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SYNTHESIS STUDY OF NEW 2- SUBSTITUTED IMIDAZOLINES WITH POTENTIAL HYPOTENSIVE ACTIVITY

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ABSTRACT: *A theoretical study based on molecular mechanics and semi-empirical calculations of the condensation mechanism of methyl p-amidosulphonyl phenoxyacetate with ethylene diamine is reported. Synthesis of 17 new imidazolines derived from sulphonamidated phenoxyacetic acids is also described.*

RESUMO *Este trabalho relata os resultados de um estudo teórico baseado em mecânica molecular e cálculos semiempíricos para o mecanismo de condensação do metil-p-amidosulfonil fenoxiacetato com etileno diamina. A síntese de 17 novas imidazolinas derivadas de ácidos fenoxiacéticos sulfonamidados é também descrita.*

KEYWORDS: 2-substituted imidazoline, sulphonamidated phenoxyacetic acid derivatives, hypotensive imidazolines

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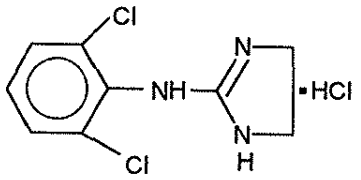
INTRODUCTION

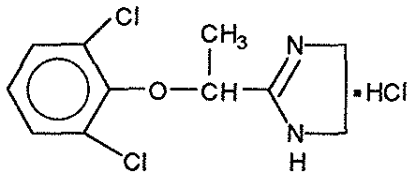
The systematic syntheses and pharmacological studies of numerous imidazolines substituted in the 2-position resulted in compounds with various biological activities (e.g. analgesic, antidepressant, antihelmintic, antihypertensive, vasopressor, hypotensive) [1].

Referring to the imidazolines acting on the high blood pressure only, these could be divided in two classes [1-3]. The first class consists in 2-substituted imidazolines with specific cardiovascular actions (e.g. Clonidine® and Lofexidine®). They have central antihypertensive properties being useful in treating the essential high blood pressure.

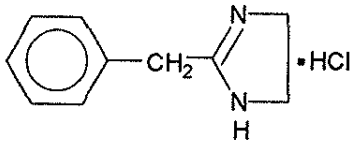
The imidazolines substituted in the 2- position which act on the vegetative nervous system are included in the second class. These ones (e.g. Periphen®) induce hypotensive responses being used for the periferic vasoconstricting disturbances.



Clonidine



Lofexidine



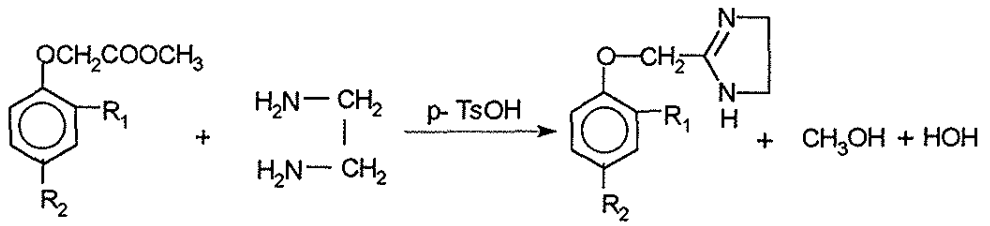
Periphen

In the present paper a study on the obtaining of some imidazolines derived from sulphonamidates phenoxyacetic acids with a possible hypotensive action (i.e. of second class type), is reported.

Some pharmacodynamical studies on such products [e.g. 2-(4-amidosulphonyl-phenoxymethylene)- imidazoline and 2-(4-amidosulphonyl-2-methyl-phenoxymethylene)-imidazoline] showed significant changes in arterial blood pressure when having been administred to dogs. In

addition, the sulphonamidated aryloxymethylene group exhibited an extremely low toxicity, even in high doses [4].

2- Substituted imidazolines have been synthesized by the condensation of ethylene diamine (EDA) with methyl esters of sulphonamidated phenoxiacetic acids in the presence of a condensing agent (p-toluenesulphonic acid, p-TsOH) and anhydrous methyl alcohol as solvent, following the scheme described below [4,5].



where: R_1= *Cl, CH*$_3$; R_2= SO_2NH_2, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2N(C_3H_7)_2$, $SO_2N(C_4H_9)_2$, *SO*$_2$*NH-i Pr, SO*$_2$*NH-t Bu, pyrrolydinosulphonyl, piperazinosulphonyl*

In order to obtain some theoretical informations on the condensation mechanism between esters and EDA in acid catalysis, a modelling study based on molecular mechanics and semi-empirical calculations has been performed.

EXPERIMENTAL AND METHODS

Computational Details

The modelling of the condensation process was done with the aid of the HyperChem 4.5 software.

All calculations have been performed after geometry optimization of the molecular systems. Both system optimization and semi- empirical calculations were carried out using the AM1 method [6].

Chemistry

Melting points were determined on a Boetzius micromelting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a UNICAM SP-100 apparatus using KBr pellets. Nuclear Magnetic Resonance

(^{1}H-NMR) spectra were recorded at 300.1 MHz in deuterated dimethylsulphoxide (DMSO-d_6) as solvent, at ambient temperature. Chemical shifts were referred to hexamethyldisiloxane (HMDS) used as an internal reference. Ultraviolet (UV) spectra were recorded on a UV-Visible Spectrophotometer as diluted methanol solutions. The nitrogen content of the compounds was determined by the Dumas method. All evaporations were performed under vacuum.

General Procedure

All the compounds were synthesized starting with 0.01 mole of methyl ester of the corresponding sulphonamidated phenoxyacetic acid and 0.015 mole EDA using *p*-TsOH and traces of sulfur as catalysts and anhydrous methanol (10 ml) as solvent. The reaction mixture was refluxed for 3-4 hours and the residue remaining after methanol removal by vacuum was treated with 25 ml water and allowed to stay till crystallization. The products obtained were purified from the appropriate solvent depending on their solubility.

RESULTS AND DISCUSSION

Our approach in clarifying the condensation reaction mechanism was based on two criteria: heats of formation, (ΔH_f), analyzed comparatively for three pairs of presumably formed species (denoted by A- H in the Figure 1) and bond lengths (δ) for the intermediates from which small molecules have to be eliminated.

Thus, according to the assumed mechanism the protonation, under the catalyst influence, of the methyl ester of *p*-amidosulphonyl-phenoxyacetic acid, taken as an example, can occur on either the ether oxygen or the carbonyl one giving the isomers denoted by A and B, respectively. Due to the great difference between the two values of ΔH_f corresponding to the A and B compounds, we supposed that only the formation of intermediate B is possible. That is why, only the attack of EDA on compound E is further considered.

For the binding of EDA at the carbon atom of the ester group, three intermediates are proposed as the structures C, D and E are depicting. Analyzing the ΔH_f values for the three compounds it can be observed that for

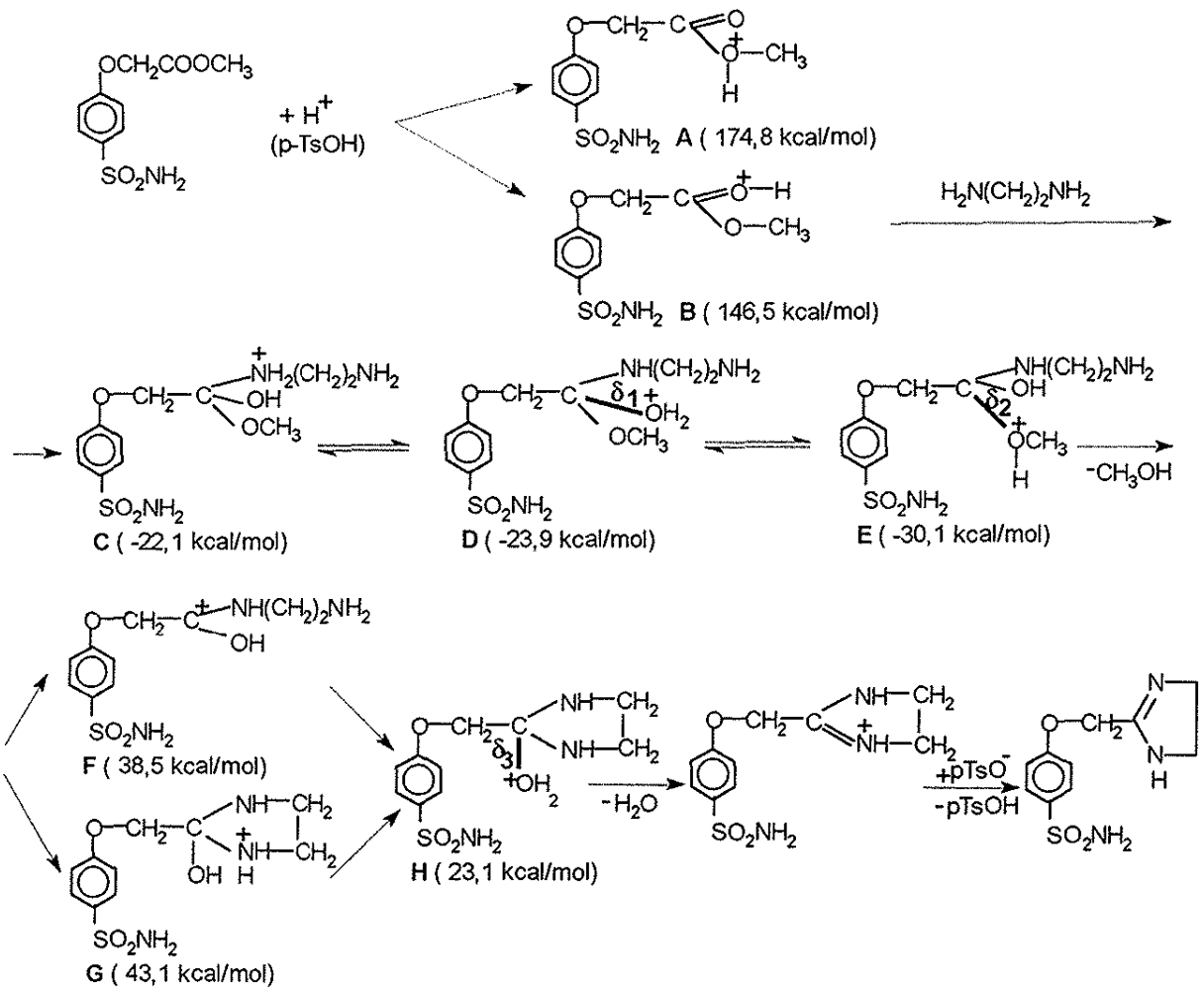


Figure 1. Acid catalyzed condensation of methyl p-amidosulphonyl phenoxyacetate with ethylene diamine.

the E intermediate the probability of formation is greatest. Consequently, we choose the E compound for the further transformation, by the elimination of one molecule of methanol. An additional argument for this choice consists in the difference between the length of the bonds δ_1 of 2,95 Å and δ_2 of 3,28Å which is indicative for the methanol molecule and not for the wateras leaving group.

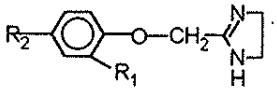
After methanol elimination from E two likely structures, denoted by F and G, respectively can be assumed. Since the difference in ΔH_f values of the two compounds is rather small (of 4.6 kcal/ mol) the conclusion that can be drawn is that both structures can be regarded as possible intermediates [7]. Thus, either carbocation F or intermediate G , obtained by a direct rearrangement of compound E , could virtually pass into the intermediate H , of lower ΔH_f value.

From the isomer H one water molecule is easily expelled, in agreement with the the abnormally great δ_3 length bond value, of 3.38 Å, giving thus the protonated 2-(4-amidosulphonyl-phenoxymethylene)-imidazoline.The expected product is obtained by exchanging proton with the conjugated base of catalyst (p-TsO^-).

In conclusion, according to the proposed mechanism, the condensation reaction of the methyl p-amidosulphonylphenoxyacetate with EDA, in acid catalysis, occurs in two main stages. The first step that involves the elimination of one molecule of methanol due to the attack of EDA on the ester and the second step, consists of cyclization and water elimination, the final product resulting by proton exchange with the catalyst.

Practically, seventeen imidazolines (Table 1) derived from sulphonamidated fenoxyacetic acids were obtained.

Table 1. Some properties of the imidazolines synthesized.



No.	R_1	R_2	Empirical Formula	M (g/mol)	M.p. (°C)	%N calc.	%N found	Recr. Solv.
1.	Cl	SO_2NH_2	$C_{10}H_{12}ClN_3O_3S$	289.5	230-231	14,5	14.25; 14.39	H_2O
2.	Cl	$SO_2NHC_2H_5$	$C_{12}H_{16}ClN_3O_3S$	317.5	172	13.22	13.05; 13.54	i-PrOH-HOH
3.	Cl	$SO_2N(C_2H_5)_2$	$C_{14}H_{20}ClN_3O_3S$	345,5	184	12,15	11,98; 12,01	i-PrOH-HOH
4.	Cl	$SO_2N(C_3H_7)_2$	$C_{16}H_{24}ClN_3O_3S$	373.5	115	11.24	11.34; 11.40	i-PrOH-H_2O
5.	Cl	$SO_2N(C_4H_9)_2$	$C_{18}H_{28}ClN_3O_3S$ HCl	438	129-130	9.59	9.47; 9.55	CH_3OH
6.	Cl	$SO_2NHCH(CH_3)_2$	$C_{13}H_{18}ClN_3O_3S$ HCl	368	183-185	11.41	11.09; 11.38	CH_3OH
7.	Cl	$SO_2NHC(CH_3)_3$	$C_{14}H_{20}ClN_3O_3S$ HCl	382	163-165	10.99	10.87; 11.03	CH_3OH
8.	Cl	pyrrolidinosulphonyl	$C_{14}H_{18}ClN_3O_3S$	333.5	167	12.59	12.25; 12.39	CH_3OH
9.	Cl	piperazinosulphonyl	$C_{14}H_{19}ClN_4O_3S$	358.5	258-260	15.62	15.49; 15.54	DMSO
10.	CH_3	$SO_2NHC_2H_5$	$C_{13}H_{19}N_3O_3S$	297	140	14.14	13.98; 14.02	C_2H_5OH-H_2O
11.	CH_3	$SO_2N(C_2H_5)_2$	$C_{15}H_{23}N_3O_3S$	325	189 - 190	12.92	12.55; 12.78	C_2H_5OH
12.	CH_3	$SO_2N(C_3H_7)_2$	$C_{17}H_{27}N_3O_3S$ HCl	389.5	175	10.78	10.69; 10.71	CH_3OH
13.	CH_3	$SO_2N(C_4H_9)_2$	$C_{19}H_{31}N_3O_3S$ HCl	417.5	171	10.059	9.98; 10.01	CH_3OH
14.	CH_3	$SO_2NHCH(CH_3)_2$	$C_{14}H_{21}N_3O_3S$ HCl	347.5	217	12.086	11.98; 12.05	CH_3OH
15.	CH_3	$SO_2NHC(CH_3)_3$	$C_{15}H_{24}N_3O_3S$ HCl	362.5	210	11.58	11.62; 11.52	CH_3OH
16.	CH_3	pyrrolidinosulphonyl	$C_{15}H_{21}N_3O_3S$	323	183-184	13.00	13.12; 13.08	CH_3OH- H_2O
17.	CH_3	piperazinosulphonyl	$C_{15}H_{22}N_4O_3S$	337	232	16.61	16.54; 16.59	DMF- H_2O

The imidazolines obtained are solid, amorphous substances with characteristic melting points. As free bases they are soluble in ethyl and methyl alcohol, acetone, dimethylsulfoxide, dimethylformamide, tetrahydrofuran and hot water.

The IR spectra, show characteristic bands as follows: 3050-3100, 2930-2950, 1600-1610, 1450-1490 cm^{-1} (imidazoline), 1080-1100 cm^{-1} (C⋯S); 1020- 1040 cm^{-1} (S⋯O); 1040- 1080 cm^{-1} (S⋯N); 1160-1180, 1300-1360 cm^{-1} (SO_2); 1200-1260 cm^{-1} (C⋯O) and 805-825, 870-885 cm^{-1} (1,2,4- substituted aromatic ring) [8-10].

The UV spectra show broad bands at approximately 220 nm.

The structures of 2-substituted imidazolines were finally confirmed by ^{1}H- NMR spectra. The chemical shifts assignments supported the expected structures being in close agreement with the Lofexidine® spectrum, taken as reference for the imidazoline ring [1].

CONCLUSIONS

The studies on the aryloxyalkylcarboxylic acids derivatives were continued by the synthesis of new compounds with potential hypotensive actions.

Seventheen new imidazolines have been prepared by the reaction of some methylic esters of sulphonamidated aryloxyalkylcarboxilic acids with ethylene diamine using acid catalysis.

A theoretically study based on molecular mechanics and semi-empirical calculations of the condensation mechanism of methyl p-amidosulphonyl phenoxyacetate with ethylene diamine is reported.

The structure of the compounds obtained have been elucidated by means of elementary analysis data and IR, UV and ^{1}H- NMR measurements.

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