STEREOCHEMISTRY OF SILYCHRISTIN

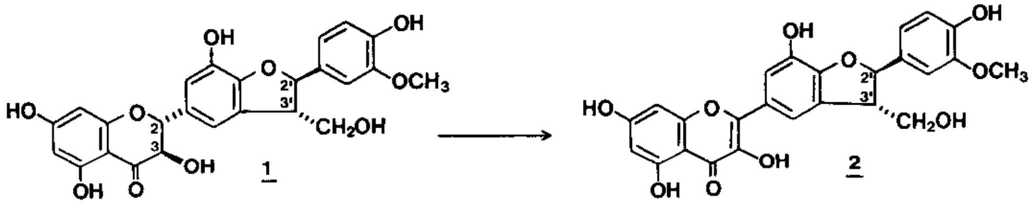
MILD DEHYDROGENATION OF FLAVANONOLS

Antonio Zanarotti

Centro CNR per le Sostanze Organiche Naturali, Istituto di Chimica,
Politecnico, Piazza Leonardo da Vinci 32, I-20133 Milano, Italy

Abstract —— 3-Hydroxyflavanones can be quantitatively dehydrogenated by air in pyridine to 2,3-dehydro derivatives. The reaction has been performed on silychristin (1) in order to remove the chirality at the flavanonol ring and to allow the assignment of the stereochemistry of the dihydrobenzofuran ring as 2'R,3'S.

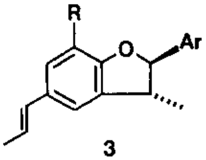
Seed extract of Silybum marianum Gaertn.,[1] largely used as an antihepatotoxic drug, contains as main components silybin,[2,3] isosilybin,[3] silychristin[4] (1) and silydianin.[5] All four compounds appear to be derived biosynthetically by the coupling of a dihydroquercetin molecule with coniferyl alcohol. The structure of silychristin (1) has been the object of some discussion;[6,7] while the stereochemistry of the flavanonol moiety has been established by Wagner et al.,[8] the absolute configuration of the trans-dihydrobenzofuran ring remained still unsolved. In order to establish the latter configuration it was necessary to remove first the chirality of the flavanonol ring. The methods available in the literature, which utilize iodine[9] or aqueous basic conditions,[10] were completely unable to perform this task. I have found a new procedure which allows an efficient dehydrogenation of the flavanonol ring without affecting the phenol moietis present in the molecule. The reaction is performed simply by refluxing the flavanonol in dry pyridine in the presence of air:



Thus silychristin (1) (400 mg) was dissolved in dry pyridine (40 ml) and refluxed to complete reaction (20 h; tlc, silica gel, $CHCl_3$/acetone/HCOOH 9/2/1; (1) Rf 0.16, (2) Rf 0.25). Then pyridine was removed in vacuo and the residue was dissolved in ethyl acetate and filtered through silica gel (3 g). By evaporation of the solvent dehydrosilychristin (2) ($[\alpha]_D^{20}$ +71.2[11]) was obtained with a 94% yield. The absolute configuration of the dihydrobenzofuran moiety of (2) is proved by the CD spectrum:[12] c 0.119; MeOH; $|\theta|_{220}\,0$; $|\theta|_{237}\,-5590$; $|\theta|_{243}\,0$; $|\theta|_{255}\,+7454$; $|\theta|_{264-280}\simeq 0$; $|\theta|_{280-410}$ positive.

According to Gottlieb,[13,14] in every case with no exceptions, the sign of the Cotton effect above 290 nm can be taken as reference mark for the absolute configuration of the C-2 chiral center in 2-aryl-2,3-dihydrobenzofuran-type derivative (3). Now, the Cotton effect shown by (3) and (2) above 290 nm is positive thus assigning the chirality of (2) as 2'R. Furthermore, the relative 2'-3' configuration being trans, the absolute configuration of silychristin must be 2'R,3'S. Moreover, at shorter wavelength, the CD spectrum of (2) is practically identical for shape and values to that of (+)-acuminatin[15] (4) whose absolute configuration has been established by El-Feraly et al.[16]

The method used for the described dehydrogenation proved to be of general application to 3-hydroxyflavanones, as shown below. Yields were nearly quantitative in all the cases tested: (5)-(10).



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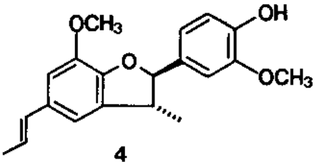

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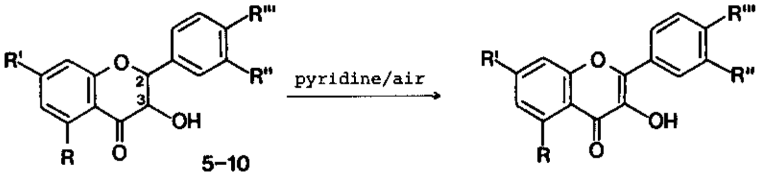

5–10

(5) R=R'=R''=R''' =OH
(6) R=H R'=R''=R''' =OH
(7) R=R'=R''=H R''' =OCH_3
(8) R=R'=R''=H R''' =Cl
(9) R=R'=R''=H R''' =Br
(10) R=R'=R''=H R''' =NO_2

The dehydro derivatives may be readily distinguished from the starting flavanonols in that the two doublets at 5.3 and 4.8 ppm due to the protons in the 2- and 3- position have disappeared in their nmr spectra (pyridine).

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