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A PHENOLIC ISOFLAV-3-ENE FROM GLIRICIDIA SEPIUM

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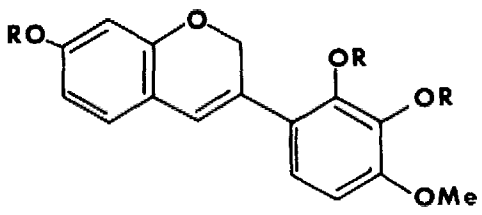
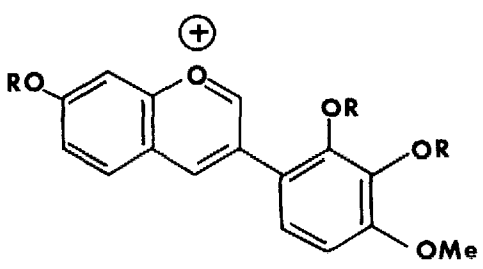
Constituents of the Panamanian timber, Gliricidia sepium (Leguminosae) have not previously been reported, although a flavonol, robinetin[1], has been detected in a related Indian wood, Gliricidia maculata.

The sodium borate soluble fraction of ether extracts of the heartwood of Gliricidia sepium yields robinetin and a new, colorless phenol, $C_{16}H_{14}O_5$, m.p. 209-210°, now called sepiol and identified as 2',3',7-trihydroxy-4'-methoxy-isoflav-3-ene Ia.

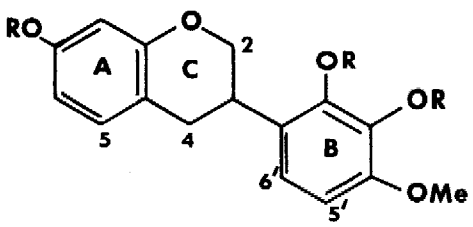


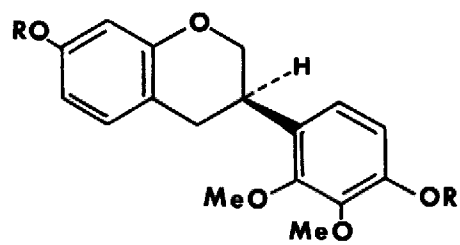


Ia, R = H c, R = COMe IIa, R = H

b, R = Me d, R = Et b, R = Me

In accord with structure Ia sepiol is optically inactive, contains one methoxyl group, and forms tri-O-acetyl and tri-O-alkyl derivatives, whose mass and n.m.r. spectra[2] clearly indicate an isoflav-3-ene nucleus. Thus, the mass spectra of sepiol and sepiol trimethyl ether Ib (m.p. 102-103°) show, in addition to the parent ions at m/e 286 and m/e 328, prominent ions at m/e 285 (43%) and m/e 327 (27%), indicative of the expected, facile formation of isoflavylium salts IIa and IIb respectively. The 100 Mhz n.m.r. spectrum of Ib in $CDCl_3$ shows the presence of a C_2 methylene group at δ5.02 (2H, d, J = 1 Hz), allylically coupled to a C_4 methine proton at δ6.42, four methoxyl groups (3H, s, δ3.80; 3H, s, δ3.85; 3H, s δ3.88; 3H, s, δ3.91), and five aromatic protons (2H, m, δ6.42-δ6.58; 1H, d, J = 8 Hz, δ6.66; 1H, d, J = 8 Hz, δ6.98; 1H, d, J = 8Hz, δ7.01).





IIIa, R = H c, R = COMe

b, R = Me d, R = Et

IVa, R = H

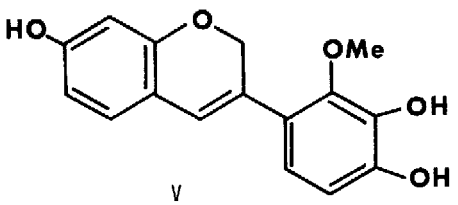
b, R = Me

Catalytic hydrogenation of sepiol yields a dihydro- derivative, m.p. 172°, identified as an isoflavan (IIIa) on the basis of the n.m.r. spectra of its derivatives which reveal the characteristic splitting pattern previously reported[3,4] for the C ring protons of isoflavans, e.g. in the n.m.r. spectrum ($CDCl_3$) of triacetyldihydrosepiol IIIc a methylene group at C_4 appears as two, broad, 1H singlets δ2.89 and δ2.98, a methine proton at C_3 as a multiplet at δ3.20-δ3.44, and a methylene group at C_2 as a 1H dd (J = 10,10 Hz) at δ3.97 and 1H double doublet (J = 10,3 Hz) at δ4.29. Furthermore, in the mass spectrum of dihydrosepiol prominent peaks at m/e 123 (7%) and at m/e 153 (43%), 154 (56%), 166 (100%) show that ring A of the isoflavan carries one hydroxyl group, and ring B one methoxyl and two hydroxyl groups.

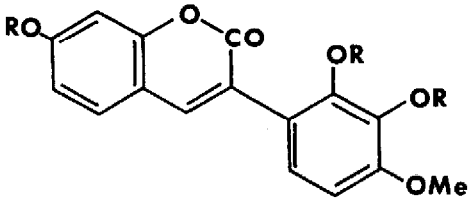
The n.m.r. spectrum of dihydrosepiol trimethyl ether indicates that the four methoxyl groups are located at positions 7,2',3',4' on the isoflavan nucleus as in IIIb. The aromatic protons at $C_{5'}$ and $C_{6'}$ appear as ortho-coupled doublets (J = 8 Hz) at δ6.64 and δ6.81, the C_5 proton as a doublet (J = 8 Hz) at δ6.97, the C_6 proton as a dd (J = 8,2 Hz) at δ6.48 and the C_8 proton as a doublet (J = 2 Hz) at δ6.44. Methoxyl protons appear as 3H singlets at δ3.78, 3.86, 3.90, 3.92, and C_4 methylene group as broad 1H singlets at δ2.88 and δ2.96, the C_2 methylene group as a 1H dd (J = 10,10 Hz) at δ4.00 and a 1H dd (J = 10, 3 Hz) at δ4.31, and the C_3 methine proton as a multiplet at δ3.34 - δ3.80. Dihydrosepiol trimethyl ether has λ_{max}^{EtOH} 288 (3.60) 280 (3.70) nm (log ε), and its mass spectrum shows peaks at m/e 330 (37%), 194 (100%), 182 (40%), 181 (26%), 179 (44%), 149 (36%). All of these spectral data closely agree with those reported[5] for a di-O-methyl derivative IVb of optically active laxifloran IVa, an isoflavan constituent of Lonchocarpus laxiflorus. Tri-O-methyl dihydrosepiol, m.p. 76-77°, is considered, therefore, to be the higher melting racemate of laxifloran dimethyl ether (m.p. 65-67°).

It remains to establish the location of the methoxyl relative to the two hydroxyl groups in the B ring of sepiol. Sepiol is soluble in aqueous borax, rapidly reduces silver nitrate, and its λ_{max} in alcohol (323 nm, log ε 4.44) shifts to 338 nm in the presence of boric acid - sodium

acetate. The B ring, therefore, contains an ortho-dihydroxy system and the methoxyl is located at the 4^1 position as in Ia, or at the 2^1 position as in the possible alternate structure V. Although unreliable with free phenols, the signals from methoxy groups ortho- to hydrogen in fully methylated derivatives[5] move upfield >0.3 ppm on changing solvent from $CDCl_3$ to C_6D_6. This procedure has now been extended to ethylated derivatives of sepiol, which unambiguously locate the methoxyl at the 4^1 position. Thus, with tri-O-ethyl sepiol Id the methoxyl signal appears at δ3.87 in $CDCl_3$, and the three methylene signals of the ethoxyl groups appear as quartets at δ4.00, 4.07 and 4.13. In C_6D_6 the methoxyl and <u>one</u> of the methylene signals shift upfield by 0.43 and 0.38 ppm respectively to δ3.40 and δ3.62. The other two methylene signals shift less than .08 ppm. Similar large shifts of the methoxyl and one methylene group are observed with tri-O-ethyldihydrosepiol IIId and with the derived ethylated coumarin VId. These data exclude structure V for sepiol, since ethyl derivatives of V would show large shifts of <u>two</u> methylene groups, the methoxyl and one methylene group shifting inappreciably. It is clear that this



V



VIa, R = H c, R = $COCH_3$

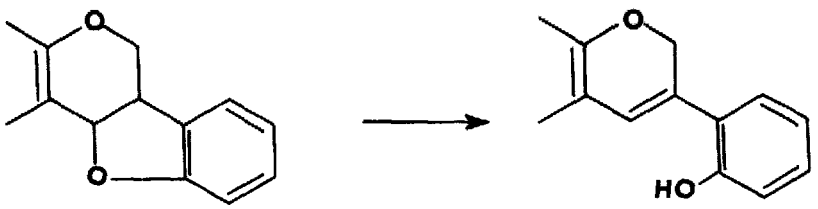
b, R = Me d, R = Et

simple modificaition, employing solvent shifts of O-ethyl derivatives, should prove to be a versatile and generally useful procedure for locating methoxyl groups in other phenolic natural products.

The isoflav-3-ene structure of sepiol was confirmed by CrO_3 oxidation of its trimethyl ether to the 3-phenylcoumarin VIb, m.p. 141-2°. Similar oxidation of triacetylsepiol gave VIc, which was hydrolysed to the phenolic coumarin VIa, m.p. 262-263°, and subsequently ethylated to yield 3-(2,3-diethoxy-4-methoxyphenyl)-7- ethoxycoumarin VId, m.p. 93-94°. The structure of VId (and, therefore, of sepiol) was confirmed unequivocally by its synthesis from 2,4-dihydroxybenzaldehyde and 2,3-diethoxy-4- methoxyphenylacetic acid.

Isoflavenes are highly reactive intermediates which may play a central role in the biosynthesis of isoflavans and other types of isoflavanoids in the Leguminosae. The natural occurence of isoflavenes, which has now been demonstrated,[9] lends support to the recent theory of Donnelly

and Kavanagh[6] that the biosynthesis of natural 3-phenylcoumarins may involve allylic oxidation of "an isoflav-3-ene". Although sepiol may arise by reduction and dehydration of an isoflavanone, its 2' - hydroxylation pattern suggests a more probably biosynthetic origin involves opening of the furano-ring[7,8] of a pterocarpan, e.g. VII→VIII.



VII VIII

Attempts to cyclise sepiol to a pterocarpan by reversing this reaction have not yet been successful.

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