STRUCTURE AND SYNTHESIS OF BISSANTANOLIDES**

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2-Hydroxy-hexahydro-ℓ-α-santonins (1) and (2) were transformed in reasonable yield to the corresponding bissantanolides (3) and (4) using p-toluenesulfonic acid, respectively. The structures and conformations of (3) and (4) were determined on the basis of their spectral data and X-ray crystallographic analysis of (3).

In an attempt to synthesize the antitumor bifunctional santenolide, "β"- and "α"-bissantanolide (3) and (4) as the key intermediate were prepared from 2β-hydroxy-3αH- and 2α-hydroxy-3βH-hyxahydro-ℓ-α-santonins, that is, cis-2β,3β- and 2α,3α-diol (1) and (2), respectively.

2β- and 2α-Acetoxytetrahydrosantonin[1] readily available from α-tetrahydrosantonin (5)[2] were subjected to a medium-pressure catalytic hydrogenation in the presence of platinum in ethyl acetate followed by hydrolysis with 5% potassium hydroxide in methanol yielding desired cis-diols (1) and (2)[3]. When 2β,3β-diol (1) was refluxed with p-toluenesulfonic acid in dry benzene for 6 hr, a mixture of β-bis- (3) and 3-keto-santanolide (5) (1:1) was quantitatively obtained. Trituration followed by recrystallization of this mixture from ether gave (3) as prisms, m.p. 302-304°; IR (KBr) ν 1770 cm^{-1} (lactone); CI(NH_3)-MS m/e 268 ($(M/2+NH_4)^+$, 100%), m/e 518 (QM^+, 4%); FD-MS (emitter current 17 mA) m/e 250 ($M/2^+$, 5%), m/e 500 (M^+, 100%); pmr ($CDCl_3$) δ 1.00 (3H, s, C(10')-CH_3), 1.12 (3H, s, C(10)-CH_3), 1.18 (12H, each d, J=7, >CH-CH_3×4), 3.58 (1H, dd, J=7, 8, C(3α)-H), 3.80 (2H, t, J=10, C(6β), C(6'β)-H), 4.26 (1H, t, J=4, C(2α)-H). The ether linkage

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between the two dihydroxysantanolide moieties in (3) should not constitute the ordinary 1,4-dioxane type, but reveal 1,3-dioxalane structure. Because the ketone (5) was produced besides the original diol (1) on the treatment of (3) with 5N sulfonic acid in acetone.

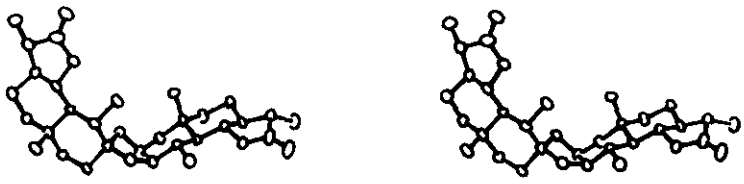


Fig. 1 Stereoscopic view of β-bissantanolide (3)

In order to settle the stereochemistry at the spiro carbon, which could not be determined merely on the basis of the aforementioned spectral data, an X-ray crystallographic analysis was carried out. Crystal data: $C_{30}H_{44}O_6$, MW= 500, orthorhombic, space group $P2_12_12_1$, Z= 4, a= 27.35, b= 11.69, c= 8.53 Å, U= 2726.9 $Å^3$, Dx= 1.22 g/cm^3. 2398 intensities ($2\theta_{max}$= 156°) were measured on a four-circle diffractometer with graphite-monochromated Cu-Kα radiation. The crystal structure was solved by the direct method using MULTAN.[4] The refinement by the block-diagonal least-squares method gave the final R value of 0.088. A stereoscopic view of the molecular structure of (3) is illustrated in Fig. 1. The 1,3-dioxalane system is located between the ketone and diol moieties as mentioned above, and the configuration of the two moieties in (3) is identical with every respect with that in the original diol (1). The configuration of the two ether bonds is deduced to be C(2β)-O-C(3'α) (axial-axial) and C(3β)-O-C(3'β) (equatorial-equatorial).

The reaction mechanism for the formation of β-bissantanolide (3) is considered as shown in Chart 1. (5) is produced by the trans-elimination of the hydroxy group axially oriented at C(2) position in diol (1) attacks nucleophilically from less hindered β side against carbonyl carbon of (5), and finally β-bissantanolide (3) is formed by the dehydration between 2β- and 3'α-hydroxy group.

A mixture of α-bis-(4) and 2-keto-santanolide (6)[5] (1:4) was quantitatively prepared from 2α,3α-diol (2) by the same procedure as above. (4) was separated from (6) by HPLC (μPorasil 1/4"×1', chloroform/n-hexane (4/1), 1 ml/min). Recrystallization from ether afforded prisms, m.p. 205~207°; IR (KBr) ν 1775 cm^{-1}

Chart 1

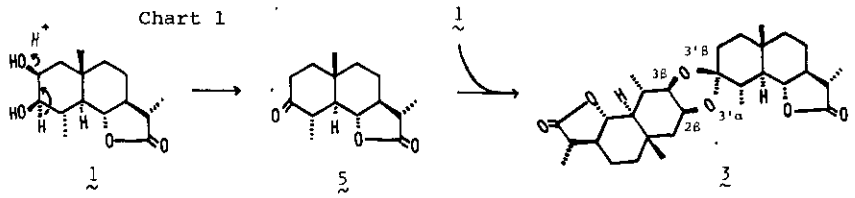
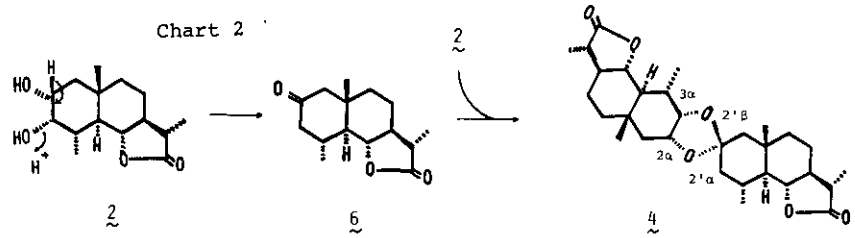


Chart 2



(lactone); CI(isobutane)-MS m/e 251 ($(M/2+H)^+$, 100%), m/e 501 (MH^+, 20%); pmr ($CDCl_3$) δ 0.89, 1.04 (6H, each s, →C-C<u>H</u>$_3$×2), 1.14 (3H, d, J=6, >CH-C<u>H</u>$_3$, 1.20 (6H, d, J=6, >CH-C<u>H</u>$_3$×2), 1.24 (3H, d, J=6, >CH-C<u>H</u>$_3$), 3.74 (2H, t, J=10, C(6β), C(6'β)-<u>H</u>), 4.04 (1H, t, J=4, C(3α)-<u>H</u>), 4.20 (1H, m, C(2β)-<u>H</u>). The acetal structure of (4) is also supported by the similar evidence as above, in which diol (2) and 2-keto-santanolide (6) were produced by the acid hydrolysis. The structure of α-bissantanolide (4) was deduced from the view point of the same reaction mechanism as above shown in Chart 2.

In conclusion it is evident that bissantanolide (3, 4) is formed by the condensation between <u>cis</u>-2β,3β- and 2α,3α-diol (1, 2) and the primarily dehydrated 3- and 2-ketone (5, 6), respectively, and that the ether bonds between the two moieties are oriented in the form of <u>axial</u>-<u>axial</u> and <u>equatorial</u>-<u>equatorial</u> configuration in (3) and (4).

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