Tetrahedron Letters Vol. 21, pp 2561 - 2564
0040-4039/80/0622-2561$02.00/0

EQUILIBRATED STEREOSTRUCTURES OF HYDRATED GERANIIN AND MALLOTUSINIC ACID

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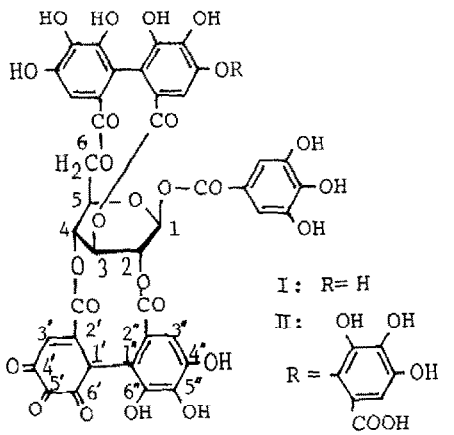
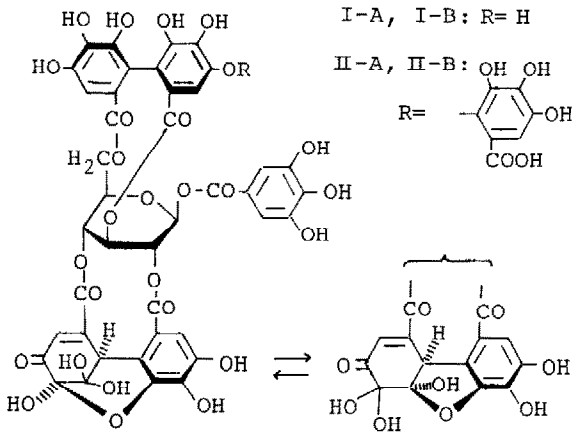
Summary: Partial revision of the hydrated structure, and determination of the absolute configurations of geraniin and mallotusinic acid lead to structures I-A and II-A, respectively.

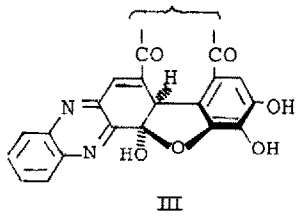
Structure of geraniin, the main tannin of plants of Geranium species, and of several species of Euphorbiaceae[1], is represented by I[2]. Structure of mallotusinic acid which occurs in several species of Euphorbiaceae[1], can be fundamentally shown by II[3].

Crystalline geraniin exhibits mutarotation in acetone containing water to give an equilibrium mixture which is shown by PMR and CMR spectra to be composed of two isomers[2]. Mallotusinic acid, which is obtained as an amorphous powder, forms an analogous equilibrium mixture[3]. Two of three carbonyl groups in the cyclohexenetrione moiety in these tannins were presumed to be hydrated, based on the CMR spectra[2,3]. These structures have now been re-investigated, as the PMR spectra showed that the methine proton at $C_{1'}$ is not substituted by deuterium upon mutarotation of dried geraniin in the presence of D_2O, to indicate that the mutarotation of geraniin is not due to epimerization[2,3] at the methine carbon.

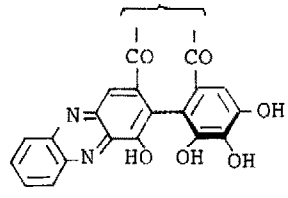


Equilibrated geraniin shows in the region of hydrated ketone and acetal of the CMR spectrum, four peaks which are singlets in the off-resonance spectrum, and doublets or triplets in the spectrum obtained by gated-decoupling technique as indicated by d and t in Fig. 1. Two solid lines indicate the peaks observed when the spectrum was measured in a short time after dissolution of crystalline geraniin





III



IV

in acetone-d_6. Since these couplings are attributable to the couplings of ^{13}C-C-H and ^{13}C-C-C-H on the cyclohexene ring, the doublets can be assigned to $C_{6'}$, and the triplets to $C_{5'}$. The downfield shift of $C_{6'}$ peak from 92.5 ppm to 108.9 ppm upon the mutarotation may be attributed to formation of an ether linkage, or transformation similar to that from pyranose to furanose[4].

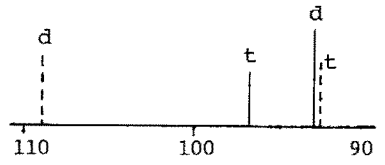
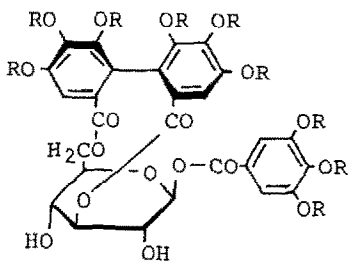


Fig. 1

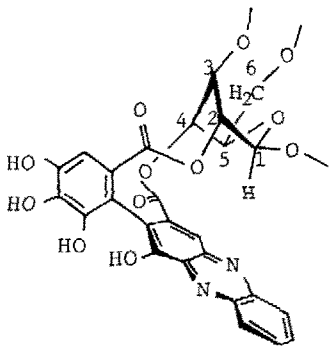
Formation of a five-membered hemiacetal ring as shown by I-B is supported by the analogous chemical shift of $C_{6'}$ peak (106.6 ppm) in the CMR spectrum of phenazine A (III) which is obtained by condensation with o-phenylenediamine at $C_{4'}$ and $C_{5'}$ of geraniin[5]. Further support to structure I-B is given by the allyl coupling between $H_{1'}$ and $H_{3'}$ in the PMR spectra of mutarotated geraniin (J=1.5 Hz) and phenazine A (J=1.5 Hz), which are in accord with the conformation induced by the ring closure of five-membered hemiacetal in I-B.

A six-membered hemiacetal structure as shown by I-A, or presence of two gem-diol groups is then presumed for geraniin before the mutarotation. Between these two structures, the former is supported by the deuterium-induced differential isotope shift (DIS) measurement as follows: As DIS technique was originally applied to carbohydrates[6], in the preliminary experiment we tested applicability of this technique to phenolic compounds using those of lower molecular weights such as arbutin and corilagin (V). The results showed that the aromatic carbon which carries free hydroxyl group is clearly differentiated from that carrying ether oxygen, by a dual peak (difference of shift, 0.1 - 0.25 ppm) of the former, and a single peak of the latter.

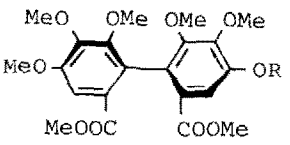


V: R= H

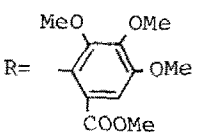
VII: R= Me



IV-A



VI: R= Me

VIII: 

Upon DIS measurement of geraniin, only $C_{6''}$ was exhibited as a single peak before (143.4 ppm) and after (147.3 ppm) the equilibration, while the other phenolic carbons were shown as dual peaks (difference of shift, 0.13 ppm for $C_{4''}$, in acetone-d_6 - water, 1:1). This result indicates that a hemiacetal ring is formed in both of isomeric geraniin. The formation of a six-membered hemiacetal ring of geraniin before the equilibration is also supported by sharp singlets of $H_{1'}$ and $H_{3'}$ in the PMR spectrum, as bondings $H_{1'}$-$C_{1'}$ and $H_{3'}$-$C_{3'}$ in this structure are almost in the same plane. The upfield shift of $C_{5'}$ peak in the CMR spectra upon the mutarotation (96.3 → 92.3 ppm) is also in accord with the structural correlation of I-A and I-B.

The configuration of $H_{1'}$ in geraniin is regarded as α based on the following data: The large upfield shift of H_1 of the glucose moiety (6.62 → 6.14 ppm) upon the aromatization of phenazine A to phenazine B (IV) should be attributed to shielding effect by newly formed aromatic ring in the conformation shown by IV-A. In this structure, the atropisomerism at the phenylphenazine moiety is R. This atropisomerism in phenazine B could be induced when the configuration of $H_{1'}$ in phenazine A is α.

As for the atropisomerism at the hexahydroxydiphenoyl (HHDP) group in corilagin, any unambiguous evidence has not been presented although S configuration was proposed[7] in the attempts to apply the amide rule of glyconic acids to biphenyls. In the present experiment, dimethyl hexamethoxydiphenoate (VI) ($[\alpha]_D^{25}$ +21°, $CHCl_3$) obtained by methanolysis of nona-O-methylcorilagin (VII), and dihydroxymethylhexamethoxybiphenyl ($[\alpha]_{240}^{25}$ +2800°, MeOH) which is produced by reduction of VI, have been found optically identical with those derived from schizandrin for which atropisomerism was determined to be R[8].

The determination of R configuration of the HHDP moiety in corilagin which is produced by hydrolysis of geraniin[5], establishes the atropisomerism at the HHDP moiety in geraniin to be R. The absolute stereostructure of equilibrated geraniin is therefore shown by I-A ⇄ I-B.

The PMR and CMR spectra of mallotusinic acid and its phenazine derivatives exhibit peaks corresponding to those of equilibrated geraniin, to show that the structure of this tannin is identical as that of geraniin except the presence of an additional gallic acid bonded via an ether linkage. The hydrated stereostructure of mallotusinic acid is then shown by II-A ⇄ II-B[9]. The direction of optical rotation of trimethyl octa-O-methylvaloneate (VIII)[3] derived from mallotusinic acid is identical with that of dimethyl hexamethoxydiphenoate produced from corilagin. The R configuration of valoneoyl group in the above structure of mallotusinic acid is based on this optical property and also on the co-occurrence of this tannin and geraniin as the main constituents in the leaf of Mallotus japonicus.

Acknowledgements – We thank Dr. H. Taguchi of Tsumura Laboratory for offering the ORD data, and staffs of Hitachi, Ltd. and JEOL for measuring some of the CMR spectra.

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9. Orientation of valoneoyl group is not determined.

(Received in Japan 5 April 1980)