Tetrahedron Letters No. 12, pp 979 - 981, 1974. Pergamon Press. Printed in Great Britain.

REVISED STRUCTURE FOR SIDERIN

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(Received in UK 30 January 1974; accepted for publication 8 February 1974)

Some years ago, during a search for diterpenes on Sideritis romana L. (Labiatae), we extracted a very small amount (5 mg) of a $C_{12}H_{12}O_4$ product, m.p. 194-195°, that on the basis of MS, IR, UV and NMR data was tentatively regarded as a methyl-dimethoxy-coumarin. As the compound was available in too little amount for any chemical degradation to be performed, its study had been abandoned.

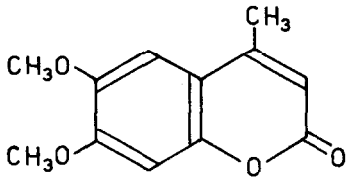
Recently, González et al. ([1]) reported the isolation from Sideritis canariensis Ait. of a product, whose physical and spectroscopic data were identical to those of our substance. From the interpretation of the spectra they attributed it the structure [I] of 4-methyl-6,7-dimethoxy-coumarin, and named the substance siderin, regarding it as a new natural coumarin.

As we pointed out in a preliminary note ([2]), structure [I] is clearly untenable for siderin. In fact, the authentic 4-methyl-6,7-dimethoxy-coumarin [I] has been well known since 1911 ([3-6]) and is also listed in Beilstein's Handbuch ([7]): it has m.p. 136-137°, as we checked on a synthetic sample ([8]). Moreover, synthetic [I] differs from siderin in the NMR spectrum, see Table: the most striking difference is the occurrence of an allylic coupling (J 0.8 Hz) between H-3 and the methyl group, that is totally missing in siderin ([9]).

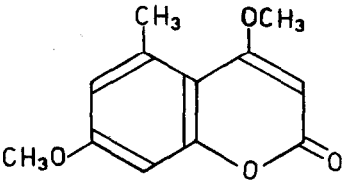
A reinvestigation of the NMR spectrum of siderin (see Table) casts a serious doubt on the occurrence of the para coupling suggested by González ([1]): the slightly broadened signal for the two aromatic protons does not rule out a meta coupling, as it was observed on other similar coumarins ([10]). Moreover, H-3 is usually reported to resonate at 6.05-6.28 δ when a methyl group is present on C-4 ([9,11,12]), whereas it resonates at 5.56 δ when a methoxy group is on C-4 ([13]). Furthermore, a signal for H-5 should appear at a field lower than those of the other aromatic protons, i.e. in the 7.28-7.39 δ range ([12]) or even at 7.71 δ ([13]): but such a signal is clearly missing in siderin.

These remarks led to the following hypotheses: occurrence of OCH_3 instead

of CH_3 on C-4, and presence of the other substituents on C-5 and C-7. Also on the basis of biogenetical grounds, we took in consideration the structure [II] of 4,7-dimethoxy-5-methyl-coumarin for siderin.



[I]



[II]

The synthesis of [II] was performed as follows. Orcinol (3.1 g), malonic acid (2.6 g), anhydrous $ZnCl_2$ (10.2 g) and $POCl_3$ (6.85 ml) were heated at 65° for 36 hr with stirring ([14]). Decomposition with ice water gave 4,7-dihydroxy--5-methyl-coumarin ([15]), which was dissolved in aqueous Na_2CO_3 and precipitated with acids: m.p. 265-267° (from ethanol), yield 50%. UV (ethanol): λ_{max} 318 nm (sh, log ε 4.18), 308 (4.24), 290 (sh, 4.15), 234 (sh, 4.13), 218 (4.30). NMR (60 MHz, DMSO-d_6): 2.56 δ (s, Ar-CH_3), 5.31 δ (s, H-3), 6.48 δ (broad s, H-6 and H-8), 10.3 and 12 δ (broad, 2 OH).

The above coumarin (0.5 g) dissolved in acetone was treated with K_2CO_3 (2g) and $(CH_3)_2SO_4$ (0.5 g) at reflux for 2 hr. Dilution with water gave a precipitate of 4,7-dimethoxy-5-methyl-coumarin, m.p. 194-195° (from methanol), yield 90%. UV (ethanol): λ_{max} 314 nm (sh, log ε 4.05), 305 (4.12), 288 (sh, 4.03), 232 (sh, 4.04), 219 (4.25). NMR (60 MHz, $CDCl_3$): see Table. UV, IR and NMR spectra are superimposable with those of our natural siderin; m.m.p. does not depress.

Table

	Ar-CH_3	2 O-CH_3	H-3	2 Ar-H
siderin (S.canariensis)	2.65	3.88 and 3.98	5.64	6.76
siderin (S.romana)	2.60	3.84 and 3.94	5.53	6.64
synthetic [I]	2.42*	3.92	6.15**	6.80 and 6.92
synthetic [II]	2.60	3.84 and 3.94	5.53	6.64

* d, J 0.8 Hz

** q, J 0.8 Hz

The data of synthetic [II] are in good agreement with those reported for siderin ([1]): the small difference in δ values might be attributed to the use of different spectrometers. Hence, the structure of siderin is revised to 4,7-dimethoxy-5-methyl-coumarin, which is a real new natural product.

References and footnotes.

([1]) A.G.Gonzàlez, B.M.Fraga, M.G.Hernàndez and J.G.Luis, Phytochem. 11 2115 (1972).

([2]) P.Venturella, A.Bellino and F.Piozzi, Atti Accad.Sc.Lett.Arti Palermo [IV] 32 I 35 (1973).

([3]) G.Bargellini and E.Martegiani, Gazz.Chim.Ital. 41 II 612 (1911).

([4]) R.J.Parikh and S.Sethna, J.Indian Chem.Soc. 27 369 (1950); Chem.Abstr. 45 6631 (1951).

([5]) R.D.Desai and J.V.Parghi, J.Indian Chem.Soc. 33 483 (1956); Chem.Abstr. 51 6620 (1957).

([6]) E.Cingolani, Gazz.Chim.Ital. 84 825 (1954).

([7]) Beilstein's Handbuch, vol. XVIII, Suppl. I, 351.

([8]) Prepared according to ([3]).

([9]) K.D.Kaufman, J.F.W.Keana, R.C.Kelly, D.W.McBride and G.Slomp, J.Org.Chem. 27 2567 (1962).

([10]) G.Büchi, D.M.Foulkes, M.Kurano, G.F.Mitchell and R.S.Schneider, J.Am.Chem. Soc. 89 6745 (1967).

([11]) S.K.Jain, O.P.Aggarwal, U.S.Mahnot and R.L.Mital, Monatsh. 101 1052 (1970).

([12]) R.Grigg, J.A.Knight and P.Roffey, Tetrahedron 22 3301 (1966).

([13]) G.Büchi, D.H.Klaubert, R.C.Shank, S.M.Weinreb and G.N.Wogan, J.Org.Chem. 36 1143 (1971).

([14]) General procedure of V.R.Shah, J.L.Bose and R.C.Shah, J.Org.Chem. 25 677 (1960).

([15]) This product was recently quoted by L.Simonova and A.Shamshurin, Chem. Abstr. 78 4072 h (1973), but no physical data were reported.