Tetrahedron Letters Vol. 21, pp 149 - 152
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0040-4039/80/0108-0149$02.00/0

ACAMELIN, A NEW SENSITIZING FURANO-QUINONE FROM *ACACIA MELANOXYLON* R.BR.

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Summary. From Australian blackwood *Acacia melanoxylon* R.BR., a commercial timber of West Australia, two quinones have been isolated which are responsible for the allergy-inducing properties of this species. The sensitizers have been identified as 2,6-dimethoxy-p-benzoquinone and 2-methyl-6-methoxy-furano-benzoquinone (acamelin) by X-ray analysis.

Australian blackwood *Acacia melanoxylon* R.BR. (family: Leguminosae-Mimosaceae) is one of the at least 100 wood species of commercial value which are capable of inducing an allergy of the eczematous type in men handling them. Blackwood is native to West Australia and used there mainly for high-quality furniture, panelling, joinery, turnery and even parts of musical instruments. Since 1925 it is known that this timber cause allergic contact dermatitis as well as allergic asthma bronchiale in joiners, sanders, boat-builders and other workers who come into contact with the sawdust.

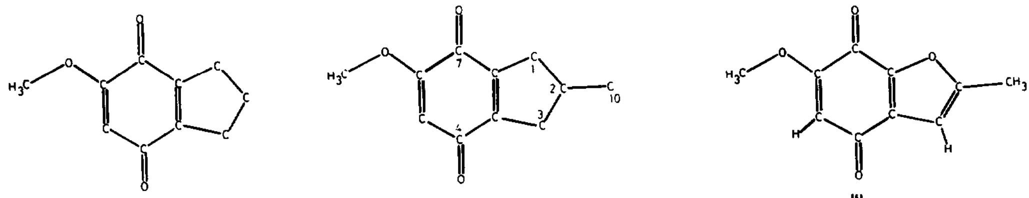
Sensitizing experiments in guinea pigs with an ethanol extract of Australian blackwood corroborated its sensitizing capacity. Different fractions obtained by preparative thin layer chromatography and challenged in the sensitized animals by application to the skin revealed that quinoid constituents were responsible for the induced contact allergy. Two quinones could be isolated in pure form and identified by X-ray analysis. The first was identified as 2,6-dimethoxy-1,4-benzoquinone[1]. The second one with a slightly stronger sensitizing capacity was a new benzo-furano-quinone of red colour.

Naturally occurring furano-quinones are rare in the plant kingdom. A quite similar but naphto-furano-quinone has been isolated and identified in 1968 from Peroba wood (*Paratecoma peroba* KUHLM., family: Bignoniaceae)[2]. Though this quinone has not been investigated experimentally with respect to its sensitizing properties, it is known that Peroba wood is responsible for causing allergic contact dermatitis too[3].

We succeeded in crystallizing the second sensitizing quinoid compound from Acacia melanoxylon R.BR.[1] out of a mixture of chloroform/acetone (v/v 1:2). The only red single crystal with sufficient dimensions (0.10x0.15x0.20 mm) was used for measurements. The intensity of the Bragg-reflexions was measured with a four-circle computer-controlled diffractometer (Syntex P 2_1) with graphite-monochromated MoKα -radiation (λ = 0.7107 Å). 1178 reflexions in the range 2.9-44.0° in 2ϑ were collected at room-temperature using the ϑ-2ϑ scan mode. Because of the small size of the crystal, only 495 reflexions were considered to be observed, for which the intensity was $I > 3\sigma(I)$, where the error $\sigma(I)$ was calculated from counting statistics. After Lorentz- and polarization corrections has been done for all intensities[4] (no absorption correction was made; μ(MoKα) = 0.73 cm^{-1}), and after the calculation of normalized structure factor amplitudes with MULTAN[5], the statistical test of the distribution of the $|E|$-values gave a strong indication for the structure to be centrosymmetric

Because the chemical formula was unknown, the density of the crystal was estimated to be 1.48 gxcm^{-3}, the corresponding molecular weight M was supposed to be 189. From these values the chemical formula was proposed to be $C_{11}H_9O_3$.

It was not possible to get a solution for the structure with the aid of centrosymmetric trials with MULTAN, neither with $|E|$-values based on K-curve normalization, nor with Debeye-curve normalized ones. Therefore, in a second step, the acentric "magic integer"-procedure in MULTAN was used successfully.



I II III

Fig. 1. Models I, II and III as steps of the structure determination

Normalized structure factor amplitudes for 186 reflexions with $|E| \geq 1.29$ were used for the calculation of 20 sets of phases. The main part of the model III (Fig.1,I), a p-quinonering with a methoxygroup and a five-membered ring was found among several similar acentric MULTAN proposals. At the first stage of refinement of this part of the acentric model with SHEL-X[6], two molecules of I (Fig.1) with 26 atomic positions were used at all. Six atoms were attached to oxygen- and 20 atoms to carbon-scattering-factors[7]. After four cycles of isotropic least-squares refinement an R_1-value of 0.32 was obtained.

By reason of the atomic positions of the two molecules, the centre of symmetry of the structure was calculated and used for further refinement. A Fourier difference synthesis[6] showed another atomic position connected with the five-membered ring (Fig.1,II). Due to the similarity of the C-, N- and O-scattering factor curves and the permutation of sp^2-sp^2-, sp^2-sp^3 and sp^3-sp^3-hybridization of the four atoms in position 1,2,3 and 10 (Fig.1,II), more than 100 isomeres should have been tested as possible models at all. Therefore the rest of the crystals (some 10 μg) was used for a mass-spectrometry[8] with the result of M = 192.17 for the sensitizing compound. The number of the isomer models to be tested was reduced to 15. After several cycles of refinement and difference syntheses (R_1 = 0.127), the H-atoms in position 3 and 5 were localized (Fig.1,III) without doubt. The interpretation of bond lengths and isotropic temperature parameters led to the identification of the compound to be 6-methoxy-2-methyl-3,5-dihydrobenzo(b)furan-4,7-dion, for which we propose the name acamelin.

Crystal data: $C_{10}H_8O_4$, triclinic, $P\bar{1}$, $\underline{a}$ = 3.846(3) Å, $\underline{b}$ = 14.381(9) Å, $\underline{c}$ = 7.980(6) Å, α = 101.75(2)°, β = 99.01(2)°, γ = 94.07(2)°, $\underline{V}$ = 424.4 Å^3, D_c = 1.50 gxcm^{-3}, Z = 2, F(000) = 200, S = 175-176°C (uncorr.).

The positions of the methylgroup H-atoms were calculated and neither their positions nor their estimated mean isotropic temperature parameters were refined. After four cycles of refinement of the positional and anisotropic temperature parameters of the non-hydrogen atoms and the positional parameters of H(3) and H(5), R_1 decreased to 0.096 and R_2 to 0.073.

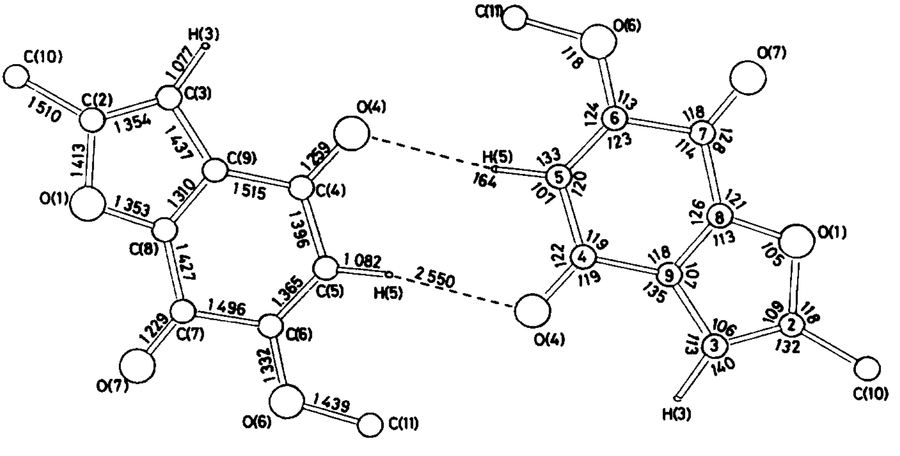


Fig. 2. ORTEP[9] -drawing of two acamelin-molecules with bond lengths and angles. Their e.s.d.'s are in the range of 0.013-0.022 Å and 1.3-1.7° for the non-hydrogen atoms.

The molecule of acamelin is relatively planar with a maximum out-of-plane deviation of 0.104 Å from the best plane: $-3.4041X + 5.9634Y + 2.8351Z - 4.2549 = 0$ (C(4) to C(9)). In the crystal, pairs of very weak hydrogen bonds of type O(4)...H(5)-C(5) and 2.55 Å in length join molecules together across centres of symmetry, while O(6)...H(3)-C(3) hydrogen bonds with 2.44 Å in length are forming endless chains along $\vec{c}$.

Table 1. Atomic coordinates ($\times 10^4$) without methylgroup-hydrogens. Their e.s.d.'s are in the range of: $\sigma(x) = 26\text{-}50 \times 10^{-4}$, $\sigma(y) = 7\text{-}12 \times 10^{-4}$, $\sigma(z) = 15\text{-}24 \times 10^{-4}$ for O(1) to C(11), for H(3) and H(5) $28\text{-}30 \times 10^{-3}$, $5\text{-}8 \times 10^{-3}$, $12\text{-}18 \times 10^{-3}$.

	x	y	z		x	y	z
O(1)	6875	8823	4664	C(5)	3439	6284	5942
O(4)	400	5864	3101	C(6)	5663	6950	7185
O(6)	6808	6838	8788	C(7)	7049	7889	6880
O(7)	9237	8414	8035	C(8)	5860	8016	5163
C(2)	5101	8706	2933	C(9)	3714	7408	3922
C(3)	3260	7828	2426	C(10)	5808	9479	1964
C(4)	2424	6462	4289	C(11)	5517	5981	9262
H(3)	1489	7390	1323	H(5)	2085	5600	5953

Acknowledgement. This research was supported by grant of 'Deutsche Forschungsgemeinschaft'. The authors thank Dr. Mary D. Tindale, Royal Botanic Gardens, Sidney, for the supply of blackwood samples. They also thank Dr. G. Adiwidjaja for the collection of the intensity data, Prof. Dr. W.A.König and Mrs. Meiners for the mass-spectrometry.

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(Received in Germany 25 October 1979)