (2.10-2.40)[b]
C-5	43.62 (4.20)[c]	50.14 (3.35)[c]	43.49 (3.70)[c]	43.42 (4.00)[c]	50.13 (2.80)[c]	43.41 (2.80)[c]
C-6	79.33 (6.50)[d]	79.17 (6.70)[d]	79.15 (6.70)[d]	78.79 (6.10)[d]	78.62 (6.45)[d]	78.64 (6.45)[d]
C-7	155.60 (6.85)[e]	155.51 (6.85)[e]	155.54 (6.80)[e]	155.67 (6.55)[e]	155.58 (6.52)[e]	155.73 (6.52)[e]
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)[f]	61.05 (4.15)[f]	61.00 (4.15)[f]	60.62 (3.48)[f]	60.95 (4.10)[f]	61.02 (4.10)[f]
C-11	13.40 (1.00)[g]	13.91 (1.25)[g]	13.94 (1.25)[g]	13.42 (0.95)[g]	13.88 (1.20)[g]	13.89 (1.21)[g]

TABLE (contd.)

		2a	2b	2c	2d	2e	2f
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 (7.35-8.00)[h]	129.07 (7.35-8.00)[h]	129.14 (7.35-8.00)[h]			
	CH_3				23.28 (2.00)[i]	23.23 (1.96)[i]	23.32 (1.95)[i]
R':	C-1'	137.53			137.48		
	C-2',3',5',6'	128.33			128.26		
	C-4'	133.03 (7.35-8.00)[h]			133.05 (7.45-7.85)[h]		
	CH_3		29.40 (2.20)[i]			29.28 (2.07)[i]	
	OCH_2CH_3			60.75 (4.08)[f]			60.72 (4.00)[f]
	OCH_2CH_3			13.82 (1.20)[g]			13.89 (1.14)[g]

[a]Nmr spectra were recorded on a Varian FT-80A pulsed Fourier transform spectrometer in DMSO-d_6 solutions and chemical shifts are given in ppm downfield from TMS. In the ^{1}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 ^{13}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_6 and TMS; all asignments were confirmed by off-resonance experiments. [b]2H, m. [c]1H, m. [d]1H, s, OH, exchangeable with D_2O. [e]2H, s, NH_2, exchangeable with D_2O. [f]2H, q, J=7. [g]3H, q, J=7. [h]5H, m. [i]3H, s.

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