REMOTE INDUCTION OF THE CONDENSATION OF p-NITROBENZALDEHYDE ON THE METHYLENE GROUP OF 5-HYDROXY-2-COUMARANONE

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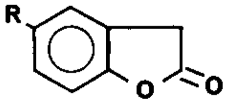
Abstract- (Z)-5-Hydroxy-3-(p-nitrobenzylidene)-2-coumaranone ((Z)-p-nitromarginalin) is obtained in 92% yield by reaction of p-nitrobenzaldehyde with 5-hydroxy-2-coumaranone. The same condensation carried out with 2-coumaranone gives a mixture of (Z)- and (E)-p-nitrobenzylidene-2-coumaranones (72% yield) in a 2:1 ratio. In a discussion taking also into account previous results in the series, it is concluded that the 5-hydroxyl group exerts a remote induction in the orientation of the intermediate secondary alcohol, stabilized through chelation with the lactone carbonyl group. Such a long distance effect is in agreement with the requirements of the Cram's rule, leading in this particular case to a high stereoselectivity in the final dehydrated ene-lactone.

The direct syntheses of 4-substituted 3-isochromanones by condensation of aliphatic or aromatic aldehydes[1] and of (Z)-marginalin 2 by reaction of p-hydroxybenzaldehyde with 5-hydroxy-2-coumaranone[2] 1 in basic media were previously reported. A difference appeared between these two series of syntheses; the former led to mixtures of syn (E)- and anti (Z)-isomers as expected, while the latter gave a 60% yield of (Z)-marginalin 2. The stereochemistry of the naturally occurring marginalin[3] isolated from the defensive (pygidial) glands of the water-beetle Dytiscus marginalis (Coleoptera) was not precised so far. By comparing the physical properties of the synthetic (Z)-marginalin 2 (in particular the ^{1}H-nmr spectrum) with the reported data[2], the (E)-stereochemistry 8 was proposed for the natural product. Due to the interaction occurring between the olefinic proton and the lactone carbonyl group in the (E)-isomers, isolations and characterizations were rather easy, resulting in greater polarities on tlc and in noticeable chemical shifts in the ^{1}H-nmr spectra. The possible role of the hydroxyl group in the case of 5-hydroxy-2-coumaranone 1 was advanced as a hypothesis, and with some reserve, because of the distance (4 carbon atoms) which separated this function from the methylene group where the condensation of the aldehyde took place. The addition of aldehydes being carried out at pH 8 (KOH) and thus in competition with the hydrolysis of the lactone ring, the eventual role of a more bulky potassium phenolate appeared to be another possibility in the orientation of the stereochemistry.

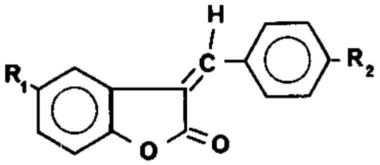
In the present paper, we report the selective condensation in the absence of any base (92% yield of (Z)-isomer) of p-nitrobenzaldehyde on the methylene group of 5-hydroxy-2-coumaranone 1. As the same reaction carried out on 2-coumaranone 5 gave the mixture of (Z)- and (E)-isomers (72% yield, 2:1 ratio) it was established that this high stereoselectivity would be at least in part, due to the 5-OH function in 1. The most favourable attack corresponds to an antiparallel situation[4-6] of the hydroxyl groups which minimizes interactions between these groups, so that the further dehydration of the intermediate secondary alcohol leads to the (Z) compound 3. The existence of this secondary alcohol was noticed at the beginning of the reaction, as a colorless spot on the tlc (it was observed in uv, Rf 0.20), attempts to extract the product from the scrapped SiO_2 layer leading to the red benzylidene derivative 3 through immediate dehydration. As from molecular model the distance between the hydroxyl groups in the intermediate 9 is big enough, repulsion alone does not seem to be a sufficient cause to avoid isomerization to the mixture of (Z)- and (E)-isomers. So that the stereoselective formation of 3 has to be related to combined effects,hydrogen bonding between the secondary alcohol once formed 10 and the lactone carbonyl group being a stabilizing force. The finding that the reaction carried out on 2-coumaranone 5 led to a 2:1 ratio of the (Z)- and (E)-isomers would be supported by a similar stabilizing role of the lactone carbonyl group on the intermediate secondary alcohol which resulted from the condensation of the aldehyde. The whole mechanism, as far as the reaction of p-nitrobenzaldehyde on 5-hydroxy-2-coumaranone 1 is concerned, fulfils the requirements of the Cram's rule[4-6] ; polar effects indeed stabilize those states in which the separation between the entering reagent group and the electronegative group is greatest, and destabilize others. It seems that this observation may be of particular interest in synthesis, when a repulsion from substituents such as hydroxyl groups can induce stereoselectivity, assisted by chelation to a carbonyl group, previous to dehydration of the secondary alcohols into their corresponding ene-lactones.

Attempts were made to prepare dinitro analogues by using 2,4-dinitrobenzaldehyde in the similar reaction. No condensation was observed, however, very likely because of the steric hindrance induced by the presence of the bulky ortho nitro substituent. Marginalin needs some comments, as being a curious and unique natural compound and having no reported biological properties so far. The product is with time, sensitive to hydrolysis at neutral, acidic or alkaline pH, so that its occurrence as such in the glands of the insects could indicate that it is protected, for example by a lipid fraction. In order to determine an eventual cytostatic effect, experiments were carried out with all the derivatives obtained through synthesis, but they led to negative results (200µg/ml of the corresponding hydroxy acids for solubilization, assayed on the inhibition of germination of water-cress seeds).



1 R = OH

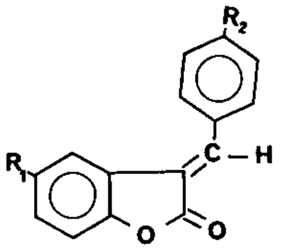
5 R = H



2 $R_1 = R_2 = OH$

3 $R_1 = OH$ $R_2 = NO_2$

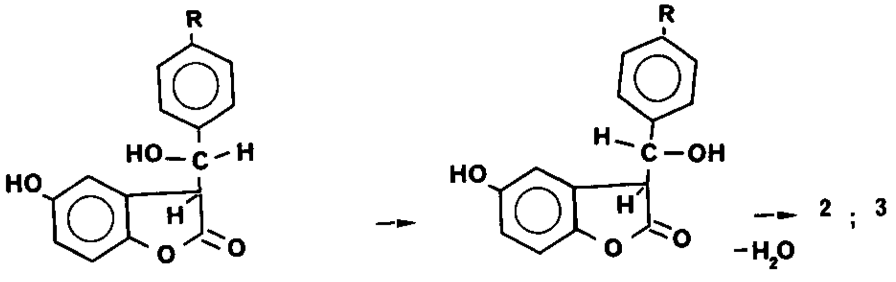
6 $R_1 = H$ $R_2 = NO_2$



4 $R_1 = OH$ $R_2 = NO_2$

7 $R_1 = H$ $R_2 = NO_2$

8 $R_1 = R_2 = OH$



9 **10**

R = OH or NO_2

EXPERIMENTAL

Mps were determined with a Kofler apparatus under the microscope and are corrected. Mass spectrometry was carried out on an AEI MS 50 apparatus and ^{1}H-nmr on a Bruker 200 MHz spectrometer in $CDCl_3$ solution (δ ppm) using TMS as an internal standard. (Z)-5-Hydroxy-3-(p-nitrobenzylidene)-2-coumaranone 3 : A solution of p-nitrobenzaldehyde (300 mg, 2.2 mM), in 10 ml absolute ethanol was added dropwise to a solution of 5-hydroxy-2-coumaranone 1 (an Aldrich-Chemie product)(150 mg, 1 mM) in 10 ml ethanol at room temperature under stirring. The mixture turned soon yellow, orange, red, and began to give a red precipitate after 1h. Controls on aliquote parts led to yields of 20% (3h), 64% (6h), and 92% (20h), (filtration of the crystals, washing with a little cold ethanol); Rf 0.60 SiO_2 tlc, hexane-ethyl acetate 1:1; orange-red prisms, mp. 255-260°C with recrystallization in bigger prisms between 258 and 260°C and second melting point at 262-264°C with decomposition. Recrystallization of the precipitated product from hot ethanol led to the presence of some (E)-isomer (less than 1%) observed on tlc (comparison with the isomer isolated from the mother-liquors of the reaction, occurring at a concentration of 3%). 3 : Ms m/z 283 (M^+)(100%), λ max. $HCCl_3$, nm, ε : 250, 1. 5x10^4; 280, 1. 1x10^4; 340, 1. 2x10^4; 410, 5. 4x10^3; ^{1}H-nmr, A_2B_2 system for the aromatic protons of the p-nitrobenzylidene ring at 7. 18 (d, 8Hz, 2H) and 5. 95 (d, 8Hz, 2H), ABX system for the second aromatic ring at 5. 80 (d, 3Hz, 1H), 5.70 (dd, 8Hz and 3Hz, 1H), 6.75 (d, 8Hz, 1H), olefinic proton at 6. 70 (s, 1H). Anal. Calc. for $C_{15}H_9NO_5$: C 63. 61; H 3. 20; N 4. 95; found: C 63. 28; H 3. 12; N 4.95. The position of the olefinic proton was in agreement with the reported values[1,2] for the series of (Z)-ene-lactones and this observation was corroborated by the position of this same proton in the (E)-isomer. (E)-isomer 4, isolated from the mother-liquors of the reaction by tlc (Rf 0.55), orange-red small prisms, mp. 245-248°C with recrystallization in bigger prisms during the melting, and second melting point at 258-260°C with decomposition. Ms and ^{1}H-nmr are similar to those of the (Z)-isomer 3 except for the olefinic proton now found at 6. 95. As this (E)-isomer is formed during recrystallization of the (Z)-isomer from hot ethanol, the small amount obtained from these mother-liquors may also result, at least in part, from a slow isomerization of the (Z)-isomer which is occurring first in the reaction. It is not possible to determine so far the exact yield in the (E)-isomer effectively due to the condensation itself, as we failed to detect this substance in the reaction mixture after 3h and 6h, its presence being noticed after a much longer time of reaction (20h).

(Z)-3-(p-Nitrobenzylidene)-2-coumaranone 6 and (E)-7 : These products were obtained through the same reaction carried out on 2-coumaranone 5 but during 4 days; 72% yield. Reaction for 24h led to a 28% yield of the mixture. The isomers were separated by preparative tlc (hexane-ethyl acetate 1:1); (Z)-6 : yellow, Rf 0.50 and (E)-7 Rf 0.45, obtained in a ratio of 2:1. 6 : mp. 200-204°C; ^{1}H-nmr, olefinic proton at 6. 65, ms m/z: 267 (M^+). Anal. Calc. for $C_{15}H_9NO_4$: C 67. 41; H 3. 39; N 5. 24; found : C 67. 49; H 3. 84; N 5.81. 7 : mp. 190-203°C; ms and ^{1}H-nmr similar to those of 6 except for the olefinic proton found at 6. 85. Anal. Calc. for $C_{15}H_9NO_4$: C 67. 41; H 3.39; N 5. 24; found : C 67. 48; H 3.30; N 5. 35.

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