New Isomeric *N*-substituted Hydrazones of 2-, 3- and 4-Pyridinecarboxaldehydes

Elżbieta Wyrzykiewicz* and Dorota Prukała

Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland

Received September 4, 1997

Eighteen compounds unknown in the literature, *N*-(*E*)-stilbenyloxyalkylcarbonyl- and *N*-(*E*)-stilbenyloxyalkylcarbonylaminoalkylcarbonyl-substituted hydrazones of 2-, 3- and 4-pyridinecarboxaldehydes have been prepared. The stereochemical behavior of these compounds in dimethyl-d_6 sulfoxide solution has been studied by ^{1}H-nmr technique. The *E* geometrical isomers and *cis/trans* amide conformers have been found for *N*-substituted-hydrazones **1-16**.

J. Heterocyclic Chem., **35**, 381 (1998).

The *N*-substituted hydrazones of aromatic aldehydes are well known and are of considerable interest in both spectral analysis [1-8] and analytical chemistry [9,10]. However, so far the synthesis and physicochemical properties of hydrazones of pyridinecarboxaldehydes bearing *N*-(*E*)-stilbenyloxyalkylcarbonylaminoalkylcarbonyl-substituent have not been reported. These compounds containing amide and hydrazone functions in their molecules, seemed to be suitable candidates for further chemical modifications and may be pharmacologically active and analytically useful.

We have previously reported the synthesis and biological activity, as well as mass spectrometric study of *N*-(*E*)-stilbenyloxyalkylcarbonyl-substituted derivatives of amino acids, their methyl esters and hydrazides [11,12]. Our studies have been recently extended to *N*-(*E*)-stilbenyloxyalkylcarbonyl- and *N*-(*E*)-stilbenyloxyalkylcarbonylaminoalkylcarbonyl-substituted hydrazones of 2-, 3- and 4-pyridinecarboxaldehydes **1-18** (Figure 1).

Treatment of the corresponding 2-, 3- and 4-pyridinecarboxaldehydes with the hydrazide of (*E*)-stilbenyloxyacetic acid (or (*E*)-4'-chloro-4-stilbenyloxyacetic acid) in boiling absolute ethanol afforded **1-6** (Figure 1). The same reaction of hydrazides of *N*-(*E*)-stilbenyloxyalkylcarbonyl (or *N*-(*E*)-4'-chlorostilbenyloxyalkylcarbonyl)-substituted β-phenyl-β-alanine, α-alanine and tryptophane afforded **7-9**, **10-15**, and **16-18**, respectively (Figure 1). Reaction of acetone with hydrazides of (*E*)-stilbenyloxyacetic acid, as well as with hydrazides of *N*-(*E*)-stilbenyloxymethylenecarbonyl-substituted β-phenyl-β-alanine and tryptophane provided new *N*-substituted-hydrazones of acetone, **19**, **20** and **21**, respectively (Figure 2). These compounds were included in this paper for comparative purposes. The structures of all compounds obtained were determined by examining their uv/vis, ir and ^{1}H-nmr spectra as well as by elemental analyses (Tables 1-3). The spectral analysis revealed (*E*)-configuration as the geometric isomers in the stilbene part of the molecules of **1-21**.

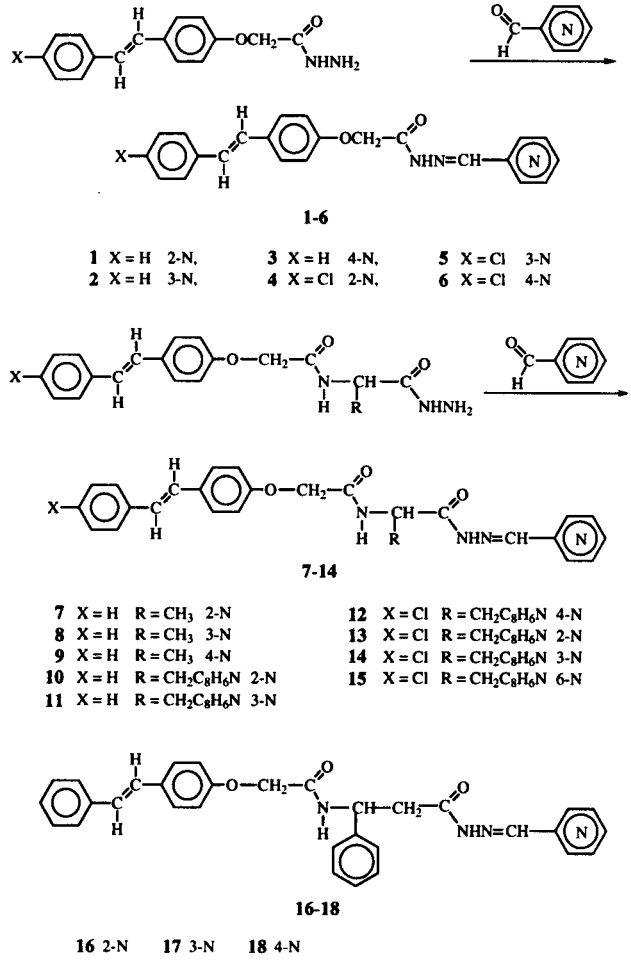


Figure 1

It has been pointed out that in the uv/vis spectra of **1-21** λ max are situated in the range 289.4-303.2 nm (lg ε = 4.52-4.75) (Table 2 and Table 3). On the other hand, the infrared spectra of **1-21** show a strong absorption at 959-968 cm^{-1} which can be attributed to C-H out of plane deformation vibration of the ethylene bridge (Table 2 and Table 3).

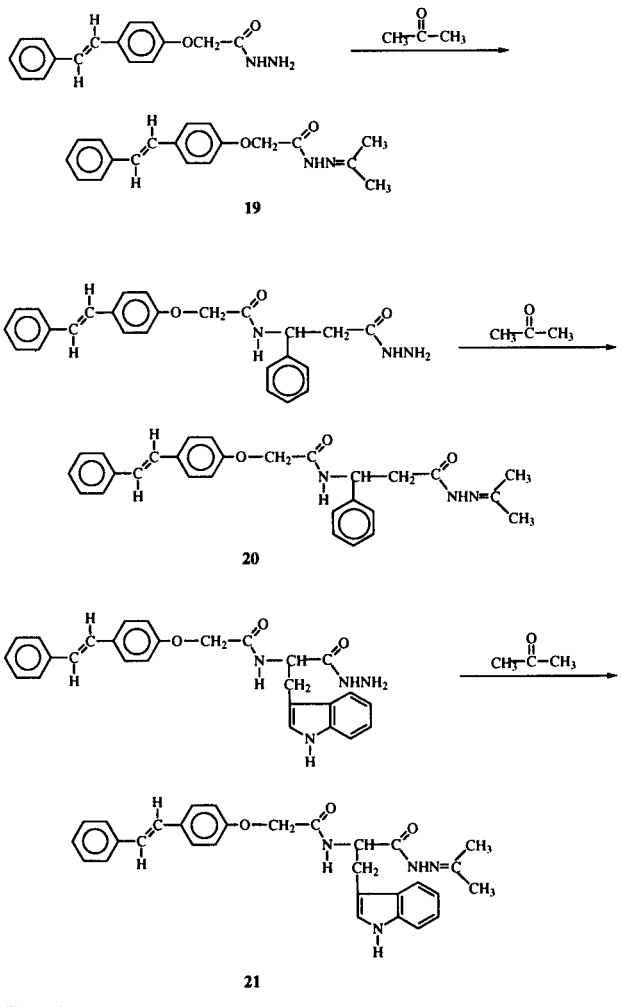


Figure 2

The hydrazones **1-21** may exist as *Z/E* geometrical isomers about C=N double bonds and *cis/trans* amide conformers (Figure 3). According to the literature [3,13] *N*-acyl substituted derivatives of hydrazones of pyridinecarboxaldehydes are present in dimethyl-d_6 sulfoxide solution in the form of geometric *E* isomer about C=N double bond.

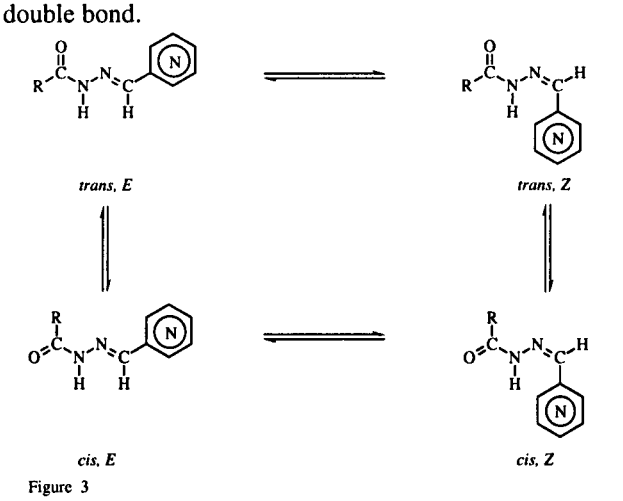


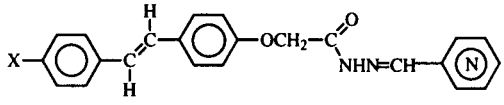
Figure 3

In the cases of *N*-substituted-hydrazones of 2-pyridylcarboxaldehydes, *Z* geometric isomers can be stabilized in less polar solvents by an intramolecular hydrogen bond [13]. The *E/Z* isomer ratio, as well as the ratio of amide *cis/trans* conformers can be easily quantified by nmr techniques. In order to acquire information about the stereochemical behavior of **1-18** in polar dimethyl-d_6 sulfoxide solution we have investigated ^{1}H-nmr spectra of these compounds. We wish to establish whether it is possible to determined from this spectral analysis the ratio of *cis/trans* amide conformers of **1-18**. Our investigations was arrived at as follows.

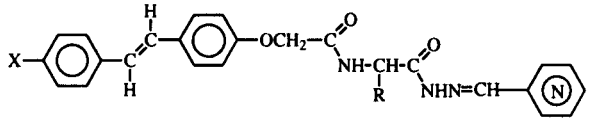
Prior studies of ^{1}H-nmr spectra in dimethyl-d_6 sulfoxide solution of *N*-(*E*)-stilbenyloxymethylenecarbonyl-substituted hydrazone of acetone (**19**) established the values of the chemical shifts of protons of the molecule investigated (Table 4). This compound shows simpler spectrum, as it lacks the possibility of *E/Z* geometrical isomers about the C=N double bond. In the investigated ^{1}H-nmr spectrum of **19** are seen two sets of singlets of methylene and imine protons around δ 5.00 and 4.67, as well as δ 10.44 and 10.22 respectively (**a** and **2**, Table 4). According to the data dealing with the ^{1}H-nmr assignments of protons of *N*-acetyl-substituted hydrazone of acetone [13] the singlets at δ 5.00 and δ 10.44 are associated with protons of the *cis* amide conformer of **19**, as well as singlets at δ 4.67 and δ 10.22 of the *trans* amide conformer of **19**. The rate of *cis/trans* isomerization of **19** in dimethyl-d_6 sulfoxide has been followed by ^{1}H-nmr at several temperatures (25, 70, 90, 100°) in order to evaluate the energy barrier of *cis→trans* conversion (Figure 4). The coalescence of methylene group of **19** conformers present in dimethyl-d_6 sulfoxide solution occured at about 100°. The ΔG# values of 18.33 and 18.06 kcal/mol were found by dynamic nmr, using the well known coalescence-temperature method [15]. The intensities of the ^{1}H signals at δ 5.00 and 4.67 ppm have allowed us to make measurements of the ratio of *cis/trans* amide conformers. Chemical shifts and percentage of conformers of **19** in dimethyl-d_6 sulfoxide are summarized in Table 4. It ought to be pointed out that the ratio of the conformers at 25° is the same as that measured at the same temperature at the end of the experiment dealing with the coalescence temperature. This is the proof that in the dimethyl-d_6 sulfoxide solution of **19** investigated, the conversion of *cis/trans* amide conformers has been the only process of isomerization.

In the ^{1}H-nmr spectra of *N*-substituted-hydrazones of acetone, **20** and **21** are seen also two sets of protons of methylene, methine as well as imine groups (a, b **1** and **2**, Table 4). According to the literature [13] the upfield lines of methylene, methine and imine protons have been assigned to amide conformers *cis*, and downfield lines of

Table 1

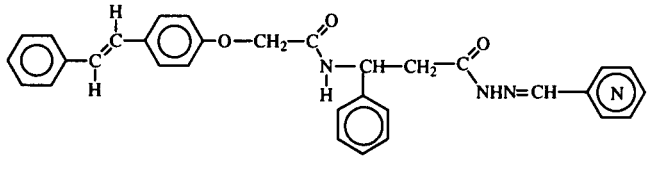


1-6



7-15

Compound	R	N	X	Formula (molecular weight)	Mp [°C]	Yield [%]	R_f TLC	Reaction time hours	Crystallization Solvent
1	-	2-	H	$C_{22}H_{19}N_3O_2$ 357.15	181-183	74	0.57	1.0	Ethanol/ dimethylformamide 100/1
2	-	3-	H	$C_{22}H_{19}N_3O_2$ 357.15	205-206	85	0.67	3.0	Ethanol
3	-	4-	H	$C_{22}H_{19}N_3O_2$ 357.15	218-220	88	0.46	2.0	Ethanol
4	-	2-	Cl	$C_{22}H_{18}N_3O_2Cl$ 391.11	211-213	83	0.75	2.0	Ethanol/ dioxane 10/1
5	-	3-	Cl	$C_{22}H_{18}N_3O_2Cl$ 391.11	243-244	71	0.62	1.5	Dioxane
6	-	4-	Cl	$C_{22}H_{18}N_3O_2Cl$ 391.11	232-234	84	0.60	1.0	Ethanol
7	CH_3	2-	H	$C_{25}H_{24}N_4O_3$ 428.49	201-203	82	0.76	2.0	Ethanol
8	CH_3	3-	H	$C_{25}H_{24}N_4O_3$ 428.49	253-255	78	0.63	2.0	Ethanol/ dimethylformamide 100/1
9	CH_3	4-	H	$C_{25}H_{24}N_4O_3$ 428.49	257-259	72	0.58	2.5	1-Propanol
10	$CH_2C_8H_6N$	2-	H	$C_{33}H_{29}N_5O_3$ 543.63	224-226	74	0.70	2.0	Ethanol/ dimethylformamide 100/1
11	$CH_2C_8H_6N$	3-	H	$C_{33}H_{29}N_5O_3$ 543.63	207-209	62	0.59	2.0	Methanol
12	$CH_2C_8H_6N$	4-	H	$C_{33}H_{29}N_5O_3$ 543.63	243-245	69	0.67	2.5	1-Propanol
13	$CH_2C_8H_6N$	2-	Cl	$C_{32}H_{28}N_5O_3Cl$ 578.08	138-140	69	0.58	2.5	Ethanol
14	$CH_2C_8H_6N$	3-	Cl	$C_{32}H_{28}N_5O_3Cl$ 578.08	228-230	83	0.54	2.0	Ethanol
15	$CH_2C_8H_6N$	4-	Cl	$C_{32}H_{28}N_5O_3Cl$ 578.08	234-246	83	0.45	2.5	Ethanol



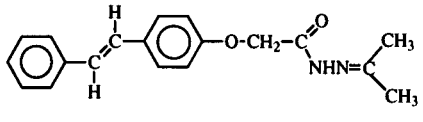
16-18

16	-	2-	H	$C_{31}H_{28}N_4O_3$ 504.59	189-191	71	0.77	1.5	1-Propanol
17	-	3-	H	$C_{31}H_{28}N_4O_3$ 504.59	236-238	75	0.84	1.0	1-Propanol
18	-	4-	H	$C_{31}H_{28}N_4O_3$ 504.59	232-234	89	0.74	1.5	1-Propanol

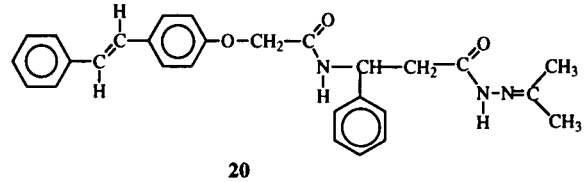
Table 2

Compound	UV/VIS λ_{max} [nm] (log ε)	IR δ_{CH} [cm^{-1}] CH=CH (*E*)	Analysis Calcd. C	H	N	Found C	H	N
1	302.0 (4.69)	966	73.95	5.32	11.76	73.54	5.00	11.80
2	302.2 (4.75)	961	73.95	5.32	11.76	73.70	5.40	11.70
3	302.2 (4.74)	966	73.95	5.32	11.76	73.80	5.10	11.52
4	302.1 (4.69)	966	67.43	4.59	10.71	67.12	4.40	10.80
5	301.8 (4.68)	966	67.43	4.59	10.71	67.60	4.32	10.31
6	301.0 (4.61)	960	67.43	4.59	10.71	67.20	4.48	10.70
7	294.6 (4.68)	964	70.08	5.65	13.08	69.90	5.30	13.10
8	298.2 (4.65)	962	70.08	5.65	13.08	69.80	5.60	13.10
9	291.4 (4.69)	965	70.08	5.65	13.08	69.90	5.50	13.11
10	291.8 (4.68)	963	72.93	5.34	12.89	72.60	5.60	12.60
11	289.6 (4.73)	967	72.93	5.34	12.89	72.70	5.20	12.70
12	289.8 (4.69)	961	72.93	5.34	12.89	72.80	5.40	12.50
13	303.0 (4.58)	966	68.56	4.88	12.12	68.20	4.80	11.90
14	290.8 (4.52)	967	68.56	4.88	12.12	68.25	4.70	11.90
15	289.4 (4.66)	966	68.56	4.88	12.12	68.25	4.80	11.80
16	294.6 (4.71)	964	73.81	5.56	11.12	73.60	5.50	11.10
17	289.4 (4.63)	959	73.81	5.56	11.12	73.50	5.30	11.10
18	289.4 (4.63)	961	73.81	5.56	11.12	73.50	5.50	10.90

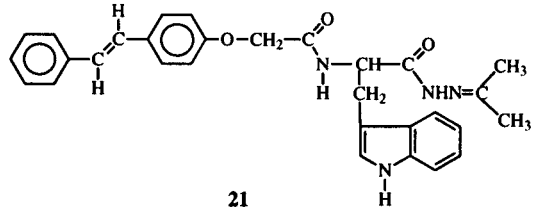
Table 3



19



20

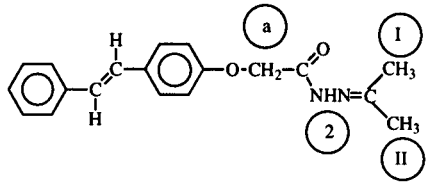


21

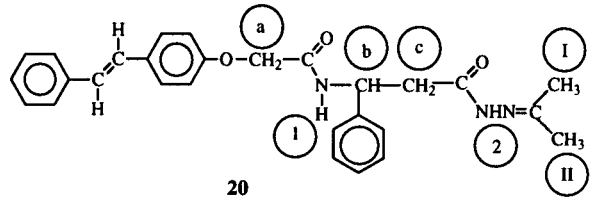
Compound	Formula (molecular weight)	Mp [°C]	Yield [%]	R_f TLC	Solvent	UV/VIS λ_{max} [nm] (log ε)	IR δ_{CH} [cm^{-1}] CH=CH (*E*)	Analysis (Calcd./Found) C	H	N
19	$C_{22}H_{19}N_3O_2$ 357.15	175-177	89	0.85	1-Propanol	303.2 (4.61)	966	74.03 74.21	6.49 6.42	9.09 8.98
20	$C_{22}H_{19}N_3O_2$ 357.15	200-202	79	0.89	1-Propanol	303.0 (4.66)	965	73.85 73.62	6.37 6.38	9.23 9.19
21	$C_{22}H_{19}N_3O_2$ 357.15	249-251	85	0.84	1-Propanol	302.8 (4.62)	966	72.87 72.69	6.07 5.98	11.34 11.06

Table 4

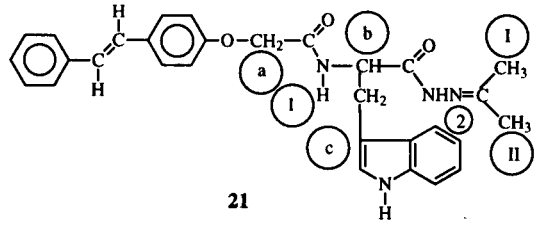
^{1}H NMR Chemical Shifts of *N*-substituted Hydrazones of Acetone **19-21** [a]



19



20



21

Compound	a	b	c	l	2	3	Ar	I	II	Percentage of Conformer
19	5.00 s	-	-	-	10.44 s	-	6.86-7.57 m	1.88 s	1.95 s	59 *cis*
	4.67 s	-	-	-	10.22 s	-				41 *trans*
20	4.51 s	5.36 q	2.86-3.09 m	8.29 d	10.37 s	-	6.87-7.62 m	1.89 s	2.00 s	59 *cis*
	4.49 s	4.85 q	-	8.40 d	10.23 s	-		1.80 s	1.94 s	41 *trans*
21	4.51 s	5.36 q	2.86-3.09 m	8.23 d	10.29 s	10.87 d	6.83-7.70 m	1.87 s	2.00 s	51 *cis*
	4.49 s	4.85 q	1.37 d	8.40 d	10.22 s	-		1.74 s	1.91 s	49 *trans*

s - singlet, d - doublet, q - quartet, m - multiplet.

[a] Spectra determined in dimethyl-d_6 sulfoxide at 25° and shifts are reported in ppm (δ) downfield from tetramethylsilane.

protons of the same groups to amide conformers *trans*. The chemical shifts and percentage of conformers of **20**, **21** in dimethyl-d_6 sulfoxide solution are summarized in Table 4. The *cis* and *trans* amide conformers of **21** are present in the solution investigated in about the same amount, however in the cases of **19** and **20** the *cis* form is predominant. Having established the ratio of *cis/trans* the conformers of **19-21** in dimethyl-d_6 sulfoxide solution, we have applied the similar methodology in establishing the ratio of conformers **1-16** in the same solution; compounds **17** and **18** are insoluble in dimethyl-d_6 sulfoxide. The chemical shifts and percentage of conformers **1-16** are summarized in Table 5.

The investigation of ^{1}H-nmr spectra of **1-16** and **19-21** demonstrated that these hydrazones behave similarly in dimethyl-d_6 sulfoxide solution. When dissolved in this solvent, the *E* geometrical isomers of these compounds undergo a rapid *cis/trans* amide equilibrium, with the *cis* conformer predominating.

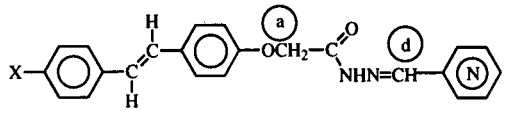
It is also clear that the position of the annular nitrogen atom in the phenyl ring of hydrazones **1-16** has no influence on the ratio of *cis/trans* amide conformers of these compounds.

EXPERIMENTAL

The purity of all described compounds was monitored by mp and tlc. The melting points (uncorrected) were determined on a Böetius microscope hot stage. R_f values to silica gel F_{254} tlc plates (Merck) were developed with chloroform/methanol 5:1 and observed under uv light (λ = 254 and 366 nm). The uv-vis spectra were recorded on a Specord uv/vis spectrophotometer in methanol solution. The ir spectra were recorded on a Perkin-Elmer M-180 Spectrophotometer in potassium bromide pellets. The ^{1}H-nmr spectra were determined on a Varian Gemini 300 (300 MHz) in dimethyl-d_6 sulfoxide solution with tetramethylsilane as internal standard. All chemical shifts are quoted in δ values. Elementary analyses were performed on a Perkin-Elmer 240C-CHN analyzer.

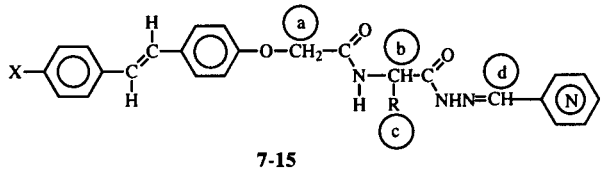
Table 5

^{1}H NMR Chemical Shifts of *N*-substituted Hydrazones of Pyridinecarboxaldehydes **1-16**



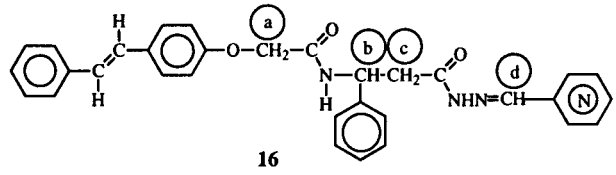
1-6

Compound	a	d	Ar	Percentage of Conformer	
1	5.23 s	8.83 s	6.97-8.61 m	*cis*	64
	4.76 s	8.39 s		*trans*	36
2	5.15 s	8.02 s	6.94-8.83 m	*cis*	63
	4.69 s	8.45 s		*trans*	37
3	5.22 s	8.01 s	6.96-8.66 m	*cis*	64
	4.74 s	8.35 s		*trans*	36
4	5.23 s	8.08 s	6.97-8.62 m	*cis*	64
	4.76 s	8.39 s		*trans*	36
5	5.22 s	8.07 s	6.97-8.94 m	*cis*	64
	4.74 s	8.42 s		*trans*	36
6	5.22 s	8.01 s	6.96-8.65 m	*cis*	65
	4.75 s	8.34 s		*trans*	35



7-15

Compound	a	b	c	d	Ar	Percentage of Conformer	
7	4.59 s	5.24 q	1.38 d	8.83 s	6.97-7.58 m	*cis*	57
	4.60 s	4.45 q	1.37 d	8.39 s		*trans*	43
8	4.58 s	5.22 q	1.38 d	8.02 s	6.97-8.84 m	*cis*	52
	4.59 s	4.44 q	1.37 d	8.45 s		*trans*	48
9	4.58 s	5.22 q	1.38 d	8.01 s	6.97-8.64 m	*cis*	54
	4.59 s	4.44 q	1.37 d	8.35 s		*trans*	46
10	4.55 s	5.57 q	1.38 d	8.08 s	6.86-8.63 m	*cis*	56
	4.54 s	4.72 q	1.37 d	8.39 s		*trans*	44
11	4.53 s	5.56 q	3.1 d	8.07 s	6.85-8.36 m	*cis*	56
	4.52 s	4.72 q	3.3 d	8.42 s		*trans*	44
12	4.54 s	5.56 q	3.1 d	8.01 s	6.85-8.66 m	*cis*	57
	4.52 s	4.70 q	3.3 d	8.34 s		*trans*	43
13	4.54 s	5.56 q	3.1 d	-	6.86-8.42 m	*cis*	56
	4.53 s	4.71 q	3.3 d			*trans*	44
14	4.58 s	5.60 q	3.1 d	-	6.86-8.63 m	*cis*	54
	4.57 s	4.76 q	3.3 d			*trans*	46
15	4.54 s	5.56 q	3.1 d	-	6.86-8.64 m	*cis*	56
	4.53 s	4.71 q	3.3 d			*trans*	44



16

16	4.54 s	5.50 q	3.0 d	8.05 s	6.86-8.63 m	*cis*	51
	4.53 s	4.69 q	3.2 d	8.25 s	-	*trans*	49

Compounds **17** and **18** are insoluble in dimethyl-d_6 sulfoxide.

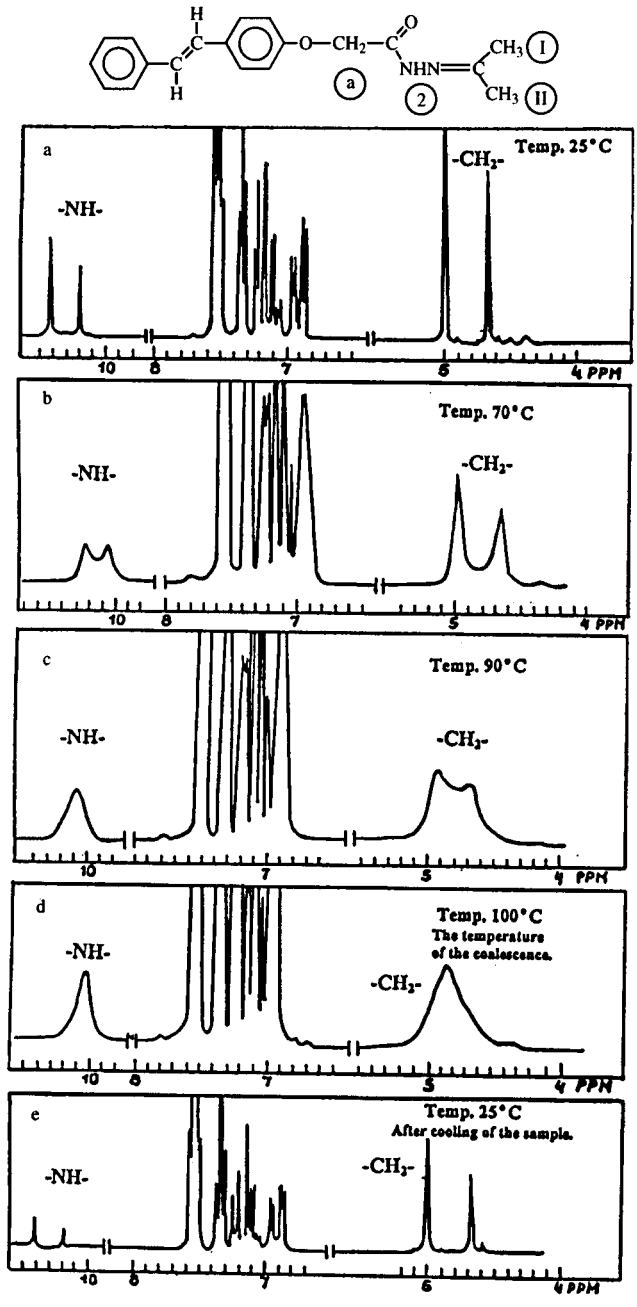


Figure 4.

Hydrazides of (*E*)-stilbenyloxyalkylcarboxylic acids [16] and hydrazides of *N*-(*E*)-stilbenyloxyalkylcarbonyl-substituted β-phenyl-β-alanine [11] and tryptophane were obtained as reported in the literature.

Synthesis of *N*-(*E*)-stilbenyloxyalkylcarbonyl-substituted Hydrazones of 2-, 3- and 4-Pyridinecarboxaldehydes **1-6**.

General Procedure.

To a boiling solution of 10^{-3} mole of the corresponding hydrazide of (*E*)-stilbenyloxyalkylcarboxylic acid in 50 ml of absolute ethanol the solution of 3 x 10^{-3} mole of the corresponding 2-, 3- and 4-pyridinecarboxaldehyde was added dropwise. The reaction mixture was refluxed for 1-3 hours (Table 5). Then the half of volume of solvent was evaporated on a rotatory evaporator and the residue was cooled and the precipitated solid was filtered, dried and recrystallized from the solvent selected (Table 3).

The Synthesis of *N*-(*E*)-stilbenyloxyalkylcarbonylaminoalkylcarbonyl-substituted Hydrazones of 2-, 3- and 4-Pyridinecarboxaldehydes **7-18**.

To a boiling solution of 1 x 10^{-3} mole of the corresponding hydrazide of *N*-(*E*)-stilbenyloxyalkylcarbonyl-substituted β-phenyl-β-alanine (α-alanine, tryptophane) in 50 ml of absolute ethanol, a solution of 3 x 10^{-3} mole of the selected 2-, 3- or 4-pyridinecarboxaldehyde in 30 ml of absolute ethanol was added. The mixture reaction was then refluxed for 1-2.5 hours (Table 1). Then half of the volume of solvent was evaporated and the residues were cooled in the refrigerator for 24 hours. The precipitated solids of **7-18** were filtered, dried and recrystallized from solvent noted (Table 1).

The Synthesis of *N*-(*E*)-stilbenyloxymethylenecarbonylaminoalkylcarbonyl-substituted Hydrazones of Acetone **19-21**.

General Procedure.

A solution of 1 x 10^{-3} mole of the hydrazide of (*E*)-stilbenyloxyacetic acid or hydrazide of *N*-(*E*)-stilbenyloxymethylenecarbonyl-substituted β-phenyl-β-alanine (tryptophane) in 60 ml of acetone was refluxed for 3 hours. Then half of the volume of acetone was evaporated on a rotatory evaporator and the residue was cooled in the refrigerator for 3 hours. The crystals which formed were filtered, dried and recrystallized from solvent reported (Table 2).

REFERENCES AND NOTES

[1] C. Colonna, A. Cosé-Barbi, A. Massat, R. Ben Abdelmoumene and J. P. Doucet, *Bull. Soc. Chim. Belg.*, **102**, 58 (1993).

[2] D. Hadži and J. Jan, *Spectrochim Acta*, **23A**, 577 (1967).

[3] G. Palla, L. Pellizi and G. Predieri, *Gazz. Chim. Ital.*, **112**, 339 (1982).

[4] G. Ostrogovich, F. Kerek and Z. Simon, *Rev. Roum. Chim.*, **15**, 1453 (1970).

[5] G. Ostrogovich, F. Kerek and Z. Simon, *J. Chem. Soc. (B)*, 541 (1971).

[6] E. Hückel, *Z. Physik.*, 423 (1930).

[7] D. Y. Curtin, E. J. Grubbe and C. G. McCarty, *J. Am. Chem. Soc.*, **88**, 2775 (1966).

[8] H.-O. Kalinowski and H. Kessler, *Top. Stereochem.*, **7**, 295 (1973).

[9] A. Casoli, A. Mangis and G. Predieri, *Anal. Chem.*, **57**, 561 (1985).

[10] M. Gallego, M. Garcia Vargas and M. Valcarcel, *Analyst*, **104**, 613 (1979).

[11] E. Wyrzykiewicz and D. Prukała, *Pol. J. Chem.*, **66**, 763 (1992).

[12] E. Wyrzykiewicz and D. Prukała, *Org. Mass Spectrom.*, **29**, 347 (1994).

[13] G. Palla, G. Predieri and P. Domiano, *Tetrahedron*, **42**, 3649 (1986).

[14] I. A. Litwinov, O. N. Kataeva, L. V. Ermolaeva, G. A. Vagina, T. V. Troepol'skaya and V. A. Naumov, *Izv. Akad. Nauk SSSR*, 75 (1991).

[15] H. Shanan-Atidi and K. H. Bar-Eli, *J. Phys. Chem.*, **74**, 961 (1970).

[16] E. Wyrzykiewicz, J. Kępka and W. Prukała, *Pol. J. Chem.*, **62**, 25 (1988).