**Tetrahedron Letters No.24, pp. 2669-2673, 1966. Pergamon Press Ltd.
Printed in Great Britain.**

SYNTHETIC PROANTHOCYANIDIN

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(Received 10 March 1966)

We wish to report supporting evidence for the carbon to carbon type of condensation of polyhydroxyflavan-3,4-diols with catechins proposed in a previous publication.[1] Under mild acidic conditions, both phloroglucinol and (+) catechin condense with a flavan-3,4-diol to give proanthocyanidin products which, when heated with acid, yield the characteristic red color of flavylium salts. Based on analytical results and their NMR spectra, these products have been assigned structures that are condensation products linked by a carbon-carbon bond formed by replacement of the hydroxyl group in the 4-position of the flavan-3,4-diol.[1,2] The condensations were effected by allowing equimolar amounts of the flavan-3,4-diol and phloroglucinol or (+) catechin to react at 0° in a dioxane-water solution that was approximately 0.1N in HCl. The course of the reaction was followed by thin-layer chromatography, and the products were separated by preparative thin-layer chromatography.

In the case of the acid-catalyzed condensation of tetra-O-methyl 3',4',5,7-tetrahydroxyflavan-3,4-diol with phloroglucinol, two major products (formed in approximately equal amounts) were partially separated by fractional precipitation. A chromatographically homogenous sample of one of the products was obtained by vacuum sublimation of its trimethylsilyl ether followed by passage through a short column of silica gel. Its NMR spectrum (Fig. 1) showed a total of seven aromatic protons: three of the catechol type (ring B) and four of the phloroglucinol type (ring A + 2). Out of the six lines clearly visible in the region of from 5.80 to 6.04 ppm, four are assignable to the 6 and 8 hydrogens ($J_{6H,8H}$=2.5 cps.) of the flavan residue. The remaining two lines must be part of a second AB pattern arising from the two meta protons on the phloroglucinol residue. The group of signals integrates for a total of four protons. In addition, the NMR spectrum shows a distorted triplet centered at 4.48 (3H), four singlets between 3.33 and 3.85 ppm (12 H; four OMe) and another set of four singlets between -0.6 and 0.37 ppm (36 H; four $SiMe_3$). Structure I (Fig. 1) accommodates this information and the corresponding phenol (Fig. 1, R=H) is proposed as one of the products of the condensation. Possibly the other product is of identical structure, epimeric at the 4 position, but this was not purified for detailed study.

Under identical acidic conditions as those used in the phloroglucinol case, tetra-O-methyl 3',4",5,7 tetrahydroxyflavan-3,4-diol and (+) catechin also give two major proanthocyanidin products in 67% yield. Preparative thin layer chromatography of their methyl ether acetates yielded two chromatographically homogenous products, SD-1 (dec. 122-128°) and SD-2 (dec. 138-146°), which analyzed for compounds both having the molecular formula $C_{42}H_{46}O_{14}$.

The NMR spectrum of SD-2 (Fig. 2) integrated for a total of 46 protons and is in complete agreement with the requirements for an octamethyl ether diacetate. Aside from this information, the most

Fig. 1

NMR Spectrum in $CDCl_3$.

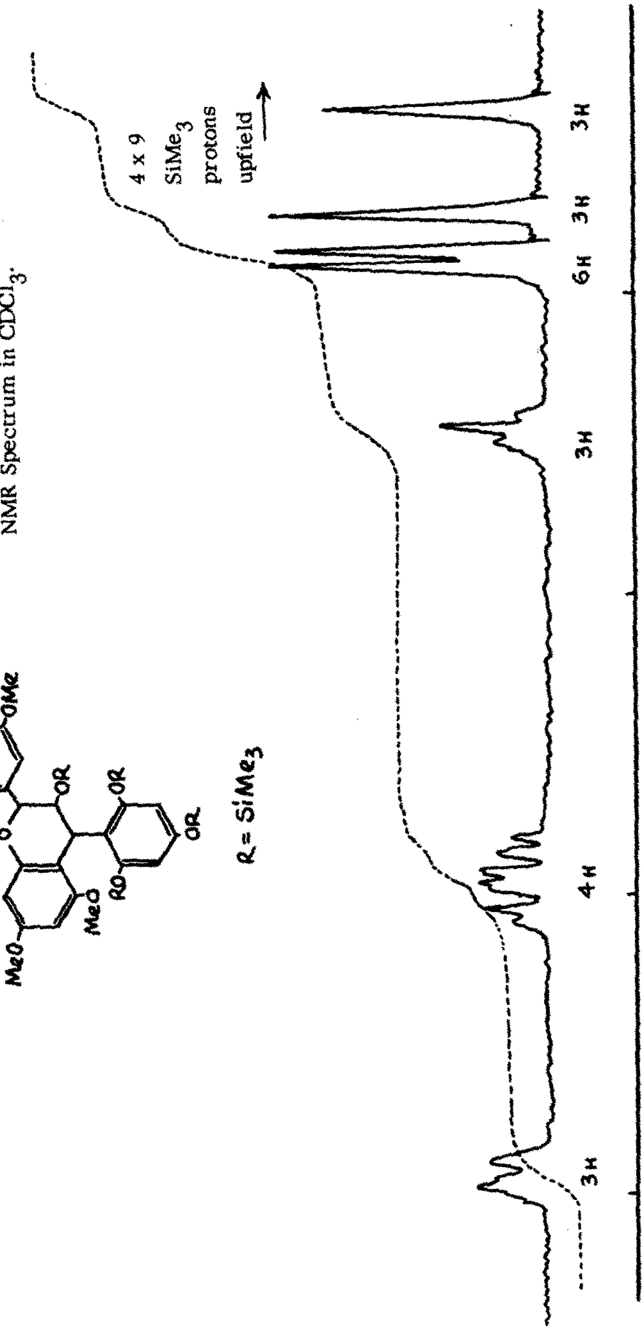
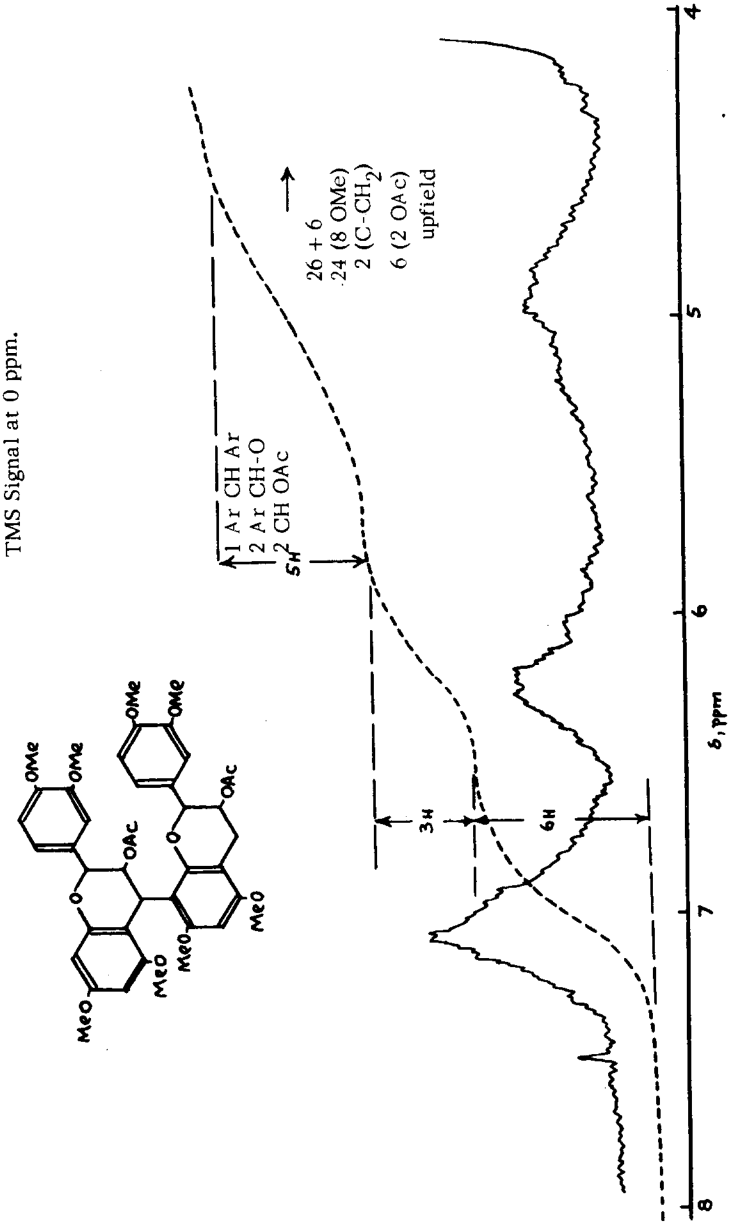


Fig. 2

NMR Spectrum in CD Cl_3.

TMS Signal at 0 ppm.



significant feature of the NMR was in the aromatic region between 5.8 and 7.5 ppm. There are two clearly discernable complex multiplets of lines assignable to three ring-A-type protons (5.8-6.6) and six ring-B-type protons (6.6-7.5). The observed ratio of 3:6 for the ring A:ring B protons is accounted for only if ring A of the catechin molecule carries a substituent other than hydrogen at the 6 or 8 position as in Structure II (Fig. 2). The corresponding tetramethyl ether is proposed as a product of the condensation. Likewise, as in the phloroglucinol case, it is probable that the second product, formed in approximately equal amount, is of the same structure, but epimeric at the 4 position.

The ease with which these condensations occur under mildly acidic conditions is consistent with the ease of production of an electrophilic center at the 4-position of the flavan-3,4-diol and the high degree of nucleophilic character of the phloroglucinol nucleus, and furnishes additional support for the suggestion[1,2] that the natural flavonoid tannins are polymers formed by similar condensations.

REFERENCES:

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Acknowledgment. -This work was supported by a Research and Service Contract USDA-12-14-100-7160(74) and in part by USPHS Grant GM 03667-12. This paper is Contribution No. 1925 from the Department of Chemistry, U. C. L. A.