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ABOUT THE SYNTHESIS OF HETEROCYCLIC ANALOGUES OF MARGINALIN AND THEIR TRANSFORMATION PRODUCTS

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Abstract- Pyridine-2 or 4-carboxaldehyde,furan-2-aldehyde,were condensed on 2-coumaranone and on 5-hydroxy 2-coumaranone to give new ene-lactones analogues of the natural marginalin.Only the addition compounds issued from 2-coumaranone could give stilbene methyl esters and no rearrangement into benzo[b]furan carboxylates could be observed.These observations are discussed in relation with previous results in the series.

The simple access to new molecules through addition of aldehydes on aromatic lactones under controlled pH was previously considered. With this respect,the direct syntheses of 4-substituted 3-isochromanones by condensation of aliphatic or aromatic aldehydes were first reported[1]. The reaction between 5-hydroxy 2-coumaranone 1b and 4-hydroxybenzaldehyde gave (Z)-marginalin 2b with a high stereospecificity[2]. ((E)-marginalin is a product which was previously isolated from the pygidial glands of the water beetle Dytiscus marginalis,Coleoptera[3]). In these series,the (E)-isomers could be easily distinguished from the (Z) due to interaction between the

olefinic proton and the lactone carbonyl group.The result was a greater polarity on TLC and a distinct chemical shift in the ^{1}H NMR spectra. This same reaction gave a direct access to 2-hydroxymethyl-phenylglyoxylic acid[4]. It also lead to a series of 2-phenyl $\alpha\beta$-unsaturated aliphatic acids[5] and thus revealed to offer a particularly rich field of possibilities concerning the synthesis of new compounds. 4-Nitrobenzaldehyde was found to condense on 1b without addition of any base[6] to give the nitro analogue of marginalin with an excellent yield. By difference,when carried out on 2-coumaranone 1a instead of 1b,these reactions always gave mixtures of (E)- and (Z)-isomers,as previously[1,2,5] observed in other cases. It was concluded[6] that the 5-hydroxy group in 1b exerted a remote induction of the orientation of the secondary alcohol issued from the addition of the aldehyde on the methylene group of the lactone,stabilized through chelation with the carbonyl function. These conditions, leading after dehydration to the ene-lactones,fulfilled the requirements of the Cram's rule,namely the combination of two forces:the antiparallel situation of the hydroxyl groups in order to minimize electronic interactions[7-9] plus the stabilizing effect due to chelation between the tertiary OH proton and the lactone carbonyl group. It was clear that in these conditions,the condensations carried out on substance 1b would furnish the isomer in which the

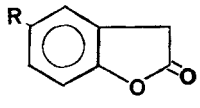
olefinic proton would be opposed to the carbonyl function, that is the (Z)-isomer (such as 2b) while the additions on 1a would give the mixture of the two isomers such as 2a and 2b.

Due to the self-basicity induced by the nitrogen atom in the pyridine carboxaldehydes, the condensations did not require another base such as KOH to give the expected ene-lactones. This was not the case with furan-2-aldehyde for which the reaction had to be base catalyzed to promote the formation of the corresponding ene-lactones. In all cases, when the condensation was carried out on 5-hydroxy 2-coumaranone 1b, a single isomer could be isolated and it was unexpectedly the (E) (TLC, ^{1}H NMR). With 1a, a mixture of (E)- and (Z)- isomers were isolated, but here again the (E) was the most abundant product. These results are of course in opposition with the previous observations and point out the predominant influence of the heteroaromatic group on the stereospecificity. The possible perturbating role of the reagent acting as a base was ruled out by carrying out a base-catalyzed condensation of p-hydroxybenzaldehyde on 1b in which pyridine was choosen as the base: (Z)-marginalin was obtained. The conclusion is that the heteroatom in the aldehyde annihilates the repulsion between the hydroxy groups of the intermediate tertiary alcohol, giving priority to a privileged interaction between the carbonyl group of the lactone and the ole-

finic proton. By this method, the ene-lactones issued from reaction on 1a or 1b and pyridine-2 carboxaldehyde (4a and b) or pyridine-4 carboxaldehyde (8a and b) or furan 2-aldehyde (5a and b) could be obtained ((E) as main product, the (Z)-isomer was present as a minor product with condensations carried out on 1a: 6a, 7a and 9a.)

A previous work on marginalin had shown that a rearrangement of the ene-lactone structure into a benzo[b] furan was obtained under prolonged action of a base[10]. With sodium carbonate, the strongly fluorescent compound 10a could be isolated. With sodium methylate, the corresponding methyl ester methylated at position C-7 10b was produced. More recently (unpublished) it was observed that marginalin 2b could be simply rearranged into the benzo[b] furan carboxylic acid 10a by warming with water at 110°C in a pressure tight tube. It is with the idea of synthesizing the parallel series of heteroaromatic benzo[b] furans that similar reactions were carried out on the ene-lactones described in this publication. By none of the methods cited could a benzo[b] furan derivative be isolated from the reaction mixture so that marginalin appears to be the most fitted compound in the series to give this rearrangement. The heterocyclic stilbenes issued from the action of sodium methylate on the ene-lactones could be obtained from 4a (11a), 7a (13a), and could not be found on reactions carried out on the

corresponding 4b (12b) and 7b (14b),and it is not possible at the present to explain this difference.



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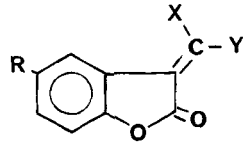


2-9

2:X=H Y=p-C_6H_5OH 3:X=p-C_6H_5OH Y=H

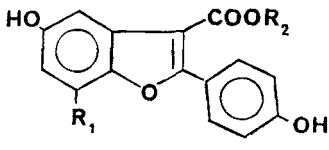
4:X=2-Py Y=H 5:X=2-furyl Y=H

6:X=H Y=2-Py 7:X=H Y=2-furyl

8:X=4-Py Y=H 9:X=H Y=4-Py

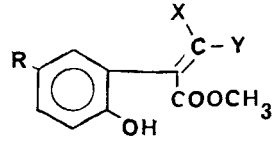
Series a: R=H

Series b : R=OH



10a: $R_1=R_2=H$

10b: $R_1=OCH_3$ $R_2=CH_3$



11:X=2-Py Y=H 12:X=H Y=2-Py

13:X=2-furan Y=H

14:X=H Y=2-furan

EXPERIMENTAL

General- Mp.:Kofler microscope,corrected;TLC:thin-layer chromatography on Schleicher-Schüll SiO_2 fluorescent films for analytical purposes,1 mm thickness for preparative,UV observation at 254 or 366 nm with a

Desaga ramp,extractions from scrapped SiO_2 layers with ethyl acetate.UV:Perkin-Elmer Lambda-5 automatic recorder;^{1}H NMR:Bruker 250 MHz,ppm,zero TMS;MS:AEI MS 50 spectrometer.

Synthesis of the pyridine analogues of marginalin 4a and b: In a typical experiment,2-coumaranone 1a (an Aldrich-Chemie product)(268mg,2mM) was suspended in absolute ethanol (2ml) and pyridine-2-carboxaldehyde (a Janssen Chimica reagent)(642mg,6mM) in ethanol (8ml) was added under stirring.The final solution which was homogenous,was kept for 72h at room temp.The resulting 4a precipitated out slowly (357mg,80%).This product was recrystallized from ethanol for analytical purposes (308mg,69%).A small amount of the (Z)-isomer 6a could be obtained from the motherliquors by preparative TLC (Rf 0.80 in ethyl acetate-pentane 1:1,25mg,7%).

4a:Rf 0.75 (ethyl acetate-pentane 1:1),mp. 134-136°C, pale yellow long needles with a greenish glance,MS,m/z, (%),223,M^+ (100);195(80);168(50);145(16);139(18);UV, MeOH,nm,(ε):208(2.3×10^4),245 (1.2×10^4),270 (7.8×10^3), 340 (1.7×10^3).^{1}H NMR ($CDCl_3$):olefinic proton at 7.70. Anal.Elem.,Calcd.for $C_{14}H_9NO_2$ (%):C 75.32 H 3.06 N 6.28; found C 75.25 H 3.98 N 6.33.

4b:This product was obtained according to the same reaction carried out on 5-hydroxy-2-coumaranone 1b (300mg, 2mM).It does not crystallize out and had to be extrac-

ted from the mixture by ethyl acetate (35mlx2) after addition of water (30ml).The crude substance was crystallized from ethanol giving 286mg (60%).Rf 0.45 (ethyl acetate-pentane 1:1,mp.orange yellow prisms 160-162°C; MS m/z (%):239 M^+(100),210 (70),182 (22),153 (48);UV, MeOH,nm,(ε):204 ($2.98x10^4$),260 ($1.1x10^4$),270 ($1.1x10^4$), 333 ($2.03x10^4$);^{1}H NMR (CD_3OD):olefinic proton at 7.22, s,1H.Element.anal.:calcd.for $C_{14}H_9NO_3$ C 70.29 H 3.79 N 5.86;found C 70.32 H 3.73 N 6.00.

Synthesis of the pyridine analogues of marginalin 8a and 8b:

The same method as for the pyridine analogue 7a was used and the product crystallized out as grains (pale orange, yield 60%,mp.dec.above 250°C;MS m/z (%):223 M^+ (100); Rf 0.25 (ethyl acetate);^{1}H NMR olefinic proton at 7.30 (DMSO-D_6);Element.anal.:Calcd.for $C_{14}H_9N\ O_2$:C 75.32 H 4.06 N 6.28;found C 75.29 H 3.98 N 6.18.

The (Z)-isomer 9a could be isolated from the mother-liquors (10%) together with some more 8a,by preparative TLC (Rf 0.30,orange grains,mp.dec.above 250°C;MS m/z (%) 223 M^+(100);^{1}H NMR olefinic proton at 6.9ppm.

8b:This product of addition of pyridine-4-carboxaldehyde on 5-hydroxy-2-coumaranone 1b was obtained as for 4a but the reaction was achieved after 6h at 20°C,giving a 70% yield in pale orange grains which crystallized out from the mixture.It was recrystallized from ethyl acetate, yield 46%,Rf 0.20 (ethyl acetate),mp.dec above 250°C,

UV,MeOH,nm,(ε),203 (2.1×10^4),265 ($8.\times10^3$),309 (7.2×10^3) MS m/z (%):239 M^+(100) ,211 (70);^{1}H NMR DMSO-D_6:olefinic proton found at 7.86ppm;Element.anal:Calcd.for $C_{14}H_9NO_3$ C 70.29 H 3.79 N 5.86;found C 69.89 H 3.90 N 5.81.

Syntheses of the furan analogues of marginalin 5a and b: 2-coumaranone (268mg,2mM) was suspended in 2ml absolute ethanol and a solution of furan-2-aldehyde (576mg,6mM, an Aldrich-Chemie reagent) in ethanol (8ml) was added under stirring.A dilute solution of KOH (100mg) in ethanol (10ml) was added dropwise until pH 8.The substance 5a began to crystallize out after 1h at 20°C and was recovered by filtration after 4h of reaction.Water was added to the mother liquors until turbid to get a second crop which was joined to the preceding previous to recrystallisation from ethanol (251mg,48%).

5a: yellow prisms Rf 0.65 in ethyl acetate-pentane 7:3, mp.119-121°C;MS m/z (%):212 M^+(100),184 (22),155 M^+-furan (20),128 (18);UV,MeOH,nm,(ε):203 (1.4×10^4),236 (8.5×10^3),242 (8×10^3);^{1}H NMR ($CDCl_3$):olefinic proton at 7.45ppm;Element.anal.:Calcd.for $C_{13}H_8O_3$ C73.58 H 3.80 ; found C 73.42 H 3.59.Examination of the mother liquors of crystallization by TLC showed the presence of the less polar (Z)-isomer 7a Rf 0.70 which was isolated (obtained 52mg,10%);mp.142-144°C,MS m/z (%):212 M^+(100); ^{1}H NMR ($CDCl_3$) olefinic proton found at 6.72ppm.

5b:the similar reaction carried out on 5-hydroxy-2-cou-

maranone 1b gave 30.2% of 5b,Rf 0.55 on TLC (ethyl acetate-pentane 1:1),orange red plates mp.207-208°C,UV, MeOH,nm,(ε),205 ($1.03x10^4$),230 ($4.3x10^3$),256 ($3.7x10^3$) ; MS m/z (%):228 M^+ (100),201 (20),171 (16),144 (8),115 (18);^{1}H NMR (DMSO-D_6):olefinic proton at 7.49ppm. Element.anal.:Calcd.for $C_{13}H_8O_4$ C 68.42 H 3.53;found C 68.29 H 3.49.

Syntheses of the stilbene methyl esters 11a and 13a : These substances were prepared according to the following general process:50mg of the substituted lactones were dissolved in 10ml absolute methanol at 50° C and sodium methylate (150mg Na in 10ml MeOH) was added.The reaction mixture was kept for 2h at room temp.,brought to pH 2 by HCl 4N,then to pH 7.5 by sodium bicarbonate. The methyl esters were extracted by ethyl acetate after adding water,the usual work up leading to a 100% yield.

11a : off-white prisms Rf 0.20 (TLC ethyl acetate-pentane 1:1),mp.148-151°C,MS m/z (%):255 M^+ (20),238 (41),223 (100),195 (40),167 (42);UV,MeOH,nm (ε),208 ($3.7x10^4$), 255 ($1.6x10^4$),283 ($2x10^4$)((E)-stilbene);^{1}H NMR ($CDCl_3$): olefinic proton at 7.90 (s,1H),CH_3 methyl ester at 3.86, (s,3H);Element.anal.Calcd. for $C_{15}H_{13}NO_3$ (%) C 70.58 H 5.13 N 5.49;found C 70.66 H 5.14 N 5.61.

13a: The same reaction was carried out on the furan derivative 5a leading to a nearly quantitative yield in the stilbene methyl ester 13a;colourless grains,Rf 0.55

(TLC ethyl acetate-pentane 7:3),mp.142-144°C,UV,MeOH, nm (ε),207 (1.7×10^4),309 (2.5×10^4);MS m/z (%):244 M^+ (30),213 (100),184 (20),176 (15),155 (15),128 (36);^1H NMR ($CDCl_3$):olefinic proton present at 7.44.Element. anal.:Calcd.for $C_{14}H_{12}O_4$ (%) C 68.84 H 4.95;found C 68.74 H 4.92.

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