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THE FIRST NATURALLY OCCURRING
4-ARYL FLAVAN-3-OL

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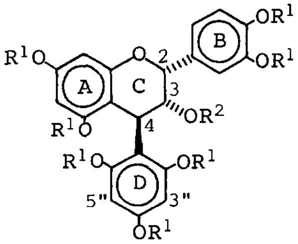
Abstract: (2R, 3R, 4S)-4-(2,4,6-trihydroxyphenyl)flavan-3,3',4',5,7-pentaol, the first natural 4-aryl flavan-3-ol, was isolated from *Nelia meyeri* Schwant., and its structure and stereochemistry determined by spectroscopic investigation and synthesis.

From previous studies on the chemical composition of *Nelia meyeri* Schwant. the flavonoids astragalin, isoquercitrin, luteolin, and its 7-O-glucoside have been characterized.[2] However, procyanidins possessing mainly (-)-epicatechin units predominate in the extracts of the leaves of this plant.[3] With regard to the attention directed at the chemistry of condensed tannins, continued investigations afforded a previously overlooked compound. This report now provides the first evidence of a natural 4-aryl flavan-3-ol, isolated from *Nelia meyeri* Schwant..

While re-investigating a mixture of mainly biflavanoids obtained by chromatography on Sephadex LH-20 compound (1a) was isolated and characterized by methylation followed by acetylation and p.l.c. separation as its heptamethyl ether mono acetate (1b).[4]



(1a) $R^1 = R^2 = H$
(1b) $R^1 = Me$; $R^2 = Ac$
(1c) $R^1 = R^2 = Me$

Mass fragmentation spectra are in agreement with structure (1b), showing the molecular ion m/e 554 (M^+, 1.3%) substantiated by loss of acetic acid, m/e 494 (M^+ -60, 100%), and fragment m/e 387 (M^+ -167, 2.9%), the fore-mentioned due to elimination of the 4-aryl group. The ratio M^+ -60 : M^+ (77 : 1) obtained for the methyl ether acetate correlates with a 3,4-*trans*-stereochemistry.[5]

The ^1H n.m.r. spectrum displays temperature - dependent line widths (Fig. B) due to 'slow' rotation about the C (4) - aryl group bond, as evidenced by sharpening of the broadened resonances at elevated temperature (Fig. A), particularly the signal at δ 5.37 which exhibits abnormal secondary couplings.[6] The absence of line-broadening at elevated temperatures is indicative of 'fast' rotation about the point of linkage and magnetic equivalence of D-ring protons (H-3", H-5") as reflected by a two-proton singulet at δ 6.12. While the multiplet centred at δ 5.28 was readily assigned to H-3 by its characteristic splitting

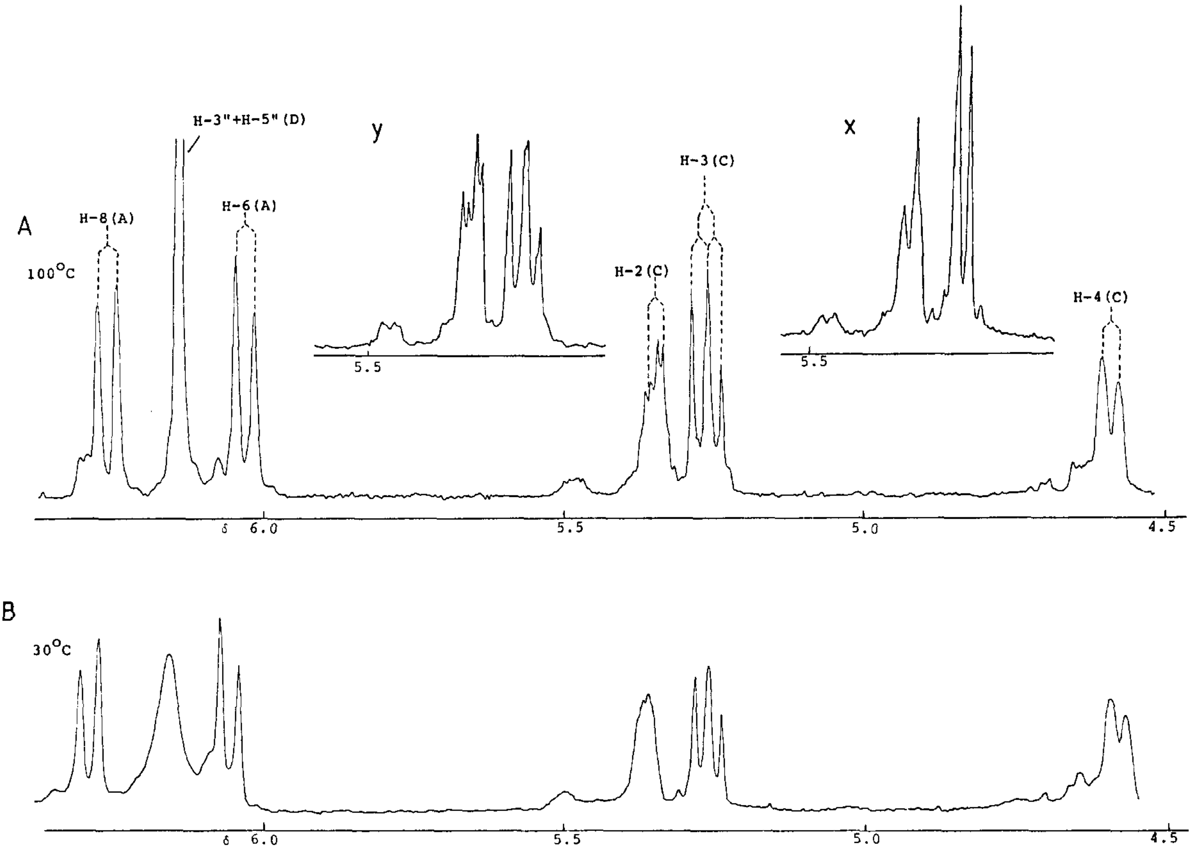


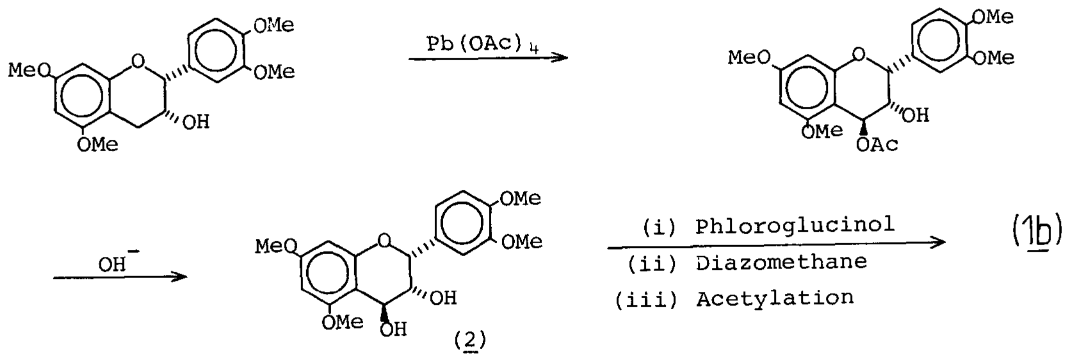
Figure A) and B). Expanded resonances from ^1H n.m.r. spectra of the methyl ether acetate of (1a), recorded at 100°C (A) and 30°C (B); spin-decouplings are shown in (x) and (y).

patterns, unequivocal assessment of the remaining resonances in the heterocyclic region was confirmed by means of spin-decoupling experiments involving the resonance for H-3 and the doublet of doublets at δ 5.37 (H-2) by irradiation of the line broadened doublet at δ 4.59, assigned to H-4, and of the B-ring protons. Irradiation of the latter intensifies the resonance at δ 5.37 and enhances its fine structure (cf. spectrum y), while decoupling of H-4 leads to sharpening of both H-3 and H-2, while H-3 is reduced to a sharp doublet (cf. spectrum x). The H-2 signal, attached to oxygen, is expected to appear downfield, and hence these results are consistent with the downfield position of H-2 relative to H-4.

Spin-decouplings establish for the first time that secondary couplings of H-2 may be attributed to long range couplings with H-4 rather than influence of B-ring protons. This observation is explicable in terms of an exception to the W-rule[7] (coupling through σ - bonds; J_4 0.75 Hz).

^{1}H n.m.r. coupling constants of the heterocyclic protons are consistent with the relative stereochemistry for 2,3-*cis*-3,4-*trans* flavan derivatives ($J_{2.3}$ 1.8 Hz, $J_{3.4}$ 2.0 Hz).[8] The 3,4-*trans* configuration is also supported by its positive Cotton effect in the low wavelength region of the c.d. spectrum indicative of a quasi-*axial* orientation of the 4-substituted aryl group.[9]

Synthesis of (1b) is summarized in Scheme 1. The flavan-3,4-diol (2), prepared from tetramethyl ether (-)-epicatechin according to Bett's procedure[10] , was



SCHEME 1

obtained in 23% yield. As expected, condensation of (2) with phloroglucinol[11] yielded (1b), after methylation followed by acetylation. Comparison of spectroscopic data (^{1}H n.m.r., m.s., c.d.) showed the synthetic substance to be identical with the natural product. Synthesis, coupling constants, and circular dichroism support the 4 S configuration at the point of linkage, and thus the 2R, 3R, 4S absolute configuration of the natural product. The 3-O-methyl derivative (1c) obtained during methylation as side reaction for both the synthetic and natural product again confirms structure and stereochemistry of (1a).

The characterization of the 4-aryl flavan-3-ol (1b) represents an extension of the series of natural biflavanoids. It may be regarded as a prototype of biflavanoids with (-)-epicatechin as 'upper' part and phloroglucinol as aryl derivative for the 'lower' moiety. Compound (1a) occurs in low concentration amongst the biflavanoid analogues present in the leaves of *Nelia meyeri* Schwant..

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11) L. Jurd and R. Lundin, *Tetrahedron 24, 2653 (1968);* method modified: Flavan-3,4-diol (2) (100 mg) and phloroglucinol (200 mg) were dissolved in 70% EtOH (20 ml) and HOAc (5 ml), heated (50^{o}C; 5 min.), and diluted with H$_2$O (100 ml). The precipitate (48 h; + 4^{o}C) was converted into the appropiate derivative.

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