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NEO-OLIVIL, A NEW LIGNAN FROM *THYMUS LONGIFLORUS*

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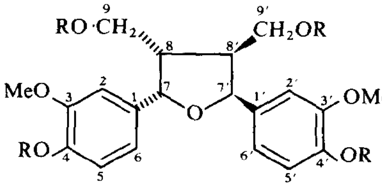
The genus *Thymus*, numerous species of which are to be found in the Iberian Peninsula, has been the subject of several studies, aimed primarily at determining the contents of its essential oils [1–3], flavonoids [4] and triterpenes [5]. In the course of a research project in our Institute, involving the study of several Spanish species of *Thymus* [3], we have isolated from *T. longiflorus*, collected on the east coast of Spain, a new lignan which we propose to name neo-olivil. From the spectral evidence discussed below, structure **1** was assigned to neo-olivil.



1 R = H
2 R = Ac

Since neo-olivil (**1**) was found to be extremely difficult to purify, it was converted into its tetraacetate (**2**) for purification and structure elucidation. However, the mass spectrometric analysis of crude neo-olivil had already suggested the molecular formula $C_{20}H_{24}O_7$ and shown a fragmentation pattern characteristic of a lignan of the tetrahydrofuran type [6]: *m/e* 376 (M^+) (25%), 224 ($\text{ArCH—CH(CH}_2\text{OH)—CH—CH}_2\text{OH}^+$) (60%), 196 ($\text{ArCOCH}_2\text{—CH}_2\text{OH}^+$) (70%), 180 ($\text{ArCH=CH—CH}_2\text{OH}^+$) (100%). Furthermore, its IR spectrum (nujol) showed very strong OH absorption and no carbonyl band.

Combustion analysis and mass spectrometry indicated the molecular formula $C_{28}H_{32}O_{11}$ for neo-olivil tetraacetate (**2**). Its IR spectrum (nujol) showed two carbonyl bands, at 1735 and 1765 cm^{-1}, corresponding to aliphatic and aromatic acetates, respectively. No OH absorption could be observed in the IR spectrum. The ^1H NMR spectrum (90 MHz, $CDCl_3$) of **2** provided the first evidence for the presence of a symmetry element in the molecule, since only seven signals could be observed. A multiplet at δ 7.0 (6H) was due to the aromatic protons. A doublet at δ 4.25 (2 × 2H, J = 4 Hz) was attributed to two equivalent $—CH_2—OAc$ groups. A singlet at δ 3.86 (2 × 3H) was due to two aromatic methoxy groups. A two-proton multiplet at δ 2.49 was assigned to H-8 and H-8'; its irradiation in a double resonance experiment resulted in the collapse of the two doublets at δ 5.0 and 4.25 to singlets. A singlet at δ 2.30 (2 × 3H) corresponded to two equivalent $\underline{CH}_3—COOAr$ groups and another singlet at δ 2.0 (2 × 3H) to two equivalent $\underline{CH}_3—COOCH_2—$ groups.

The ^{13}C NMR spectrum (25.2 MHz, $CDCl_3$) of **2** provided further evidence for the presence of a symmetry element in the molecule, confirmed the tetrahydrofuran structure of the lignan, and indicated the substitution pattern in the aromatic rings. Only 13 signals were observed in the spectrum, which were assigned as follows: δ 20.6 (*q*, 2 × $\underline{C}H_3—CO_2Ar$ and 2 × $\underline{C}H_3—CO_2CH_2—$), 50.4 (*d*, C-8 and C-8'), 56.0 (*q*, 2 × CH_3OAr), 63.4 (*t*, C-9 and C-9'), 82.6 (*d*, C-7 and C-7'), 110.0 (*d*, C-2 and C-2'), 118.0 (*d*, C-6 and C-6'), 127.7 (*d*, C-5 and C-5'), 139.4 (*s*, C-4 and C-4' or C-1 and C-1'), 140.0 (*s*, C-1 and C-1' or C-4 and C-4'), 151.2 (*s*, C-3 and C-3'), 168.6 (*s*, 2 × $CH_3—\underline{C}O_2Ar$) and 170.4 (*s*, 2 × $CH_3—\underline{C}O_2CH_2—$).

As a result of all above spectroscopic data, structure **2** is proposed for the neo-olivil tetraacetate. As regards the stereochemistry, the relative configuration of centres C-7, C-7', C-8 and C-8' was assigned on the basis of the following considerations. The molecular symmetry required by the ^1H NMR and ^{13}C NMR spectra, and the fact that neo-olivil tetraacetate (**2**) is optically active are only compatible with either an all-*trans* or a *cis–trans–cis* arrangement of the 4 substituents on the tetrahydrofuran ring. However, the two structures can be differentiated by comparing the ^1H NMR data with those reported for related compounds, namely the 4 lignans of the 2,5-*bis*-(aryl)-3,4-dimethyl-tetrahydrofuran type [7, 8]: grandinsin, galgravin, veraguensin and galbelgin. The ^1H NMR data of these compounds indicate that when the vicinal methyl and aryl groups are *trans*-oriented, the benzylic proton has a chemical shift of δ 4.48–4.6. When, on the other hand, these two substituents are *cis*-oriented, the benzylic proton is deshielded and resonates at δ 5.1. These same shift values have been observed in a dihydroxy derivative (9,9'-dihydroxy-veraguensin) [9]. This compound, which was obtained as an intermediate product in the synthesis of veraguensin, has a *trans–trans–cis* arrangement of its 4 substituents and its ^1H NMR spectrum [9] shows two signals for the benzylic protons at δ 4.5 and 5.12. The benzylic protons H-7 and H-7' in neo-olivil tetraacetate have a chemical shift of δ 5.0, suggesting a *cis–trans–cis* configuration. We, therefore, propose structure **1** or its antipode for neo-olivil.

It should be mentioned that in 1937 Vanzetti [10] proposed structure **1**, without specifying the configuration, for a lignan, which he named olivil, isolated from the resin of an olive tree. However, olivil was later reexamined by several authors [11–14] and the structure then found differed from that proposed by Vanzetti. For this reason we decided to name compound **1** neo-olivil.

EXPERIMENTAL

Dried plant (400 g), which was collected in Villajoyosa (Alicante, Spain) in June 1978, was pulverized and subjected to extraction with 2 l. of cold Me_2CO for 72 hr. The Me_2CO extract was concd *in vacuo* and, on cooling, a solid residue separated, the main component of which was identified as the triterpene oleanolic acid. The residue was filtered off and the filtrate was concd to dryness and chromatographed on a Si gel column (Merck, Kieselgel 60, 70–230 mesh). Elution with *n*-hexane–EtOAc (varying proportions, 9:1–1:1) yielded fractions containing the monoterpenes thymol, carvacrol and camphor, as well as oleanolic acid. Further elution with $CHCl_3$–MeOH (4:1) yielded crude neo-olivil (**1**) (135 mg), which could not be purified satisfactorily. The product was therefore acetylated.

Neo-olivil tetraacetate (**2**). Treatment of crude neo-olivil with Ac_2O–pyridine for 2 hr at 80° gave the tetraacetate **2**, which was purified by prep-TLC, yielding an amorphous solid. (Found: C, 61.42; H, 6.28. Calc. for $C_{28}H_{32}O_{11}$: C, 61.76; H, 5.88 %). UV λ_{max} nm: MeOH, 282, 235, 213 sh. IR, ^1H NMR and ^{13}C NMR: see text.

$$[\alpha]^{\lambda}_{24^\circ} \frac{589 \quad\quad 578 \quad\quad 546 \quad\quad 436\,\text{nm}}{-9.0 \quad -12.6 \quad -14.4 \quad -28.8} \; (c = 1.1).$$

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