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Usnic Acid. XII.[1] The Oxidation of Dihydrousnic Acid. (1)

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Two new oxidation products of dihydrousnic acid, III and IV were assumed to be 3-acetyl-5-methylcyclopentane-1,2,4-trione and α-acetyl-γ-methylteronic acid by the chemical and spectral evidences, respectively.

The mechanism of the formation III and IV from dihydrousnic acid was discussed.

It was reported in a previous paper[3] that 7-acetyl-3,5-dimethyl-6-hydroxycoumaran-2-one, a resorcinol type of compound, obtained from dihydrousnic acid (I) by dry distillation with $CaCl_2$, was formed from the ring B of I. Asahina and Yanagita[4] reported that I afforded 2,6-dihydroxy-3-methylacetophenone (II), another resorcinol type of compound, by oxidation with potassium permanganate followed by distillation. Later Schöpf and Ross[5] assumed that II was formed from the ring B of I by the mechanism as shown in Chart 1. But any oxidation products from the ring A of I have not been reported as yet. This paper deals with new potassium permanganate oxidation products III and IV, obtained from I and the reaction mechanism. In alkaline solution, I was oxidised with potassium permanganate to afford yellow needles $C_8H_8O_4$ (III) of mp 218° (decomp.) and colorless needles $C_7H_8O_4$ (IV) of mp 54°. III was strongly acidic and soluble in $NaHCO_3$ solution under bubbling and gave violet coloration with $FeCl_3$ and the positive 1,3-diketone reaction (orange-red) with *o*-phenylenediamine. The ultraviolet (UV) spectra of III in both acidic and alkaline ethanolic solutions were closely similar to those of 3-acetyl-5-methylcyclopentane-1,2,4-trione,[6–9] respectively. The infrared (IR) spectra[6] of both compounds were similar. III shows nuclear magnetic resonance (NMR) signals (δ-value, ppm) in $CDCl_3$ (110°) at 1.94 (s, 3H, $-CH_3$), 2.39 (s, 3H, $COCH_3$), 6.37—7.13 (broad, about one proton) and 11.6—12.24 (broad, about one proton). In 98% CF_3COOD, III shows NMR signals only at 1.80 (s, 3H, $-CH_3$), 2.41 (s, 3H, $COCH_3$) and at 10.87 (CF_3COOH), probably due to rapid proton exchange between enolic OH and CF_3COOH. So the signals at 11.6—12.24 and 6.37—7.13 could be assigned to enolic OH groups, *i.e.* to an acidic enol OH and a less acidic enol OH, as in the case of 3-acylcyclopentane-1,2,4-trione type of compound such as isohumulinic acid which exists in the dienolised form,[10] respectively. III showed an isosbestic point at 295 nm (ε=5500) and the pK_a value of III was 2.60, UV-spectrophotometrically. The second dissociation of III might be too weak to be measured.[6] These chemical and spectral data suggest that III is 3-acetyl-5-methylcyclopentane-1,2,4-trione. The analysis of the fragmentation of the mass spectrum (MS) of III could be interpreted as shown in Chart 2, supporting the formula for the compound

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2) Location: *Takaramachi, Kanazawa, 920, Japan.*
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5) C. Schöpf and F. Ross, *Ann.*, **541**, 1 (1941).
6) J.A. Elvidge and R. Stevens, *J. Chem. Soc.*, **1965**, 2251.
7) E. Leucht and W. Riedl, *Ann.*, **669**, 55 (1963).
8) P.M. Brown and G.A. Howard, *J. Chem. Soc.*, **1960**, 164. The authentic sample of 3-acetyl-5-methylcyclopentane-1,2,4-trione was not available.
9) P.R. Ashurst, P.M. Brown, J.A. Elvidge and R. Stevens, *J. Chem. Soc.*, **1965**, 6543.
10) S. Forsen and M. Nilsson, *Acta. Chem. Scand.*, **18**, 513 (1964).

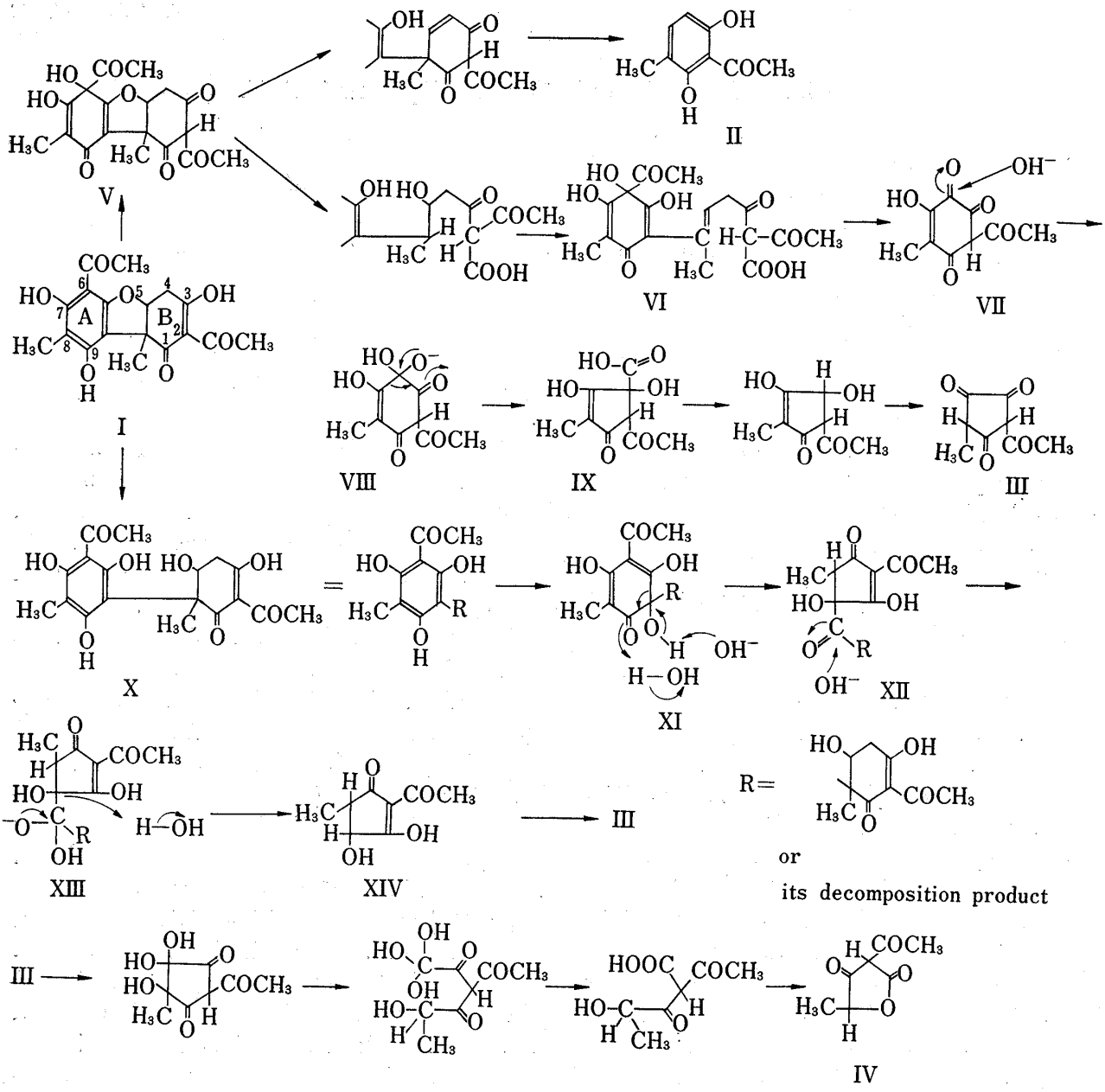

Chart 1

(Chart 1). The UV and IR of IV and α-acetyl-γ-methyltetronic acid[11–13] were almost superimposable, respectively and the MS of IV could be interpreted as shown in Chart 3, suggesting that IV is α-acetyl-γ-methyltetronic acid. The NMR indicate that IV exists in isomeric forms as α-acetyltetronic acid.[14]

The reaction mechanism of the formation of III and IV from I could be tentatively postulated in Chart 1. Namely, the first stage of the reaction might be the formation of dihydrousnonic acid (V), which might give II by the Schöpf's mechanism. On the other hand, the difference of the mode of dehydration would change the reaction course and VI thus formed, might be oxidised to give VII. Then VII might give III through VIII and IX by

11) R. Sudo, A. Kaneda and N. Itoh, *J. Org. Chem.*, **32**, 1844 (1967). The authentic sample of α-acetyl-γ-methyltetronic acid was not available.
12) P.M. Boll, E. Sorensen and E. Balieu, *Acta. Chem. Scand.*, **22**, 3251 (1968).
13) R.N. Lacey, *J. Chem. Soc.*, **1954**, 832.
14) F. Merenyl and M. Nilsson, *Acta. Chem. Scand.*, **18**, 1208 (1964).

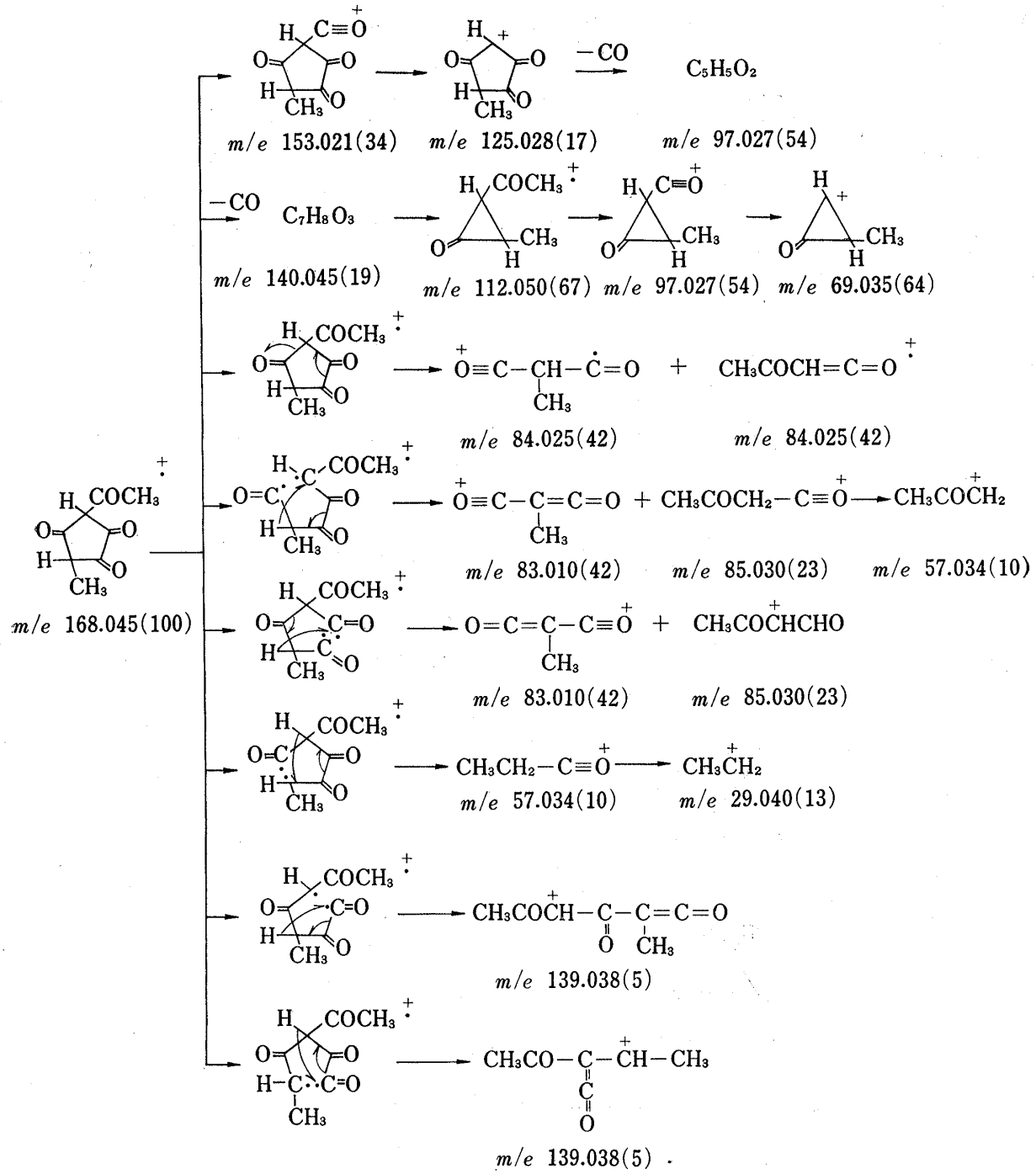

Chart 2. The Fragmentation of III

The figures in roued brackets are the relative intensities of the fragment ions.

the benzil-benzilic acid type of rearrangement. III might be further oxidised, hydrolysed and again oxidised to give IV. In this reaction mechanism, dihydrousnonic acid, the intermediate, was assumed to be formulated as V. But dihydrousnonic acid has not been reported and was not isolated in this study. So the structure of usnonic acid, forwarded by Schöpf and Ross[5] was reinvestigated by the spectral data. Usnonic acid exhibits the IR bands at 1550—1530 (triketone), 1690 (C=O) and 1660 which could be assigned to an $\alpha\beta$-$\alpha'\beta'$-unsaturated C=O and 3500 (OH), while usnic acid exhibits the IR bands at 1545—1530 (triketone), 1690 (C=O), 1630 which could be assigned to the chelated aromatic $COCH_3$, but does not the IR bands of OH. These spectral data suggest that usnic- and usnonic-acids are different in regard to the structure of the ring A and that all the OH groups of usnic acid are chelated, but usnonic

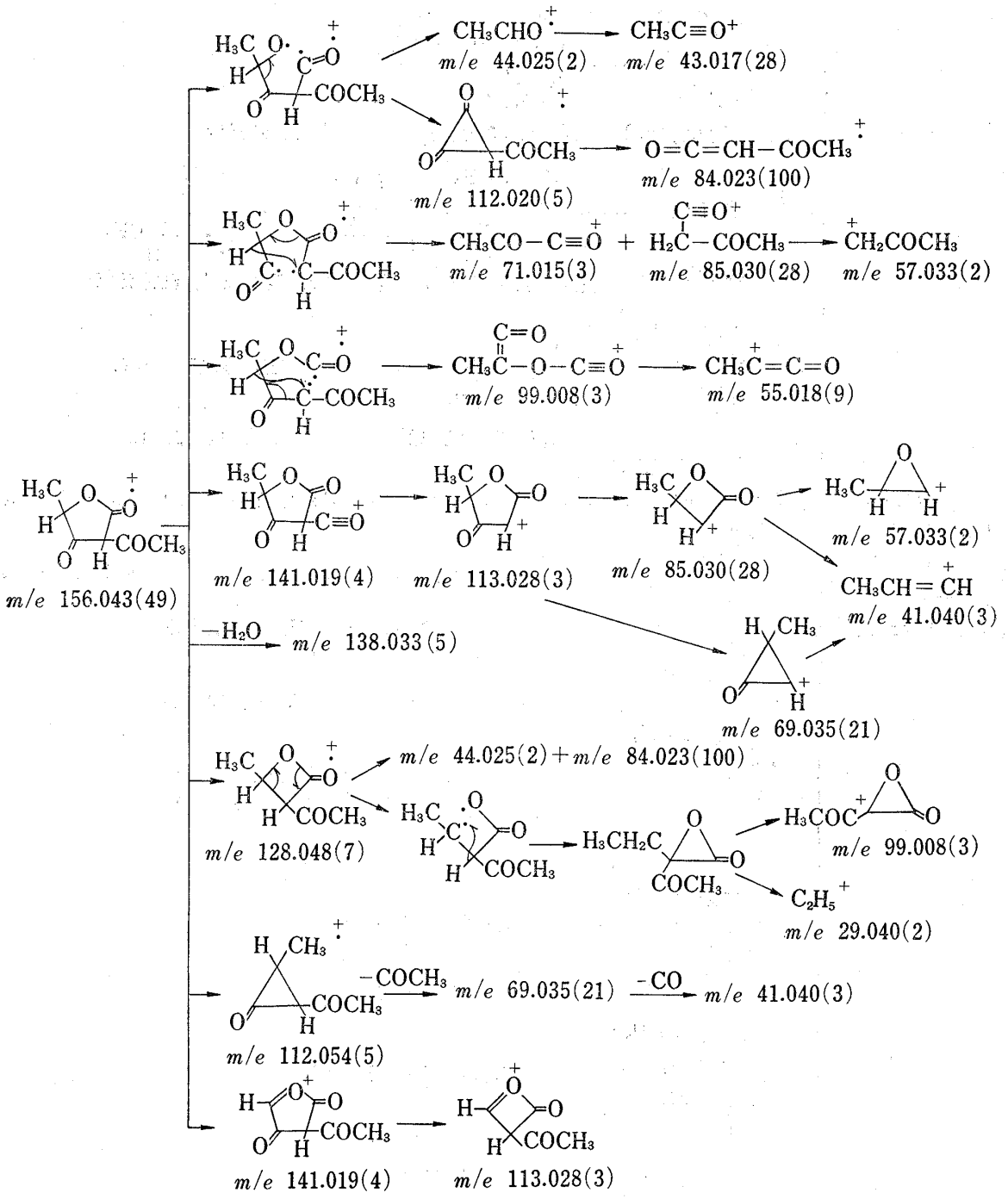

Chart 3. The MS Fragmentation of IV

The figures in brackets are the intensities of the fragment ions.

acid has at least a free OH group. Usnonic acid exhibits the NMR signals of an ang-CH_3, one of $COCH_3$, >CH=C– and chelated enol OH, the chemical shifts of which are similar to those of corresponding groups of the ring B of usnic acid, respectively, suggesting that usnonic acid has the same ring B as usnic acid. Usnonic acid shows also the signal of a non-chelated OH, but does not show, unlike usnic acid, the signal of the aromatic chelated OH group. The absence of the signal[15] at 11.0 on the NMR of usnonic acid denies the presence of the chelation between C_1=O and C_9-OH groups. These spectral evidence indicates that usnonic acid could be formulated as Schöpf's formula[5] and dihydrousnonic acid as V.

15) M. Takani and K. Takahashi, *Chem. Pharm. Bull.* (Tokyo), 19, 2072 (1971).

Table I. NMR of Usnonic- and Usnic-acids (δ-value)

	ang-CH_3	$-CH_3$	$COCH_3$	$COCH_3$	=CH–	OH	Chelated aromatic OH	Chelated enol OH
Usnonic acid	1.70 (s)	1.91 (s)	2.66 (s)	2.63 (s)	5.96 (s)	4.65—4.25	—	16.20 18.20
Usnic acid[15]	1.8 (s)	2.2 (s)	2.70 (s) 6H		6.0 (s)	—	13.3 (C_7) 11.0 (C_9)	18.8

abbreviation: s: singlet; d: doublet; t: triplet; m: multiplet

However, it is reported[16] that humulones are easily rearranged to isohumulones under both natural and laboratory conditions, so another mechanism as shown in Chart 1 might not be excluded. Namely, dihydrousnic acid might give XI through X by the fission of the furan ring, followed by oxidation, which isomerises to XII as in the case of the isomerisation of humulones to isohumulones. Then XII might give III through XIII and XIV by hydrolysis, followed by oxidation. This is the first example of obtaining of oxidation products from the ring A of I. In this oxidation reaction of I, pale yellow needles $C_9H_9O_3Cl$ (XV) of mp 151° and yellow plates $C_{10}H_{12}O_3$ (XVI) of mp 58° were obtained. By chemical and spectral evidences and finally by synthesis, XV was proved to be identical with 2,6-dihydroxy-3-methyl-5-chlor-acetophenone and XVI, 2-hydroxy-3-methyl-6-methoxyacetophenone. XV and XVI might be produced as secondary products from II during the process of the purification of the oxidation products of I.

Experimental

The IR were taken with a Nippon Bunko IR-G spectrometer, the UV with a Hitachi Recording spectrometer 323, the NMR with a JEOL PS-100 NMR instrument at 100 Mc in $CDCl_3$ with $(CH_3)_4$ Si as internal reference and the MS with a JMS-01SG mass spectrometer, the ionizing current kept at 200 μA (III), 200 μA (IV), while the ionisation energy being maintained at 75 eV (III), 75 eV (IV) and source temperature at 150° (III) and 30° (IV).

Oxidation of I——A solution of 4.8 g of I in 60 ml of 10% KOH was diluted to 1.5 liter with water. To this solution, 150 ml of 4% $KMnO_4$ was added in drops during 3 hr under vigorous stirring at room temperature. The filtered solution was acidified with dil. HCl and then filtered. The solution was salted out with NaCl and extracted with $CHCl_3$ several times. The $CHCl_3$ solution was evaporated to give brown oil (2 g), which was treated with CH_3OH. The oil was chromatographed over 300 g of silicic acid with $CHCl_3$-ethylacetate (3: 1).

2,6-Dihydroxy-3-methylacetophenone (II)——The fractions (17 g each) from No. 9 to 14 gave yellow plates (II) of mp 138° from benzene. (125 mg). *Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found. C, 65.41; H, 6.02.

3-Acetyl-5-methylcyclopentane-1,2,4-trione (III)——The fractions from No. 27 to 29 gave 74 mg of substance, which was sublimated at 80° under 2 mmHg pressure to give yellow needles (III) of mp 218° (decomp.) from benzene. (12.5 mg). It sublimates at 170°. $FeCl_3$ reaction: violet.[17] UV λ_{max} (nm, ε): 253.5 (26300), 274 (18000) in HCl-acidic EtOH; 273.5 (30000), 298.5 (26000) in NaOH-alkaline EtOH. IR ν_{max}^{Nujol} (cm^{-1}): 3150, 1725, 1665, 1615, 1460, 1375, 1325, 1235, 1175, 1120, 1025, 990, 875, 820, 795, 760, 725. *Anal.* Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80. Found. C, 57.10; H, 4.96.

Isosbestic Point and pK_a Value of III——A stock solution of containing 1 mg of III in 10 ml of EtOH was prepared. Various solution having different pH (0.34—4.82) were prepared as follow: One normal solution of HCl was diluted suitably to make a solution having desired pH. The stock solution (0.4 ml) was exactly added to 5.6 ml of the solution, prepared as mentioned above and then the absorption curve at various pH were measured. There thus exists the isosbestic point at 295 nm (ε=5500). The pK_a value was 2.60 from the spectra at 320 nm or 253 nm.

α-Acetyl-γ-methyltetronic Acid (IV)——The fractions from No. 17 to 26 gave 186 mg of substance, which was chromatographed over 40 g of silicic acid with *n*-hexane–ethylacetate (2: 1). The fractions (4 g each)

16) J.S. Burton, R. Stevens and J.A. Elvidge, *J. Inst. Brewing*, **70**, 345 (1964).
17) Howard, *et al.*[8] reported "green" and Leucht, *et al.*[7] "blue."

from No. 7 to 10 gave substance, which was sublimated at 50° under 2 mmHg pressure to give colorless needles (IV) of mp 55—55.5°. (42 mg). UV[11] λ_{max}^{EtOH} (nm, log ε): 231 (3.96), 265 (4.07). IR ν_{max}^{KBr} (cm^{-1})[13]: 3410 (OH), 2960, 2920, 1755 (lactone), 1660 (C=O), 1625 (chelated $COCH_3$), 1390, 1370, 1345, 1315, 1235, 1175, 1115, 1080, 1060, 1020, 995, 875, 795. NMR[12] ($CDCl_3$) (δ, ppm): 1.52 (d, J=7 Hz) and 1.54 (d, J=7 Hz) (3H, $-CH\underline{CH_3}$), 2.58 (s, 3H, $COCH_3$), 4.71 (q, J=7 Hz) and 4.82 (q, J=7 Hz) (1H, $-\underline{CH}CH_3$), 12.61 (s, 1H, chelated enol OH). *Anal.* Calcd. for $C_7H_8O_4$: C, 53.84; H, 5.16. Found. C, 53.81; H, 5.14.

2,6-Dihydroxy-3-methyl-5-chloracetophenone (XV)——The fractions from No. 1 to 8 from five runs were distilled under reduced pressure and the distilate was treated with ether and then benzene. The soluble part (3.4 g) was chromatographed over 300 g of silicic acid with $CHCl_3$–C_6H_6 (10: 1). The fractions of Rf=0.7 gave 180 mg of substance, which was treated with *n*-hexane and separated into *n*-hexane unsoluble part A and soluble part B at room temperature. The part A was sublimated under 2 mmHg at 85° to give pale yellow needles of mp 151° from *n*-hexane. (23 mg). $FeCl_3$ reaction: blue. The Beilstein reaction: green. Chlorine reaction: positive (Na-fusion and $AgNO_3$). The Gibb's reaction: negative. IR ν_{max}^{KBr} (cm^{-1}): 3380 (OH), 1620 (C=O), 710 (C–Cl). NMR (CCl_4) (δ, ppm): 2.17 (d, 3H, $-CH_3$), 2.75 (s, 3H, $COCH_3$), 6.15 (s, 1H, OH), 7.21 (m, 1H, aromatic proton), 13.20 (s, 1H, chelated OH). Mass Spectrum: $(M^+ + 2)/M^+ = 0.32$ (indicative of a chlorine atom). *Anal.* Calcd. for $C_9H_9O_3Cl$: C, 53.9; H, 4.52. Found. C, 53.75; H, 4.48.

Chlorination of II——II (150 mg) was added to chlorine-saturated acetic acid at room temperature and the mixture was poured into water and filtered. The product (120 mg) was chromatographed over silica gel (20 g) with *n*-hexane–ethylacetate (10: 1). The fraction of Rf 0.38 gave 2,6-dihydroxy-3-methyl-4-chloracetophenone of mp 152° from benzene, which was proved to be identical with XV by the mixed fusion, IR and thin-layer chromatography. *Anal.* Found: C, 54.07; H, 4.55.

2-Hydroxy-3-methyl-6-methoxyacetophenone (XVI)——The *n*-hexane soluble part B, mentioned above, gave 76 mg of substance, which was chromatographed over 40 g of silica gel with *n*-hexane–ethylacetate (20: 1). The fraction of Rf 0.65 (40 mg) was sublimated under 2 mmHg at 55° to give yellow crystals of mp 58° (XVI). 17 mg. $FeCl_3$ reaction: blue. The Gibb's reaction: pale blue. (II showed red-violet coloration). IR ν_{max}^{KBr} (cm^{-1}): 3400 (OH), 1610 ($COCH_3$). NMR ($CDCl_3$) (δ, ppm): 2.16 (d, 3H, $-CH_3$), 2.66 (s, 3H, $COCH_3$), 3.81 (s, 3H, OCH_3), 6.24, 6.32 and 7.16, 7.24 (d-d, 2H, aromatic protons), 13.52 (chelated OH). *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found. C, 66.51; H, 6.58.

Methylation of II——II (500 mg) in ether was methylated with diazomethane for 48 hr at room temperature and the solution was treated as usual. The product was chromatographed over silica gel (100 g) with *n*-hexane–ethylacetate (50: 1). The fraction of Rf 0.57 was sublimated under 2 mmHg at 55° to give yellow plates of mp 57.5° (86 mg), which was proved to be identical with XVI by the mixed fusion and IR. *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found. C, 66.42; H, 6.55.

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