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THE STRUCTURE OF SILYDIANIN, AN ISOMER OF SILYMARIN (SILYBIN), BY X-RAY ANALYSIS

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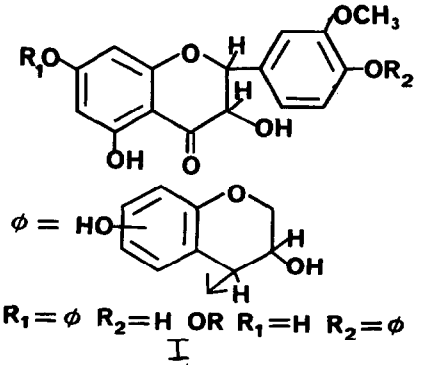
The natural product silymarin (silybin) $C_{25}H_{22}O_{10}$ (1,2) was isolated from the fruits of Silybum marianum Gaertn. several years ago. The structure of silymarin, a antihepatotoxic agent (3), has been under investigation by several workers, and two groups have proposed structures for this substance.

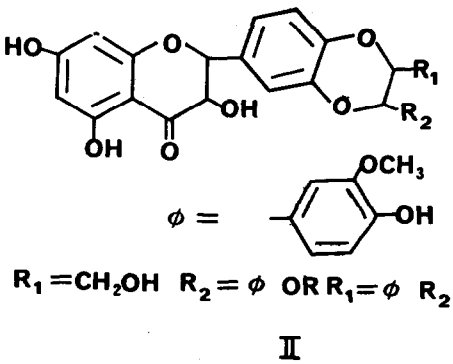
Wagner et al. (4) suggested structure I for Silymarin. Pelter and Hänsel (5) proposed structure II for Silymarin primarily from N.M.R. and mass spectrometric fragmentation patterns of derivatives. These studies supposedly showed that II contained a 1,4-dioxane moiety. Syntheses (6) of 1,4-dioxane derivatives as model compounds were also used by these workers to verify the structure.

We now wish to present the structure of a silymarin isomer, silydianin, which is quite distinct from the silymarin structure. This compound [M.P. 191°C $[\alpha]_D^{24} = +175°$ (Acetone)] was obtained from the defatted seeds by acetone extraction and polyamide chromatography. A Silydianin IR was found to be superimposable with the IR spectrum of the earlier isolated compound E 5 (7).



$R_1 = \phi$ $R_2 = H$ OR $R_1 = H$ $R_2 = \phi$

I



$R_1 = CH_2OH$ $R_2 = \phi$ OR $R_1 = \phi$ $R_2 = CH_2OH$

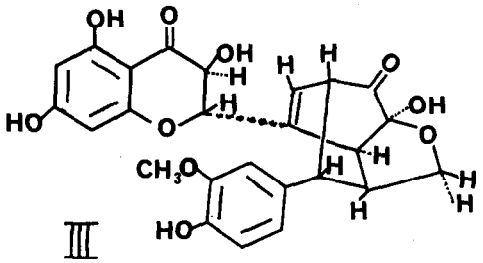
II

*To whom inquiries should be submitted.

Because of the biological and chemical interest in II and its isomers, it was decided to attempt the structure of this Silybin substance (Silydianin) by X-ray single crystal analysis. The ensuing analysis showed the structure of silydianin to be a new class of natural occurring substances.

Crystallization of 3 mg of III by slow evaporation of a methanol solution produced small colorless blades which were found to be orthorhombic, a = 24.872, b = 6.978, c = 13.293 Å, with 4 molecules*/unit cell (D cal = 1.481, D meas = 1.508 by flotation in $CHCl_3$-CCl_4). The space group is $P2_12_12_1$, from systematic absences. Three-dimensional CuKa data were measured with θ-2θ scans of 2° up to 110° in 2θ, using a four-circle automatic diffractometer. A total of 1013 reflections were found to be observed out of 1710 independent reflections. The structure was solved using one crystal of approximately 0.15 x 0.1 x < 0.05 mm.

Normalized structure factors were calculated using Wilson statistics and renormalized by an IBM 1130 program (8). The phase determination was accomplished by the tangent refinement procedure**. An E-synthesis showed the terminal flavanone and substituted benzene ring systems, and difference syntheses based on this part of the molecule revealed the remainder of the structure, including a molecule of methanol. Two cycles of isotropic full-matrix least squires (10) produced an R-factor of 9.8% for the observed reflections. It is not possible at present to decide the absolute configuration from the X-ray data. The final structure for Silydianin (III) is shown below.



III

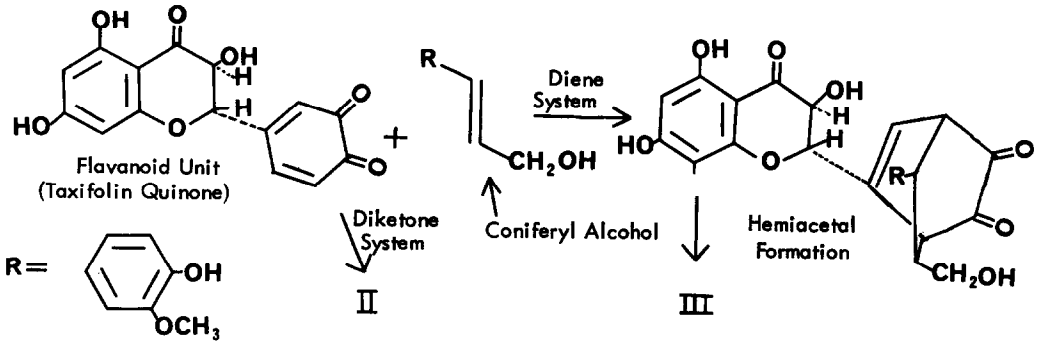
Further anisotropic refinement is being performed and will be reported in a full paper on the X-ray analysis (at present the R-factor is now 5.8% for observed reflections only).

The structure III is not only novel but could be quite interesting from a biogenetic standpoint. Pelter

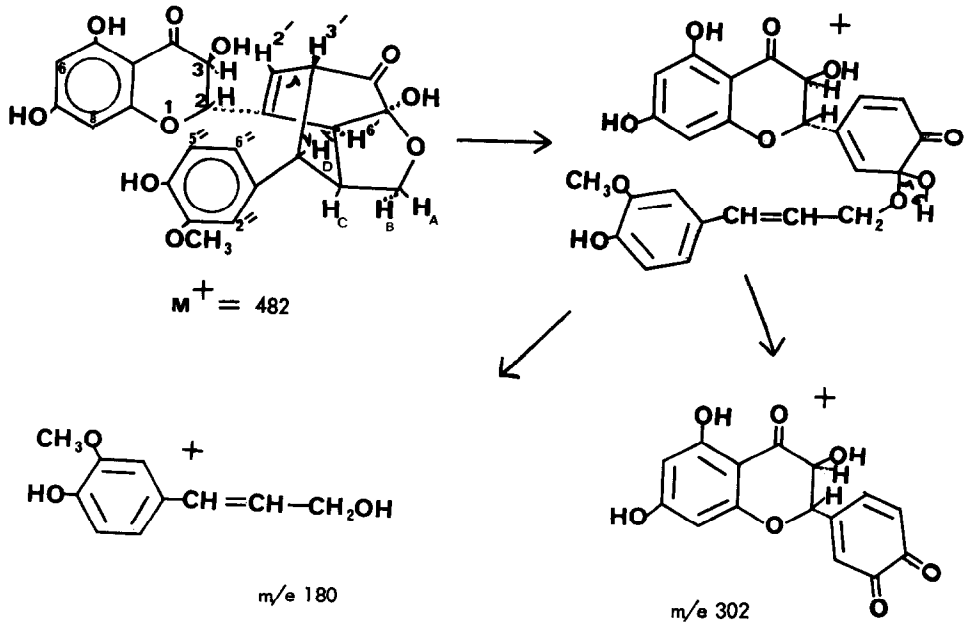
*$C_{25}H_{22}O_{10} \cdot CH_3OH$

**Three origin phases and one enantiomorph phase were chosen from equatorial reflections in such a way that they combined to yield highly interacting general phases. These four phases alone were used as input to the tangent refinement and extension program (9).

and Hänsel (4) pointed out that de Stevens and Nord (11) implicated flavanones as possible constitutive elements in bagasse native lignin, the mode of linkage of the flavanone and C_9 being unknown. This is now confirmed by structure (III) for Silydianin. A possible biogenetic scheme for formation of the bridged ring-system of III can be seen in the following proposed sequence by Diels-Alder formation. If the reaction involves the diketone instead of the diene system, a silymarin type of structure is obtained.



The mass spectral fragmentation products are easily interpreted below. The relationship of the Diels-Alder reaction in the biogenetic scheme and retro-Diels-Alder of the mass spectrometry fragmentation is a clear one.



The 100 megacycle N.M.R. values for the protons are given below with TMS being used as an internal standard.

100 Mc. N.M.R. in $(CD_3)_2CO$:

$\delta = 6.73 - 7.0$ m (H-2", H-5", H-6"); $\delta = 6.27$ d (J = 7.0) (H-2'); $\delta = 6.06$ s (H-6, H-8); $\delta = 4.98$ d (J = 11.0) (H-2); $\delta = 4.63$ d (J = 11.0) (H-3); $\delta = 4.32$ q (H-D); $\delta = 3.88$ d (J = 8.0) (H-6'); $\delta = 3.87$ s (OCH_3); $\delta = 3.70$ q (H-3'); $\delta = 3.40$ m (H-B); $\delta = 3.27$ d (H-A); $\delta = 2.97$ m (H-C); $\delta = 11.7$ (H-5 OH).

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