SOUTHERN BRAZILIAN JOURNAL OF CHEMISTRY
SOUTH. BRAZ. J. CHEM., Vol. 7, N° 8, 1999

BIOLOGICAL ACTIVE ACYLHYDRAZIDE I. THE O-ACYL-DERIVATIVES NATURE OF MONOACYLATION PRODUCTS OF CYCLIC MALEIC- AND PHTHALIC-HYDRAZIDE.

I. Panea[a], Lucia Bodochi[b], Teodora Panea[b], Daniela Zinveliu[b] and Violeta Paşcalău[b]

a) "Babeş-Bolyai" University, Department of Organic Chemistry, Arany Janos 11, 3400 Cluj-Napoca, Romania

b) Research and Production Center "BIOS", Academy of Agricultural and Forest Sciences, OP 1 CP 2, 3400 Cluj-Napoca, Romania

ABSTRACT

We confirmed, on the basis of chemical and physico-chemical (melting points, IR- and ^{1}H-NMR-spectra) data, that the products isolated by monoacylation of cyclic maleic- and phthalic-hydrazides have only the O-acylderivatives nature although owing to tautomerism these hydrazides may give rise to N- or/and O-acylderivatives in such reactions. Simultaneously, we showed that the claims for the obtainment of N-acylderivatives of cyclic maleic- and phthalic-hydrazides were not valid. Also by reacting the cyclic maleic-, respectively phthalic-hydrazide, with 4-chlorobenzoylchloride two new O-monoacylderivatives [3-(4-chlorobenzoyloxy)-1-H-pyridazin-6-one and 1-(4-chlorobenzoyloxy)-3-H-phthalazin-1-one] were obtained.

RESUMO

Através de estudos químicos e físico-químicos confirmamos que os produtos isolados da monoacilação de hidrazidas maléica e ftálica cíclicas tem somente o caráter de O-acil-derivados. Devido a tautomerismo, estas hidrazidas podem resultar em derivados de N- ou O-acila. Também demonstramos que as pretensões de obtenção de N-acil derivados de hidrazidas cíclicas maléica e ftálica não são válidas. A reação de hidrazida maléica e ftálica cíclicas com cloreto de 4-clorobenzoila leva a dois novos O-monoacil derivados: 3-(4-benzoiloxi)-1-H-piridazina-6-ona e 1-(4-clorobenzoiloxi)-3-H-ftalazina-1-ona, respectivamente.

KEYWORDS : O-acylderivatives of cyclic maleic- and phthalic-hydrazides. Melting points, IR- and ^{1}H-NMR-spectra.

DOI: 10.48141/SBJCHEM.v7.n8.1999.27_1999.pdf

INTRODUCTION

Many acylated acyclic (1)[1-12], semicyclic (2)[1,5,8,9,12b,c,13-16] and cyclic (3, 4)[3,4,12b,13a,14,17-34] hydrazides of 1,4-dicarboxylic acids have been described. Most of these have various useful biological actions like: tuberculostatic[2a], herbicide[6-8], plant growth regulation[9,10,12,22,25a,26,29a,b,30,32,34], of thrombocytes antiagregation[11], cytostatic[24a,28], bactericide[27c], respectively are intermediary or component parts of some useful products, inclusively biological ones[2a,5,8,12d,17c,26,30].

The structure of these acylhydrazides is uncertain, respectively controversial[3,4,12-15,17-34]. Thus, for the products obtained by the monoacylation of acyclic hydrazides (5, R^1 = acyl) with the cyclic anhydrides of 1,4-dicarboxylic acids (6), some authors assigned an acyclic acylhydrazide (1)[2-12] structure, while others considered that under given conditions a semicyclic (2, R=H; R^1=acyl)[12c,13,14b], respectively cyclic (3, R=H; R^1=acyl; Y=H, H) (7)[3a,26] N-acylhydrazides (for acyl see the R^1 significances from Scheme 1) would result. According to other authors, the type 7 derivatives have not been isolated till now[4,12b,c] contrary to other affirmations[3,14a,24,26,28,29c,30-32].

Likewise, the nature of the obtained products by cyclic hydrazides (8) acylation with acyclic anhydrides (9) or acid chlorides (10), namely the O-[3,4,12b,17b,18-20,21-25,27,33,34] or/and N-[4,13a,17a,24,27,28,31,32] -acylderivatives nature (3, 4, 11), by the monoacylation, respectively diacylation [4,13a,17a,18-20,27,28], is uncertain[14d,22,29a] or controversial.

The possibility of N-(3) or/and O-acyl (4, 11) derivatives formation from cyclic hydrazides (8) of dicarboxylic acids is based on their tautomerism[3a,4,17b,18-20,23,25,27,35] (see Scheme 1).

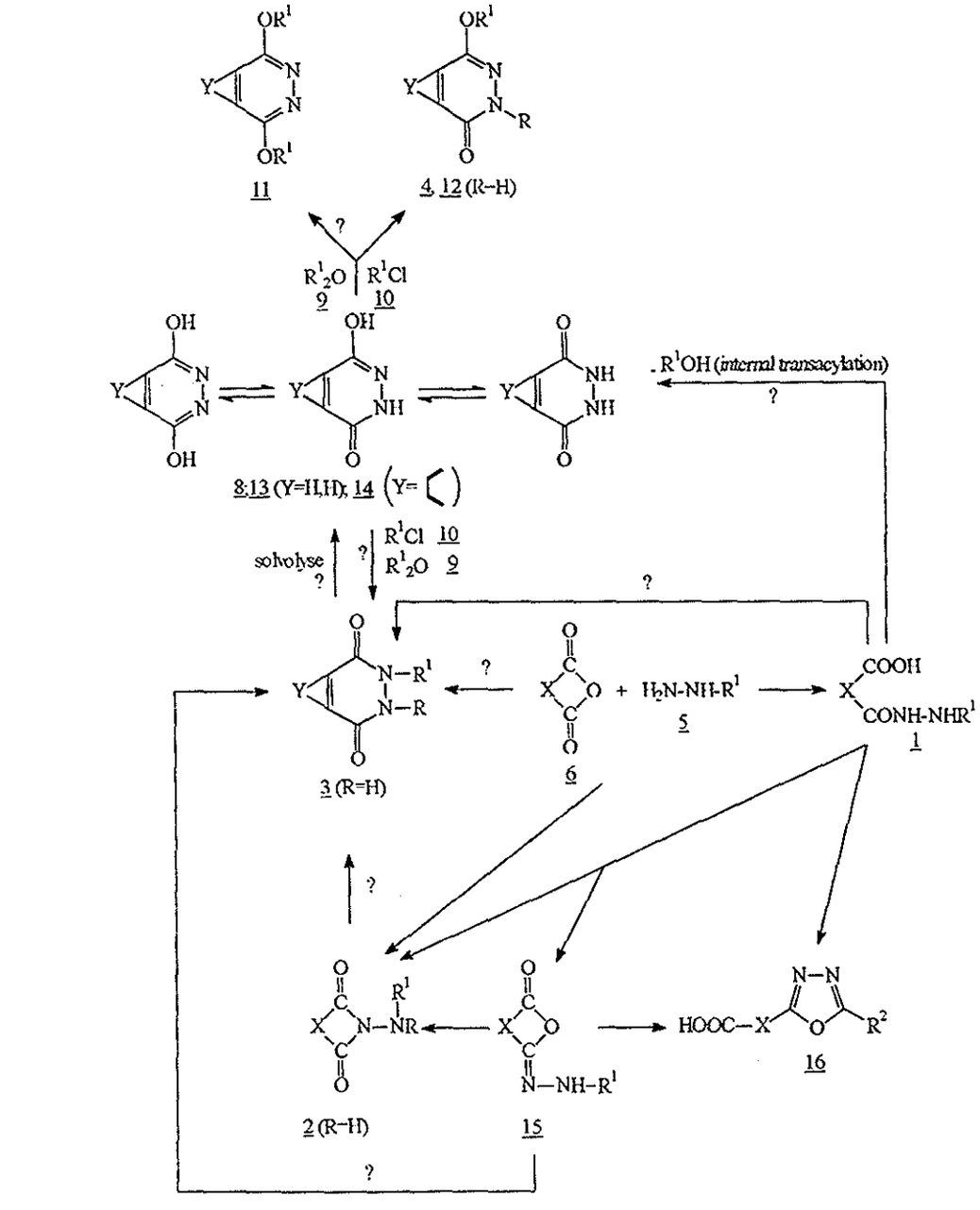
The unclear situation and controversies on acylhydrazides structure (1-4, 11), prompted us to undertake a systematic study on them.

We consider that the study is necessary in as much as it concerns substances of biological interest and a knowledge of the exact structure is an absolute requirement for establishing structure-activity relationship.

In this paper we discuss the O-acyl derivatives nature (4, R=H) (12) of the products obtained by us[34], by monoacylation of cyclic hydrazides 8 (Y=H, H; maleic; Y = ⟨ ; phthalic) and in this context we deal with all of the monoacylation products of cyclic hydrazides (8).

EXPERIMENTAL

The cyclic maleic hydrazide (13)[3b,17a,36], the cyclic phthalic hydrazide (14)[13a,17a] and the acid chlorides (10)[37] have been obtained in accordance with cited references. The cyclic anhydrides (6) were commercial products. The monoacylation products (12) were prepared by treating to reflux cyclic maleic-(13) or phthalic-(14) hydrazide (0,012 moles), suspended in toluene (30 ml), with acid chloride (0,0133 moles) (10)[34]. The mixture was refluxed in addition 2-4 hours, then cooled at room temperature, filtered off, washed with ethanol and dried (yield 83-87%). The purity was checked by thin layer chromatography. The elemental analysis data agreed with that of monoacylation products. Under similar conditions, working instead in the presence of equimolar quantities of pyridine, one new monoacylation product was obtained from each of cyclic



R=H, CH_3-CO ; X= CH_2—CH_2 ; CH=CH ; . Y=H, H; .

R^1=R^2-CO; R^2=CH_3; C_2H_5; $ClCH_2$; C_6H_5; (2-or 4-)ClC_6H_4; 4-O_2N-C_6H_4; 4-H_2N-C_6H_4; 2-HO-C_6H_4; 2-CH_3-$OCOC_6H_4$; H_5C_6-CH_2; α-naphthyl-CH_2; H_5C_6-OCH_2; 4-ClC_6H_4-OCH_2; 2,4-$Cl_2C_6H_3OCH_2$; β-naphthoxy-CH_2; 4-pyridyl; indolyl-CH_2; H_2N; CH_3-O; C_2H_5-O, etc.

Scheme 1.

hydrazide (13, 14), through their reaction with p-chlorobenzoic acid chloride (10, R^1=OC-C_6H_4-4-Cl).

6-(4-chlorobenzoyloxy)-2,3-dihydro-3-oxo-pyridazine (12, Y=H, H; R^1=4-Cl-C_6H_4-CO) formed colorless needles from ethanol. Yield : 77%, m.p. = 227-230°C

Anal. : Calcd. for $C_{11}H_7N_2O_3Cl$ (250.5); MS 250
C-52.60; H-2.8; N-11.9; Cl-14.5;
Found : C-52.80; H-3.15; N-11.94; Cl-14.4.

1-(4-Chlorobenzoyloxy)-3,4-dihydro-4-oxo-phthalazine (12, Y= ; R^1=4-Cl-C_6H_4-CO) formed colorless needles from ethanol. Yield : 65%, m.p. = 193-195°C

Anal. : Calcd. for $C_{15}H_9N_2O_3Cl$ (300.5); MS 300
C-69.3; H-4.4; N-8.09; Cl-10.3;
Found : C-69.2; H-4.5; N-8.20; Cl-10.23.

In order to determine the spectra of compounds claimed to be O-[23,25,26] (12) or N-[3,17b,24a,26,32] (3, R=H) monoacylderivatives of cyclic hydrazides (8), respectively of the monoacylderivatives of hydrazides (8) with no specified O- or N-derivatives nature[22], we prepared a series of them using the same conditions described by previous authors.

With the purpose to have spectra for comparison we synthesized, in accordance with references[2a,3a,b,4,6-8,11-13a,16b], a series of acyclic hydrazides (5)[3b], their acyclic acylation products (1) with dicarboxylic acid anhydrides (6) and also the transformation products (2, 15, 16) of initial acyclic acylderivatives (1) (see Scheme 1).

The ^{1}H-NMR spectra were recorded with a Brucker Fourier Transform NMR spectrometer of 90 MHz, respectively Varian FT-80A NMR of 80 MHz, respectively Varian Gemini 300 (300 MHz), in deuterated solvents at room temperature.

Mass spectra were registered with a Matt 311 mass spectrometer with double focussing and inverse Nier geometry.

IR spectra were registered as KBr pellets with a UR-20 spectrophotometer (C. Zeiss-Jena). The melting points are uncorrected.

RESULTS AND DISCUSSIONS

Some of physico-chemical data of the compunds under consideration and other related ones are presented in Tables 1, 2. Relative to the alkylation products of cyclic hydrazides – maleic-(13) and phthalic-(14) – the exact nature of N-, respectively O-alkyl derivative was succesfully established based on structure proof synthesis[3a,4c,20,28,35, 38].

From literature works[4c,20,28,38] it results that O-alkylderivatives of maleic-(13) and phthalic-(14) hydrazide have much lower melting points (about 150°C) than the cyclic unsubstituted hydrazides and lower (about 50°C) than the N-alkylderivatives (see Table 1). The reason is that O-alkylderivatives are ethers and the initial hydrazides (8) and their N-alkylderivatives are amides. It is well-known that ethers are a class of compounds more volatile than amides, the latter having high melting points.

The monoacylated products of maleic-(13) and phthalic-(14) hydrazides also have much lower melting points (some of them more than 150°C lower) than starting hydrazides (see Table 1). This situation is more consistent with the O-acylderivatives (12) than the N-acylderivatives (3, R=H) structure of cyclic monacylated hydrazides (compare[17b]). The option for O-acylderivatives (12) takes into consideration their relation to esters, which are more volatile compunds (see[25b]) than amides, to which the starting hydrazides and their N-acylderivatives (3, R=H, R^1= acyl) belong.

Table 1. Physical-chemical data of acylhydrazides with controversial structure and of some related compounds. References are given in square brackets.

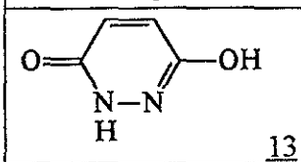
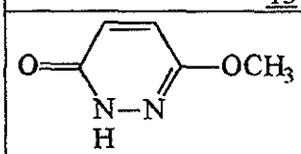
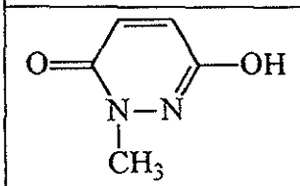
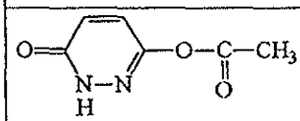
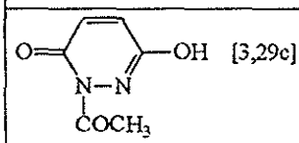
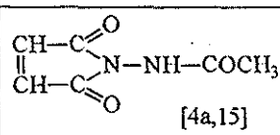
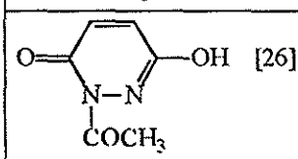
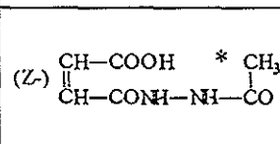
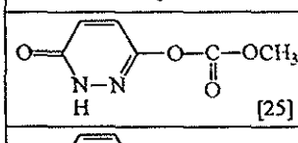
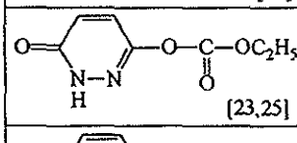
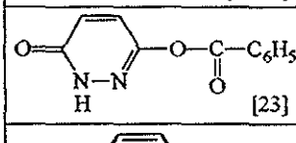
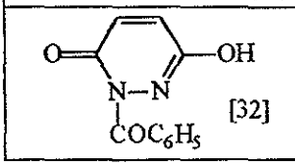
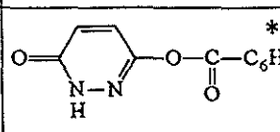
Structure according to reference	The structure confirmed for the compound by present study	Melting point [°C]	I.R. -$\nu_{C=O}$ with highest wave number [cm^{-1}]	Molecular peak from mass spectra
1	2	3	4	5
 13	as in first column [35]	300 [3a,4a]	1660 [15] 1676 [4a]	-
	as in first column [4c,38]	154 [38]	-	-
	as in first column [4c,35,38]	210 [38]	-	-
	as in first column [3a,4]	122-123 [3a,4]	1755 [4a]	-
 [3,29c]	 [4a,15]	164-166 [4a] 160-162 [3]	1725 [4a] 1715 [15]	-
 [26]		176 [26] 173-175*	1718* for COOH	-
 [25]	as in first column*	118-120* 121-122[25b] 105-107[25a]	1790*	170*
 [23,25]	as in first column*	103-105* 106-108 [23] 101-103[25b]	1765*	184*
 [23]	as in first column*	154-156* 162-164 [23]	1745*	-
 [32]		154-156*	1745*	-

Table 1 (continued)

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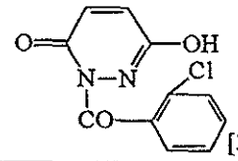
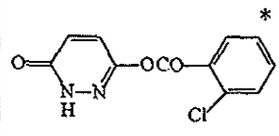
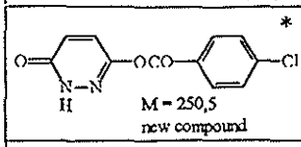
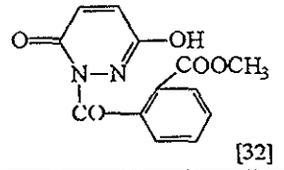
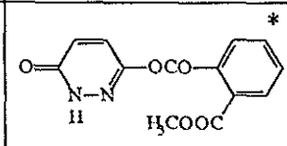
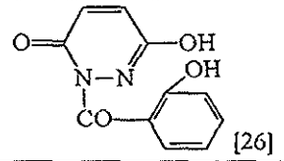
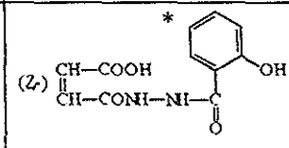
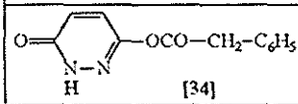
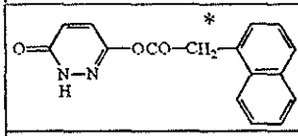
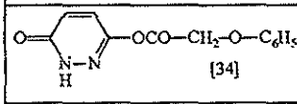
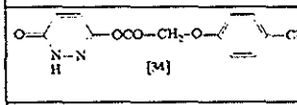
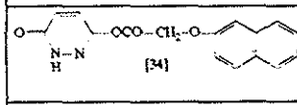
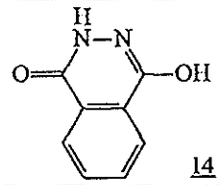
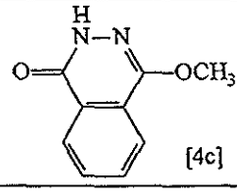
 [32]	 *	>210 [32]	-	-
 M = 250,5 new compound	as in first column*	226-228*	1735*	250*
 [32]	 *	144-146* 144-145 [32]	1770*	-
 [26]	 *	192 [26] 189-191*	1710* for COOH	-
 [34]	as in first column*	136-138* [34]	1767* [34]	-
 *	as in first column*	177-178*	1775*	280*
 [34]	as in first column*	143-145* [34]	1780* [34]	-
 [34]	as in first column*	146-147* [34]	1787* [34]	-
 [34]	as in first column*	124-126* [34]	1775* [34]	-
 14	as in first column [27]	344 [4] 341-344[13a]	1660 [4,27]	-
 [4c]	as in first column [4c]	188-189 [4c,20]	-	-

Table 1 (continued)

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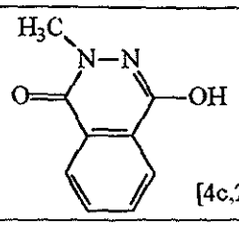
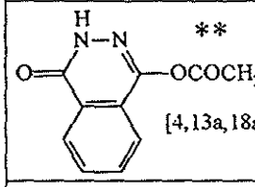
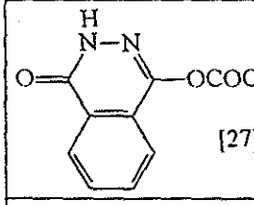
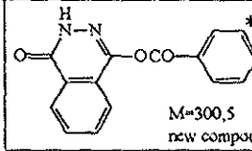
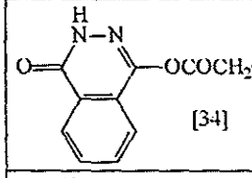
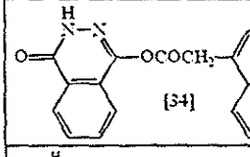
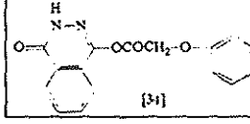
 [4c,20]	as in first column [4c,20a]	238-240 [4c,20a]	-	-
 ** [4,13a,18a,27]	as in first column [4c,27]	175 [27] 172-173 [13a,20a] 170 [18a]	1770 [4a] 1765 [27]	-
 [27]	as in first column [27]	227-228 [27]	1745 [27]	-
 M=300,5 new compound	as in first column*	193-195*	1765*	300*
 [34]	as in first column*	178-180 [34]	1760*	-
 [34]	as in first column*	199-200 [34]	1762*	330*
 [34]	as in first column*	212-213 [34]	1745*	346*

* Structure assigned (see Discussion and compare also with Table 2), respectively data obtained, by authors of this work.

** Among the cyclic phthalic hydrazide monoacylations, one in which the N-acylderivative formation is claimed, but only beside O-acylderivative, is the acetylation [4a, 4b, 13a]. However we point out that in a subsequent work [4c] of Le Berre and coworkers, concerning this acetylation, there is no reference to the N-acetylderivative. Other authors [27a] also deny the N-acetylated phthalic hydrazide formation on the basis of IR data.

The O-acylderivative nature of monoacylation products of cyclic hydrazides (8) is also supported by the presence of an absorbtion band between 1735-1790 cm^{-1} in their IR spectra (see Table 1). This band is characteristic for carbonyl stretching frequency ($\nu_{C=O}$) within a ester group[26,27a,39], which is present in all O-acylderivatives. The O-acylderivative nature (12) of monoacylation products is sustained by the parameters of their ^{1}H-NMR spectra too (see Table 2).

It was found in published ^{1}H-NMR data[4c,35] of maleic hydrazide alkylderivatives (13) that the chemical shift (δ) for the olefinic hydrogens signals have bigger and more differentiated values for O-alkyl than N-alkylderivatives. These chemical shift values for O-alkylderivatives are also bigger than those of maleic hydrazide. On the other hand, for N-alkylderivatives, only the chemical shift (δ) for olefinic hydrogen of distant position to N-alkylsubstitute is sometimes slightly bigger than in maleic hydrazide.

In ^{1}H-NMR spectra registered by us for maleic hydrazide monoacylderivatives (see Table 2) the signals for olefinic protons have sensible differentiated chemical shifts values (Δδ~ 0,5 ppm) and are allways bigger than those of maleic hydrazide (13). These results correlated with the debates upon maleic hydrazide alkylderivatives support the O-acylderivatives nature (12) for examined monoacylderivatives (see reference 4).

The sensible differentiation of chemical shifts for olefinic protons and their bigger chemical shift values, especially for the hydrogen atom close to O-substitute in O-derivatives towards maleic hydrazide and N-alkylderivatives is due to a deshielding steric effect. In the case of O-derivatives (see 12), the O-substitute is much nearer in space to olefinic protons than N-substitute in N-derivatives (see 3, R=H). Probably the N-substitute has no deshielding steric effect upon olefinic protons since for its manifestation the very close steric proximity is important (see reference 40a).

Also, the O-acylderivative nature of monoacylated cyclic hydrazides-8 is sustained indirectly by a series of other data. One of these arguments is that the authors who claimed[17c,24a,29c,32] the obtainment of N-acylated cyclic maleic hydrazide or suggested[14d,29a] the N-acylderivatives formation besides O-acylderivatives in the monoacylation reaction of cyclic maleic hydrazide do not give any proof for their claim or suggestion. On the contrary, many authors[3a,4,12b,17b,23,26,27,33,34] who claimed only O-acylderivatives (12) formation, in the monoacylation reaction of cyclic maleic hydrazide (13), presented more or less convincing proofs for this. In accordance with the last authors our IR and ^{1}H-NMR spectral data (see Table 1, 2) for cyclic maleic hydrazide monoacylderivatives, claimed to be N-acylderivatives[17c,29c,32] or O-acylderivatives[23,25,34], respectively with unspecified structure[22], are compatible only with O-acylderivatives structures (12). Thus, the monoacylation products of cyclic maleic hydrazide (13) with carbonic acid monochlorides-monoesters (10, R^1=OC-OCH_3; OC-OC_2H_5)[23,25], α-naphthylacetic (10, R^1= OC- α-naphthyl[22,34]), benzoic (10, R^1=CO-C_6H_5[23]) or 2-carbomethoxy-benzoic (10, R^1=CO-C_6H_4-(2)$COOCH_3$)[32] chlorides – reproduced by us under the conditions described by the authors[22,23,25,32,34] – all show an absorbtion band in the IR, specific of esters $\nu_{C=O}$ stretching vibrations, between 1745-1790 cm^{-1} as well as two ^{1}H-NMR signals, as doublets – for the olefinic hydrogens – with well differentiated chemical shifts (Δδ~0,4ppm) that are bigger than in maleic hydrazide (δ> 7ppm).

We point out that regardless the O- or N-acylderivative claimed, respectively unspecified nature, all the monoacylated cyclic maleic hydrazide compunds show similar properties: low melting points, IR band specific to ester carbonyl group and ^{1}H-NMR signals almost identical for each type of olefinic protons (see Table 1, 2).

Table 2. ^{1}H-NMR Data (Chemical shift - δ, in ppm, multiplicity*, number of hydrogens and coupling constant - J, in Hz) of acylhydrazides with controversial structure and of some related compounds.

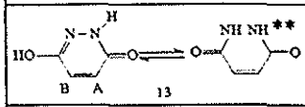
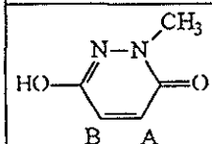
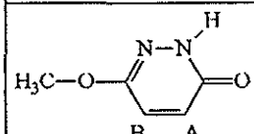
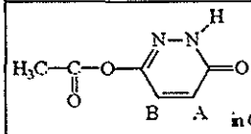
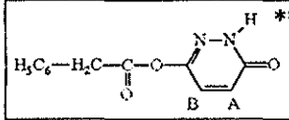
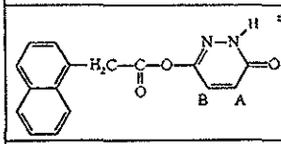
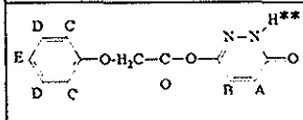
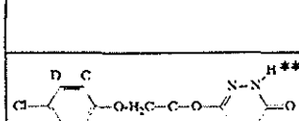
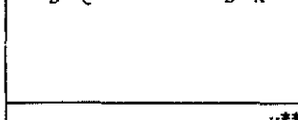
Compound	Methylic and Methylenic hydrogens	Olefinic hydrogens	Aromatic hydrogens	Hydrazidic hydrogens (NH or OH)
1	2	3	4	5
 13	-	$\delta_{HA,B}$ = 6,94 (s)	-	11,55 (b)
 [35a,4c]	δ_{CH3-N} = 3,50 (s) 3H	δ_{HA} = 6,87 (d); 1H δ_{HB} = 7,04 (d); 1H J_{AB} = 9,4	-	11,06 (b)
 [4c]	δ_{CH3-O} = 3,76 (s) 3H	δ_{HA} = 7,06 (d); 1H δ_{HB} = 7,29 (d); 1H J_{AB} = 10	-	-
 [4] in $CDCl_3$	δ_{CH3-CO} = 2,3 (s) 3H	δ_{HA} = 7,07 (d); 1H δ_{HB} = 7,22 (d); 1H J_{AB} = 10	-	-
	δ_{CH2-CO} = 3,97 (s) 2H	δ_{HA} = 6,99 (d); 1H δ_{HB} = 7,4 (d); 1H J_{AB} = 9,8	δ_{C6H5} = 7,33 (s) 5H	-
	δ_{CH2-CO} = 4,45 (s) 2H	δ_{HA} = 7,0 (d); 1H δ_{HB} = 7,4 (d); 1H J_{AB} = 9,7	δ_{C10H7} = 7,35-8,2 (m) 7H	-
	δ_{CH2-O} = 5,06 (s) 2H	δ_{HA} = 7,01 (d); 1H δ_{HB} = 7,44 (d); 1H J_{AB} = 10	$\delta_{HC,E}$ = 6,85-7,1 (m) δ_{HD} = 7,2-7,4 (m) 2H	-
	δ_{CH2-O} = 5,1 (s) 2H	δ_{HA} = 7,0 (d); 1H δ_{HB} = 7,45 (d); 1H J_{AB} = 10	δ_{HC} = 7,01 (d); 2H δ_{HD} = 7,33 (d); 2H J_{CD} = 8,5	-
	δ_{CH2-O} = 5,25 (s) 2H	δ_{HA} = 7,01 (d); 1H δ_{HB} = 7,45 (d); 1H J_{AB} = 10	δ_{OC10H7} = 7,1-7,9 (m) 7H	-

Table 2 (continued)

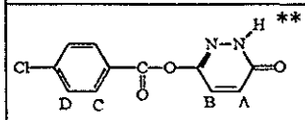
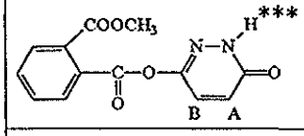
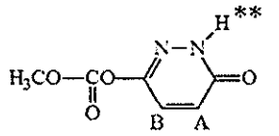
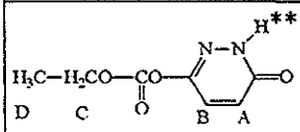
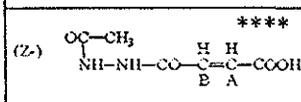
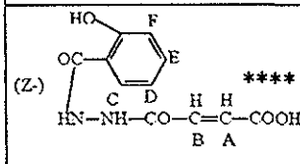
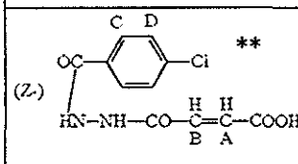
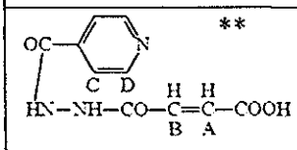
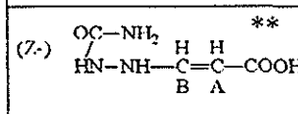
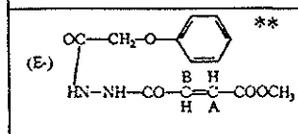
1	2	3	4	5
	-	δ_{HA} = 7,01 (d); 1H δ_{HB} = 7,53 (d); 1H J_{AB} = 10	δ_{HC} = 8,06 (d); 2H δ_{HD} = 7,63 (d); 2H J_{CD} = 8,6	-
	δ_{OCH_3} = 3,81 (s) 3H	δ_{HA} = 7,05 (d); 1H δ_{HB} = 7,47 (d); 1H J_{AB} = 10	$\delta_{C_6H_4}$ = 7,6-8,0 (m) 4H	-
	δ_{OCH_3} = 3,81 (s) 3H	δ_{HA} = 7,0 (d); 1H δ_{HB} = 7,49 (d); 1H J_{AB} = 10	-	-
	δ_{CH_3} = 1,24 (t) 3H δ_{CH_2-O} = 4,23 (q) 2H J_{CD} = 7	δ_{HA} = 7,0 (d); 1H δ_{HB} = 7,49 (d); 1H J_{AB} = 10	-	12,8 (b)
	δ_{CH_3-CO} = 1,9 (s) 3H	$\delta_{HA,B}$ =6,31 (s) 2H	-	10,1 (b)
	-	$\delta_{HA,B}$ =6,35 (s) 2H	δ_{HC} =7,85 (d);1H δ_{HD} = 6,94 (t);1H δ_{HE} = 7,4 (t); 1H δ_{HF} =6,93 (d);1H J_{orto} = 8	10,7 (b)
	-	δ_{HA} = 6,26 (d); 1H δ_{HB} = 6,41 (d); 1H J_{AB} = 11	δ_{HC} = 7,86 (d); 2H δ_{HD} = 7,51 (d); 2H J_{CD} = 8,7	10,7 (b)
	-	δ_{HA} = 6,32 (d); 1H δ_{HB} = 6,43 (d); 1H J_{AB} = 12	δ_{HC} = 7,75-7,85 (m) 2H δ_{HD} = 8,7-8,9 (m) 2H	10,92 (b)
	-	δ_{HA} = 6,22 (d); 1H δ_{HB} = 6,4 (d); 1H J_{AB} = 12,2	-	8,03 (b)
	δ_{CH_3-O} = 3,65 (s) 3H δ_{CH_2-O} = 4,6 (s) 2H	δ_{HA} = 6,6 (d); 1H δ_{HB} = 7,0 (d); 1H J_{AB} = 15,5	$\delta_{OC_6H_5}$ = 6,65-7,25 (m) 5H	10,5 (b)

Table 2 (continued)

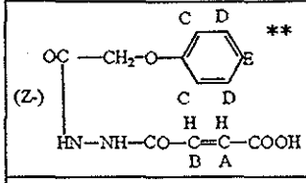
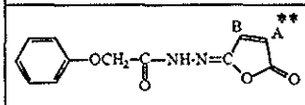
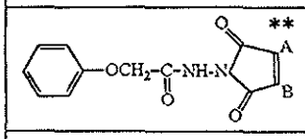
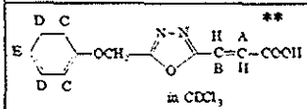
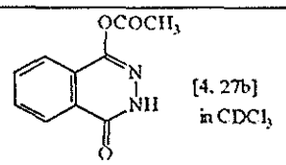
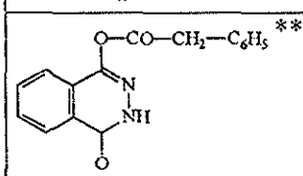
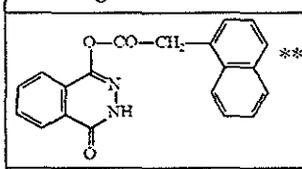
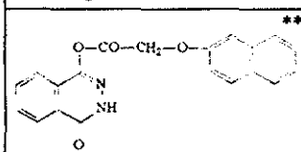
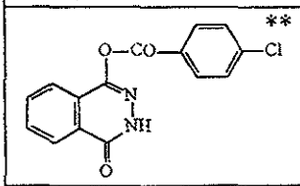
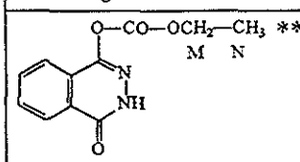
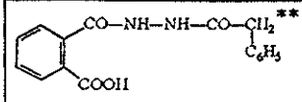
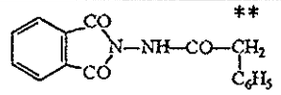
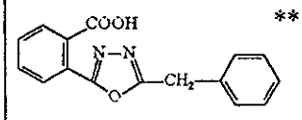
1	2	3	4	5
	δ_{CH_2-O} = 4,58 (s) 2H	δ_{HA} = 6,2 (d); 1H δ_{HB} = 6,37 (d); 1H J_{AB} = 12	$\delta_{HC,E}$ =6,75-7,15 (m) 3H δ_{HD} = 7,2 (t) 2H	10,35 (b)
	δ_{CH_2-O} = 4,74 (s) 2H	δ_{HA} = 6,82 (d); 1H δ_{HB} = 7,8 (d); 1H J_{AB} = 5,6	$\delta_{OC_6H_5}$ = 6,75-7,26 (m) 5H	11,54 (b)
	δ_{CH_2-O} = 4,7 (s) 2H	$\delta_{HA,B}$ = 7,09 (s) 2H	$\delta_{OC_6H_5}$ = 6,9-7,0;7,2-7,35 (m); 5H	10,82 (b)
	δ_{CH_2-O} = 5,32 (s) 2H	δ_{HA} = 6,87 (d); 1H δ_{HB} = 7,63 (d); 1H J_{AB} = 16	δ_{HC} =7,02 (d);2H δ_{HD} =7,34 (t); 2H δ_{HE} = 7,05 (t);1H J_{CD}=8,6; J_{DE}=8	-
	δ_{CH_3-CO} = 2,47 (s) 3H	-	$\delta_{C_6H_4}$ = 7,80 (m); 3H 8,47 (m); 1H	-
	δ_{CH_2-CO} = 4,14 (s) 2H	-	$\delta_{C_6H_5}$ = 7,34 (m); 5H $\delta_{C_6H_4}$ = 7,75-8,5 (m); 4H	-
	δ_{CH_2-CO} = 4,62 (s) 2H	-	$\delta_{C_{10}H_7;\ C_6H_4}$ = 7,35-8,5 (m); 11H	-
	δ_{CH_2-O} = 5,50 (s) 2H	-	$\delta_{C_{10}H_7;\ C_6H_4}$ = 7,1-8,5 (m); 11H	-
	-	-	$\delta_{C_6H_4;\ C_6H_4}$ = 7,4-8,4 (m);	-
	δ_{CH_2-O} = 4,31 (q) 2H δ_{CH_3} = 1,3 (t) 3H J_{MN} = 7,0	-	$\delta_{C_6H_4}$ = 8,4 (m) 1H 7,7-8,2 (m); 3H	-

Table 2 (continued)

1	2	3	4	5
	δ_{CH_2-CO} = 3,56 (s) 2H	-	$\delta_{C_6H_5}$ = 7,3 (s); 5H $\delta_{C_6H_4}$ = 7,45-7,7 (m); 3H 7,75 (m); 1H	10,32 (b)
	δ_{CH_2-CO} = 3,72 (s) 2H	-	$\delta_{C_6H_5}$ =7,3 (s);5H $\delta_{C_6H_4}$ = 7,85 (m); 4H	11,0 (b)
	δ_{CH_2} = 4,32 (s) 2H	-	$\delta_{C_6H_5}$ = 7,25-7,4 (m); 5H $\delta_{C_6H_4}$ = 7,7-7,75 (m); 3H 7,9-7,94 (m); 1H	-

* s=singlet; d=doublet; t=triplet; q=quartet; m=complex multiplet; b=broad
CD_3SOCD_3 was used as solvent with two exceptions that are mentioned beside the respective formula
** data obtained by authors of this article
*** for this compound Hoffmann and Patel [32] have claimed the N-acylated cyclic maleic hydrazide structure but the properties of the reproduced compound are compatible only with isomeric O-acylated structure (see Discussion and also Table 1)
**** for these compounds Kühle [26] has claimed the N-acylated cyclic maleic hydrazide structure but their ^{1}H-NMR spectra show that they are N-acylaminomaleamic acids (see Discussion)
The cited references are given in square brackets.

Evidently, this indicates the same type of structure, namely that of O-acylderivative (12).

The fact that the N-acylderivatives (3, R=H) of the cyclic maleic-(13) and phthalic-(14) hydrazides were not found among the products of reactions that begin by treating the acyclic hydrazides (5, R^1=acyl) with maleic-, respectively phthalic-anhydride[4,12b,c,13a] (see Scheme 1) is another indirect argument for the O-acylderivatives (12) structure of monoacylation products of cyclic maleic-(13) and phthalic-(14) hydrazides.

The acylation with maleic-, respectively phthalic-anhydride of alkyl- and aryl-hydrazines (5, R^1=alkyl, aryl) is considered a structure proof synthesis for N-alkyl, respectively N-aryl- cyclic maleic-[15,28,38,41-43] or phthalic-[20a] hydrazides (3, R=H, R^1=alkyl, aryl). For this reason it was considered that the analogue acylation of acylhydrazines – namely the acyclic hydrazides (5, R^1=acyl) – with dicarboxylic acid anhydrides (6) led to cyclic N-acylhydrazides (3, R=H)[3,26]. Le Berre and co-workers[4] contested the statemants of Feuer and co-workers[3,14a] by invalidation of the N-acetylated cyclic maleic hydrazide structure (3, R=H, R^1=$COCH_3$) for a product formed as a result of transformations involving, as a first step, the reaction between acethydrazide (5, R^1=acetyl) and maleic anhydride (6, X=-CH=CH). This polemic and other dissagrements[14c,43b] concerning the structure of compounds formed in the

reactions that begin by treating substituted hydrazines (5) and maleic anhydride (see Scheme 1) have determined Feuer research group[15,44] to reconsidered previous apreciations. Furthermore, they tried to explain why the formation of some N-substituted cyclic maleic hydrazide with electron acceptor substitutes, including acyl groups (3, R=H, R^1=acyl) failed[15,44].

To check if N-acylated cyclic hydrazides (3, R=H, R^1=acyl) can be formed under Kühle's given conditions[26] we reproduced his acylation of acethyl hydrazide (5, R^1=$COCH_3$) and of salicylic acid hydrazide (5, R^1=OC-C_6H_4-2-OH) with maleic anhydride. Our products had the Kühle's physical constants (melting points, IR spectra) (see Table 1). Yet, the ^{1}H-NMR spectra of these products (see Table 2) prove unequivocally their acyclic structure, namely that of N-acylaminomaleamic acids (1, R^1=OC-CH_3; OC-C_6H_4-2-OH). Thus, the chemical shift for the olefinic hydrogens ($\delta_{CH=CH}$ ~ 6,35 ppm) has a close value to that of maleic acid ($\delta_{CH=CH}$ ~ 6,2 ppm) and of other N-substituted maleamic or 3-aminocarbonyl propenoic acids ($\delta_{CH=CH}$= 6,25-6,7ppm)[4,12a,15,44,45]. On the other hand, for N-acylated cyclic maleic hydrazides (3, R=H; Y=H, H; R^2=acyl) it would be expected that the chemical shift of olefinic hydrogens ($\delta_{CH=CH}$), have values correspondent to maleic hydrazide (13), respectively their N-alkyl and N-aryl derivatives (3, R=H; Y=H,H; R^2= alkyl, aryl) which are about 7 ppm (see[4,15,35,43a,44,47]). Furthermore, extending the acylation with maleic anhydride, under Kühle's[26] conditions to other acyclic hydrazides (5, R^1 = acyl with the meanings from Scheme 1) we obtained N-acyl-aminomaleamic acids (1, R^1=CO-C_6H_4-4-Cl; izonicotinyl; OC-NH_2) that show in their ^{1}H-NMR spectra a pair of doublets, for the olefinic hydrogens, with a vicinal coupling constant $J^{1,3}_{CH-CH}$ = 11-12 Hz (see Table 2). This value is known to be characteristic for acyclic olefinic hydrogens with Z-(cis) configuration[40b,44]. Otherwise, the N-acylated cyclic maleic hydrazide structure (3, R=H) for Kühle's[26] products is contradicted by the position of IR band, due to $\nu_{C=O}$ stretching vibration, recorded by Kühle at 1708 cm^{-1} for the derivative obtained from p-nitrobenzoic acid hydrazide. This value is characteristic for $\nu_{C=O}$ within the carboxylic group of α,β-unsaturated acids (see[3a,4a,15,39b,44]) to which N-acyl aminomaleamic acids (1) also belong.

We could not obtain[12b] N-acylated cyclic hydrazides (3, R=H, R^1=acyl) either by submission the N-acylaminoamic acids (1, R^1=acyl) to some conditions in which the N-alkyl or N-arylaminoamic acids are cyclocondensed[15,41-46], for instance, to imides (2), isoimides (15) or N-alkylated or N-arylated cyclic hydrazides (3, R=H, R^1=alkyl, aryl)* or to conditions under which the N-acylaminomaleamic acids (1, R^1=acyl; X=-CH=CH) transformation – directly[3] or through the N-acetylaminomaleinimide (2, R=H, R^1=acetyl; X=-CH=CH)[14a] or through the N-acetylaminoisomaleinimide (15, R^1=acetyl; X=-CH=CH)[14c] – to N-acetylated maleic hydrazides (3, R=H; R^1= $COCH_3$; X=-CH=CH) is claimed. In these experiments we however obtained, in accordance with Scheme 1 (see Table 2), a series of new N-acylamino-imides (2) and -isoimides (15)[12b,16b], respectively oxadiazole derivatives (16)[12b,d].

Very probably, the N-acylated cyclic maleic- and phthalic-hydrazides (3, R=H, R^1=acyl) were not found neither in cyclic maleic-(13) and phthalic-(14) hydrazides acylation experiments, or in acylations of acyclic hydrazides (5, R^1=acyl) with

dicarboxylic acid anhydrides (6).This is because of their (3) instability, knowing that they would correspond to triacylhydrazines (N-acylated cyclic diacylhydrazines[31,47]) which are very sensible to solvolysis[3b,4a,b,13a,20a].

In conclussion, we have shown that the claims of those who affirmed the obtainment of N-acylated cyclic hydrazides (3, R=H; R^1=acyl) were not valid.

Simultaneously we have confirmed the O-acyl-derivatives nature (12) of the products isolated by monoacylation of cyclic maleic-(13) and phtalic-(14) hydrazide. This conclussion is entirely compatible with the melting points, IR and ^{1}H-NMR spectra of cyclic maleic-(13) and phthalic-(14) hydrazide monoacylation products.

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* We must also point out here that there are wrong assignments concerning the ^{1}H-NMR published data on the products formed in the transformations that begin by treating maleic anhydride and aryl hydrazine (5, R^1=aryl, Scheme 1). Thus, the characteristic parameters for N-arylaminoisomaleinimides (15, R^1=aryl; X=-CH=CH), respectively for N-arylaminomaleinimide (2, R=H, R^1=aryl; X=-CH=CH) (see[15, 44]), are wrongly assigned[43a, 45] for N-arylated cyclic maleic hydrazides (3, R=H, R^1=aryl; X=-CH=CH).

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The SOUTHERN BRAZILIAN JOURNAL OF CHEMISTRY (ISSN: 2674-6891; 0104-5431) is an open-access journal since 1993. Journal DOI: 10.48141/SBJCHEM.
http://www.sbjchem.com.
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