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In our laboratory, many studies have been made on the synthesis, stereochemistry, the complexing power and biological properties of various pyrazolic and pyrazolinic structures.

The new pyrazolines presented in this work were prepared by cycloaddition of 1,3-dipole (the diarylnitrilimine) on eugenol and acetyleugenol which are two natural extracted dipolarophiles from cloves.

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Biological tests, Complexity trials and synthesis using the rest of the series diarylnitrilimines are in progress.

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I. Introduction

Since its development by Huisgen and al. Dipolar cycloaddition reaction appears among the most applied reactions for the synthesis of heterocyclic compounds not readily accessible by other synthetic methods [1-8].

In our laboratory, the synthesis of new pyrazolinic and pyrazolic heterocycles via such cycloaddition with diary lnitrilimines (DANI) as a dipole has been the subject of several theoretical and experimental studies [9-13].

Furthermore several cycloadducts, or derivatives thereof, synthesized showed very interesting biological activities.

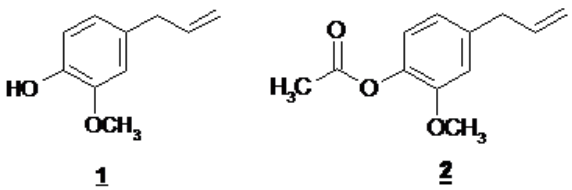
These compounds have in fact antimicrobial, antifungal and antileishmanial [14-16]. In order to continue this work and to broaden the scope of investigation of our research team, we diversify the nature of used dipolarophiles (natural instead of synthetic), we have opposed DANI to two dipolarophiles eugenol and acetyleugenol which are extracted from a natural substance "nails chanterelle."

II. Bibliographic Details

Cloves are the dried buds, unhatched, the clove and are among the oldest spices and drugs described in the story. They have antiseptic, analgesic and are widely used in dentistry against toothache. They are also antibacterial, antifungal and prevent infectious diseases and helps to eliminate intestinal parasites.

Eugenol 1 and acetyleugenol 2 are natural compounds that can be extracted from natural oil of cloves.

They belong to a class of compounds called vanilloid. They are known for their antioxidant properties and may reduce the risk of diseases such as cancer, cardiovascular disorders and also malaria, AIDS and the effects of aging [17-20].



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Cycloaddition Reaction

To develop essential oils and compounds 1 and 2 whose structures have activated ethylenic dipolarophiliques sites similar to the 7-allyl-8-hydroxyquinoline studied in our laboratory [13], we have opposed them to 1,3-dipole : the diarylnitrilimine (DANI) 3.

In fact, heating at reflux in dry benzene for 48 hours, eugenol 1 or acetyleugenol 2 with DANI 3, generated "in situ" by means of triethylamine after reaction with the precursor 3' gives in regiospecific manner both single cycloadducts with a good yield varying from 50 to 67%.

The structure of the compounds obtained was established on the basis of spectroscopic data of IR, 1H NMR (300 MHz), 13C NMR (50 MHz) and DEPT (Distortionless Enhanced Polarization Transfer).

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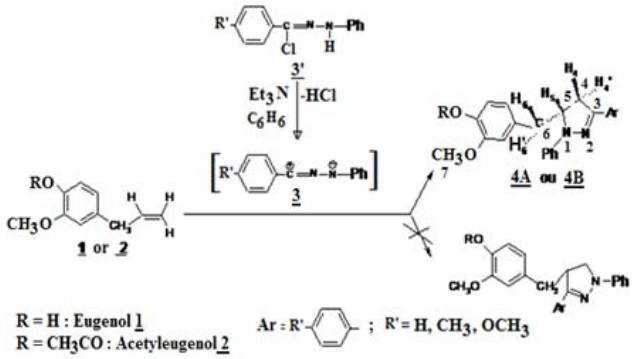

Eugenol and Acetyleugenol structures

III. Results and Discussion

On the IR spectrum of cycloadducts 4A (we note the absorption bands, which are characteristics bands due to C = N vibration around 1600 cm^{-1} and OH vibration at about 3475 cm^{-1} (Table 1).

The ^1H NMR spectrum of all compounds 4A in $CDCl_3$ at 300 MHz (Table 1) has four split doublets. We discuss the cycloadduct A1 for example. Indeed, we assigned the two split doublets centered at 2.63 and 3.20 ppm respectively protons H_4 and H'_4, and the two split doublets centered at 3.07 and 3.28 ppm respectively in two protons H_6 and H'_6. The transitions 12 which degenerates multiplet centered at 4.69 ppm characteristic of a proton bound to a carbon adjacent to a heteroatom which cannot be that the H_5 proton bound to a heteroatom. Protons H_4, H'_4, H_5, H_6 and H'_6 thus form a ABMXY system. As the most intense peak at 3.87 ppm; we attributed to the methoxy protons 3. It should also be noted that another intense peak at 3.22 ppm result of a union between two transitions, the H'_4 and H'_6.

We can also note that the protons H_6 and H_4 are respectively more armored than H'_6 and H'_4.

On the other hand the four values of the coupling constants characterizing H_4 and H_6 protons show that H_6 and H_4 are in cis position relative to the H_5 proton while H'_4 and H'_6 are in transposition compared to the same proton. Indeed, protons H6 and H4 have values larger coupling constant respectively, found $^3J_{H6-H5}$ = 10.8 Hz; $^3J_{H4-H5}$ = 9.6 Hz, H'_6 and H'_4 give respectively $^3J_{H'6-H5}$ = 4,5 Hz and $^3J_{H'4-H5}$ = 3,3 Hz (Table 2).

The structure 4A was also confirmed after examining the parameters 13C NMR (50 MHz) (Table 3). In case of cycloadduct 4A (R'=H), the signals corresponding to the pyrazolinic carbon C^4, C^5 and méthylenic C^6 are 37.36; 60.91 and 37.06 ppm, with respect to the carbon of methoxy function, it resonates at 56 ppm. DEPT spectrum further confirms the proposed structure since we observe reversal of carbons C^4 and C^6.

Regarding the adducts 4B, its IR spectrum (Table 1) shows in addition to the C = N band, another characteristic band at 1700 cm-1 corresponding to the vibration of C=O.

The ^1H NMR spectrum at 300 MHz of cycloadducts 4B (Table 1) were substantially identical to that of cycloadducts 4A, only one difference in that a single corresponding to the methyl group of acetyl is observed.

Furthermore the 13C NMR spectrum at 50 MHz cycloadducts 4B (Table 3) shows, in addition to signals attributable to carbons pyrazoliniques C^4, C^5 and C^6 methylenic carbon two significant signals to 20.69 ppm and 168 ppm respectively corresponding to the carbon of the methyl group acetyl and of carbonyl carbon C=O.

Table 1 : IR & ^1H NMR Characteristics of cycloadducts 4A and 4B

		NMR ^1H (δ in ppm)							Infra Red (ν in cm^{-1})	
		R'	H_4	H'_4	H_5	H_6	H'_6	H_7	$\nu_{C=N}$	ν_{O-H}
4A	4A1 (R'=H)	----	2,63	3,20	4,69	3,07	3,28	3,87	1597	3476
	4A2 $(R'=OCH)_3$	3,78	2,65	3,32	4,70	3,11	3,36	3,92	1596	3475
		R'	H_4	H'_4	H_5	H_6	H'_6	H_7	$\nu_{C=N}$	$\nu_{C=O}$
4B	4B1 (R'=H)	----	2,6	3,15	4,70	3,03	3,24	3,96	1596	1700
	4B2	2,34	2,58	3,10	4,76	3,00	3,20	3,82	1600	1700
	$(R'=CH_3)$									

Table 2 : Values of the coupling constants

	J (Hz)					
	H_4-H'_4	H_4-H_5	H'_4-H_5	H_6-H'_6	H_6-H_5	H'_6-H_5
4A1 (R'=H)	14,6	9,6	3,3	17,1	10,8	4,5
4B1 (R'=H)	13,98	9,1	2,89	17,28	10,92	4,62

Table 3 : ^{13}C NMR Characteristics of cycloadducts 4A and 4B

		NMR^{13}C (δ in ppm)					
	R'	C_4	C_5	C_6	C_7	R = O<u>C</u>H$_3$ R = <u>C</u>H$_3$-<u>C</u>=O	R' = CH_3
4A1	H	29,75	60,9	37,06	59,99	56,12 --------	--------
4A2	OCH_3	29, 79	61,02	37,17	58,79	55,86 -------	--------
4B1	H	37 ,1	60,45	29,7	58,96	56,15 20, 76; 168,65	--------
4B2	CH_3	37 ,0	60,5	30,0	58,86	56,10 20, 96; 170,0	21,5

IV. Experimental

a) Extraction of eugenol A and acetyleugenol B

We place in a 250 ml three ground cloves mixed with water and we proceed to a steam distillation. The distillated essential oil being transferred to a separator funnel and extracted three times with dichloromethane, and will be finally collected.

The collected organic layer contains the mixture of the two main constituents eugenol A and acetyleugenol B.

To separate the mixture, the organic phase is treated in a separator funnel, two times with a solution of 5 % sodium hydroxide.

The thus obtained organic phase, containing the acetyleugenol B, dried over anhydrous magnesium. Acetyleugenol B is recovered after evaporation of dichloromethane in a rotary evaporator.

Furthermore, the aqueous phase containing eugenol A as eugenolate sodium, is treated with concentrated hydrochloric acid until about pH = 3.

We Dry over magnesium sulphate or anhydrous sodium. The removal of solvent on a rotary evaporator recovers the Eugenol A.

V. Cycloaddition : General Procedure

In a 100 ml flask equipped with a condenser and a CaCl2 guard are successively introduced 6,6 mmol of eugenol A or acetyleugenol B and 6 mmol of hydrazonoyle chloride in 40 ml of anhydrous benzene. 4 ml of triethylamine was added through a dropping funnel.

Magnetic stirring this mixture was heated to reflux for 48 hours after complete addition of triethylamine. The triethylamine hydrochloride formed is filtered hot and the benzene and excess triethylamine are removed in a rotary evaporator. The oil obtained crystallized from ethanol in a refrigerator. The crystal of cycloadducts obtained are filtered and washed with cold ethanol (Table 4).

Table 4 : Yield and physical caracteristics

	F° C	yield%	Aspect
4A1	150	67	Pale yellow crystals
4A2	162	63	Pale yellow crystals
4B1	158	58	Beige Crystals
4B2	160	50	Beige Crystals

VI. Conclusion

Cycloaddition of arylnitrilimine with eugenol or acetyleugenol is a regiospecific reaction whose sense of direction resulting steric effects theoretically expected. The structure of obtained adducts and the regiochemistry of the reaction was confirmed on the basis of spectroscopic parameters IR, 1H NMR (300 MHz) and 13C NMR (50 MHz) are in perfect agreement with literature data. Biological tests and tests of complexation are in progress as well as the synthesis using the rest of the series diary Initrilimines (DANI).

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