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NMR STUDY OF TRIMETHYLSILYL ETHERS OF FLAVONOID COMPOUNDS

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Since flavonoid compounds contain, in general, very few protons, proton magnetic resonance (PMR) spectroscopy is a useful tool in the structural elucidation of this class of compounds. Several correlations of the PMR spectra of flavonoid compounds and their ethers and esters have been published .[1-4] Many flavonoids, especially the glycosides, have low solubility in solvents suitable for PMR study. Moreover the ethers and esters often suffer molecular rearrangements during their synthesis and subsequent hydrolysis to the parent compounds. In addition, naturally occurring O-methyl groups are indistinguishable from synthetic ones in the PMR spectrum.

This report presents some preliminary results on the usefulness of trimethylsilyl ethers in structural determination of flavonoid compounds by PMR spectroscopy. A full report together with critical discussion on the chemical shifts and coupling constants of the protons in flavonoid compounds will be presented later.

We have used in our study trimethylsilyl ethers of flavonoid compounds because of several important advantages which they offer.[5,6] The synthesis and hydrolysis of these ethers may be carried out quantitatively under relatively mild conditions. All hydroxy groups are silylated as indicated by the absence of OH peaks and by the integration of trimethylsilyl groups in the NMR spectra. Optically active dihydroquercetin, II has been silylated and hydrolysed back to the parent compounds without loss in optical activity. The recovery of unracemized dihydroquercetin from its silyl ether demonstrates that silylation does not alter the basic structure of the flavonoids. The trimethylsilyl ethers are miscible with CCl_4 in all proportions, a property of definite advantage in NMR spectroscopy. Unlike methyl ethers and esters the protons in trimethylsilyl group absorb at fields higher than 0.5 p.p.m. (δ) and therefore do not interfere with absorptions of aliphatic protons in the hetercyclic ring, naturally occurring methyl ethers, and other side chains attached to the flavonoid nucleus. The silyl ethers are thermally stable and volatile so that purification by gas-liquid chromatography and examination by mass spectrometry can be done.[7]

The protons at the 6 and 8 positions of 7-trimethylsiloxyflavonoid compounds are found to absorb exclusively in the region of 5.8-6.7 p.p.m. (δ), as illustrated by the dotted lines in Chart I. In the presence of 5,7-bis-(trimethylsiloxy) substitutions H_6 and H_8 appear as two doublets displaying a typical meta spin-spin splitting (J = 2.5 c.p.s.) with H_6 at slightly higher field, as reported by Massicot and Marthe.[1] As shown by spin multiplets the positions of H_6 and H_8 are reversed in 7-trimethylsiloxy compounds, apparently because of a slight difference in shielding produced by ortho and para oxygen substitution. The positions of H_6 and H_8 of 5,7-bis-(trimethylsioxyl)-flavanes and flavanones are located 0.3-0.5 p.p.m. higher field than their corresponding flavones because of a more effective electron donating power by the oxygen of the heterocyclic ring in flavanes.

The protons in the 3 position of flavones appear as singlets in the region of 6.2-6.4 p.p.m. (δ).

All protons in ring B absorb in a region separate from H_6 and H_8 of ring A (6.7-8.0 p.p.m.). A careful examination of Chart I reveals that their absorptions are rather characteristic of the hydroxylation pattern.

In flavones, the proton in the 5 position absorbs in the region of 7.6-8.2 p.p.m. and may be recognized readily, especially in the presence of H_6, by its ortho coupling (J = 9 c.p.s.).

The aliphatic protons in the heterocyclic ring and glycosidic side chains, whose hydroxy groups are silylated, appear expectedly at fields above 5.5 p.p.m. The stereochemistry of the heterocyclic ring may be readily determined by their coupling constants.[2-4]

It is important to note that the 3-trimethylsilyl groups of flavanes and flavanones appear at -5 and -10 c.p.s., respectively. The exact position of other phenolic trimethylsilyl groups cannot be assigned without further investigation.

A typical procedure for the preparation of the trimethylsilyl ethers is described as follows. While under an atmosphere of nitrogen, 1 ml. of redistilled hexamethyldisilazane was added slowly to the solution of 100 mg. of (+) catechin, I, flavonoid in 2 ml. of anhydrous pyridine. The solution was then heated in an oil bath of 80° for 2 hrs. Upon cooling to room temperature the solvent and excess hexamethyldisilazane were removed under high vacuum at room temperature. In order to remove last traces of pyridine the product was redissolved in 1 ml. of anhydrous CCl_4 and then removed under vacuum. This process was repeated twice and the product, m.p. 99-100°, is ready for NMR and elemental analyses.[8,9] The yield of the trimethylsilyl ether is quantitative.

Anal. Calcd. for $C_{30}H_{54}O_6Si_5$: C,55.4; H, 8.29. Found: C,55.5; H, 8.24.

The silyl ethers from 100 mg. of flavonoid compounds, may be hydrolysed by heating in 5 ml. of 50% aqueous methanol at reflux temperature for 2 hrs.

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[7] Some preliminary work on liquid-gas chromatographic separation and mass spectroscopic analysis of flavonoid silyl ethers is in progress in the laboratory.

[8] The NMR spectra were recorded in CCl_4 solution using TMS as internal reference with the Varian A-60 or HR-60 NMR spectrometers.

[9] Satisfactory elemental analyses have been obtained for all trimethylsilyl ether presented in this paper.

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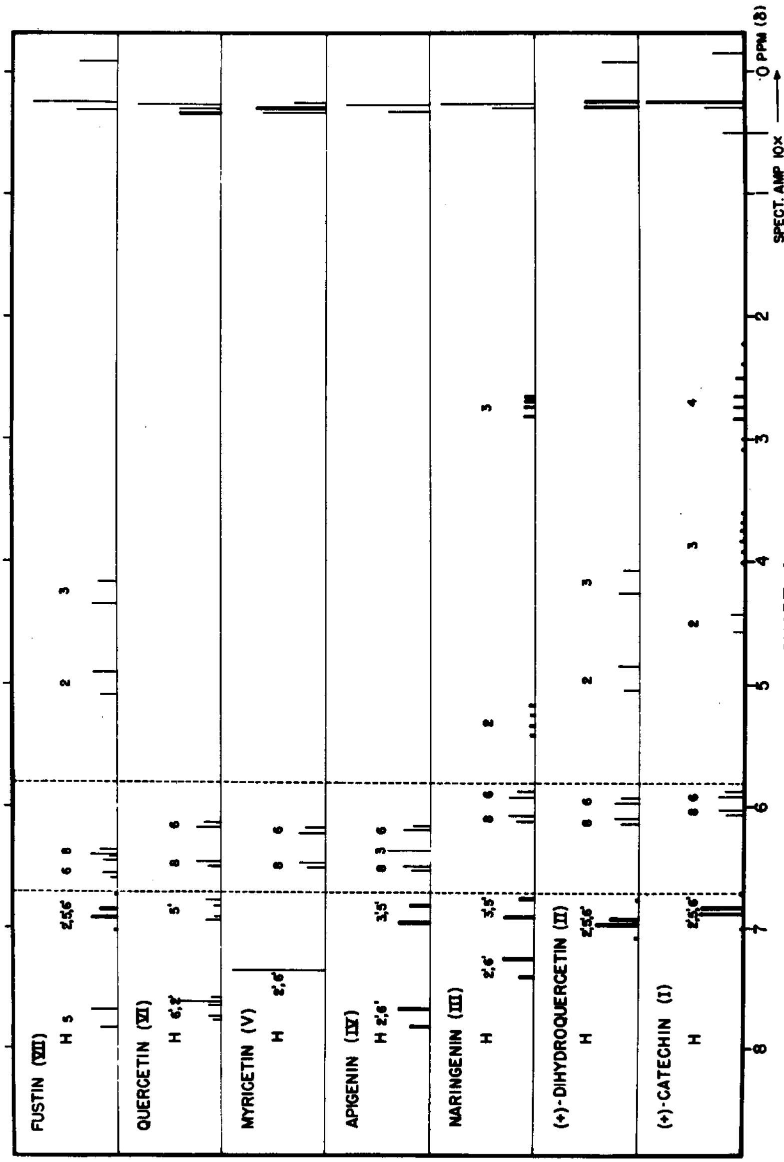
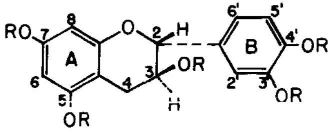

FUSTIN (VII)
H 5 2',5',6' 6 8 2 3
QUERCETIN (VI)
H 6',2' 5' 8 6
MYRICETIN (V)
H 2',6' 8 6
APIGENIN (IV)
H 2',6' 3',5' 8 3 6
NARINGENIN (III)
H 2',6' 3',5' 8 6 2 3
(+)-DIHYDROQUERCETIN (II)
H 2',5',6' 8 6 2 3
(+)-CATECHIN (I)
H 2',5',6' 8 6 2 3 4
8 7 6 5 4 3 2 1 0 PPM (δ)
SPECT. AMP 10X

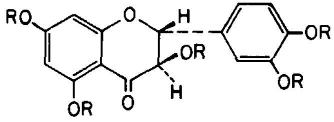
CHART I

I



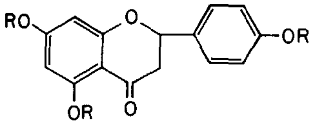
(+)-CATECHIN

II



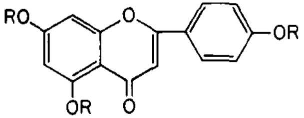
(+)-DIHYDROQUERCETIN

III



(±)-NARINGENIN

IV



APIGENIN

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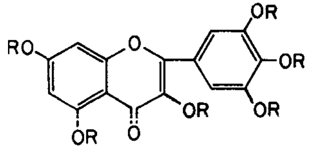
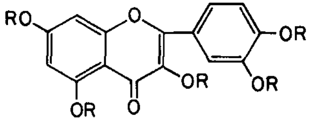


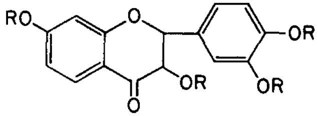
MYRICETIN

VI



QUERCETIN

VII



FUSTIN

R = $(CH_3)_3Si-$