

Filtrate was evaporated to obtain a crude crystalline product. Recrystallization from EtOH afforded colorless prisms, m.p. 169~171°. Yield 0.6 g. (80%). *Anal.* Calcd. for  $C_{12}H_{14}ON_4S$ : C, 54.95; H, 5.38; N, 21.37. Found: C, 55.17; H, 5.36; N, 21.44. IR  $\nu_{NH}$   $cm^{-1}$ : 3300 (KBr).

**3-Acetylthiomethyl-2,4-dimethyl-1-phenyl-3-pyrazolin-5-one (XVIII)**—A solution of 2.8 g. (0.01 mole) of compound (I) in 3 ml. of thioacetic acid was refluxed for 1 hr. on an oil bath. After cooling ether was added to obtain white solid, m.p. 156~158°, colorless needles (from EtOH-ether (1:1)). Then this was dissolved in water, extracted with benzene, dried over anhyd.  $Na_2SO_4$ , benzene was evaporated to obtain colorless needles (from ether), m.p. 81~82°, yield 2.6 g. (94%). *Anal.* Calcd. for  $C_{14}H_{16}O_2N_2S$ : C, 64.60; H, 6.20; N, 10.76. Found: C, 64.15; H, 5.93; N, 10.43. IR  $\nu_{C=O}$   $cm^{-1}$ : 1690 (KBr).

**Reaction of Compound (XVIII) and Concentrated Ammonia**—To 10 ml. of conc.  $NH_3$  (25%) 0.5 g. of compound (XVIII) was dissolved and the solution was kept at room temp. for 1 hr. in a nitrogen atmosphere. White flocky substance which appeared was removed by filtration. The filtrate was concentrated under reduced pressure, water was added and this operation was repeated three times. The resulting crystalline product was extracted with ether, dried over anhyd.  $Na_2SO_4$ . By distilling ether white solid was obtained, m.p. 82~84° (0.3 g.). The IR spectrum of this compound was identical with that of starting material (XVIII) and the mixed melting point of this substance and the compound (XVIII) showed no depression. The small amount of flocky substance which was obtained in the above procedure was confirmed to be disulfide (VI) from the comparison of the IR spectrum and the mixed melting point determination.

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### Summary

As a part of studies on syntheses of pyrazolone derivatives, 3-mercaptomethyl-2-methyl-4-substituted-1-phenyl-3-pyrazolin-5-one were prepared by the reaction of 3-bromomethyl-2-methyl-4-substituted-1-phenyl-3-pyrazolin-5-one with thiourea and alkaline treatment, the reduction of 1,1-bis(2-methyl-4-substituted-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl disulfide and (2-methyl-4-substituted-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl thiocyanate.

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### 169. Hiroshi Hikino, Kanji Meguro, Yojiro Sakurai, and Tsunematsu Takemoto: Structure of Curcumol.\*<sup>1</sup>

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The rhizome of zedoary (*Curcuma zedoaria* ROSCOE (Zingiberaceae)) has been used medicinally since olden times. Although investigations directed towards a study of its composition have spread over many years, knowledge concerning the nature of its constituents has remained scanty.<sup>1)</sup> We have undertaken an analysis of it and, by chromatography of the extract, isolated a new sesquiterpenoid, curcumol. A

\*<sup>1</sup> This paper is Part V in the series on Sesquiterpenoids. Preceding paper, Part IV, H. Hikino, K. Aota, T. Takemoto: This Bulletin, 14, 890 (1966).

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1) For a historical background of early works, see E. Gildemeister, F. Hoffmann: Die Ätherischen Öle," Vol. IV, 477 (1956), Akademie Verlag, Berlin.

preliminary account of the structural elucidation has already been reported.<sup>2)</sup> The work is now discussed in full detail in terms of the structure elucidated (I; R=H).

Curcumol melts at 141~142° and analyzed for C<sub>15</sub>H<sub>24</sub>O<sub>2</sub>. These data indicated that it might be identical with the substance (m.p. 142.5°, C<sub>15</sub>H<sub>24</sub>O<sub>2</sub> (?)) isolated from this plant by Haensel<sup>3)</sup>; however, identification could not be carried out since no original specimen appeared available.

The presence of an exocyclic methylene grouping in curcumol was indicated by infrared bands at 1645 and 882 cm<sup>-1</sup> and an NMR (nuclear magnetic resonance) signal equivalent to two protons at 5.15τ, and further confirmed by the formation of formaldehyde on ozonolysis. That curcumol contains no other centers of unsaturation was shown by its conversion on hydrogenation to a saturated dihydro-derivative (*vide infra*) and on perbenzoic acid oxidation to two saturated monoepoxides (IIa and b), which are considered to be the epimers arising by approach of the reagent from the different sides of the molecule.

The nature of the oxygen functions was elucidated as follows. Curcumol is an alcohol as shown by hydroxyl absorption at 3420 cm<sup>-1</sup> in the infrared spectrum. The NMR spectrum exhibits a singlet equivalent to one proton at 7.25τ which disappears upon addition of deuterium oxide suggesting curcumol to be a mono-ol. Since no bands can be observed in the infrared attributable to a carbonyl grouping, the second oxygen function is, therefore, presumed to be oxidic. In order to confirm this assignment it was desirable to prepare its acetate. However, on refluxing with acetic anhydride in the presence of sodium acetate or on heating with acetic anhydride in pyridine at 100° curcumol was recovered unchanged. The acetate (I; R=COCH<sub>3</sub>) was ultimately obtained by refluxing curcumol with acetic anhydride and pyridine. The infrared spectrum shows acetoxy absorption at 1757 and 1214 cm<sup>-1</sup>, while the NMR spectrum exhibits a singlet at 8.06τ indicating the presence of the methyl moiety of an acetoxy group. This spectral evidence and the empirical formula C<sub>17</sub>H<sub>26</sub>O<sub>3</sub> clearly define it to be the monoacetate. The previously presumed ethereal nature of the second oxygen atom in curcumol was confirmed by the absence of any bands associated with a hydroxyl group in the infrared spectrum of the monoacetate. The NMR spectra of curcumol and its acetate lack the hydrogen signal of an  $\text{H}-\text{C}\leftarrow\text{O}-\text{C}-$  system; this indicates the oxide linkage of curcumol as being tertiary.

The hemiketal relationship between the two oxygen functions in curcumol was then deduced in the following manner. On treatment with methanolic or ethanolic hydrochloric acid curcumol was converted into a compound which no longer showed the infrared band due to the hydroxyl group and, from the empirical formula and NMR spectrum showing the presence of a methoxyl or an ethoxyl group, was revealed to be the corresponding ether (I; R=CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>). When treated with hydrochloric acid in aqueous acetone the ether (I; R=CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>) reverted to curcumol. Reduction of curcumol with lithium aluminum hydride gave two diols (IIIa and b), which have a secondary and a tertiary hydroxyl group, respectively; the latter must be present in some masked form in curcumol. Both the alcohols are, therefore, epimers about the carbon which participated to form the masked carbonyl in curcumol and which is now bearing the secondary hydroxyl group. In confirmation, oxidation of each alcohol (IIIa or b) with chromic acid led to the conversion of the secondary hydroxyl group into a carbonyl which on simultaneous ring closure with the tertiary hydroxyl group regenerated the hemiketal, curcumol. The two oxygen atoms have been thereby satisfactorily related.

2) H. Hikino, K. Meguro, Y. Sakurai, T. Takemoto: This Bulletin, **13**, 1484 (1965).

3) H. Haensel: Pharm. Ztg., **44**, 752 (1899).

The next objective was to establish the carbon skeleton of curcumol. Of the four double-bond equivalents indicated by the molecular formula of curcumol, two have been accounted for as a double bond and a hemiketal system. It must, therefore, be concluded that curcumol contains two carbocyclic rings. This conclusion was substantiated when it was found that, on dehydrogenation with palladium-on-carbon, curcumol gave S-guaiazulene (IV) together with a small amount of Se-guaiazulene (V), showing curcumol to be a member in the guaiane series. The NMR spectra of curcumol and its derivatives reveal that the number and splitting patterns of the methyl groups are in agreement with this carbon skeleton; *i. e.*, a vinylidene group or equivalent and three secondary methyls, two of which are to be attributed to an isopropyl grouping. The results so far obtained coupled with the established carbon skeleton of curcumol enable a partial structure to be written down as described below. The vinylidene system must be placed at the C-4 or C-10 position because of the presence of the isopropyl group in the molecule. Further, the tertiary nature of the hemiketal linkage defines position C-1, C-5, or C-7 for one terminus of the linkage (*i. e.*, the masked hydroxyl). The remaining problem is to fix the functional groupings on the skeleton.

Curcumol was hydrogenated over platinum oxide in methanol, with the uptake of one molecule of hydrogen, to give the dihydro-derivative (VI), while on hydrogenation over palladized charcoal (freshly prepared from palladium chloride by hydrogenation) in methanol curcumol suffered hydrogenolysis as well as hydrogenation to yield dihydrocurcumol (VI), a ketol, and a ketone. The second, the ketol, which had infrared bands at  $3448\text{ cm}^{-1}$  due to a hydroxyl and at  $1698$  and  $1435\text{ cm}^{-1}$  due to a carbonyl group in a six-membered or larger ring and having a methylene grouping  $\alpha$  to it, is considered to be a stereoisomer (VII) of the tautomeric ketol form of dihydrocurcumol (VI). The ketone (VIII), the third product, showed infrared absorption at  $1704$  and  $1435\text{ cm}^{-1}$ , indicating the presence of a carbonyl in a six-membered or larger ring and a methylene grouping flanking the carbonyl, and under alkaline equilibrating conditions incorporated three deuterium atoms. These observations indicate that the carbonyl group in the ketones, VII and VIII, or the masked carbonyl in curcumol, must be present at C-8 or C-9 in the guaiane skeleton. This arrangement renders the position of the remaining terminus of the hemiketal linkage (*i. e.*, the masked hydroxyl) in curcumol at C-7 improbable since a ketal bridge cannot be easily formed between them. Hydrogenolysis seems to imply that the masked hydroxyl in curcumol is more likely bound to the allylic position, C-1. However, hydrogenolysis of an isolated tertiary hydroxyl group under acidic conditions is also known, and so, the remaining possible position C-5 cannot be immediately precluded by this fact alone.

Ozonolysis of curcumol gave the norketone (X; R=H) with concomitant loss of one carbon atom as formaldehyde. Although the norketone (X; R=H) had been isolated by chromatography, it could not be finally distilled since on heating further ring cleavage took place (*vide infra*). The infrared spectrum of the norketone (X; R=H) exhibits hydroxyl absorption at  $3413\text{ cm}^{-1}$  and carbonyl absorption at  $1704\text{ cm}^{-1}$ . The appropriate absorption at  $280\text{ m}\mu$  ( $\log \epsilon 1.37$ ) in neutral solution is evident in the ultraviolet spectrum. However, its maximum in alkaline solution could not be determined since it suffered immediate ring cleavage to give a product (X; R=H) having a maximum at  $263\text{ m}\mu$  (*vide infra*). In the NMR spectrum of the norketone (X; R=H) there can be observed a singlet at  $7.40\tau$  which is attributable to the methylenic protons at C-9; this line position is consistent with that of the C-9 methylene in curcumol and its derivatives (*e. g.*,  $7.47\tau$  for curcumol,  $7.63\tau$  for the methyl ether (I; R=CH<sub>3</sub>), and  $7.60\tau$  for the ethyl ether (I; R=C<sub>2</sub>H<sub>5</sub>)), but incompatible

with that of a C-2 methylene in 1,3-diones (*e.g.*, 6.53 $\tau$  for cycloheptane-1,3-dione<sup>4</sup>). This NMR evidence excludes the alternative possibility, namely, the tautomeric diketo-alcohol. The ketonic carbonyl band of the norketone (X; R=H) at 1704 cm<sup>-1</sup>, confirming the size of the ring as being six-membered or larger, fixes not only the position of the carbonyl at C-10 but also the situation of the hemiketal bridge between C-5 and C-8. Thus the possibilities that the carbonyl is located at C-4 and that the hemiketal bridge is situated between C-1 and C-8, C-1 and C-9, and C-5 and C-9 are excluded. The observation that the size of the carbonyl bearing ring of the norketone (X) is six-membered was also made in the acetate (X; R=COCH<sub>3</sub>) (1704 cm<sup>-1</sup>) and the ethyl ether (X; R=C<sub>2</sub>H<sub>5</sub>) (1718 cm<sup>-1</sup>). Therefore, curcumol is represented by structure I (R=H).

This assignment was further confirmed by the following series of experiments.

As has been described above the keto-hemiketal (X; R=H) is extremely unstable to alkali. Thus treatment with alkali gave an acidic product which has been characterized as a methyl ester. The presence of the carbomethoxyl grouping in the ester was revealed by an infrared absorption at 1736 cm<sup>-1</sup> and an NMR singlet at 6.43 $\tau$ . The infrared bands at 1678 and 1605 cm<sup>-1</sup> and ultraviolet maximum at 257 m $\mu$  give indication of the presence of an enone system, which can be further expanded to a fully substituted  $\alpha,\beta$ -unsaturated methyl ketone by the following NMR evidence. The presence of a hydrogen or a methyl group as one of the substituents on the ethylenic linkage is excluded since no signal attributable to a vinyl hydrogen or a vinyl methyl is found in the appropriate regions. In addition, a singlet at 7.89 $\tau$  shows the presence of a methyl attached to carbonyl; this was supported by a positive iodoform test. These observations, together with the presence of a secondary methyl and an isopropyl group revealed by the NMR spectrum lead to the conclusion that structure X (R=H) must be ascribed to the alkali cleavage product. The transformation of the keto-hemiketal (X; R=H) into the keto-acid (X; R=H) can be reasonably rationalized in terms of mechanistic considerations provided that the masked hydroxyl is situated  $\beta$  position (*i.e.*, C-5) to the C-10 carbonyl and the masked carbonyl situated  $\beta'$  position (*i.e.*, C-8) to the C-10 carbonyl in the 15-norketone (X; R=H).

The heat labile nature of the keto-hemiketal (X; R=H) has been mentioned above, two products being obtained. The one is assumed to be the enedione (XI) based on its ultraviolet absorption at 262 m $\mu$ , infrared bands at 1709 (carbonyl in six-membered ring or larger), 1658 and 1623 cm<sup>-1</sup> ( $\alpha,\beta$ -unsaturated carbonyl), and an AB quadruplet at 6.79 and 5.94 $\tau$ . The other product is deduced to have the structure XII from the following spectral properties. It exhibited a band at 1764 cm<sup>-1</sup> which bespoke the presence of a  $\gamma$ -lactone system, however, no signal due to a hydrogen on carbon bearing a lactonic oxygen is visible, whilst a band at 1709 cm<sup>-1</sup> and a singlet at 7.92 $\tau$  indicated the presence of an acetyl group. In addition, the presence of a secondary methyl and an isopropyl group is evident from the NMR spectrum. The structures XI and XII are also compatible with mechanistic speculation. The keto-lactone (XII) is also obtainable from the unsaturated keto-acid (X; R=H) by acid catalysis or even on standing. The  $\gamma$ -lactonic feature of the keto-lactone (XII) also verified the situation of the masked hydroxyl at C-5 and the masked carbonyl group at C-8 in curcumol.

In order to confirm the presence of a hydrogen at C-1 in curcumol the following sequences of experiments were further attempted.

Curcumol acetate (I; R=COCH<sub>3</sub>) underwent ozonolysis to the 15-norketone (X; R=COCH<sub>3</sub>) which on Baeyer-Villiger oxidation gave not the desired product, a lactone bearing the lactonic oxygen at C-1, but rather the starting ketone (X; R=COCH<sub>3</sub>).

4) I. Maclean, R. P. A. Sneeden : Tetrahedron, **21**, 31 (1965).

On ozonolysis ethylcurcumol (I;  $R=C_2H_5$ ) yielded the 15-norketone (IX;  $R=C_2H_5$ ) which was deuterated in positions  $\alpha$  to the C-10 carbonyl group. A detailed and comparative study of the mass spectra of undeuterated and deuterated compounds revealed that the incorporation of up to three atoms of deuterium had occurred. The fact that the ketone (IX;  $R=C_2H_5$ ) contains three exchangeable hydrogens also precludes the attachment of the oxygen at C-1 in curcumol.

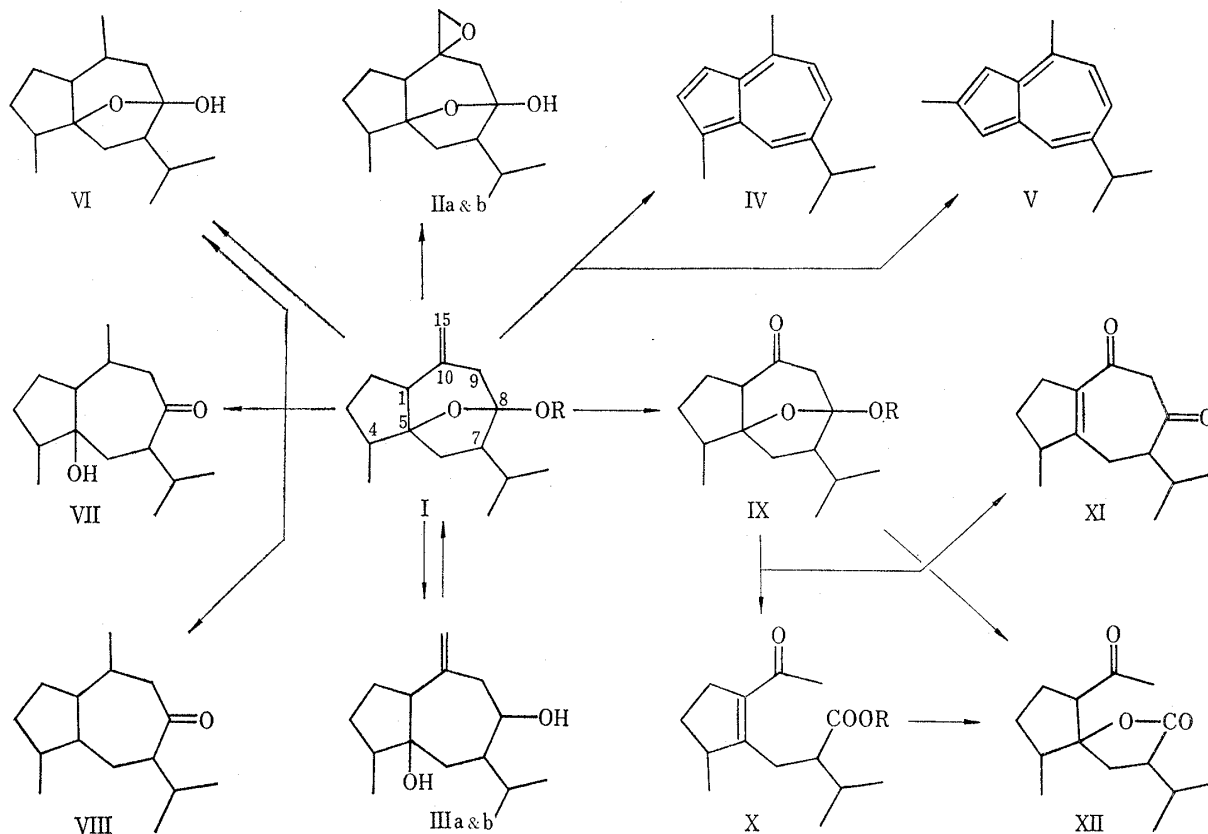


Chart 1.

### Experimental<sup>\*3</sup>

**Isolation of Curcumol**—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. Benzene eluate gave a crystalline substance which was crystallized from AcOEt to yield curcumol (I;  $R=H$ ) as colorless needles, m.p.  $141\sim 142^\circ$ ,  $[\alpha]_D -40.8^\circ$  ( $c=6.7$ ), mol. wt. 236 (mass spec.), *Anal.* Calcd. for  $C_{15}H_{24}O_2$ : C, 76.22; H, 10.24. Found: C, 75.91; H, 10.35, IR (KBr)  $cm^{-1}$ : 3420 (hydroxyl), 3067, 1645, 882 (vinylidene), NMR ( $CDCl_3$ ): doublet (3H) at  $9.14\tau$  ( $J=5.5$ ,  $CH_3-CH<$ ), doublet (6H) at  $8.99\tau$  ( $J=7.0$ ,  $CH_3-CH<$ ), triplet (2H) at  $7.47\tau$  ( $J=1.5$ ,  $H_2C=C-CH_2-C(OH)-O-$ ), singlet (1H) at  $7.25\tau$  ( $HO-$ ), triplet (2H) at  $5.15\tau$  ( $J=1.5$ ,  $H_2C=C-CH_2-$ ).

**Acetylation of Curcumol**—Curcumol (103 mg.) in pyridine (2.5 ml.) and  $Ac_2O$  (2.5 ml.) was refluxed for 4 hr. The reaction mixture was warmed with  $H_2O$  and extracted with ether. The ethereal extract in light petroleum-benzene (1:1) was filtered through alumina (1 g.). The filtrate (113 mg.) was distilled under reduced pressure to give curcumyl acetate (I;  $R=COCH_3$ ) as a colorless oil,  $n_D^{25} 1.482$ ,  $[\alpha]_D -23.3^\circ$  ( $c=5.5$ ), *Anal.* Calcd. for  $C_{17}H_{26}O_3$ : C, 73.34; H, 9.41. Found: C, 73.34; H, 9.36, IR (liquid)  $cm^{-1}$ : 1757, 1214 (acetoxyl), 3096, 1647, 886 (vinylidene), NMR: two doublets (3H, respectively) at  $9.15$  and  $9.08\tau$  ( $J=6.0$ ,  $(CH_3)_2CH-$ ), doublet (3H) at  $9.02\tau$  ( $J=5.4$ ,  $CH_3-CH<$ ), singlet (3H) at  $8.06\tau$  ( $CH_3-CO-O-$ ), doublet (2H) at  $5.23$  and  $5.19\tau$  ( $H_2C=C<$ ).

<sup>\*3</sup> Melting points are uncorrected. Specific rotations were measured in  $CHCl_3$  solution. NMR spectra were determined at 60 Mc.p.s. in  $CCl_4$  solution relative to internal  $(CH_3)_4Si$  unless indicated otherwise. Chemical shifts are given in  $\tau$ -values and coupling constants ( $J$ ) in c. p. s.

**Hydrolysis of Curcumyl Acetate**—Curcumyl acetate (I; R=COCH<sub>3</sub>) (31 mg.) and oxalic acid (200 mg.) in EtOH (8 ml.) and H<sub>2</sub>O (1 ml.) were refluxed for 8 hr. Upon isolation, the product was crystallized from AcOEt to give curcumol (I; R=H) as colorless needles, m.p. 140~141°, undepressed on admixture with an authentic specimen.

**Epoxidation of Curcumol**—Curcumol (0.50 g.) and BzO<sub>2</sub>H (0.31 g.) in CHCl<sub>3</sub> (25 ml.) was kept at 0° for 4 days. The mixture was washed successively with 5% NaOH solution and H<sub>2</sub>O, and evaporated. The residue in light petroleum was chromatographed over silica gel (10 g.).

Elution with benzene afforded a crystalline mass (260 mg.) which on crystallization from AcOEt gave the monoepoxide A (IIa) as colorless needles, m.p. 129.5~131°,  $[\alpha]_D -42.2^\circ$  (c=5.1), *Anal.* Calcd. for C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.62, IR (KBr) cm<sup>-1</sup>: 3448 (hydroxyl), NMR: multiplet (9H) in the region of 9.20 and 9.07  $\tau$  ( $\text{CH}_3\text{-CH}\langle$ ), singlet (2H) at 7.54  $\tau$  ( $\text{H}_2\text{C}=\text{C}\rangle$ ).

Successive elution with benzene gave another crystalline mass (133 mg.) which was crystallized from AcOEt-light petroleum to yield the monoepoxide B (IIb) as colorless prisms, m.p. 109~110.5°,  $[\alpha]_D -48.6^\circ$  (c=4.2), *Anal.* Calcd. for C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>: C, 71.39; H, 9.59. Found: C, 71.15; H, 9.31, IR (KBr) cm<sup>-1</sup>: 3431, 3300 (hydroxyl), NMR: multiplet (9H) in the region of 9.12~8.96  $\tau$  ( $\text{CH}_3\text{-CH}\langle$ ), singlet (2H) at 7.29  $\tau$  ( $\text{H}_2\text{C}=\text{C}\rangle$ ).

**Methylation of Curcumol**—Curcumol (400 mg.) in MeOH (40 ml.) and conc. HCl (4 ml.) was set aside at room temperature for 1 week. The mixture was diluted with H<sub>2</sub>O and extracted with ether. The ethereal solution was washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to give an oil (418 mg.) which was chromatographed over silica gel (7 g.). The eluate (247 mg.) with light petroleum was distilled under diminished pressure yielding methylcurcumol (I; R=CH<sub>3</sub>) as a colorless oil,  $n_D^{25}$  1.483,  $[\alpha]_D +8.3^\circ$  (c=5.3), mol. wt. 250 (mass spec.), *Anal.* Calcd. for C<sub>16</sub>H<sub>26</sub>O<sub>2</sub>: C, 76.75; H, 10.48. Found: C, 76.93; H, 10.44, IR (liquid) cm<sup>-1</sup>: 3096, 1647, 888 (vinylidene), NMR: two doublets (3H, respectively) at 9.17 and 9.09  $\tau$  (J=5.9,  $\text{CH}_3\text{-CH-}$ ), doublet (3H) at 9.03  $\tau$  (J=5.3,  $\text{CH}_3\text{-CH}\langle$ ), unresolved band (2H) at 7.63  $\tau$  ( $\text{CH}_2=\text{C-CH}_2\text{-C(OCH}_3\text{)-O-}$ ), singlet (3H) at 6.75  $\tau$  ( $\text{CH}_3\text{-O-}$ ), unresolved band (2H) at 5.22  $\tau$  ( $\text{H}_2\text{C}=\text{C}\rangle$ ).

**Ethylation of Curcumol**—Curcumol (2.0 g.) in EtOH (160 ml.) and conc. HCl (16 ml.) was let standing at room temperature for 13 days. Upon isolation, the product (2.26 g.) was chromatographed over silica gel (40 g.). Elution with light petroleum and distillation under reduced pressure gave ethylcurcumol (I; R=C<sub>2</sub>H<sub>5</sub>) as a colorless oil (0.94 g.),  $n_D^{25}$  1.479,  $[\alpha]_D -18.3^\circ$  (c=4.6), mol. wt. 264 (mass spec.), *Anal.* Calcd. for C<sub>17</sub>H<sub>28</sub>O<sub>2</sub>: C, 77.22; H, 10.67. Found: C, 77.30; H, 10.33, IR (liquid) cm<sup>-1</sup>: 3086, 1645, 888 (vinylidene), NMR: two doublets (3H, respectively) at 9.16 and 9.07  $\tau$  (J=5.6,  $\text{CH}_3\text{-CH-}$ ), doublet (3H) at 9.05  $\tau$  (J=5.9,  $\text{CH}_3\text{-CH}\langle$ ), triplet (3H) at 8.86  $\tau$  (J=7.1,  $\text{CH}_3\text{-CH}_2\text{-O-}$ ), two quartets (2H) at 6.37 and 6.42  $\tau$  (J=7.1,  $\text{CH}_3\text{-CH}_2\text{-O-}$ ), unresolved band (2H) at 5.20  $\tau$  ( $\text{H}_2\text{C}=\text{C}\rangle$ ).

**Hydrolysis of Methylcurcumol**—Methylcurcumol (I; R=CH<sub>3</sub>) (107 mg.) and conc. HCl (1 ml.) in dil. acetone (acetone: H<sub>2</sub>O=9:1) (10 ml.) were set aside at room temperature for 10 days. The mixture was diluted with H<sub>2</sub>O and extracted with ether. The product in light petroleum was chromatographed over alumina (2 g.). Elution with benzene and crystallization from AcOEt gave curcumol (I; R=H) as colorless needles, m.p. 141~142°. Identity was confirmed by mixed m.p. and IR comparison.

**Hydrolysis of Ethylcurcumol**—Ethylcurcumol (I; R=C<sub>2</sub>H<sub>5</sub>) (102 mg.) and conc. HCl (2 ml.) in dil. acetone (acetone: H<sub>2</sub>O=4:1) (20 ml.) were left standing at room temperature for 10 days. Extraction with ether and crystallization from AcOEt yielded curcumol (I; R=H) as colorless needles, m.p. 141~142°. Identification was carried out by mixed m.p. and IR comparison.

**Reduction of Curcumol with Lithium Aluminum Hydride**—To curcumol (4.0 g.) in anhydr. ether (100 ml.) was added LiAlH<sub>4</sub> (1.0 g.) in anhydr. ether (50 ml.) in 30 min. with stirring at room temperature. The stirring was continued for a further 3 hr. Upon isolation, the product was chromatographed over silica gel (70 g.).

Light petroleum-benzene (1:1) eluted an oil (1.89 g.) which on distillation under reduced pressure gave the diol A (IIIa) as a colorless oil,  $n_D^{25}$  1.505,  $[\alpha]_D -5.9^\circ$  (c=5.4), *Anal.* Calcd. for C<sub>15</sub>H<sub>26</sub>O<sub>2</sub>: C, 75.58; H, 11.00. Found: C, 75.31; H, 11.08, IR (liquid) cm<sup>-1</sup>: 3472 (hydroxyl), 3086, 1631, 895 (vinylidene), NMR: doublet (6H) at 9.10  $\tau$  (J=5.9,  $\text{CH}_3\text{-CH}\langle$ ), doublet (3H) at 9.07  $\tau$  (J=5.6,  $\text{CH}_3\text{-CH}\langle$ ), triplet (1H) at 5.99  $\tau$  (J=3.9,  $\text{H-C}\leq\text{OH}$ ), triplet (2H) at 5.15  $\tau$  (J=1.2,  $\text{H}_2\text{C}=\text{C}\rangle$ ).

Elution with benzene gave crystals (1.31 g.) which was crystallized from light petroleum to afford the diol B (IIIb) as colorless needles, m.p. 78~79°,  $[\alpha]_D +3.2^\circ$  (c=3.8), *Anal.* Calcd. for C<sub>15</sub>H<sub>26</sub>O<sub>2</sub>: C, 75.58; H, 11.00. Found: C, 75.68; H, 10.77, IR (KBr) cm<sup>-1</sup>: 3268 (hydroxyl), 3096, 1642, 883 (vinylidene), NMR: doublet (9H) at 9.16  $\tau$  (J=5.3,  $\text{CH}_3\text{-CH}\langle$ ), unresolved doublet (1H) at 6.23  $\tau$  (J=5.0,  $\text{H-C}\leq\text{OH}$ ), unresolved band (2H) at 5.15  $\tau$  ( $\text{H}_2\text{C}=\text{C}\rangle$ ).

**Oxidation of the Diols with Chromic Acid**—a) To a CrO<sub>3</sub>-pyridine complex (made from CrO<sub>3</sub> (0.6 g.) and pyridine (12 ml.)) was added the diol A (IIIa) (260 mg.) in pyridine (3 ml.) with cooling by ice. The mixture was set aside at room temperature overnight, diluted with H<sub>2</sub>O, and extracted with ether. The product (250 mg.) was crystallized from AcOEt to give curcumol (I; R=H) as colorless needles, m.p. 141~142°,  $[\alpha]_D -41.7^\circ$  (c=10.0). Identity was confirmed by mixed m.p. and IR comparison.

b) To a  $\text{CrO}_3$ -pyridine complex (made from  $\text{CrO}_3$  (0.4 g.) and pyridine (8 ml.)) was added the diol B (IIIb) (200 mg.) in pyridine (3 ml.) with cooling by ice. The mixture was let standing at room temperature overnight. After isolation, the product (186 mg.) on crystallization from AcOEt gave curcumol (I; R=H) as colorless needles, m.p. 141~142°, identified by mixed m.p. and IR spectrum.

**Dehydrogenation of Curcumol with Palladized Carbon**—Curcumol (50 mg.) and Pd-C (5%; 100 mg.) was heated at 280~300° for 10 min. The same experiment was repeated further four times. The combined product in light petroleum was chromatographed on alumina (5 g.).

Elution with the same solvent gave S-guaiazulene (IV) as a blue oil, identified by TLC (silica gel-light petroleum) with an authentic sample. The trinitrobenzene adduct crystallized from EtOH as violet needles, m.p. 145°, UV  $\lambda_{\text{max}}^{\text{EtOH}}$   $m\mu$  (log  $\epsilon$ ): 241 (4.17), 289 (4.24), 308  $i^*4$  (3.50), 350 (3.15), 368  $i$  (2.67), ca. 600. The identity was confirmed by the usual criteria.

Successive elution with the same solvent afforded Se-guaiazulene (V) as a violet oil, identified by TLC (silica gel-light petroleum) with an authentic specimen. The trinitrobenzene adduct crystallized from EtOH as violet needles, m.p. 140°, UV  $\lambda_{\text{max}}^{\text{EtOH}}$   $m\mu$  (log  $\epsilon$ ): 230 (4.12), 279  $i$  (4.01), 290  $i$  (4.09), 298 (4.12), 323 (3.68), 357  $i$  (3.18), 368 (3.20), 386  $i$  (2.95), ca. 550. Identification was carried out in the usual criteria.

**Hydrogenation of Curcumol over Palladized Carbon in Methanol**—Curcumol (1.0 g.) in MeOH (15 ml.) was stirred in the presence of Pd-C (5%; 0.5 g.), freshly prepared from  $\text{PdCl}_2$  by hydrogenation, under  $\text{H}_2$ , when 1.54 moles of  $\text{H}_2$  were absorbed. The product was chromatographed over silica gel (40 g.).

Light petroleum eluted an oil (0.60 g.) which on distillation under reduced pressure gave the ketone (VIII) as a colorless oil,  $n_D^{25}$  1.477,  $[\alpha]_D -39.9^\circ$  ( $c=7.2$ ), mol. wt. 222 (mass spec.), *Anal.* Calcd. for  $\text{C}_{15}\text{H}_{26}\text{O}$ : C, 81.02; H, 11.79. Found: C, 81.16; H, 11.76, IR (liquid)  $\text{cm}^{-1}$ : 1704 (cycloheptanone), 1435 (methylene  $\alpha$  to carbonyl), NMR: multiplet (12H) in the region of 9.23~8.97  $\tau$  ( $\text{CH}_3\text{-CH}$ ).

Benzene eluted a crystalline mass which was crystallized from light petroleum to give dihydrocurcumol (VI) as colorless prisms, m.p. 102~104°,  $[\alpha]_D +5.2^\circ$  ( $c=4.6$ ), *Anal.* Calcd. for  $\text{C}_{15}\text{H}_{26}\text{O}_2$ : C, 75.58; H, 11.00. Found: C, 75.73; H, 10.79, IR (KBr)  $\text{cm}^{-1}$ : 3390 (hydroxyl), NMR: multiplet (12H) in the region of 9.28~8.67  $\tau$  ( $\text{CH}_3\text{-CH}$ ).

MeOH eluted an oil which on distillation under reduced pressure afforded the ketol (VII) as a colorless oil,  $n_D^{25}$  1.487,  $[\alpha]_D -94.7^\circ$  ( $c=4.9$ ), *Anal.* Calcd. for  $\text{C}_{15}\text{H}_{26}\text{O}_2$ : C, 75.58; H, 11.00. Found: C, 76.39; H, 11.21, IR (liquid)  $\text{cm}^{-1}$ : 3448 (hydroxyl), 1698 (carbonyl), 1435 (methylene adjacent to carbonyl), NMR: multiplet (12H) in the region of 9.16~9.02  $\tau$  ( $\text{CH}_3\text{-CH}$ ).

**Hydrogenation of Curcumol over Platinum in Methanol**—Curcumol (0.10 g.) in MeOH (8 ml.) was stirred with  $\text{PtO}_2$  (0.01 g.) under  $\text{H}_2$ , when it consumed ca. 1 mole of  $\text{H}_2$ . The product was chromatographed on silica gel (5 g.).

Elution with benzene and crystallization from light petroleum gave dihydrocurcumol (VI) as colorless prisms, m.p. 102~104°, IR (KBr)  $\text{cm}^{-1}$ : 3390 (hydroxyl), NMR: multiplet (12H) in the region 9.28~8.67  $\tau$  ( $\text{CH}_3\text{-CH}$ ). The identity with the dihydro-derivative (VI) obtained in the preceding experiment was confirmed by the usual criteria.

Successive elution with benzene gave an oil whose behaviors on VPC and TLC were identical with those of the ketol (VII) obtained in the preceding experiment.

**Deuteration of the Ketone**—Deuterium exchange was performed by treating the ketone (VIII) (28 mg.) in dil. NaOD (made from Na (10 g.) and  $\text{D}_2\text{O}$  (1 ml.)) and dioxane (1 ml.) under reflux for 10 min. After cooling, the solvent was distilled off under diminished pressure. The cycle of experiment was repeated further three times, the mixture being protected from outside moisture throughout the operations. Extraction with ether followed by distillation *in vacuo* afforded the trideuterioketone as a colorless oil, mol. wt. 225 (mass spec.), IR (liquid)  $\text{cm}^{-1}$ : 1692 (cycloheptanone).

**Ozonolysis of Curcumol**—Curcumol (1.0 g.) in AcOEt (30 ml.) was ozonized at  $-5^\circ$  for 2 hr. The mixture was heated with  $\text{H}_2\text{O}$  (30 ml.), Zn dust (0.6 g.), hydroquinone (trace), and  $\text{AgNO}_3$  (trace) at 100° for 1 hr. After cooling, Zn dust was filtered off. The AcOEt layer was washed with  $\text{H}_2\text{O}$  and the washings were combined with the  $\text{H}_2\text{O}$  layer.

The  $\text{H}_2\text{O}$  solution was treated with dimedone to give formaldimedone as colorless needles (from EtOH), m.p. 187~188°, *Anal.* Calcd. for  $\text{C}_{17}\text{H}_{24}\text{O}_4$ : C, 69.83; H, 8.27. Found: C, 69.64; H, 8.54, undepressed on admixture with an authentic sample.

The AcOEt solution gave a brown oil which was chromatographed on silica gel (20 g.). Fractions eluted with benzene afforded the keto-hemiketal (IX; R=H) as a colorless oil, UV  $\lambda_{\text{max}}^{\text{EtOH}}$   $m\mu$  (log  $\epsilon$ ): 280 (1.37), IR (liquid)  $\text{cm}^{-1}$ : 3413 (hydroxyl), 1704 (carbonyl in a six-membered ring), NMR: multiplet (9H) in the region of 9.12~8.96  $\tau$  ( $\text{CH}_3\text{-CH}$ ), singlet (2H) at 7.40  $\tau$  ( $-\text{CO}-\text{CH}_2\text{-C}(\text{OH})-\text{O}-$ ), singlet (1H) at 6.23  $\tau$  ( $\text{HO}-$ ). UV maximum in 0.1N NaOH-EtOH at 263  $m\mu$  (log  $\epsilon$  3.83) is, in fact, due to the enone (X; R=H).

The keto-hemiketal (IX; R=H) on distillation under reduced pressure yielded a mixture of the keto-hemiketal (IX; R=H) and the keto-lactone (XII) as a colorless oil,  $n_D^{25}$  1.496,  $[\alpha]_D -46.4^\circ$  ( $c=5.0$ ), *Anal.* Calcd.

\*4  $i$ : inflection.

for  $C_{14}H_{22}O_3$ : C, 70.55; H, 9.31. Found: C, 70.55; H, 9.39, IR (liquid)  $cm^{-1}$ : 3413 (hydroxyl), 1751 ( $\gamma$ -lactone), 1704 (carbonyl in a six-membered ring), NMR: singlet at 7.41  $\tau$  ( $-CO-CH_2-C(OH)-O-$ ), singlet at 7.91  $\tau$  ( $CH_3-CO-$ ).

**Ozonolysis of Ethylcurcumol**—Ethylcurcumol (I;  $R=C_2H_5$ ) (210 mg.) in AcOEt (20 ml.) was ozonized at  $0^\circ$  for 1.5 hr. The ozonide was decomposed as described in ozonolysis of curcumol. The product obtained from the AcOEt layer was chromatographed on alumina (5 g.). Light petroleum eluate (96 mg.) was distilled *in vacuo* to yield the keto-ethylketal (X;  $R=C_2H_5$ ) as a colorless oil,  $n_D^{25}$  1.478,  $[\alpha]_D -58.2^\circ(c=4.4)$ , MS  $m/e$  (relative intensity): 266 (100), 267 (19), 268 (2), IR (liquid)  $cm^{-1}$ : 1718 (carbonyl in a six-membered ring), 1408 (methylene  $\alpha$  to carbonyl), NMR: doublet (3H) at 9.07  $\tau$  ( $J=5.0$ ,  $CH_3-CH<$ ), doublet (3H) at 9.01  $\tau$  ( $J=5.3$ ,  $CH_3-CH<$ ), doublet (3H) at 8.99  $\tau$  ( $J=5.4$ ,  $CH_3-CH<$ ), triplet (3H) at 8.83  $\tau$  ( $J=7.2$ ,  $CH_3-CH_2-O-$ ), singlet (2H) at 7.47  $\tau$  ( $-CO-CH_2-C(OR)-O-$ ), quadruplet (2H) at 6.36  $\tau$  (unresolved,  $J=7$ ,  $CH_3-CH_2-O-$ ).

**Ozonolysis of Curcumol Acetate**—Curcumol acetate (I;  $R=COCH_3$ ) (1.17 g.) in AcOEt (40 ml.) was ozonized at  $0^\circ$  for 2 hr. The ozonide was decomposed with  $H_2O$  in the presence of Zn, hydroquinone, and  $AgNO_3$  by refluxing for 1 hr. The AcOEt gave an oil (0.44 g.) which on distillation under reduced pressure afforded the keto-acetylketal (X;  $R=COCH_3$ ) as a colorless oil,  $n_D^{25}$  1.482,  $[\alpha]_D -30.5^\circ(c=2.6)$ , Anal. Calcd. for  $C_{16}H_{24}O_4$ : C, 68.54; H, 8.63. Found: C, 68.32; H, 8.76, IR (liquid)  $cm^{-1}$ : 1745, 1202 (acetoxyl), 1704 (carbonyl in a six-membered ring), NMR: doublet (3H) at 9.07  $\tau$  ( $J=5.6$ ,  $CH_3-CH<$ ), doublet (6H) at 8.99  $\tau$  ( $J=7.5$ ,  $CH_3-CH<$ ), quadruplet (2H) in an AB type at 7.56 and 6.75  $\tau$  ( $J=16.0$ ,  $-CO-CH_2-C(OAc)-O-$ ).

**Alkaline Cleavage of the Keto-hemiketal**—The keto-hemiketal (X;  $R=H$ ) (0.9 g.) in MeOH (40 ml.) and 5% KOH (10 ml.) was refluxed for 1 hr. The mixture was concentrated under reduced pressure, diluted with  $H_2O$ , washed with ether, acidified with AcOH, and extracted with ether. The acid (X;  $R=H$ ) (730 mg.) thus obtained, IR ( $CHCl_3$ )  $cm^{-1}$ : 3500~2400, 1600 (carbonyl), 1661, 1592 (enone), NMR: doublet (6H) at 9.13  $\tau$  ( $J=7.0$ ,  $CH_3-CH<$ ), doublet (3H) at 9.01  $\tau$  ( $J=7.5$ ,  $CH_3-CH<$ ), singlet (3H) at 7.92  $\tau$  ( $CH_3-CO-$ ), no vinyl signal, was methylated with  $CH_2N_2$  and chromatographed on silica gel (15 g.). Elution with light petroleum-benzene (1:1) afforded an oil (580 mg.) which on distillation *in vacuo* gave the ester (X;  $R=CH_3$ ) as a colorless oil,  $n_D^{25}$  1.487,  $[\alpha]_D -196.2^\circ(c=5.2)$ , Anal. Calcd. for  $C_{15}H_{24}O_3$ : C, 71.39; H, 9.59. Found: C, 71.22; H, 9.43, UV  $\lambda_{max}^{EtOH}$   $m\mu$  ( $\log \epsilon$ ): 257 (3.67), IR (liquid)  $cm^{-1}$ : 1736, 1253 (ester), 1678, 1605 (enone), NMR: doublet (3H) at 9.08  $\tau$  ( $J=6.3$ ,  $CH_3-CH<$ ), doublet (3H) at 8.99  $\tau$  ( $J=6.2$ ,  $CH_3-CH<$ ), doublet (3H) at 8.97  $\tau$  ( $J=7$ ,  $CH_3-CH<$ ), singlet (3H) at 7.89  $\tau$  ( $CH_3-CO-$ ), singlet (3H) at 6.43  $\tau$  ( $CH_3-O-CO-$ ), iodoform test: positive.

**Lactonization of the Unsaturated Acid**—a) The unsaturated acid (X;  $R=H$ ) (0.50 g.) in AcOH (5 ml.) and conc.  $H_2SO_4$  (1 drop) was kept at  $50^\circ$  for 7 days. The mixture was diluted with  $H_2O$ , made alkaline with  $NaHCO_3$ , and extracted with ether. The product (0.30 g.) was chromatographed on silica gel (12 g.). Elution with benzene and distillation under diminished pressure gave the keto-lactone (XII) as a colorless oil,  $n_D^{25}$  1.470,  $[\alpha]_D +12.6^\circ(c=3.2)$ , Anal. Calcd. for  $C_{14}H_{22}O_3$ : C, 70.55; H, 9.31. Found: C, 70.52; H, 9.57, IR (liquid)  $cm^{-1}$ : 1761 ( $\gamma$ -lactone), 1712 (acetyl), NMR: singlet (3H) at 7.93  $\tau$  ( $CH_3-CO-$ ), iodoform test: positive.

b) The unsaturated acid (X;  $R=H$ ) was set aside at  $50^\circ$  for 7 days. The product was identified as that obtained in the preceding experiment in the usual criteria.

**Pyrolysis of the Keto-hemiketal**—The keto-hemiketal (X;  $R=H$ ) (2.8 g.) was heated at  $165\sim 170^\circ$  for 1.5 hr. The product was chromatographed over silica gel (30 g.). Light petroleum-benzene (1:1) eluted an oil (0.20 g.) which was distilled under diminished pressure to yield the unsaturated dione (XI) as a colorless oil, UV  $\lambda_{max}^{EtOH}$   $m\mu$ : 262, IR (liquid)  $cm^{-1}$ : 1709 (cycloheptanone), 1658, 1623 (enone), NMR: quadruplet (2H) in an AB type at 6.79 and 5.94  $\tau$  ( $J=13.4$ ,  $-CO-CH_2-CO-$ ).

Benzene eluted an oil (0.16 g.) which on distillation under reduced pressure gave the keto-lactone (XII) as a colorless oil, Anal. Calcd. for  $C_{14}H_{22}O_3$ : C, 70.55; H, 9.31. Found: C, 69.99; H, 9.28, IR (liquid)  $cm^{-1}$ : 1764 ( $\gamma$ -lactone), 1709 (acetyl), NMR: singlet (3H) at 7.92  $\tau$  ( $CH_3-CO-$ ). Identification was carried out by IR and NMR spectra.

**Attempted Oxidation of the Keto-acetylketal with Perbenzoic Acid**—The keto-acetylketal (X;  $R=COCH_3$ ) (420 mg.) and  $BzO_2H$  (540 mg.) in  $CHCl_3$  (14 ml.) was let standing at  $25^\circ$  for 40 days. Upon isolation, the product was identified as the starting material (X;  $R=Ac$ ) in the usual criteria.

**Deuteration of the Keto-ethylketal**—The ketone (IX;  $R=C_2H_5$ ) (17 mg.) was deutrated as described in deuteration of the ketone (VIII). The product was chromatographed on silica gel (0.7 g.). Light petroleum eluted the deuterioketone, MS  $m/e$  (relative intensity): 267 (7), 268 (100), 269 (37), 270 (4), IR (liquid)  $cm^{-1}$ : 1712 (carbonyl in a six-membered ring), no band due to a methylene  $\alpha$  to carbonyl.

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### Summary

Extraction of zedoary (*Curcuma zedoaria* (Zingiberaceae)) has afforded a new sesquiterpenoid, curcumol, of the empirical formula  $C_{15}H_{24}O_2$ . It has been shown to



contain a vinylidene group and a hemiketal system. The guaiane carbon skeleton has been established by its dehydrogenation giving S-guaiazulene (IV). Curcumol has been ozonized to give the norketone (K) which has been converted into the acid (X) and the lactone (XII). Spectroscopic study of these derivatives and other evidence show curcumol to be represented by formula I (R=H).

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170. Satoshi Mizukami and Kōichi Nagata : Studies on Thiohydroxamic Acids and Their Metal Chelates. I. Syntheses of Thiohydroxamic Acids and O-Methylthiohydroxamic Acids.

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The donor atoms which form metal chelates are restricted commonly to N, O and S. Of these, the sulfur atom only has 3p electrons so that the reagents including S atom must exhibit interesting selectivities and sensitivities, which differ from those of reagents including N or O atoms. However, studies on those compounds are lagging because of their instabilities and difficulties of synthesis even though further developments are expected.

It is well known that hydroxamic acids show characteristic color reactions with some transition metals. These reactions have been applied to the colorimetric determination of  $\text{Fe}^{3+}$ ,  $\text{Ti}^{4+}$ ,  $\text{UO}^{2+}$ , and especially the forming of red  $\text{Fe}^{3+}$  chelate has been very useful for the qualitative or quantitative assay of organic compounds which can be easily converted to hydroxamic acids, such as aldehyde, carboxylic acid, ester, anhydride and amide. There is too much literature on such analytical applications and the structures of their  $\text{Fe}^{3+}$  chelates to refer here in detail. We have also reported on the colorimetric determination of alcohols by hydroxamic acid method.<sup>1)</sup> On the contrary, thiohydroxamic acids are very scarce in the literature except for a few reports on their synthesis.

From these standpoints we entered on this study in order to examine the chemical natures of thiohydroxamic acids more distinctly, and to investigate the roles of sulfur as ligand atom by comparative studies of the reactivities with metal ions and the structures of the metal chelates between thiohydroxamic acids and hydroxamic acids.

Some thiohydroxamic acids (IV) have been synthesized from dithioacids and hydroxylamine,<sup>2~5)</sup> or hydroxamoyl chlorides and sodium hydrogen sulfide<sup>6)</sup> by Cambi and Bacchetti, but these methods are not available for liquid thiohydroxamic acids

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