Structure of Silybin: Synthetic Studies

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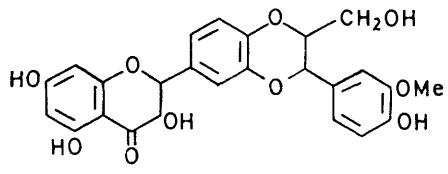
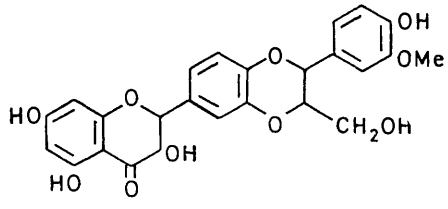
Summary The structure of silybin (E_6) has been resolved by the synthesis of the tetra- and penta-methyl ethers of the two possible derived flavanols.

DESPITE the numerous studies[1–4] on silybin [substance (E_6)] its structure has remained ambiguous. This is particularly

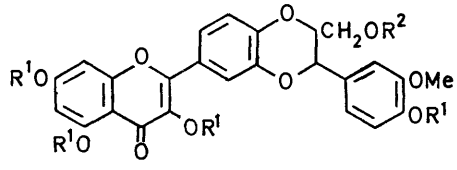


(I)

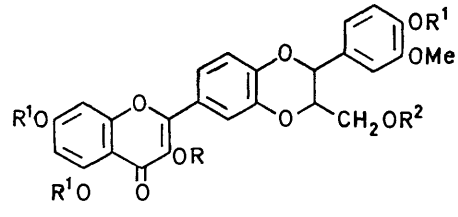


(II)

regrettable in view of its reported protective or curative effect on different hepatic toxa.[5]



(III)



(IV)

(a) $R^1 = R^2 = H$

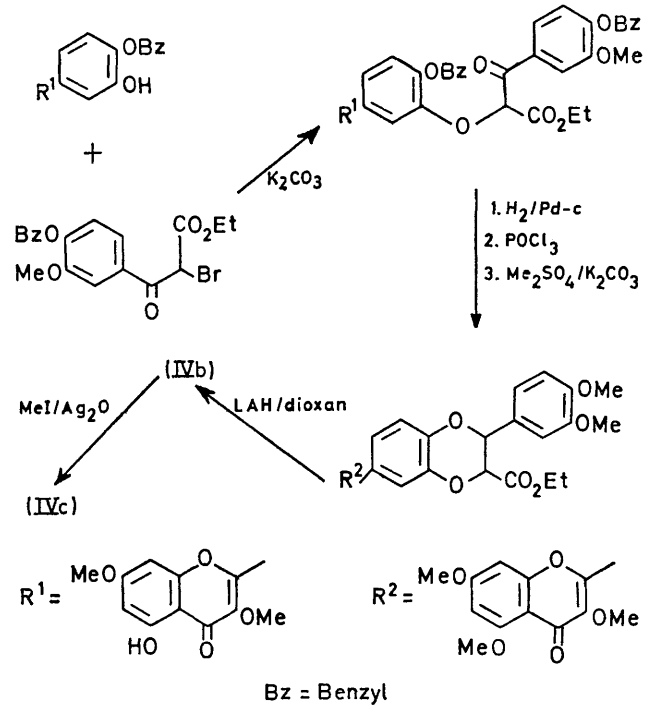
(b) $R^1 = Me$, $R^2 = H$

(c) $R^1 = R^2 = Me$

In 1968 we proposed[2] that silybin was represented by one of the two structures (I) or (II), but due to the insulating effect of the benzodioxan system as regards spectroscopic investigation and the difficulties of degrading that particular ring system we were unable to distinguish between the two possibilities. Silybin was recognised as the first of a new class of substance, the flavonolignans almost certainly produced in the plant by a radical coupling of a flavonoid and coniferyl alcohol.[6] Two other members of this class, silydianin[7] and silychristin,[8] have been characterised, and their structures may be rationalised on the same basis. In 1968 a different structure for silybin was proposed, in which taxifolin was attached as either a 7- or 4′-ether to a chroman diol system.[4]

Silybin (E_6) can be dehydrogenated to the derived flavonol, E_6F, (IIIa) or (IVa) from which the tetramethyl ether, (IIIb) or (IVb), and the pentamethyl ether (IIIc) or (IVc) can be derived.[2] It was these ethers that were the targets for our synthetic efforts.

Compounds (IVb) and (IVc) were produced by two routes, one of which is as shown in Scheme 1.



Bz = Benzyl

SCHEME 1

The substances had the same mass spectra as the corresponding compounds derived from natural sources, but there were small differences in the n.m.r. spectra and significant differences in the fingerprint region of the i.r.

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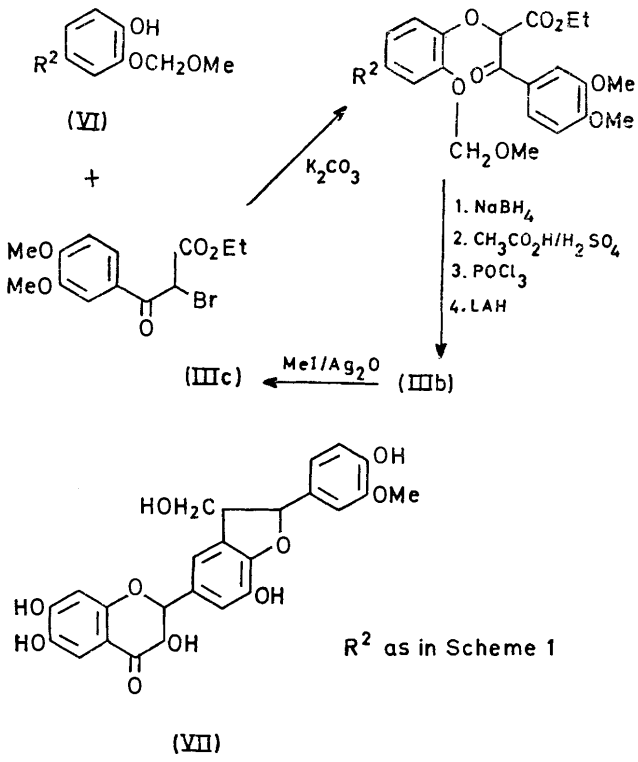

SCHEME 2

spectra. There was no doubt that E_6F and its derivative were not represented by (IVa—c) but equally the similarities were such as to exclude for silybin all structural proposals lacking a benzdioxan ring.

The substances (IIIb) and (IIIc) were synthesised as in Scheme 2.

Except with regard to optical activity the synthetic substances (IIIc) and (IIIb) were identical in all respects (mass spectra, i.r., n.m.r., m.p.) with E_6F pentamethyl and tetramethyl ethers derived from silybin. Therefore E_6F is represented by (III) and silybin by (I). The relative stereochemistry of all centres of silybin is known[2] and we shall report on the absolute configuration in our full paper, as also on the preparations of the rather inaccessible starting materials (V) and (VI).

It is difficult to reconcile this result with the report[8] that silychristin which has been assigned structure (VII), yields silybin (I) on reaction with acid.

(*Received*, 23*rd November* 1971; *Com.* 2013.)

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