PYRIDAZINE IZOMERS WITH BIOLOGICAL ACTIVITY

IZOMERI PIRIDAZINICI CU ACTIVITATE BIOLOGICĂ

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Abstract. *Isomers are chemical compounds different from each other, with individualized physical and chemical properties. Dimethyl 2-butenoate is a symmetricall substitued alkene, with two isomeric structures: cis (dimethyl maleate) and trans (dimethyl maleate). By the addition reaction of dimethyl 2-butenoate to pyridazine salts, pyridazine isomeric derivatives are obtained. The existence of isomeric structures was proven spectrally. The biological effect of pyridazine isomers was analyzed, through tests, carried out in special chambers with controlled temperature. The results proveded the influence of the tested compounds in the germination process of wheat seeds, in the development and weight of the fresh seedlings.*
Key words: isomers, synthesis of pyridazine isomers, biological properties

Rezumat. *Izomerii sunt compuși chimici diferiți între ei, cu proprietăți fizice și chimice bine individualizate. 2-butenoatului de dimetil este o achenă activată simetric substituită, cu două structuri izomere: cis (maleat de dimetil) și trans (fumarat de dimetil). Prin reacția de adiție a 2-butenoatului de dimetil la săruri de piridazină se obțin heterociclii piridazinici izomeri. Existența structurilor izomerice a fost dovedită spectral. Efectul biologic al izomerilor de piridazină a fost urmărit, prin teste minuțioase, realizate în camere speciale, cu temperatură controlată. Rezultatele au relevat influența compușilor testați în procesul de germinare a semințelor de grâu, în dezvoltarea și greutatea plantulelor în stare proaspătă.*
Cuvinte cheie: izomeri, sinteză izomeri piridazinici, proprietăți biologice.

INTRODUCTION

The concept of *Chemical structure* was introduced in 1861 by Alexander Butlerov and referred to the way in which the atoms of a molecule are connected (Leicester, 1940). So, for a chemical formula, can be several chemical structures (distinct arrangements of atoms in space).

Molecules with identical atoms, but different structures, are isomers. In other words, isomers are chemical individuals different from each other, with well individualized physical and chemical properties (Petrucci and Herring, 2002).

Dimethyl 2-butenoate is a symmetricall substitued alkene, with two isomeric structures: dimethyl maleate (cis-isomer) and dimethyl fumarate (trans-isomer).

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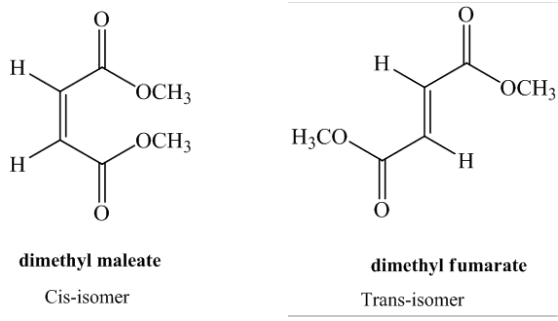


Fig. 1. DIMETHYL MALEATE AND DIMETHYL FUMARATE

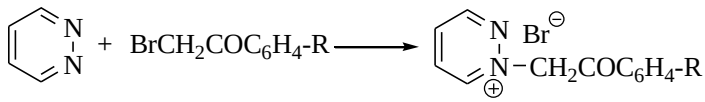
According to recent studies from the literature, the pyridazine derivatives are successfully used as intermediates in the synthesis of products with pharmacological properties (Allad, 1963), in analytical chemistry (Surpățeanu and Rucinschi, 1974), polymer chemistry (Mangalagiu, 2001) physics (Kawamura, 1990), science and technology of materials (Tanaka, 1996). Furthermore, the data presented in the literature testify the phytotoxic action of the pyridazine derivatives and demonstrates the possibility to use them as potential biostimulant in growth and development of horticultural plants with potential practical applications as insecticides, herbicides and pesticides (Mangalagiu et al., 2005; Tucaliuc *et al*., 2008).

In this respect, the study present the synthesis of isomeric pyridazine, the existence of isomeric structures by spectral analysis and their biological effect.

MATERIAL AND METHOD

For synthesis of isomeric pyridazine, according to the literature (Tucaliuc and Mangalagiu, 2009), the following steps were done:

1. *N-ALKYLATION REATIONS*, by treating pyridazine with ω-brom-acetophenone-p-R-substituited:



(**1**) R= F
(**2**) R= Cl
(**3**) R= CH_3

Fig. 2. N-ALKYLATION REATIONS

The reactions take place mole by mole, in benzene anhydrous, in 3 hours at room temperature, by stirring. After filtered off and dried *in vacuum*, were obtained compounds (**1-3**) as crystals with good yield (η>92 %). No purification required. They are stable in air and light and can be stored at room temperature for indefinite period of time.

2. *CYCLOADDITION REACTION*, by treating compounds (**1-3**) with dimethyl maleate (cis-isomer) and dimethyl fumarate (trans-isomer). The reactions take place in alkaline medium, by heating (relux), stiring and finally - solvent evaporation. Were obtained the coumponds (**4-9**).

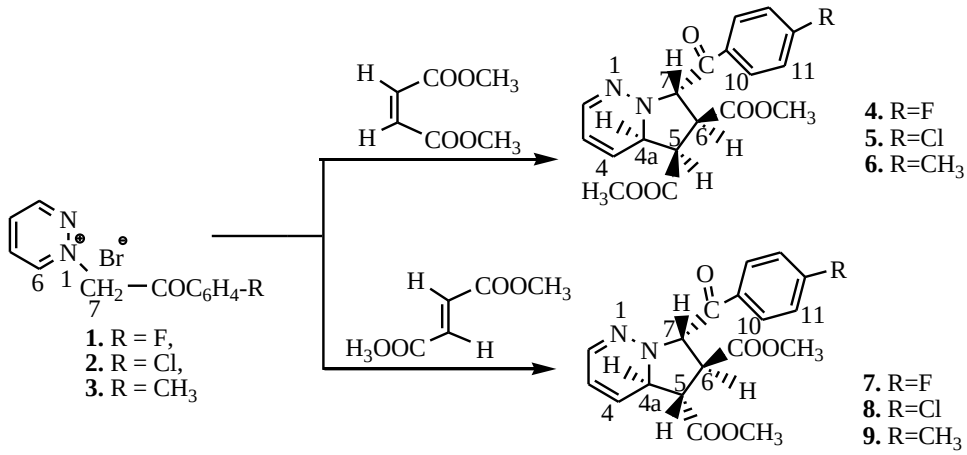


Fig. 3. CYCLOADDITION REACTION

The structures and the spectral analyses proved the existence of isomers:
- compound (**4**) is isomer with compound (**7**);
- compound (**5**) is isomer with compound (**8**);
- compound (**6**) is isomer with compound (**9**).

For the isomeric pyridazine (compounds **4**-**9**) were tested their effects on seed germination and growth of wheat seedlings. Thus, fifty seed samples of wheat were treated with 5 mL of each $5 \cdot 10^{-3}$ molar solutions of compounds (**4-9**). A blank with redistilled water was also carried out (**B**), and all the determinations were performed in triplicate or duplicate.

The seeds were periodically watered and the percent of germinated seeds were reported 3 days later (energy of germination, **EG**) and 7 days later (the germination rate, **GR**), respectively. A seed with visible coleorhizae was considered germinated. Young wheat plants were harvested from their seeds, measured (**H**, expressed as cm) and weighed (**W**, expressed as grams).

RESULTS AND DISCUSSIONS

The structure of the obtained isomeric pyridazine was proven by elemental and spectral analysis: IR, ^{1}H NMR and ^{13}C NMR.

The most informative signals are summarized in table 1.

Table 1

The representative signals for coumponds (4-9) in IR, ^{1}H NMR and ^{13}C NMR spectra.

Comp.	IR (ν, cm^{-1})	^{1}H-RMN (δ, ppm)	^{13}C-RMN (δ, ppm)
4. (R=F) ***CIS***	1728 (CO ester), 1674 (CO keto)	**H_5:** 3.45-3.42 (*J* = 7.2; 5.2) **H_6:** 3.99-3.96 (*J* = 7.2) **H_{4a}:** 4.42-4.39 (*J*= 5.2; 5.6) **H_7:** 5.87-5.85 (*J* = 7.2)	**C_6,:** 46.65 **C_5:** 51.95 **C_{4a}:** 59.27 **C_7:** 70.19
7. (R=F) ***TRANS***	1737 (CO ester), 1687 (CO keto)	**H_5,H_6:**3.79-3.72 (*J*=9.2;6.5) **H_{4a}:** 4.30-4.27 (*J*= 9.2; 5.2) **H_7:** 5.82-5.81 (*J* = 6.8)	**C_6,:** 46.65 **C_5:** 52.11 **C_{4a}:** 55.41 **C_7:** 73.53
5. (R=Cl) ***CIS***	1720 (CO eter), 1683 (CO keto)	**H_5:** 3.45-3.42 (*J* = 7.6; 5.6) **H_6:** 3.99-3.95 (*J* = 7.6) **H_{4a}:** 4.40-4.37 (*J*= 5.6; 5.2) **H_7:** 5.85-5.83 (*J* = 6.8)	**C_6,:** 42.74 **C_5:** 54.20 **C_{4a}:** 59.20 **C_7:** 70.42
8. (R=Cl) ***TRANS***	1731 (CO esterică) 1684 (CO keto)	**H_5,H_6:** 3.79-3.72 (*J* = 9.2) **H_{4a}:** 4.30-4.26 (*J* = 5.6) **H_7:** 5.81-5.79 (*J* = 6.8)	**C_6,:** 46.61 **C_5:** 52.60 **C_{4a}:** 55.41 **C_7:** 73.49
6. ($R=CH_3$) ***CIS***	1722 (CO esterică), 1672 (CO cetonică)	**H_5:** 3.45-3.42 (*J* = 7.6, 5.6) **H_6:** 3.99-3.96 (*J*= 7.6; 7.2) **H_{4a}:** 4.43-4.41 (*J*= 5.2; 4.4) **H_7:** 5.91-5.89 (*J* = 6.8)	**C_6,:** 42.80 **C_5:** 52.70 **C_{4a}:** 59.22 **C_7:** 69.88
9. ($R=CH_3$) ***TRANS***	1738 (CO ester), 1673 (CO keto)	**H_5,H_6:** 3.80-3.70 (*J* = 9.2) **H_{4a}:** 4.32-4.29 (*J* = 5.2) **H_7:** 5.86-5.84 (*J* = 7.2)	**C_6,:** 46.70 **C_5:** 52.74 **C_{4a}:** 55.70 **C_7:** 73.57

The data from tables 1 prove the proposed structures for the isomers pyridazine, because all the signals appear at correct values.

In table 2 are summarized the effect of the izomers with pyridazinic structure (compounds **4 - 9**) on wheat germination.

Table 2

Effect of isomers pyridazine on wheat germination

Coumpond	Germination Rate (GR, %)	Number of plantlets in the lot
8 (R = F) *cis*	73 ± 5	34 ± 3
11 (R = F) *trans*	0± 0	0 ± 0
9 (R = Cl) *cis*	49 ± 6	22 ± 1
12 (R = Cl) *trans*	40 ± 5	28 ± 5
10 (R = CH_3) *cis*	81± 5	37 ± 2
13 (R = CH_3) *trans*	79 ± 4	36 ± 6
B	88 ± 5	38 ± 1

In table 3 are summarized the effect of the isomers pyridazine (compounds **4-9**) on wheat seedling growth (the total height of plantlets in the lot, H, the mean height of plantlets in the lot, Hm, the weight of plantlets in the lot, W, and the mean weight of plantlets in the lot, Wm, were determined).

Table 3

Effect of isomers pyridazine on wheat germination

Coumpond	H (cm)	M (g)
4 (R = F) *cis*	185.8 ± 32.5	1.11 ± 0.19
7 (R = F) *trans*	0	0
5 (R = Cl) *cis*	41.3 ± 0.3	0.78 ± 0.01
8 (R = Cl) *trans*	38.4 ± 31.4	0.78 ± 0.08
6 (R = CH_3) *cis*	177.3 ± 9.9	0.94 ± 0,30
9 (R = CH_3) *trans*	176.4 ± 31.4	0.98 ± 0.08
B	223.7 ± 23.2	1.42 ± 0.19

The data from tables 2 and 3, indicate that the isomers pyridazine influenced the germination process of the wheat seeds and also the seedling growth.

The compound **7,** proved to be noxious, because killing all the seeds. For the compound **4 (**isomer with **7)**, a good germination rate is characteristic. The

treatments with this compound proved the best results, because it stimulated the number of seedlings, the height and the weight plants.

For compounds **6** and their isomers **9** the values for parameter proved a low germination rate and a low reduced for the number of plantlets and for the weight.

For compounds **5** and their isomers **8** the values for parameter proved a decrease in the germination, the height and the weight of the shoots.

The differences in the parameters, when fluorine and chlorine were replaced by methyl, appear probably due to the steric effects by the other groups and radicals in the molecule.

CONCLUSIONS

1. By cycloaddition reaction were synthesized isomers pyridazine (**4-9**).

2. Coumpond **7** is noxious because killing all the seeds and coumpond **4** isomer with **7**) stimulated the seedlings, the height and the weight plants.

3. Isomeric pyridazine influence germination rate, shoot and root length and fresh weights as a function of structure of each investigated compound.

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