The Crystal Structure of Cudranone, 2,6,3′-Trihydroxy-4-methoxy-2′-(3-methyl-2-butenyl)-benzophenone: A New Antimicrobial Agent from *Cudrania cochinchinensis*

T. OTTERSEN,[a] B. VANCE,[b] N. J. DOORENBOS,[c] B.-L. CHANG [c] and F. S. EL-FERALY [c]

[a] Department of Chemistry, University of Oslo, Oslo 3, Norway, [b] Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822, U.S.A. and [c] Department of Pharmacognocy, School of Pharmacy, University of Mississippi, University, Mississippi 38677, U.S.A.

Preliminary antimicrobial screening of the ethanolic extract of the Chinese plant *Cudrania cochinchinensis*, var. *gerontogea*, showed distinct activity against a wide range of microorganisms. The novel compound cudranone (2,6,3′-trihydroxy-4-methoxy-2′-(3-methyl-2-butenyl)-benzophenone), which was isolated [1] from the chloroform solubles of the ethanolic extract, was identified as one of the antimicrobial constituents. In order to confirm the structure assignment and also obtain conformational data on this novel antimicrobial agent, an X-ray crystallographic structure determination has been carried out.

A yellow prismatic crystal of approximate dimensions $0.19 \times 0.38 \times 0.48$ mm was selected for the crystallographic work. A computer-controlled Syntex P$\bar{1}$ four-circle diffractometer with graphite-monochromatized Mo$K\alpha$ radiation was utilized in the preliminary experiments and the collection of intensity data. Cell dimensions and their standard deviations were determined by a least-squares treatment of the angular coordinates of fifteen reflections. The crystal data are: 2,6,3′-trihydroxy-4-methoxy-2′-(3-methyl-2-butenyl)-benzophenone, $C_{19}H_{20}O_5$, $M = 328.35$ amu, space group Cc, $a = 9.037(2)$ Å, $b = 17.977(8)$ Å, $c = 10.402(3)$ Å, $\beta = 93.39°$ (2), $V = 1687.0(10)$ Å^3, $Z = 4$, $D_{calc} = 1.293$ g cm^{-3}, $F(000) = 696$.

Three-dimensional intensity data were recorded using the $\omega - 2\theta$ scanning mode with scan speed variable from 3 to 12° min^{-1} depending on the intensity of the reflection, and background counting time was equal to $0.7 \times$ scan time. The temperature was kept constant at 24 ± 2 °C. The variations in the intensity of three check reflections which were remeasured regularly, were random. The estimated standard deviations were taken as the square root of the total counts with a 2 % addition of the

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations for nonhydrogen atoms. The temperature factor is given by $\exp\{-2\pi^2[U_{11}(a^*h)^2 + U_{22}(b^*k)^2 + U_{33}(c^*l)^2 + 2U_{12}(a^*b^*hk) + 2U_{13}(a^*c^*hl) + 2U_{23}(b^*c^*kl)]\}$.

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	.2205(0)	.1600(2)	.4482(0)	.0385(19)	.0327(17)	.0310(17)	−.0027(14)	−.0074(15)	.0016(14)
C2	.1758(5)	.0862(2)	.4222(5)	.0469(21)	.0329(18)	.0406(20)	−.0080(16)	−.0039(17)	.0021(16)
C3	.2303(6)	.0475(2)	.3205(5)	.0607(25)	.0345(19)	.0561(25)	−.0070(18)	.0012(21)	−.0128(18)
C4	.3294(6)	.0807(2)	.2432(5)	.0645(27)	.0495(24)	.0541(25)	−.0021(21)	.0075(22)	−.0152(20)
C5	.3747(6)	.1532(2)	.2654(5)	.0474(23)	.0545(24)	.0421(20)	−.0104(19)	.0065(17)	−.0056(19)
C6	.3186(5)	.1925(2)	.3675(4)	.0354(19)	.0322(17)	.0344(19)	−.0023(15)	−.0079(15)	.0034(15)
C7	.3695(5)	.2711(2)	.3887(4)	.0368(19)	.0385(19)	.0328(19)	−.0087(15)	−.0043(16)	.0029(15)
C8	.3173(5)	.3314(2)	.3057(4)	.0342(19)	.0356(18)	.0344(17)	−.0054(14)	−.0007(14)	.0023(15)
C9	.3853(5)	.4031(2)	.3189(5)	.0346(20)	.0351(19)	.0437(21)	−.0073(15)	−.0039(17)	−.0000(16)
C10	.3449(6)	.4612(2)	.2387(5)	.0519(22)	.0307(18)	.0551(23)	−.0073(16)	−.0008(19)	.0068(16)
C11	.2308(6)	.4511(2)	.1440(5)	.0464(21)	.0382(21)	.0464(22)	.0021(17)	.0013(18)	.0106(16)
C12	.1604(6)	.3837(2)	.1278(5)	.0450(21)	.0473(22)	.0370(20)	.0015(17)	−.0065(16)	.0020(17)
C13	.2020(5)	.3244(2)	.2077(4)	.0341(18)	.0368(18)	.0339(18)	−.0052(15)	.0006(15)	−.0015(15)
C14	.1544(5)	.2015(2)	.5587(5)	.0454(21)	.0331(17)	.0408(20)	−.0036(16)	−.0020(17)	−.0047(15)
C15	.2230(6)	.1789(2)	.6869(5)	.0486(21)	.0425(20)	.0400(21)	−.0057(18)	.0016(17)	−.0028(17)
C16	.2806(6)	.2214(2)	.7819(5)	.0397(21)	.0599(24)	.0455(21)	−.0024(18)	.0002(17)	−.0110(19)
C17	.2928(6)	.3046(2)	.7764(6)	.0571(27)	.0584(26)	.0778(32)	−.0024(21)	−.0032(23)	−.0338(24)
C18	.3419(7)	.1872(3)	.9059(5)	.0706(30)	.0953(35)	.0432(24)	−.0071(28)	−.0101(22)	−.0091(24)
O19	.0771(5)	.0564(2)	.5017(4)	.0749(19)	.0439(15)	.0619(19)	−.0303(14)	.0155(16)	−.0058(13)
O20	.4609(5)	.2827(1)	.4813(4)	.0577(17)	.0444(15)	.0507(16)	−.0168(13)	−.0249(14)	.0099(13)
O21	.4923(5)	.4149(1)	.4131(4)	.0510(17)	.0366(14)	.0612(18)	−.0163(12)	−.0226(14)	.0038(12)
O22	.1989(5)	.5117(2)	.0701(4)	.0750(22)	.0461(16)	.0680(20)	−.0013(15)	−.0148(17)	.0216(15)
C23	.0859(6)	.5040(3)	−.0319(5)	.0728(32)	.0723(31)	.0574(29)	.0185(26)	−.0093(26)	.0247(24)
O24	.1302(5)	.2591(1)	.1954(4)	.0520(16)	.0463(15)	.0459(14)	−.0169(13)	−.0205(12)	.0007(12)

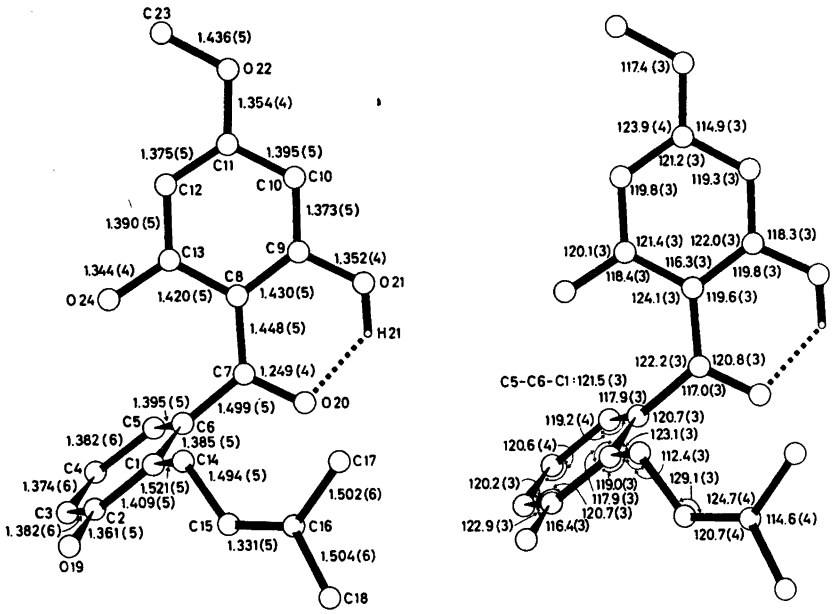


Fig. 1. Bond lengths (Å) and bond angles (°) with estimated standard deviations. The molecular conformation as seen down in the plane of the C8 – C13 ring is indicated.

net intensity for experimental uncertainties. Of the 1495 symmetry-independent reflections measured ($2\theta_{max} = 50°$), the 1408 which had intensities larger than twice their standard deviations were regarded as observed. The intensities were corrected for Lorentz and polarization effects.[2]

The phase problem was solved by the MULTAN [3] program package. The structure model with anisotropic thermal parameters for the nonhydrogen atoms was refined to a conventional R of 0.063. The computer programs used as well as programs subsequently employed, are part of a local (Oslo) assembly of programs.[4] Atomic scattering factors used were those of Doyle and Turner [5] for oxygen and carbon, and of Stewart *et al.*[6] for hydrogen. The hydrogen atoms were placed in calculated positions and included in the structure factor calculation with estimated isotropic thermal parameters. The distances indicated two *inter-* and one *intra*-molecular hydrogen bonds and the three hydrogens bonded to oxygens were placed accordingly. Full-matrix least-squares refinement of all nonhydrogen atomic parameters converged to a weighted R_w of 0.049 and an R of 0.041. Atomic parameters for nonhydrogen atoms are given in Table 1, and those used for hydrogen atoms may be obtained from the authors upon request, as may a list of observed and calculated structure factors.

Bond lengths and bond angles are listed in Fig. 1 where also the numbering of the atoms is indicated. The keto-group (C7 = O20) is nearly coplanar with the ring C8 – C13 (see Table 2), the dihedral angle O20 – C7 – C8 – C9 is only 8.4°(5). This approximate coplanarity of the keto-group with one of the phenyl rings, which is not found in other benzophenones,[7–11] is probably caused by the formation of an *intra*-molecular hydrogen bond from O21 to O20 (O – O distance: 2.501(3) Å). The strong conjugation between the keto-group and the

Table 2. Deviations from least-squares planes (Å × 10^3). The deviations for those atoms used to define the plane are given in italicized figures.

Atom	Plane A	Atom	Plane B
C1	*7*	C6	−277
C2	*−1*	C7	−57
C3	*−4*	C8	*−7*
C4	*4*	C9	*10*
C5	*2*	C10	*−8*
C6	*−7*	C11	*2*
C7	−14	C12	*0*
C8	−1195	C13	*2*
C14	−31	O20	72
C15	1297	O21	51
C16	1976	O22	−12
O19	−14	C23	−50
O20	1056	O24	48

C8 – C13 ring is reflected in a shortening of the C7 – C8 bond and a lengthening of the C8 – C9 and C8 – C13 bonds.

The angle between the planes through the phenyl rings is 77.1°, and the dihedral angle C1 – C6 – C7 – O20 is 74.0°(4) (see Fig. 1). This rotation of a phenyl ring relative to the keto-group and to the other phenyl ring is much larger than the rotations found in benzophenone,[7] 3,3′-dibromobenzophenone [9] and 4,4′-dimethoxybenzophenone,[8] where the angles between the phenyl rings and the plane defined by the atoms corresponding to C6, C7, C8 and O20 are about 25 – 35°, and the angles between the planes of the phenyl rings are about 55°. This large rotation must be a result of the *intra*-molecular crowding caused by the position of the large 3-methyl-2-butenyl group *syn* to O20 and also by the position of the hydroxyl group (O24) *syn* to the C1 – C6 ring. A similar situation is found in the molecules of *syn*- and *anti*-4-bromobenzophenone oxime *O*-picryl ethers [10] where the phenyl rings *syn* to the picryl groups are rotated 60 – 70°, relative to the plane through the oxime group, whereas the phenyl rings *anti* to the picryl groups are rotated only 18 – 23°.

The *inter*-molecular distances indicate two hydrogen bonds: one from O19 to O21 in position: $-0.5+x$, $-0.5+y$, z distance: 2.797(4) Å; and one from O24 to O20 in position: $-0.5+x$, $0.5-y$, $-0.5+z$, distance: 2.732(3) Å.

Acknowledgement. The authors thank Professor K. Seff for the use of the X-ray diffraction equipment at the Chemistry Department, University of Hawaii.

1. Chang, B.-L. *M.S. Thesis*, School of Pharmacy, University of Mississippi, December 1976.
2. Ottersen, T. *LP-76 Computer Program, Cryst. Prog. Lib.*, Department of Chemistry, University of Hawaii.
3. Germain, G., Main, P. and Woolfson, M. M. *Acta Crystallogr. A 27* (1971) 368.
4. Groth, P. *Acta Chem. Scand. 27* (1973) 1837.
5. Doyle, P. A. and Turner, P. S. *Acta Crystallogr. A 24* (1968) 390.
6. Stewart, R. F., Davidson, E. R. and Simpson, W. T. *J. Chem. Phys. 42* (1965) 3175.
7. Fleischer, E. B., Sung, N. and Hawkinson, S. *J. Phys. Chem. 72* (1968) 4311.
8. Norment, H. G. and Karle, I. L. *Acta Crystallogr. 15* (1962) 873.
9. Pattabhi, V. and Venkesatan, K. *J. Cryst. Mol. Struct. 3* (1973) 25.
10. McCullough, J. D., Jr., Paul, I. C. and Curtin, D. Y. *J. Am. Chem. Soc. 94* (1972) 883.
11. Manojlović, L. and Edmunds, I. G. *Acta Crystallogr. 18* (1965) 543.

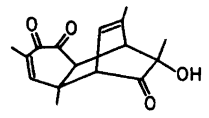
Received January 18, 1977.

On the Crystal Structure of 5,8-Etheno-3,4a,7,9-tetramethyl-4a,5,6,7,8,8a-hexahydrochromene-7,8a-diol-2,6-dione, Formed by Periodate Oxidation of 2,4-Dimethylphenol

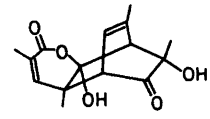
BENGT KARLSSON,[a] BENGT O. LINDGREN,[b] ANNE-MARIE PILOTTI [a] and ANNE-CHARLOTTE SÖDERHOLM [a]

[a] Department of Structural Chemistry, Arrhenius Laboratory, University of Stockholm, S-106 91 Stockholm, Sweden and [b] Swedish Forest Products Research Laboratory, S-114 86 Stockholm, Sweden

A previous study [1] has shown that the action of sodium periodate on 2,4-dimethylphenol yields three products: 2,4-dimethyl-*p*-quinol, the Diels-Alder dimerization product [2] of 2,4-dimethyl-*o*-quinol, and the Diels-Alder adduct [3] (*1*) of the *o*-quinol and 3,5-dimethyl-1,2-benzoquinone. We have now obtained from 2,4-dimethylphenol, in small yield, another periodate oxidation product, $C_{15}H_{18}O_5$, with m.p. 172.5 – 174.5 °C. Crystallographic examination shows that it is 5,8-etheno-3,4a,7,9-tetramethyl-4a,5,6,7,8,8a-hexahydrochromene-7,8a-diol-2,6-dione (*2*), evidently formed by periodate oxidation of the adduct (*1*).



1



2

Experimental. The oxidation of 2,4-dimethylphenol with periodate was carried out and the oxidation mixture was worked up essentially as described in the previous paper.[1] From the acidification of 0.5 M aqueous NaOH solution with glacial acetic acid, a precipitate of a colourless compound, m.p. 172.5 – 174.5 °C, was obtained. Its mass spectrum showed a molecular ion at *m/e* 278, calc. for $C_{15}H_{18}O_5$, 278.

X-Ray experimental and structure elucidation. Cell dimensions were determined, by least-squares refinement, from the angular positions of 25 well-centered reflexions on a Philips PW 1100 diffractometer. Crystal data are: $a = 16.513(4)$, $b = 6.987(2)$, $c = 12.146(4)$ Å, $\beta = 102.91(2)°$, $V = 1366$ Å^3, space group $P2_1/n$, $Z = 4$, $\varrho_{X-ray} = 1.35$ g cm^{-3}, $\mu(CuK\alpha) = 8.53$ cm^{-1}.

Only small single crystals were available. Data (set I) were collected using graphite monochromated Cu$K\alpha$ radiation, $\theta - 2\theta$ scan technique (scan width 1.5°(θ), scan rate 1°(θ) min^{-1}), and stationary background measurements at the ends of the scan interval. Of the