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Structure and Absolute Configuration of Curcolone[1]

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A new sesquiterpenic furano-ketol, curcolone, $C_{15}H_{18}O_3$, has been isolated from zedoary, *Curcuma zedoaria* (Zingiberaceae). Physico-chemical studies of curcolone and its derivatives have enabled a decision to be made in favor of I as a representation of the structure and stereochemistry of the ketol.

From the crude drug zedoary, the rhizome of *Curcuma zedoaria* Roscoe (Zingiberaceae), we have hitherto isolated the new sesquiterpenoids, curcumol,[3] curcumenol,[4] curdione,[5] and zederone.[6] A continuous investigation of the crude drug has resulted in the further isolation of a new sesquiterpenoid keto-alcohol containing a furan ring for which we propose the name curcolone. It has been concluded from analytical studies that curcolone has the stereostructure I (R=H). In the present paper, we wish to report evidence leading to this conclusion in full detail.

Courcolone melts at 139—139.5° and analyzed in agreement with the empirical formula $C_{15}H_{18}O_3$ which was confirmed by means of mass spectrometry.

The first objective was to establish the nature of the functional groups. The infrared spectrum shows bands at 3448 cm^{-1} indicative of a hydroxyl and at 1650 cm^{-1} assigned to a conjugated carbonyl group. The secondary nature of the hydroxyl group was elucidated by the nuclear magnetic resonance (NMR) spectrum which exhibited a 1H signal at 3.70 ppm attributed to a hydrogen on carbon carrying a hydroxyl. Since there is no peak in accord with expectance for the aldehyde grouping in the NMR spectrum, the carbonyl group is a ketonic one in a six-membered or larger ring. The presence of a furan ring obscure from the infrared absorption was suggested by positive color reactions for furan ring such as vanillin-hydrochloric acid, Ehrlich, and Liebermann-Burchard reactions. This was confirmed by the NMR spectrum which exhibited a 1H signal at 6.97 ppm and 3H signal at 2.18 ppm being characteristic of an α-proton and β-methyl protons of a furan ring, respectively.[7] Between two substitution patterns of the furan nucleus (*i.e.*, α-H and β-CH_3, and α-H and β'-CH_3), a decision as in the partial structure A was arrived at by the coupling constant (1.3 cps) with which both signals were mutually spin coupled. The presence of a methyl group as one of substituents on an ethylenic linkage is shown by a 3H signal at 1.97 ppm. The ethylenic linkage is required to be tetrasubstituted since no signal attributable to a vinyl hydrogen appears. Further, a 3H signal at 1.10 ppm gives indication of the presence of a tertiary methyl group.

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[1] This paper constitutes Part XX in the series on Sesquiterpenoids. Preceding paper, Part XIX: H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 52 (1968). Part of the material contained herein formed a preliminary communication, H. Hikino, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1065 (1967).

[2] Location: *Kita-4-bancho, Sendai.*

[3] H. Hikino, K. Meguro, Y. Sakurai, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1484 (1965); **14**, 1241 (1966).

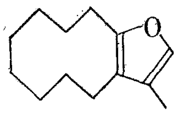
[4] H. Hikino, Y. Sakurai, S. Numabe, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 39 (1968).

[5] H. Hikino, Y. Sakurai, S. Takahashi, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 1310 (1966); **15**, 1390 (1967).

[6] H. Hikino, S. Takahashi, Y. Sakurai, T. Takemoto, and N.S. Bhacca, *Chem. Pharm. Bull.* (Tokyo), **14**, 550 (1966).

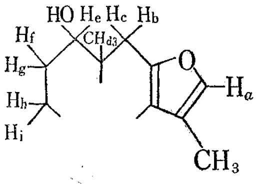
[7] This will be discussed in detail in a forthcoming paper.

Of the seven double-bond equivalents indicated by the molecular formula of curcolone, five have been accounted for as a furan ring, a ketonic carbonyl, and a double bond. Since there are no other centers of unsaturation, it must, therefore, be concluded that curcolone contains two carbocyclic rings fused with a furan nucleus. This, together with the presence of three methyls mentioned above, allow the part structure of this substance to be expressed as in A.

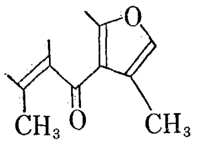


A

ring
$\geqslant C-CH_3$
$>C=C<CH_3$
$>CH-OH$
conj. $>C=O$



B



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We next examined the nature and environment of the hydroxyl group. For this purpose the NMR study was informative. Thus, the NMR spectra discloses the presence of an isolated methylene group (H_b and H_c) as two doublets (an AB quadruplet) at 2.66 and 3.05 ppm ($J=17$ cps) whose chemical shifts in the low field region imply that the methylene is flanking on the furan ring. The NMDR experiments (100 Mcps) revealed that the former signal at 2.66 ppm for one (H_b) of the methylene protons was further weakly spin coupled with the α-hydrogen (H_a) of the furan nucleus, the tertiary methyl hydrogens (H_{d3}), and the hydrogen (H_e) on carbon bearing the hydroxyl. The latter signal at 3.05 ppm due to the other proton (H_c) of the methylene group also showed weak coupling to the α-hydrogen (H_a) of the furan, and the tertiary methyl hydrogens (H_{d3}). However, the coupling constants are smaller than those in the proton (H_b). The long-range coupling of the methylenic hydrogens (H_b and H_c) to the α-hydrogen (H_a) of the furan indicates the methylene grouping to be attached to the α'-position of the furan nucleus.7) Since no homoallylic couplings are found in both signals originating from the methylene protons (H_b and H_c), the carbon which occupies the last (β'-) substitution position is suggested to carry no hydrogen. The NMR signal due to the hydrogen (H_e) on carbon attached to the hydroxyl group appears as a slightly multiplying triplet ($J=8$ cps) at 3.70 ppm. This signal is considered to be the X portion of an A_2X spectrum from the following observations. Thus, on double irradiation at this proton frequency, a 2H symmetrical octet at 1.70 ppm arising from the vicinal methylenic protons (H_f and H_g) collapsed to a symmetrical quadruplet, which resulted evidently from the couplings to the other methylene protons (H_h and H_i). On the other hand, reverse double irradiation at the frequency of the methylenic protons (H_f and H_g) caused the triplet (H_e) to degenerate to a singlet, showing that two protons (H_f and H_g) are magnetically equivalent. This finding demonstrates that the carbon bearing the hydroxyl is located between a quaternary carbon and a methylene grouping. These results may be explained in terms of the partial structure B.

The orientation of the unsaturated functions were next taken into consideration. The ultraviolet spectrum is characteristic of a cross-conjugated carbonyl system which, to a first approximation, shows maxima of separate chromophores at 261 mμ (log ε 3.92) and 292 mμ (log ε 3.85). Although no suitable analogy is available in the present case, the former absorption may be attributed to a fully substituted enone chromophore and the latter absorption assigned to a β-furoyl chromophore. This assignment was confirmed in the subsequent way. Thus, in an attempt to obtain the diol (IV) in which both chromophores, the furan nucleus and the ethylenic linkage, are insulated, curcolone was treated with sodium borohydride to give only the starting ketol (I). While reduction with lithium aluminum hydride afforded a dihydro-derivative which, however, was not the expected diol (IV) but the dihydroketol (II) formed by hydrogenation of the conjugated double bond. Formulation of the ketol (II) was verified by the infrared spectrum which showed that a hydroxyl (3497 cm^{-1}) and a conjugated carbonyl (1661 cm^{-1}) were still present and by the NMR spectrum which indicated the retention of all the functional groups present in the original ketol, curcolone, with the exception of the replacement of the olefinic methyl by a secondary methyl. The ketol (II) exhibits an ultraviolet maximum at 270.5 mμ, which indicates the disappearance of the cross-conjugation and the retention of the β-furyl ketone system, since it is consistent with that (266 mμ) of evodone (V) having the same conjugated moiety. Comparable bathochromic displacement as compared with strainless β-furoyl systems, which exhibit maxima in the region 250—255 mμ,[8] may be explained by a distorted feature of the conjugated system.

The relative locations of the olefinic methyl and furyl methyl groups with respect to the carbonyl group were confirmed by the following NMR evidence. The vinyl methyl and furyl methyl resonances of curcolone occur at 1.97 and 2.18 ppm in carbon tetrachloride and at 2.07 and 2.27 ppm in benzene solution, respectively. The shielding effects (−0.10 ppm for the vinyl methyl and −0.09 ppm for the furyl methyl) on passing from carbon tetrachloride to benzene solution are compatible with the orientation of the methyl groups as both being in the β-*cis* positions of α,β-unsaturated carbonyl systems in S-*cis* conformations.[9] These observations indicate that the part structure C is present in curcolone.

Further additonal information about the situation of the hydroxyl group in curcolone was obtained. Thus, oxidation of curcolone with chromium trioxide-pyridine complex gave the diketone (III). Since the solvent-induced shift of the NMR signal for the tertiary methyl protons of curcolone on passing from carbon tetrachloride to benzene solution is +0.10 ppm, that (+0.30 ppm) of the dione (III) shows the contribution from the newly formed carbonyl function to be estimated as +0.20 ppm suggesting that the carbonyl is adjacent to the carbon carrying the tertiary methyl group axially disposed.[10] The dione (III) exhibits bands in the infrared at 1660 and 1720 cm^{-1}, the former is to be attributed to the conjugated carbonyl originally present and the latter to that of the new cyclanone. The ultraviolet spectrum shows the essentially unchanged maxima at 258 mμ (log ε 3.82) and 291 mμ (log ε 3.71) in contrast to that of the original ketol, curcolone. These findings indicate that the newly formed carbonyl is unconjugated and oriented in a six-membered or larger ring. Curcolone is consequently concluded to have a six/six-membered ring system.

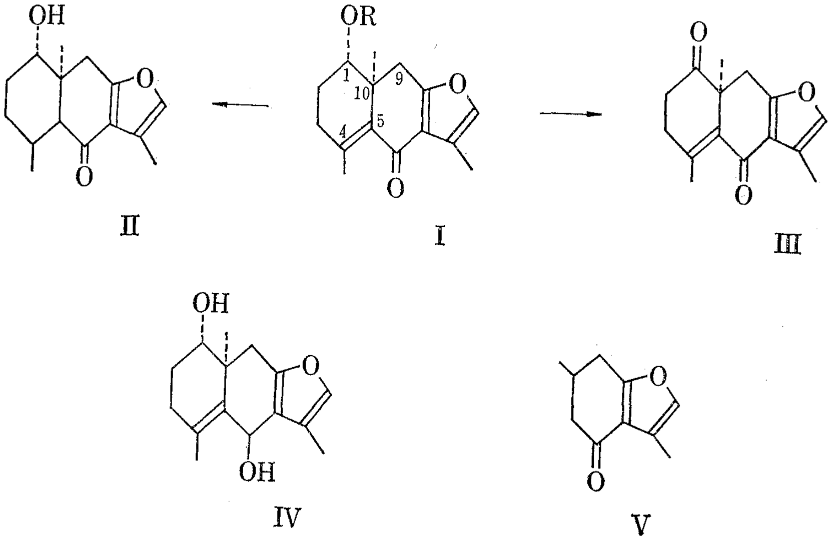

Chart 1

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[8] T. Matsuura, K. Naya, N. Ichikawa, and T. Kubota, *Bull. Chem. Soc. Japan*, 35, 1695 (1962).

[9] C.J. Timmons, *Chem. Commun.*, 576 (1965).

[10] N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964, p. 159.

As have been observed in curcolone, the similar solvent–induced shifts of the NMR signals due to the methyls (+0.07 ppm for the vinyl methyl and −0.05 ppm for the furyl methyl) are also found in the dione (III), the former shift, however, may include the effect due to the new carbonyl group.

The above evidence leads to the conclusion that curcolone has the constitution I (R=H) (without stereochemistry). With the gross structure of curcolone established the only remaining problem is to determine the absolute configuration at C–1 and C–10.

As described earlier, the splittings measured for the C–1 hydrogen signal are both equal to 8 cps. Since two protons at C–2 are located in an identical magnetic environment at 1.70 ppm, the dihedral angles between the C–1 hydrogen and the vicinal (*i.e.*, C–2) methylenic hydrogens cannot, therefore, be calculated from the observed splittings which, however, indicate that the C–1 hydrogen is oriented in an axial–like configuration in a cyclohexene ring. The C–1 hydroxyl group is, therefore, equatorially situated. Although the C–1 epimer could not be prepared, application of the benzoate rule[11] to curcolone and its benzoate (I; R=CO-C_6H_5) ($\Delta[M]_D$ +86°) demonstrates that the absolute configuration at C–1 is S, the C–1 hydroxyl group being consequently α–oriented. Inspection of Dreiding models reveals that the C–10 methyl group is located in an α–configuration, since only this arrangement can make the vicinal C–1 hydroxyl α– and equatorially situated.

On the basis of these facts, the absolute configuration of curcolone is written as formula I (R=H).

Some NMR evidence further confirmed the stereochemistry (I). Thus, of the two signals arising from the C–9 methylene protons, the one at 2.66 ppm can be assigned to the axial (*i.e.*, β–) hydrogen and the other at 3.05 ppm to the equatorial (*i.e.*, α–) hydrogen, since the couplings of the former to the protons H_a, H_{d3}, and H_e are larger than those of the latter.[12] Therefore, the low-field signal for the 9α–hydrogen is considered to suffer a downward shift by the spatial interaction effect of the 1α–hydroxyl group, and expected to move to higher field on acetylation.[13] The NMR spectrum of the acetate (I; R=$COCH_3$), in fact, shows a resonance at 2.76 ppm, attributed to both the methylenic protons, the 9α–hydrogen signal showing the expected acetylation shift (+0.29 ppm).

The structure of curcolone also enjoys biogenetic plausibility described below. From the biogenetic point of view, it is considered that both zederone (VI) and curcolone (I), present in the same plant, are derived from a common monocyclic precursor (VII). Thus, the former (VI) is formed directly by epoxidation of the ethylenic linkage at C–4:C–5, while the latter (I) by epoxidation of the other point of unsaturation at C–1:C–10 followed by a transannular cyclization and migration of the resulting double bond for conjugation, where it is unknown but tentatively assumed that formation of the furan ring and oxidation at C–6 occurs before epoxidation of an ethylenic linkage.

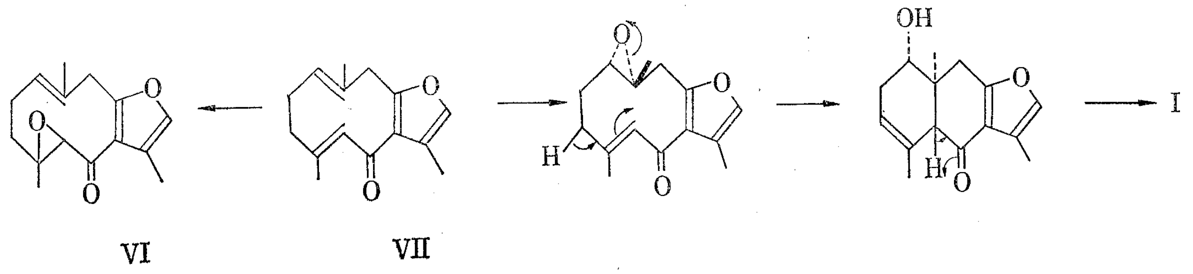

Chart 2

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[11] J.H. Brewster, *Tetrahedron*, 13, 106 (1961).

[12] Ref. 10) p. 108.

[13] T. Okamoto and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), 11, 643 (1963).

Experimental[14]

Isolation of Curcolone——The crude drug "Ga-jutsu," the dried rhizomes of *Curcuma zedoaria* ROSCOE, was extracted with MeOH. The light petroleum soluble fraction of the extract was steam-distilled. The residue was chromatographed over alumina. MeOH eluted fractions were combined and subjected to rechromatography over silica gel. Elution with benzene-AcOEt (5:1) and crystallization from AcOEt gave curcolone (I; R=H) as colorless needles, mp 139—139.5°, $[\alpha]_D$ +13.7° (c=3.8), mol. wt. 246 (mass spec.), *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.46; H, 7.66. UV λ_{max}^{EtOH} mμ (log ε): 261 (3.92), 292 (3.85), IR (KBr) cm^{-1}: 3448 (hydroxyl), 1650 (conjugated carbonyl), NMR (100 Mcps): singlet (3H) at 1.10 ($C\underline{H}_3$-C<), singlet (3H) at 1.97 ($C\underline{H}_3$-C=C-CO-), doublet (3H) at 2.18 (J=1.3, β-$C\underline{H}_3$- of furan), quadruplet (2H) in an AB spectrum at 2.66, 3.05 (J_{AB}=17, >C-$C\underline{H}_2$-furan), triplet (1H) at 3.70 (J=8, -CH_2-$C\underline{H}$(OH)-C<), quadruplet (1H) at 6.97 (J=1.3, α-$\underline{H}$- of furan), NMR (C_6H_6): singlet (3H) at 1.00 ($C\underline{H}_3$-C<), singlet (3H) at 2.07 ($C\underline{H}_3$-C=C-CO-), doublet (3H) at 2.27 (J=1.3, β-$C\underline{H}_3$- of furan), quadruplet (2H) in an AB spectrum at 2.39, 2.93 (J_{AB}=16.5, >C-$C\underline{H}_2$-furan), vanillin-HCl reaction: +(scarlet), Ehrlich reaction: +(red), Liebermann-Burchard reaction: +(purple).

Attempted Reduction of Curcolone with Sodium Borohydride——Curcolone (5 mg) in MeOH (5 ml) was stirred with $NaBH_4$ (10 mg) at room temperature for 10 hr. After isolation, the product was identified as the starting ketol (I) in the usual criteria.

Reduction of Curcolone with Lithium Aluminum Hydride——Curcolone (220 mg) in ether (12 ml) was stirred with $LiAlH_4$ (160 mg) at 0° for 40 min. Upon isolation in the customary manner, the product (200 mg) was chromatographed over silica gel (7 g). Elution with benzene and crystallization from AcOEt gave dihydrocurcolone (II) as colorless needles (50 mg), mp 152—152.5°, $[\alpha]_D$ −32.8° (c=2.4). *Anal.* Cacld. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 73.08; H, 8.27. UV λ_{max}^{EtOH} mμ (log ε): 270.5 (3.82), IR (KBr) cm^{-1}: 3497 (hydroxyl), 1661 (conjugated carbonyl). NMR ($CDCl_3$): singlet (3H) at 0.89 ($C\underline{H}_3$-C<), doublet (3H) at 1.13 (J=6, $C\underline{H}_3$-CH<), doublet (3H) at 2.17 (J=1.3, β-$C\underline{H}_3$- of furan), quadruplet (2H) in an AB spectrum at 2.75, 3.00 (J_{AB}=15, >C-$C\underline{H}_2$-furan), broad peak (1H) at 3.58 (-CH_2-$C\underline{H}$(OH)-C<).

Oxidation of Curcolone with Chromium Trioxide-Pyridine Complex——Curcolone (50 mg) was oxidized with CrO_3 (60 mg) in pyridine (4 ml) at room temperature for 4 days. After isolation with ether and washing, the product was crystallized from AcOEt to give the dione (III) as colorless needles (28 mg), mp 105.5—106°, $[\alpha]_D$ −13.1° (c=2.7). *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.92; H, 6.63. UV λ_{max}^{EtOH} mμ (log ε): 258 (3.82), 291 (3.71). IR (KBr) cm^{-1}: 1720 (carbonyl in a six-membered ring), 1660, 1620 (conjugated carbonyl). NMR: singlet (3H) at 1.33 ($C\underline{H}_3$-C<), singelt (3H) at 2.07 ($C\underline{H}_3$-C=C-CO-), doublet (3H) at 2.20 (J=1.4, β-$C\underline{H}_3$- of furan), singlet (2H) at 2.92 (>C-$C\underline{H}_2$-furan), quadruplet (1H) at 7.01 (J=1.4, α-$\underline{H}$- of furan). NMR (C_6H_6): singlet (3H) at 1.03 ($C\underline{H}_3$-C<), singlet (3H) at 2.00 ($C\underline{H}_3$-C=C-CO-), doublet (3H) at 2.25 (J=1.4, β-$C\underline{H}_3$- of furan).

Benzoylation of Curcolone——Curcolone (80 mg) in pyridine (2 ml) was treated with an excess BzCl at room temperature overnight. After dilution with water and isolation with ether followed by evaporation of the solvent an oil (90 mg) was obtained which was chromatographed over alumina (4 g). Elution with light petroleum and crystallization from light petroleum gave curcolone benzoate (I; R=COC_6H_5) as colorless needles (76 mg), mp 115—116°, $[\alpha]_D$ +34.0° (c=3.8), *Anal.* Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.39; H, 6.40. IR (KBr) cm^{-1}: 1724, 1265 (ester), 1653, 1620 (conjugated carbonyl), 1600, 1111, 711 (phenyl). NMR ($CDCl_3$): singlet (3H) at 1.34 ($C\underline{H}_3$-C<), singlet (3H) at 2.10 ($C\underline{H}_3$-C=C-CO-), doublet (3H) at 2.23 (J=1.3, β-$C\underline{H}_3$- of furan), singlet (2H) at 2.88 (>C-$C\underline{H}_2$- furan), quadruplet (1H) at 5.27 (J_1=10, J_2=6, -CH_2-$C\underline{H}$($OCOC_6H_5$)-C<).

Acetylation of Curcolone——Curcolone (45 mg) in pyridine (1 ml) was treated with Ac_2O (1 ml) at room temperature for 2 days. Isolation in the customary manner gave curcolone acetate (I; R=$COCH_3$) as a colorless oil, NMR: singlet (3H) at 1.18 ($C\underline{H}_3$-C<), triplet (3H) at 1.99 (J=1,-CH_2 -C($C\underline{H}_3$)=C-CO-), singlet (3H) at 2.06 ($C\underline{H}_3$-CO-O-), doublet (3H) at 2.18 (J=1.4, β-$C\underline{H}_3$- of furan), singlet (2H) at 2.76 (>C-$C\underline{H}_2$-furan), quadruplet (1H) at 4.93 (J_1=9, J_2=6, -CH_2-$C\underline{H}$($OCOCH_3$)-C<), quadruplet (1H) at 6.98 (J=1.4, α-$\underline{H}$- of furan).

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[14] Melting points are uncorrected. Rotations were measured in $CHCl_3$ solution. NMR spectra were determined at 60 Mcps in CCl_4 solution unless indicated otherwise. Chemical shifts are quoted as ppm from internal Me_4Si and coupling constants (J) in cps. Signals are given without fine splittings.