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THE STEREOCHEMISTRY OF MARRUBIIN

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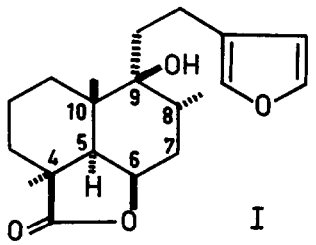
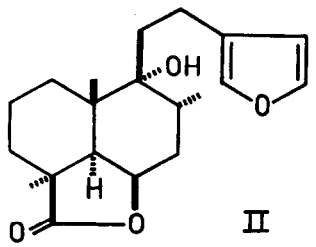
It has been recently reported that marrubiin has the stereochemistry represented in formula (I), the β-configuration of the C_9 hydroxyl being only suggested (1).

This remaining uncertainty has been now eliminated as we present evidence indicating that the C_9 hydroxyl is instead α-oriented and that actually marrubiin has steric structure (II).



I

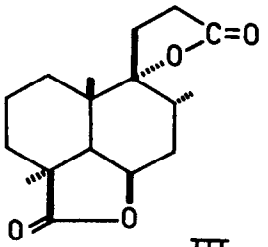


II

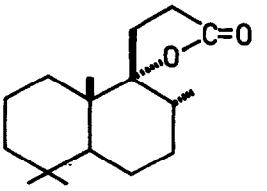
Oxidation of marrubiin is known (2) to give a dilactone m.p. 163-164° (III), that must have the same configuration of the former.

Although not self-consistent because of the tertiary nature of the hydroxyl group implied in the formation of the second lactone ring the identity of the configuration at C_9, as well as at C_4, C_5, C_6, C_8 and C_{10}, can be safely assumed, as the lactonization to the epimeric isoambreinolides (IV) and (V) has been shown (3) to take place with complete retention of configuration.

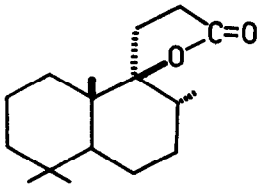
The dilactone m.p. 163-164°, on the other hand, has the stereochemistry shown in (III) owing to its conversion into the isoambreinolide m.p. 98° (4), which we have definitively proved to have structure (IV) (5).



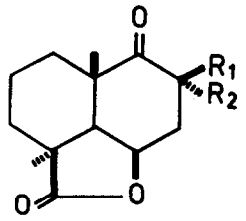
III



IV



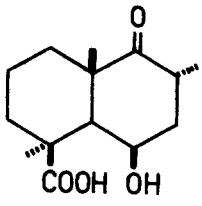
V



VI

(VIa) R_1 = H R_2 = CH_3

(VIb) R_1 = CH_3 R_2 = H



VII

However, independent evidence supporting the steric structure (III) with the potential 9-hydroxyl group α for dilactone m.p. 163-164° was obtained through its synthesis from ketolactone (VIa) m.p. 196°, $[\alpha]_D$ +119° (4).

Contrary to the findings of Cocker et al. (6) the ketolactone is not unchanged by alkali, as sodium methoxide in methanol transformed it into its 8-epimer m.p. 113-115°, $[\alpha]_D$ +149.5° (*). When hydrolized with potassium hydroxide in methyl cellosolve, both epimers yielded the same hydroxyacid m.p. 178°, $[\alpha]_D$ -43° (2) that can be assumed with confidence to have the

(*) Satisfactory analyses were obtained for all compounds reported. Melting points were determined on a Kofler block and have not been corrected. Specific rotations were determined on chloroform solutions at room temperature.

8-methyl group α-equatorial as in (VII) (7). As this in very mild conditions (ethyl chloroformate and triethylamine at 0°) quantitatively gave back the ketolactone m.p. 196°, the steric structure (VIa) with the same configuration at C_8 must be assigned to the latter and structure (VIb) to the epimer m.p. 113-115°.

In order to rationalize the alkali catalyzed (VIa)⟶(VIb) conversion formally involving an equatorial to axial epimerization, ketolactone (VIb) must be assumed to have the ring B in a "twist" form. However, this does not necessarily imply that also in the 8α-methyl epimer (VIa) the ring B has the same conformation, as the distorsion due to the presence of the lactone bridge may make (VIb) more stable than (VIa) even if in the latter the ring B is in the normal chair form (*).

When ketolactone (VIa) was reacted with the lithio-derivative of propargyl aldehyde dimethylacetal it smoothly gave an 8:1 mixture of the epimeric acetals (VIIIa) and (VIIIb) (**).

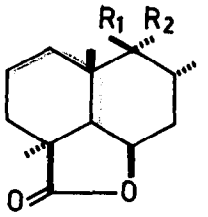
As an inspection of Dreiding models showed the β-side of ketolactone (VIa), especially if this has the ring B in the chair form, to be considerably more hindered than α-side, structure (VIIIa) was assigned to the major product m.p. 128-129°, $[\alpha]_D$ +15.3°. Hydrogenation using palladium charcoal catalyst

(*) Some 17β-methyl-D-omo-17a-oxo-steroids, but not their 17α-methyl epimers, are known to have the ring D in a "twist" form (8).

(**) Because of the easy conversion of (VIa) to (VIb) in alkaline solution, a control experiment was performed submitting (VIb) to the ethynilation reaction in the same conditions. Ketolactone (VIb) was found to give only one acetylenic hydroxyacetal, different from both (VIIIa) and (VIIIb), in poor yield.

in alkaline methanol produced the oily ethylenic acetal (VIIIc), which by chromic acid oxidation in aqueous acetic acid gave the unsaturated dilactone (IX) m.p. 324-325°, λ_{max}^{EtOH} 215mμ (ε = 10,200), $[\alpha]_D$ +24.0°.

Catalytic hydrogenation of (IX) (platinum oxide in acetic acid) gave the dilactone (X) m.p. 249-249.5°, $[\alpha]_D$ +15.0°, <u>not identical</u> with dilactone (III) from marrubiin.

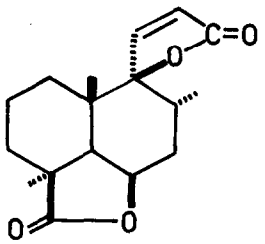


(VIIIa) R_1 = OH R_2 = C≡C-CH$(OCH_3)_2$

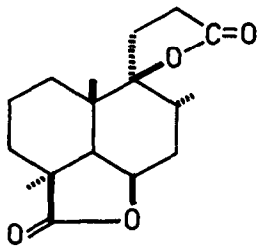
(VIIIb) R_2 = OH R_1 = C≡C-CH$(OCH_3)_2$

(VIIIc) R_1 = OH R_2 = CH=CH-CH$(OCH_3)_2$

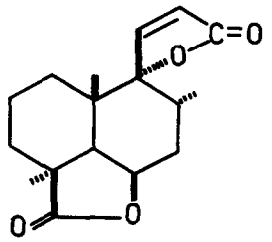
(VIIId) R_2 = OH R_1 = CH=CH-CH$(OCH_3)_2$



IX



X



XI

Analogously, the oily less abundand epimeric acetylenic acetal (VIIIb) was transformed into the ethylenic acetal (VIIId) and this oxidised to the unsaturated dilactone (XI) m.p. 153-153.5°, $[\alpha]_D$ -40.7°, λ_{max}^{EtOH} 215mμ (ε = 7,800).

Catalytic hydrogenation of (XI) gave a saturated dilactone m.p. 163.5-164°, $[\alpha]_D$ +27.3°, <u>identical</u> in all respects with dilactone (III) from marrubiin.

It is noteworthy finally that this work also provides chemical evidence indicating that in marrubiin the C_8 methyl group is α-oriented as proposed by J.W.B. Fulke and R. McCrindle (1) on spectroscopic ground.

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