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REVISED STRUCTURE OF ACID-CATALYZED REARRANGEMENT PRODUCT OF AUCUBIGENIN

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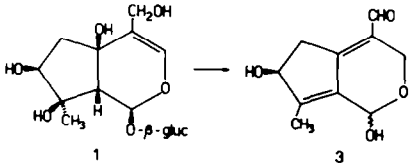
Abstract—The ^{13}C NMR spectrum of **6**, the acid-catalyzed rearrangement product of aucubigenin, has led to a critical re-examination of its ^{1}H NMR data and instead of the previous structure **6a**, the definitive structure of the acid-catalyzed rearrangement product is 1,10-anhydro, 3,4-dihydro, 4-decarbomethoxy, -3α-hydroxygardenogenin **6b**.

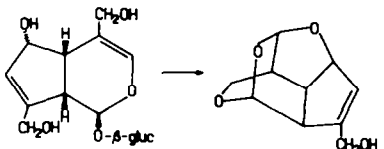
We previously described the rearrangement in mild acidic conditions of two non-natural iridoids, lamiidol **1** and asperulosidol **2**, which were transformed respectively into the conjugate cyclic aldehyde **3**[1] and the tetracyclic acetal **4**.[2] A common feature of both reactions is that the hemiacetalic system of the dihydropyrane ring is involved in the rearrangement, unlike what is reported for **6a**, the product of acid-catalyzed rearrangement of aucubigenin **5**[3], in which such system would have undergone only the epimerization of C-1 centre (structure **6a**).

Taking into account these discrepancies, we re-examined the whole problem and extended the analysis of spectral data by determining the ^{13}C NMR spectrum of **6**. The possibility of an alternative symmetrical structure **6b** for the rearrangement product suggested by the new data was corroborated by the results of its reduction with $NaBH_4$ which gave the cyclopentenpoliol **7**, clearly not obtainable from structure **6a**. Therefore, we have reached the conclusion that the structure of the rearrangement product of aucubigenin is 1,10-anhydro,-3,4-dihydro,-4-decarbomethoxy,-3α-hydroxygardenogenin **6b** and not 1,10-anhydro-6-deoxy,-7,8-dihydro-7,8-dihydroxyaucubigenin **6a**, as we reported previously.[3]



1

3



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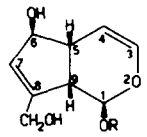
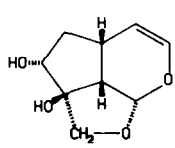
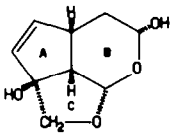
4



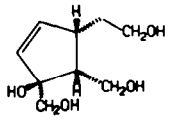
5 R=H
8 R=β-gluc



6a



6b



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RESULTS AND DISCUSSION

The acquisition of ^{13}C NMR data (PND, SFORD) of **6** has required a complete reassessment of the previous structure **6a** proposed on the basis of ^{1}H NMR arguments and hypothesized mechanism. Thus, the chemical shift values (133,8 and 140.5 ppm) of the olefinic carbons of **6** are in better agreement with those of C-6 and C-7 olefinic carbons of gardenoside[4] (134.6 and 136.0 ppm respectively) or galioside[5] (132.8 and 138.0 ppm respectively) than with those of $\Delta^{3,4}$ enol-ether system of aucubin **8** (C-3, 140.4; C-4, 106.1 ppm).[6]

Conclusive spectral evidence for the new structure **6b** is represented by the signals of two acetal carbons (102.2 and 90.1 ppm); none of the signals are attributable to the alcoholic oxymethine carbon C-7 of the previous structure **6a**.

Thus, re-examination of the original ^{1}H NMR assignments for the structure **6a** requires a reassessment on the basis of the following considerations: (i) The signal at δ 5.11 assigned in **6a** to the alcoholic oxymethine H-7 can now be assigned to the hemiacetal H-3 proton of the new structure **6b**. (ii) The resonance values of the olefinic protons (δ 6.00, dd, $J_1 = 5.7$, $J_2 = 1.9$ and δ 5.81, dd, $J_1 = 5.7$, $J_2 = 2.7$ Hz) are in better accordance with those of olefinic H-6 and H-7 protons of gardenoside (δ 6.25, H-6, dd, $J_{6,7} = 6.0$, $J_{5,6} = 2.5$; δ 5.77, H-7, dd, $J_{7,6} = 6.0$, $J_{7,5} = 1.0$ Hz)[4] or galioside (δ 6.32, H-6, dd, $J_{6,7} = 5.7$, $J_{5,6} = 3.0$; δ 5.78, H-7, dd, $J_{7,6} = 5.7$, $J_{7,5} = 1.7$ Hz)[7] than with H-3 and H-4 protons of the enolether system of aucubin **8** (δ 6.35, H-3, dd, $J_{3,4} = 6.0$, $J_{3,5} = 1.5$; δ 5.16, H-4, dd, $J_{4,3} = 6.0$, $J_{4,5} = 3.7$ Hz).[3] (iii) Both structures **6a** and **6b** have symmetrical sequences $-\underset{X}{CHOH}-\underset{AB}{CH_2}-\underset{Y}{CH}-CH=CH-$ leading to two equivalent ABXY four spin systems and there-

Table 1. ^{1}H NMR† spectra (90 MHz) and ^{13}C-NMR‡ (20 MHz) spectra assignments§

Compounds Solvents	**6b** D_2O	**7** D_2O		**6b** D_2O	**7** D_2O
H-1	5.70, d $J_{1,9} = 6.3$	4.0-3.5	C-1	90.1*	58.7*
			C-3	102.2*	61.4*
H-3	5.11, dd $J_{3,4} = 8.7$ $J_{3,4'} = 3.3$	4.0-3.5	C-4	31.4	33.4
			C-5	40.1	42.9
H-4	2.2-1.5, mc	2.1-1.2, mc	C-6	133.8	134.2
H-5	3.45, bsgf	2.98 bsg	C-7	140.5	139.1
H-6	5.81, dd $J_{6,7} = 5.7$ $J_{6,5} = 2.7$	6.20, dd $J_{6,7} = 6.0$ $J_{6,5} = 2.7$	C-8	95.4	86.7
			C-9	48.3	53.7
H-7	6.00, dd $J_{7,6} = 5.7$ $J_{7,5} = 1.9$	5.74, dd $J_{7,6} = 6.0$ $J_{7,5} = 1.5$	C-10	70.1	66.0
H-9	2.66, dd $J_{9,5} = 8.3$ $J_{9,1} = 6.3$	2.46, pq			
H-10	4.00 and 3.80 AB, $J_{AB} = 10.0$	4.0-3.5			

†Chemical shifts as δ; coupling constants in Hz; d = doublet, dd = double doublet, mc = complex multiplet, bsgf = broad signal with fine structure, bsg = broad signal, pq = pseudo quartet.

‡Values in $\delta \pm 0.1$ ppm downfield from TMS, dioxane (67.4 ppm from TMS) as internal standard. Values with the same superscript in the vertical column are interchangeable.

§To achieve a simpler comparison, the iridoid numbering has been maintained also for **7**.

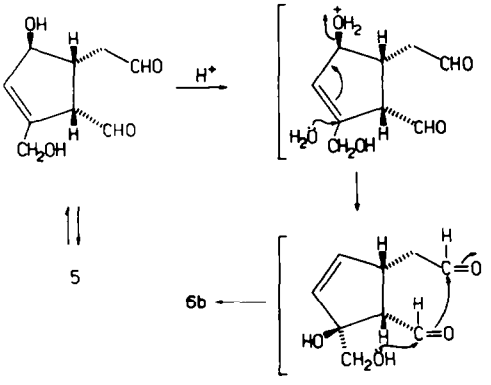
fore should exhibit similar signal multiplicities for the corresponding ABXY systems (2H-6, H-7 and H-5 in **6a**, 2H-4, H-3 and H-5 in **6b**). Clearly, however, the ABXY system of **6b** better explains the low-field value (δ 5.11) of the X part (H-3).

In order to achieve definitive chemical evidence for the hemiacetalic structure **6b**, we treated **6** with $NaBH_4$.

It was predictable that this reagent would cause the reductive opening of the hemiacetalic structure **6b**, whereas it would be ineffective on the alternative structure **6a**. As expected, **6** was easily reduced to the cyclopententetrol **7** whose structure is completely demonstrated by its ^{1}H NMR (Table 1) and ^{13}C NMR data (Table 1). The olefinic moiety of **6b** is still present in **7** (the resonance values of both olefinic carbons, 134.2 and 139.1 ppm, are practically identical with those of **6b**) while a strong upfield shift is observed for the resonance of the quaternary carbon C-8 (95.4 in **6b**, 86.7 ppm in **7**,) owing to the release of steric strain consequent on the cleavage of the acetalic rings. In addition the ^{13}C NMR data prove the disappearance of both acetalic carbons of **6** at 102.2 and 90.1 ppm and show the presence of three primary and one tertiary alcoholic functions.

As reported previously[3], the lack of any observable intermediate indicates that the whole reaction **5**→**6b** must be considered a concerted process (Scheme 1). As regards the new outlined pathway we suggest that the closure of the new acetalic ring C (clearly possible only from the α side, although with strain) may be induced by the allylic rearrangement to the more stable tertiary carbocation followed by regioselective and stereospecific closure of ring B.

The high stereospecificity of the acid-catalyzed reaction leads to the single hemiacetal compound with the C-3 in R configuration[3] (the S form is absent or present in undetectable amount via ^{1}H NMR). As regards the conformation of anomeric OH-3, the values found for the coupling constants $J_{3,4}$ and $J_{3,4'}$ (8.7 and 3.3 Hz respectively) indicate an α equatorial



Scheme 1.

orientation, in agreement with the values deducible from Dreiding models.

In fact in the alternative dihydropyrane ring conformation (OH-3 α axial), the C–H bond relative to H-3 proton ought to be the bisectrix of the angle between geminal protons at C-4 and the coupling constants $J_{3,4}$ and $J_{3,4'}$ would show the same value.

The α equatorial conformation of OH-3, on the other hand, is in contrast with the "anomeric effect" of ring B oxygen atom.[8] A possible explanation could be found considering that four interacting nearby oxygen atoms are present in the molecule. The observed stereospecificity may thus be the result of the interaction of different anomeric effects.

EXPERIMENTAL

For the materials, methods and preparation of compound **6**, see Ref. 3.

Cyclopententetrol **7**.

Compound **6** (100 mg) dissolved in water (10 ml) was treated with $NaBH_4$ (10 times molar excess) for 30 min at room temperature. Excess $NaBH_4$ was destroyed by bub-

bling CO_2 to pH ca. 7 and the solution was extracted with EtOAc (5 × 25 ml). Evaporation of organic phase gave a residue (90 mg) which, chromatographed on silica gel in $CHCl_3$/MeOH(85:15), afforded pure **7** as a colourless viscous oil.

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