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SYNTHESIS AND ANTIOXIDANT ACTIVITY OF PHENOLIC DERIVATIVES OF α-SANTONIN

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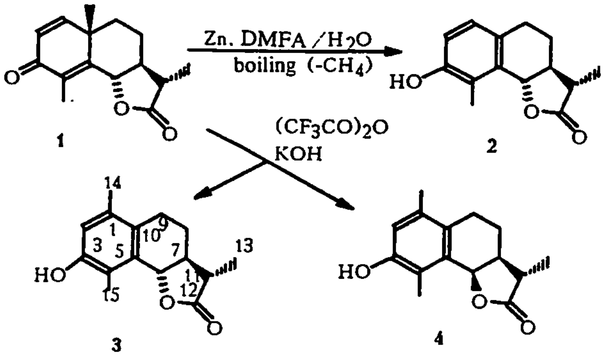
Phenolic derivatives of α-santonin have been synthesized and their antioxidant effect has been studied.

The presence in the α-santonin (**1**) molecule of a cyclohexadiene system is responsible for the tendency of this compound to undergo dienone–phenol rearrangements. The study of these rearrangements has been fairly well reported in the literature [1, 2].

We have obtained three phenolic derivatives of α-santonin (**2-4**) with the aim of studying their antioxidant activity.



The PMR spectrum of compound (**2**) (Table 1) showed doublets of the aromatic protons H-1 and H-2 at 6.83 and 7.13 ppm, respectively, and also an isolated singlet at 2.57 ppm, corresponding to the protons of the H-15 methyl group of the aromatic ring. The methyl group at C-1 was absent from product (**2**), as can be seen by comparing the spectra of compounds (**2**) and (**3**). A minor reaction product, (**4**), proved to be a *cis*-linked lactone, as was confirmed by the SSCC of the lactone proton (J = 5 Hz).

The pronounced antioxidant activity (AOA) *in vivo* of some sesquiterpene lactones has been reported previously [3], and analogous results have been obtained in our own studies [4]. It is known that the structures of many antioxidants include a phenol fragment, and we therefore investigated the change in AOA in the series: α-santonin (**1**), demethyldesmotroposantonin (**2**), and desmotroposantonin (**3**). The Fe^{+2}-initiated chemiluminescence of a model system [4] showed pronounced AOA activities of both α-santonin derivatives. While for α-santonin there was no reliable deviation of the length of the latent period from the control – i.e., it is not an antioxidant [4] – in the presence of demethyldesmotroposantonin (**2**) in a concentration of 20.7 mM the latent period increased from 1.28 ± 0.13 min in the control to 5.29 ± 0.38 min ($p < 0.05$). Desmotroposantonin (**3**) at the same concentration increased the latent period by a factor of 8, and at a concentration of 40.7 mM the slow chemiluminescence disappeared, as also in the case of the synthetic antioxidant Ionol.

Thus, *in vitro*, phenolic derivatives of α-santonin exhibit a pronounced antioxidant effect, reliably established from the increase in the latent period of Fe^{2+}-induced chemiluminescence of the lipids of a model system. Thereby the results of chemiluminescent analysis confirmed the aromatic structures of the products of the dienone–phenol rearrangement of α-santonin.

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TABLE 1. Details of the PMR Spectrum of the Phenolic Derivatives of α-Santonin (2), (3), and (4) (400 MHz, δ, pyridine-d_6)

Compound	H-1	H-2	H-6	H-11	H-13	H-14	H-15
2	6.83 (1H,d) J=8 Hz	7.13 (1H,d) J=8 Hz	4.98 (1H,d) J=10.5 Hz	2.42(1H,d.q) J_1=12.5 Hz J_2=7 Hz	1.14 (3H,d) J=7 Hz		2.57 (3H,s)
3*		6.67 (1H,s)	5.08 (1H,d) J=10 Hz	2.51(1H,d.q) J_1=12 Hz J_2–7 Hz	1.21 (3H,d) J=7 Hz	2.09 (3H, s)	2.25 (3H,s)
4		7.12 (1H, s)	5.63 (1H,d) J=5 Hz		1.29 (3H,d) J=7 Hz	2.00 (3H, s)	2.48 (3H, s)

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*Solvent acetone-d_6.

EXPERIMENTAL

6β(H),7α(H),11β(H)-1-Demethyldesmotroposantonin (2). A reaction mixture containing 490 mg (2 mmole) of activated zinc dust, 10 ml of DMFA, and 1 ml of water was boiled for 40 min. After cooling, the solution was filtered, and 20 ml of ethyl acetate and 50 ml of dilute HCl were added. The organic layer was washed with sodium bicarbonate solution and water, dried over Na_2SO_4, filtered, and evaporated in a rotary evaporator. The residue was separated by flash chromatography on Chemapol silica gel (eluent: petroleum ether–ethyl acetate (1:1)). A colorless crystalline substance was obtained with mp 224-226°C, individual according to HPLC and PMR. Yield 16%. IR spectrum (KBr, ν, cm^{-1}): 3420, 2980, 2950, 2870, 1770, 1600, 1500, 1470. UV spectrum (λ, nm, log ε): 210 (4.08), 285 (3.41).

6β(H),7α(H),11β(H)-Desmotroposantonin (3). A solution of 490 mg (2 mmole) of α-santonin in trifluoroacetic anhydride was left for three days. Then the reaction mixture was treated with aqueous dioxane containing KOH until a neutral medium had been formed. The dioxane layer was separated off, washed with saturated NaCl solution, dried over Na_2SO_4, diluted with ethyl acetate in a ratio of 1:1, and evaporated under vacuum. The residue was separated on Silpearl silica gel. Compounds (3) and (4) were isolated in the form of colorless acircular crystals with mp 175-177 and 204-205°C, respectively. Yield 70%.

IR spectrum (KBr, ν, cm^{-1}): 3350, 2950, 1750, 1580. UV spectrum (λ, nm log ε): 210 (4.16), 290 (3.56). Mass spectrum: 246 (100.0), 231 (71.5), 203 (17.9), 189 (10.1), 173 (61.9), 149 (15.9), 135 (31.1), 91 (14.7), 32 (10.1), 28 (43.8).

6α(H),7α(H),11β(H)-Desmotroposantonin (4). IR spectrum ($CHCl_3$, ν, cm^{-1}): 3600, 3030, 3400, 2950, 1760, 1600, 1470. Mass spectrum: 246 (48.9), 187 (13.7), 173 (100.0), 135 (8.3), 91 (7.0), 31 (10.5), 28 (22.2).

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