Keto–Enol Tautomerism in Santonene and Dihydrosantonene

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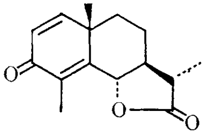
SOME years ago, we had shown[1] that santonin (I) could be converted into an enol acetate (IIa). Treatment of the enol acetate with methanolic hydrogen chloride afforded an *O*-methyl derivative which, with aqueous acid, gave a hydroxy-compound. N.m.r. spectra confirm the structure (IIa) for the enol acetate but require revision of the structure of the *O*-methyl derivative from (III) to (IIb). By analogy, the hydroxy-compound originally formulated as (IV), becomes (IIc).

Nishikawa *et al.*[2] obtained a compound with similar physical properties to the hydroxy-compound (IIc) and indeed assigned (IIc) as one of two possible structures. Their preparation involved the conversion of the diketo-acid (V) into santonene (VI) and subsequent partial reduction. We have found that the products obtained by the two routes are identical. In addition we have reduced the enol acetate (VIIa) from santonene[2] to (IIa) and the *O*-methyl ether (VIIb)[2] to (IIb). The structures (VIIa) and (VIIb) are assigned on the basis of n.m.r. spectra.

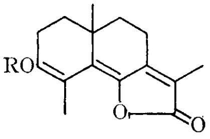
Santonene (VI) can exist in keto- (VI) and enolic forms (VIIc), and the same is true for its dihydro-derivative (VIII) and (IIc). The two compounds provide interesting contrasts. In the solid state, santonene exists in the keto-form (VI) while dihydrosantonene exists as the enol (IIc). This follows from the two carbonyl peaks in the infrared spectrum (Nujol) of the former; and the hydroxyl and one carbonyl peak of the latter.

In solution however both compounds exist as an equilibrium mixture of keto- and enol forms (*cf.* ref. 2), the position of equilibrium depending on the solvent. In chloroform both compounds exist largely in the keto-form at equilibrium. The specific rotation of santonene is unchanged with time in chloroform, but dihydrosantonene undergoes mutarotation, becoming dextrorotatory, as the enol form is converted into the keto-form.

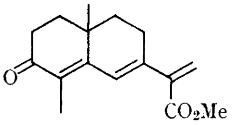
This change in dihydrosantonene can also be followed in the infrared (disappearance of hydroxyl peak; appearance of second carbonyl) and ultraviolet spectra. N.m.r. spectra are not so useful due to solubility difficulties, but bear out our other results.



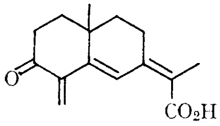
(I)



(II) a; R=Ac
b; R=Me
c; R=H

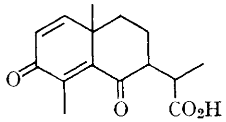


(III)

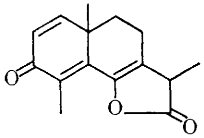


(IV)

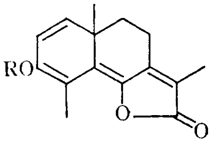
In methanol dihydrosantonene undergoes only minor changes in rotation but santonene becomes strongly lævorotatory.[2] Changes can be observed in the ultraviolet spectrum, corresponding to an isomerisation to the enolic form.



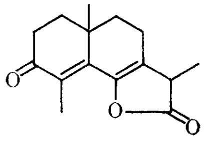
(V)



(VI)



(VII) a; R=Ac
b; R=Me
c; R=H



(VIII)

In pyridine, the rotations of both santonene and dihydrosantonene are lævorotatory indicating a high proportion of enolic form and this is confirmed by their n.m.r. spectra in this solvent.

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[1] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 1955, 4430.

[2] M. Nishikawa, K. Morita, and H. Hagiwara, *J. Pharm. Soc. Japan*, 1955, **75**, 1199, 1202.