Unusual Bromination of Tetrahydro-(—)-α-santonins and New Santonin Isomers: *X*-Ray Crystal and Molecular Structure of 2β,14-Dibromo-4α,5β,6β,11βH-tetrahydrosantonin

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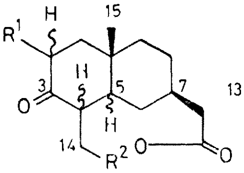
Summary A novel bromination–dehydrobromination reaction of tetrahydro-(—)-α-santonins is reported which has led, *via* the 2α,14- and 2β,14-dibromo ketones (**2a,b**), to two new dienone isomers of (—)-α-santonin whose structures were established by *X*-ray diffraction and c.d. studies of (**2b**).

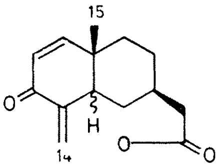
endo–exo-CROSS-DIENONES are seldom found but this unit does occur in a few natural products (*e g* encelin and farinosin)[1] and in a synthetic steroid [2] Certain sesquiterpenoids (*e g* santonin) and steroids (*e g* prednisolone) containing a normal cyclohexadienone unit are well known to exhibit cytotoxic and anti-inflammatory activity, respectively, and from a chemico-pharmacological point of view *endo–exo*-cross-dienones seem to be much more reactive against biological nucleophiles than the normal ones The present paper describes the preparation of dienone isomers (**3a,b**) of (−)-α-santonin (**4**) that possess the *endo-exo* cross-dienone group It was achieved by simple dehydrobromination of the appropriate dibromo-ketones (**2a,b**), which have become readily available through an unusual 2,14-dibromination of 4β,5α,6β,11βH- (**1a**) and 4α,5β,6β,-11βH-tetrahydrosantonin (**1b**)

Compounds (**1a**) and (**1b**) were treated in chloroform with 2 mol equiv of bromine (0 °C, 2—6 h) The reaction mixture, left preferably in a deep freeze (−15 to −20 °C, 7—21 days), afforded the unusual bromination products 2α,14- (**2a**) and 2β,14-dibromide (**2b**)‡ in average yields of 44 and 77%, respectively Treatment of (**2a**) and (**2b**) with lithium bromide and lithium carbonate in dimethylformamide (80—95 °C, 2 h) gave the double bond isomers of santonin ($\Delta^{4(5)}$) (**4**) which we have called alloisosantonin ($\Delta^{4(14)}$, 5αH) (**3a**) and isosantonin ($\Delta^{4(14)}$, 5βH) (**3b**) in *ca* 30 and 20% yields, respectively The isomers (**3a**) and (**3b**) were found from gas chromatography–mass spectrometry to undergo isomerization to (**4**) in yields of 46 and 44%, respectively, under the same reaction conditions as above, except at 130 °C In order to prove this unusual introduction of the bromine atom at the inactive C(14) position unequivocally in (**1a**) and (**1b**), and to compare its configuration in the crystal and the solution, *X*-ray crystallographic analysis and c d spectroscopic measurements of (**2b**) were carried out



(**1**) R¹ = R² = H
a, 4β, 5α
b, 4α, 5β

(**2**) R¹ = R² = Br
a, 2β, 4β, 5α
b, 2α, 4α, 5β



(**3**) **a**, 5α
b, 5β

(**4**) $\Delta^{4(5)}$

Crystal data $C_{15}H_{20}Br_2O_3$, *M* 408 1, orthorhombic, a = 12 835(4), b = 14 371(4), c = 8 783(3) Å, U = 1620 2 Å³, $Z = 4$, D_c = 1 673 g cm⁻³, space group $P2_12_12_1$ 1808 intensities ($2\theta_{max}$ = 156°) were measured on a four-circle diffractometer with graphite-monochromated Cu-K_α radiation The crystal structure was solved by the heavy-atom method and anisotropic refinement by block-diagonal least-squares, excluding the hydrogen atoms, gave *R* 0 062 In this calculation the anomalous scattering of the Cu-K_α radiation from the bromine atoms was taken into account The same refinement for the inverted structure yielded *R* 0 068 The absolute configuration of (**2b**) thus established accords with that deduced from its structural relationship to (**4**) and (**1b**) Perspective views of the molecule structure are shown in the Figure.§

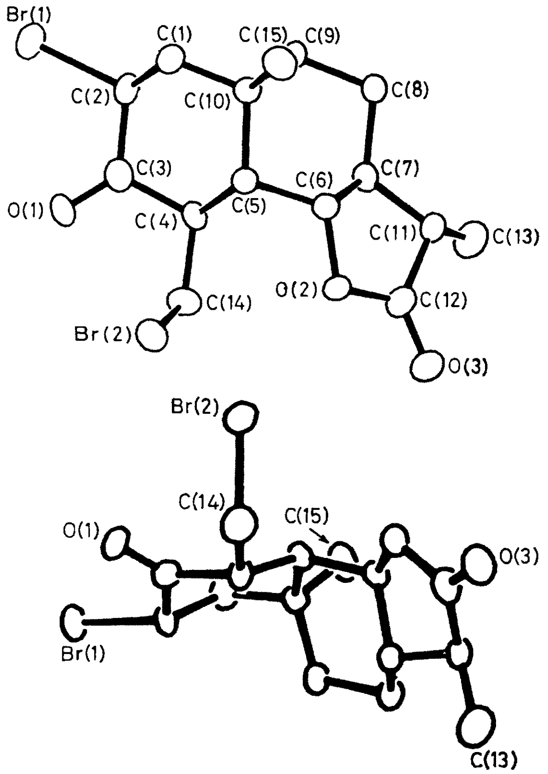


FIGURE Perspective views of (**2b**)

The *X*-ray crystal analysis of (**2b**) establishes the unique dibromination of (**1b**) and reveals that in the crystal the torsion angle of the C(14)–Br bond is 75 5° This *anti*-like stereochemistry of C(4)–H and C(14)–Br should facilitate the *trans* elimination of hydrogen bromide in a solution of (**2b**) to yield the target dienone (**3b**) The negative c d Cotton effect in ether–isopentane–ethanol (5·5 2), *e g* $[\theta]_{289}$ − 2163 (−72 °C), −1886 (−30 °C), and −1422 (27 °C), suggests that in solution the torsion angle of the C(14)–Br increases to approximately 120° at normal temperatures The observed sign of the Cotton effect is consistent with that predicted from the octant sector diagram for the conformation shown

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‡ All new compounds exhibited satisfactory spectroscopic and analytical data consistent with the proposed structures

§ The atomic co ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory Lensfield Road, Cambridge CB2 1EW Any request should be accompanied by the full literature citation for this communication

[1] T A Geissman and R Mukherjee, *J Org Chem* , 1968, **33**, 656

[2] W H W Lunn, *J Org Chem* , 1965, **30**, 2925