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THE STRUCTURE OF DIGACETIGENIN

A CORRECTION OF A RECENT PUBLICATION BY CHANDLER, COOMBE, AND WATSON IN THIS JOURNAL [1]

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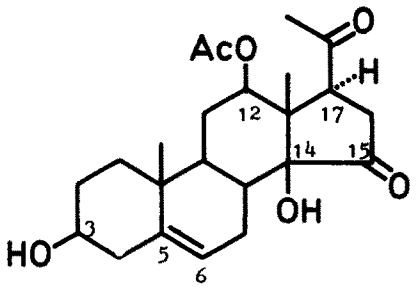
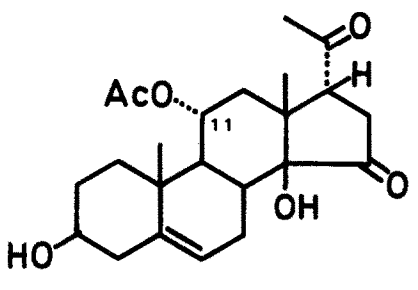
Last year we [2] elucidated the structure of digacetigenin (I) which is in agreement with a proposal made by Shoppee et al. [3]. Recently Chandler, Coombe, and Watson [1] suggested - mainly on the basis of the mass spectrum - that its structure should be changed to II. This is, however, in disagreement with most of the chemical and spectroscopical data [2], due to several misinterpretations by these authors [1].



I



II

1) From the high relative intensity of the peaks M - 18 and m/e 43 in the mass spectrum they [1] deduced the 17β-H configuration for digacetigenin. As a reference they used some of our previously published [4] mass spectra (in three cases intensities have been cited incorrectly from our plots) of compounds which in contrast to digacetigenin do not contain a 15-ketone group.

Since this keto group, however, completely changes the fragmentation pattern of 14ß-hydroxy-20-keto steroids [2, 5], the comparison of these data is not conclusive at all. Furthermore, it is assumed [1] that the high abundance of the M - 18 ion arises from the loss of the 14ß-OH group. In fact, it is mainly the homoallylic 3ß-OH group which is eliminated, as can clearly be seen from a comparison with the mass spectra of 5.6-dihydro digacetigenin [2] and its 4-en-3-one derivative. In these latter cases the intensity of the M - 18 peak (relative to the intensity of the molecular peak) is smaller by a factor of about 100 than in the mass spectrum of the genin. Any conclusions drawn upon the stereochemistry at C-17 from the intensity of the M - 18 peak are, therefore, meaningless.

2) In their "main fragmentation pathway of digacetigenin" Chandler et al. [1] assigned, inter alia, fragment ions to the peaks m/e 316, 273, and 258, which have, according to our high resolution mass measurements, other elemental compositions. They contain one oxygen atom less than assumed [1], and have to be assigned as M - CO - AcOH [2], M - CO - AcOH - $COCH_3$, and M - CO - AcOH - $COCH_3$ - CH_3.

3) Numerous peaks discussed by Chandler et al. [1] are either absent in the mass spectrum of pure digacetigenin [2] or so small that a reliable correlation is impossible (particularly without extensive high resolution mass measurements). This is the case for the peaks m/e 155, 137, 122 (interpreted as caused by the 15-ketone [1]), 266, 138, and their daughter ions (assumpted retro-Diels-Alder reaction of ring B [1]), and especially 154, 189, and secondary fragments thereof. These have been taken [1] as an indication for the 11-position of the acetoxy group on the assumption that acetic acid is first eliminated, and ring C of the thus generated 9(11)-ene is cleaved by a retro-Diels-Alder reaction (how this could lead to a fragment with odd mass number, m/e 189, is not explained). Since both peaks are virtually absent in the mass spectrum of pure digacetigenin [2], they cannot be discussed as an indication for the position of the acetoxy group. We suppose that a specimen not carefully enough purified may have been used by Chandler et al. [1].

4) The similarity of the ORD curves of digacetigenin and α-digiprogenin [6] cannot be taken as a hint to identical stereochemistry in both compounds as long as the influence of an 11-keto group, which is present only in the latter case, is not taken into account (by its contribution to the Cotton effect and the change of the conformation of the skeleton).

5) Further support for the 11α-acetoxy structure is taken [1] from the positions of the methyl signals in the cited [3, 7] NMR spectrum of digacetigenin, which have been calculated [1] using the published increments [8]. In general, such calculations are not very reliable, if many oxygen functions are accumulated in one ring [9]. In the special case of the NMR spectrum of digacetigenin published by Shoppee et al. [3, 7], these calculations cannot be used at all, since the assignement of the methyl signals has to be inversed (see ref. [2]). Besides this, Shoppee et al. [7] have allready pointed out that the shape of the geminal Proton rules out the 11α-position for the AcO-group.

In conclusion it may be said that the arguments presented by Chandler et al. [1] give no evidence whatsoever for a reassignement of the now accepted structure I of digacetigenin [2, 3]. A detailed discussion of the IR, NMR, CD, and mass spectra of pure digacetigenin and its derivatives is given in our full paper [2].

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