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Usnic Acid. VI.[1] The Ozonolysis of Anhydromethyldihydrousnic Acid Monoacetate

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1) Two new ozonolysis products of anhydromethyldihydrousnic acid monoacetate were proved to have structures Va and VI.

2) The mechanism of the formation of the three ozonolysis products, II, Va and VI from anhydromethyldihydrousnic acid monoacetate was discussed.

It was reported in a previous paper[3] that anhydromethyldihydrousinc acid monoacetate, one of the products which were obtained from methyldihydrousnic acid by treatment with acetic anhydride and conc. H_2SO_4, was formulated as I and that it gave, on ozonolysis, colorless crystals, $C_{18}H_{18}O_7$ (II), mp 193—195° (decomp.) as the main product.

The present paper will deal with the constitutions of the two of other ozonolysis products of anhydromethyldihydrousnic acid monoacetate (I) and the reaction mechanism of the ozonolysis.

The ozonolysis reaction products, after removal of II, was concentrated *in vacuo* and treated with 8% sodium hydrogen carbonate solution and then the mixture was extracted with $CHCl_3$. The sodium hydrogen carbonate solution gave, on acidification with dil. HCl, $C_{16}H_{16}O_6$ (III), mp 235—237°. The $CHCl_3$ solution was treated with 8% sodium hydroxide solution. By bubbling of CO_2 gas into the aqueous layer a crystalline substance precipitated out. It was separated into two portions, $C_{12}H_{14}O_5$ (IVa), mp 89—90° and $C_{18}H_{18}O_6$ (Va), mp 191—192°, by the chromatography as mentioned in the experimental part. The sodium carbonate solution, obtained by bubbling of CO_2 gas into the sodium hydroxide solution above mentioned, gave on acidification with dil. HCl, a resinous substance, which gave, on vacuum distillation, $C_{16}H_{14}O_6$ (VI), mp 211—212°. Of these products, II,[3] III[3] and IVa[4] are proved to be formulated as shown Chart 1, by the mixed melting point determination and the infrared (IR) spectra.

VI is not soluble in $NaHCO_3$ solution and gives red-violet coloration with $FeCl_3$ solution and was hydrolyzed to $C_{16}H_{16}O_7$ (VII), mp 211—212° (a change of the crystal form was observed at about 180—190° by the micromelting point determination) by 10% alc. KOH and converted to VI by treatment with conc. H_2SO_4 or vacuum distillation. The conversion suggests that a β-ketocarboxylic acid type group is not present in the molecule of VII. The ozonolysis of VII, followed by treatment with MeOH and H_2O, gave $C_{11}H_{12}O_5$ (IVb), mp 98—99°, which was proved to be identical with methyl 2,4-dihydroxy-3-acetyl-6-methylbenzoate[3] by the mixed melting point determination and the IR spectra. These data indicate the presence of 4-methyl-2,6-dihydroxyacetophenone nucleus and a lactone group in VI. VI has the IR bands at 1740 (α,β-unsatd. δ-lactone); 1695 (α,β-unsatd. C=O); 1635 (chelated C=O); 1590, 1565 (sh.), 1510 (C=C of phenyl and furan); 1395, 1375 (gem-dimethyl); 1245, 1078 (C-O-C) cm^{-1}. VII has IR bands at 3260 (chelated OH); 2700, 2630, 2560 (OH of COOH); 1705 (COOH); 1685 (α,β-unsatd. C=O); 1635 (chelated C=O); 1575, 1550 (sh.), 1510 (C=C of

1) Part V: *Chem. Pharm. Bull.* (Tokyo), **11**, 1229 (1963).
2) Location: *Takaramachi, Kanazawa.*
3) K. Takahashi and S. Miyashita, *Chem. Pharm. Bull.* (Tokyo), **11**, 209 (1963).
4) K. Takahashi, S. Miyashita, and Y. Ueda, *Chem. Pharm. Bull.* (Tokyo), **11**, 473 (1963).

phenyl and furan); 1380, 1350 (gem-dimethyl); 1250, 1095 (C–O–C) cm^{-1}. The fact that the band at 1740 cm^{-1} in VI is not observed in the spectrum of VII and that the bands at 3260, 2700—2560 and 1705 cm^{-1} are observed in that of VII indicates the presence of a lactone group in the molecule of VI. The position of the lactone group in VI was determined by the studies of the ultraviolet (UV) and the nuclear magnetic resonance (NMR) spectra as follows.

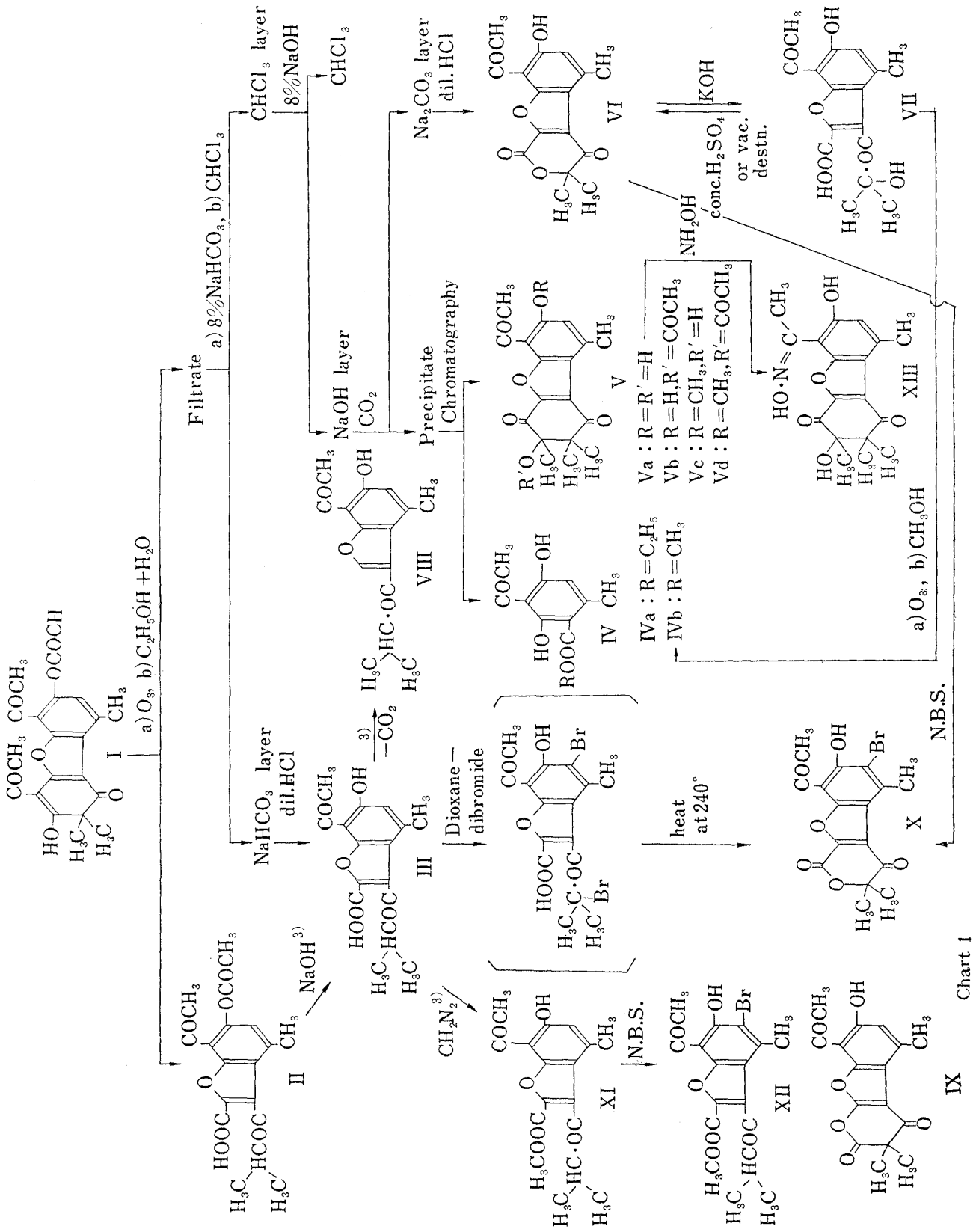


Chart 1

The substitution of α-hydrogen of the benzofuran nucleus by a carbonyl group causes the shift of the absorption maxima bathochromically, as observed in the spectra of benzofuran and α-acetylbenzofuran.[5]

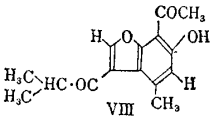
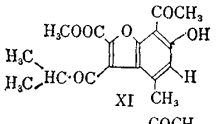
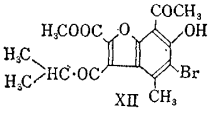
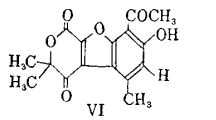
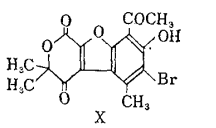
VIII,[3] not having a conjugated carbonyl radical at α-position of benzofuran nucleus, has the UV maxima at 229.5 mμ (log ε, 4.50), 282 mμ (log ε, 4.26) and 340 mμ (log ε, 3.82). VI has the UV maxima at 238.5 mμ (log ε, 4.53), 289 mμ (log ε, 4.01) and 347 mμ (log ε, 4.03) and the shape of the UV absorption spectrum is closely similar to that of VIII, but the bathochromic shift of the maxima by 7—9 mμ is observed, suggesting the presence of a benzofuran nucleus with a conjugated carbonyl function at α-position.

The NMR data, 8.26 τ(s, 6H, gem-dimethyl), 7.18 τ (s, 3H, arom.-methyl), 7.06 τ (s, 3H, Ar-$COCH_3$), 3.10 τ (s, 1H, arom.-H) and —3.33 τ (s, 1H, chelated OH), correspond to the proposed structure VI and might exclude the possibility of a formula IX as follows.

The position of the methyl signal in the NMR spectrum is changed sensitively by the effects of substituents attached to the same carbon as a methyl group generally to a lower magnetic filed. In general, -O-CO-R substitution causes the diamagnetic shift of the methyl signal by about 0.37 ppm and -CO-O-R substitution by about 0.25 ppm.[6] VIII exhibits the gem-dimethyl signal at 8.73 τ (center) (Table I). By the above mentioned data, VI might be calculated to exhibit the gem-dimethyl signal at 8.36 τ (8.73—0.37) and IX at 8.48 τ (8.73—0.25). The fact that the τ-value of the gem-dimethyl signal of VI is 8.26 τ might indicate that the substitution of the type of -O-CO-R takes place at the C-atom bearing a gem-dimethyl and so VI could be formulated as shown in Chart 1.

The structure of VI was finally confirmed by the synthesis of the bromo-derivative. III was brominated with dioxane-dibromide reagent to give a powderly substance. It

Table I. Chemical Shifts (τ-unit)

	CH_3>CH-	CH_3>C<	Ph-CH_3	Ph-$COCH_3$	>CH-	-$COOCH_3$	Ph-H	>=<H O-	-OH
 VIII	8.73 (d) J=7.2 cps	—	7.35 (s)	7.16 (s)	6.80 (m)	—	3.23 (s)	1.83 (s)	−2.93 (s)
 XI	8.73 (d) J=7.2 cps	—	7.65 (s)	7.08 (s)	6.71 (m)	6.04 (s)	3.26 (s)	—	−3.24 (s)
 XII	8.73 (d) J=7.2 cps	—	7.51 (s)	7.03 (s)	6.75 (m)	6.03 (s)	—	—	−4.24 (s)
 VI	—	8.26 (s)	7.18 (s)	7.06 (s)	—	—	3.10 (s)	—	−3.33 (s)
 X	—	8.24 (s)	7.01 (s)	6.98 (s)	—	—	—	—	−4.30 (s)

The NMR spectra were measured by JNM-C-6OH high resolution NMR instrument in $CDCl_3$ at 60 Mc, tetramethylsilane as internal reference.

5) Pauline Ramart-Lucas and Modeste Martynoff, *Compt. Rend.*, **232**, 517 (1951).
6) L.M. Jackmann, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," p. 53 (1959).

was heated at 200°, and liberating HBr gas, gave crystals $C_{16}H_{13}O_6Br$, mp 244—245°, after purification by the thin-layer chromatography. It was proved to be identical with $C_{16}H_{13}O_6Br$ (X, bromo-derivative of VI), mp 244—245°, by the mixed melting point determination and the comparison of their IR and UV sepctra. X was obtained by the bromination of VI with N-bromosuccinimide. The NMR data were summarized as follows (Table I).

The lactonisation which is observed in the change from XI to VI causes the deshielding effects on a gem-dimethyl, Ph-CH_3, Ph-$COCH_3$ and Ph-OH by 0.47 ppm, 0.47 ppm, 0.02 ppm and 0.09 ppm, respectively and the bromination of the phenyl proton which is observed in the change from XI to XII also causes the deshielding effects on a gem-dimethyl Ph-CH_3, Ph-$COCH_3$ and Ph-OH by 0 ppm, 0.15 ppm, 0.05 ppm and 1.00 ppm, respectively. So it might be expected that X exhibits the signals of the gem-dimethyl, Ph-CH_3, Ph-$COCH_3$ and Ph-OH at 8.26 τ (8.73—0.47—0), 7.03 τ (7.65—0.47—0.15), 7.10 τ (7.08—0.02—0.05) and —4.33 τ (—3.24—1.00—0.09), repsectively, by the deshielding effects of both the lactonisation and the bromination in the change from XI to X. In fact, the signals of the gem-dimethyl, Ph-CH_3, Ph-$COCH_3$ and Ph-OH of X are observed at 8.24 τ (Δ −0.02 ppm), 7.01 τ (Δ −0.02 ppm), 6.98 τ (Δ −0.03 ppm) and −4.30 τ (Δ +0.03 ppm), respectively. These NMR spectral data also support the proposed structure of VI.

Va, $C_{18}H_{18}O_6$, mp 191—192°, gave monoacetate $C_{20}H_{20}O_7$ (Vb), mp 196°, methylether $C_{19}H_{20}O_6$ (Vc), mp 225—227°, methylether-acetate $C_{21}H_{22}O_7$ (Vd), mp 109—111° and monixme $C_{18}H_{19}O_6N$ (XIII), mp 235—236° (decomp.).

Va has the IR bands at 3440 (non-chelated OH); 1705 and 1696 (α,β-unsatd. C-O); 1643 (chelated C=O); 1600, 1565 and 1507 (C=C of phenyl and furan); 1377 and 1350 (gem-dimethyl); 1250 and 1086 (C-O-C) cm^{-1}, and the UV spectrum (240.5 mμ (log ε, 4.45), 292.5 mμ (log ε, 4.03) and 354 mμ (log ε, 4.17)) is closely similar to that of VI. Va has the NMR signals at 8.73 τ (s, 3H), 8.62 τ (s, 3H), 8.58 τ (s, 3H), (a gem-dimethyl and a C-CH_3), (the two methyl radicals of a gem-dimethyl might be considered to be non-equivalent and have two different chemical shifts); 7.21 τ (s, 3H, arom.-CH_3); 7.06 τ (s, 3H, Ph-$COCH_3$); 6.23 τ (s, broad, 1H, OH); 3.13 τ (s, 1H, arom.-H); −3.37 τ (s, 1H, chelated OH). The signal of a multiplet at 6.71 τ (center) due to >CH- of the isopropyl radical which is observable in the spectrum of XI[3] is not observed. The signals at 6.23 τ (OH) and −3.37 τ (chelated OH) are not observed in the $CDCl_3$, and D_2SO_4 solution.

The acetate (Vb) gives green-brown colorlation with $FeCl_3$ and has the IR absorption bands at 1750 and 1730 (O-$COCH_3$), 1695 (α,β-unsatd. C=O) and 1640 (chalted C=O) cm^{-1}. These data indicate that an alcoholic OH radical was acetylated. The methylether (Vc) gives no coloration with $FeCl_3$ and has the IR bands at 1695 (α,β-unsatd. C=O) and 1685 ($COCH_3$) cm^{-1} and do not have a band at 1640 (chelated C=O) cm^{-1}. These data indicate that a phenolic OH radical was methylated. The methylether-acetate (Vd) was formed by acetylation of Vc. It gives no coloration with $FeCl_3$ and has the IR bands at 1740 (O=$COCH_3$), 1705, 1690 and 1670 (α,β-unsatd. C=O and arom.-$COCH_3$) cm^{-1}, and no bands at 3440 (non-chelated OH) and 1640 (chelated C=O) cm^{-1}. These data indicate that a phenolic OH radical was methylated an an alcoholic OH radical was acetylated. The monoxime (XIII) gives violet-brown coloration with $FeCl_3$ and has the IR bands at 1704 (sh.), 1692 and 1678 (α,β-unsatd. C=O and nonchelated $COCH_3$) cm^{-1}, and not a band at 1640 (chlated C=O) cm^{-1}. These data indicate that $COCH_3$ of benzene ring was oximated. The fact that the dehydrations of Va with conc. H_2SO_4, by the vacuum distillation, by the $POCl_3$ and pyridine method and by the P_2O_5 and toluene method were unsuccessful suggests that the alkoholic OH radical might be present as an α-ketol system which is resistant to dehydration. So, Va could be formulated as shown in Chart 1.

It has been confirmed that the ozonolysis of anhydromethyldihydrousnic acid monoacetate (I) affords three oxidation products II, Va and VI.

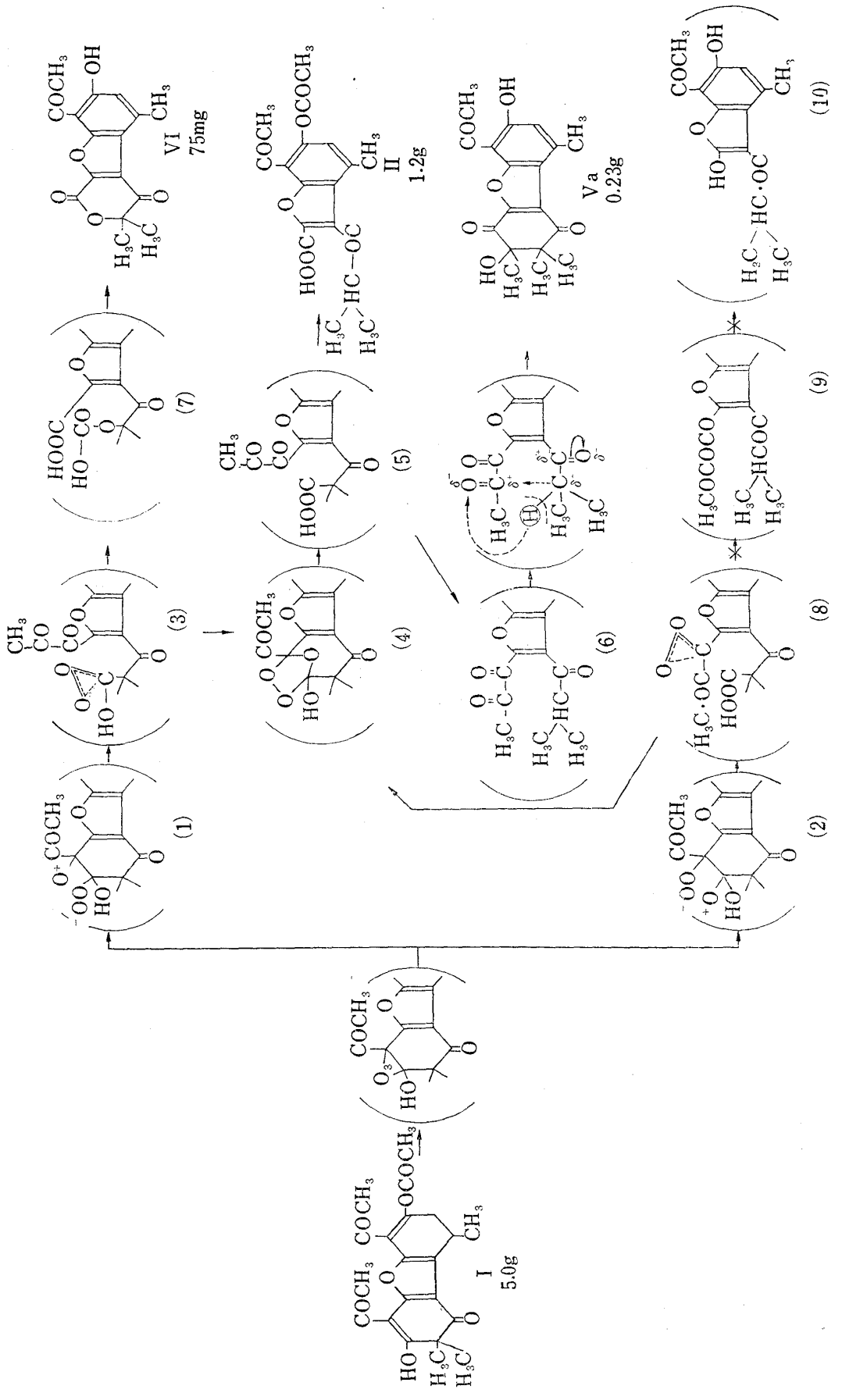
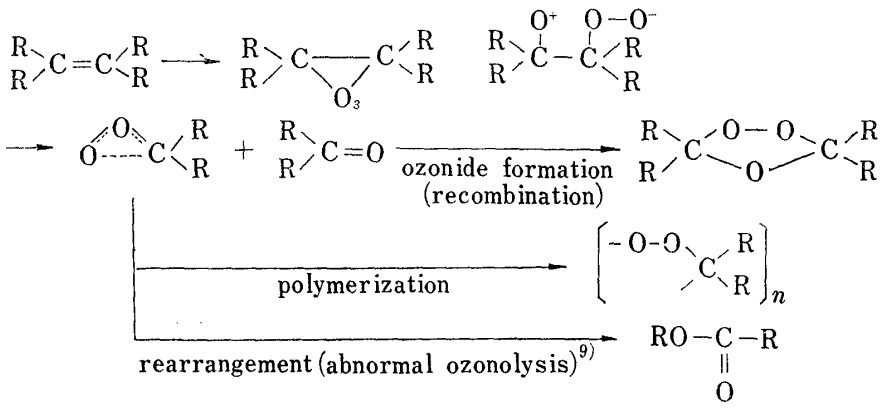


Chart 2

The mechanism of ozonolysis of the carbon–carbon double bond is usually interpreted as involving formation of an unstable primary ozonide followed by its decomposition into ampho-ion and carbonyl fragments. Recombination of these fragments is then considered to lead to the normal ozonide. Many of the abnormal ozonolysis involving rearrangement have been reported.[7]

In view of the following scheme by Criegee,[7] which has been accepted as one of the most probable mechanism for ozonolysis reaction, although R.W. Murray, *et al.*[8] have recently



reported that the Criegee ampho-ion cannot constitute the sole pathway to ozonide formation upon ozonolysis of the carbon–carbon double bond, a possible explanation might be advanced for the result of our present study as follows (Chart 2).

Firstly, the primary ozonide formation would lead to the ampho-ions, (1) or (2). (1) would lead to the diketo ampho-ion (3), which, through the formation of the five-memebred ring intermediate ozonide (4), would be hydrolyzed to the diketo acid (5). The decarboxylation of the β-ketocarboxylic acid group and the oxidation of the diketo group to a carboxylic acid function would then yield II as the stable and major product. Non-occurrence of the oxidation of the diketo group in the last step, on the other hand, would change the reaction course and the isomerization of the thus formed decarboxylated intermediate (6) by intramolecular rearrangement would lead to the cyclic and minor product Va.

With respect to the formation of the lactonic minor product VI, the intermediate (3), which would result from (1), followed by the anionic transformation to (7) by abnormal ozonolysis might be involved in the reaction processes.

We cannot exclude the ampho-ion (2) as a key intermediate in the reaction course as shown in Chart 2. However, even if the proposal of the formation of (2) as an intermediate be accepted, the anionic transformation (8)→(9) seems not to have occurred in this case, for the hydroxyisobutyryl compound (10) could not be found in the reaction product.

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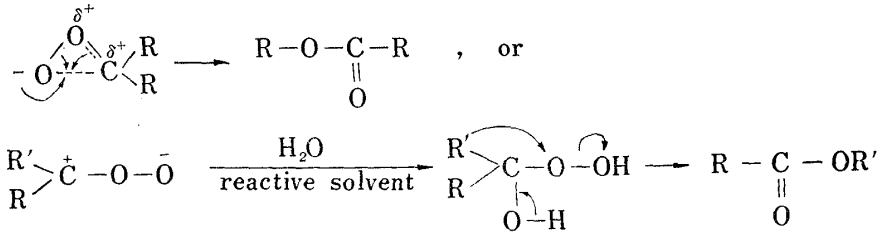
7) For a thorough discussion of the mechanism of ozonolysis, including the Criegee formulation; P.S. Baily, *Chem. Rev.*, **58**, 925 (1958).

8) R.W. Murray, R.D. Youssefyeh and P.R. Story, *J. Am. Chem. Soc.*, **88**, 3143, 3145 (1966).

9) Some anionic transformations as modes of rearangements of the ampho-ion might be shown as follows;



Experimental[10]

Ozonolysis of I. Formation of II, III, IVa, Va and VI——Five grams of I was dissolved in $CHCl_3$ (50 ml) and the ozonized O_2 was passed through for 5 hr under ice cooling and then EtOH (18 ml) and H_2O (2 ml) were added to the $CHCl_3$ solution. The mixture was warmed on a steam bath for 30 min. The greater part of the solvent was distilled off to give $C_{18}H_{18}O_7$ (II), mp 193—195° (from EtOH), as reported previously.[3] Yield 1.2 g. The solution, from which II was filtered off, was concentrated *in vacuo* to give a resinous substance, which was treated with 8% $NaHCO_3$ solution (50 ml) and allowed to stand overnight. The $NaHCO_3$ solution was then shaken with $CHCl_3$ (30 ml) twice to extract $NaHCO_3$-insoluble part. The $NaHCO_3$ solution gave, on acidification with dil. HCl, $C_{16}H_{16}O_6$ (III), mp 235—237°. Yield 0.55 g. III was proved to be identical with an authentic sample[3] by the mixed melting point determination and the IR spectra.

The $CHCl_3$ solution was extracted with 8% NaOH solution (30 ml) twice and the bubbling of CO_2 gas into the alkaline solution gave crystalline precipitate, which was chromatographed on silica gel column with benzene as solvent. The benzene eluate was evaporated to give $C_{12}H_{14}O_5$ (IVa), mp 89—90°. Yield 60 mg. $FeCl_3$ reaction: red-violet. IVa was proved to be identical with ethyl 2,4-dihydroxy-3-acetyl-6-methylbenzoate[4] by the mixed melting point determination and IR spectra.

The silica gel was then extracted with ether and the ether solution was evaporated to give colorless crystals, $C_{18}H_{18}O_6$ (Va), mp 191—192° (from EtOH). Yield 0.23 g. $FeCl_3$ reaction: red-brown. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.39, 65.50; H, 5.60, 5.87. M.W. Calcd: 330. Found: 341 (camphor). UV λ_{max} mμ (log ε): 240.5 (4.45), 292.5 (4.03), 354 (4.17). IR ν_{max} cm^{-1}: 3440 (m, OH); 1705 (s), 1696 (s) (α,β-unsatd. C=O); 1643 (s, chelated C=O); 1600 (w), 1565 (s), 1507 (w) (C=C of phenyl and furan); 1448 (m); 1406 (w); 1384 (m); 1377 (m), 1350 (w) (gem-dimethyl); 1312 (s); 1250 (s, C-O-C); 1217 (m); 1182 (w); 1162 (w); 1130 (m); 1086 (s, C-O-C); 1028 (s); 1002 (m); 962 (w); 932 (s); 887 (w); 865 (m, broad); 764 (w); 728 (w); 687 (w).

The sodium carbonate solution, obtained from 8% sodium hydroxide solution by the bubbling of CO_2 gas as mentioned above, was acidified with dil. HCl and extracted with $CHCl_3$ to give a resinous substance, which was distilled *in vacuo* at 190—240° (1 mmHg) to give colorless needles, $C_{16}H_{14}O_6$ (VI), mp 211—212° (from EtOH). Yield 75 mg. $FeCl_3$ reaction: red-violet. *Anal.* Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.76, 63.70; H, 4.63, 4.60. M.W. Calcd: 302. Found: 304 (camphor). UV λ_{max} mμ (log ε): 238.5 (4.53), 289 (4.01), 347 (4.03). IR ν_{max} cm^{-1}: 1740 (s, α,β-unsatd. δ-lactone); 1695 (s, α,β-unsatd. C=O); 1635 (s, chelated C=O); 1590 (s), 1565 (sh.), 1510 (m) (C=C of phenyl and furan); 1470 (w); 1450 (m); 1410 (w); 1395 (m), 1375 (m) (gem-dimethyl); 1320 (s); 1275 (m); 1245 (s, C-O-C); 1198 (w); 1182 (s); 1142 (s); 1132 (s); 1078 (w, C-O-C); 1030 (w); 1015 (w); 1001 (m); 961 (w); 932 (w); 882 (w); 871 (w); 845 (s); 775 (w); 760 (w); 743 (w); 702 (w).

Hydrolysis of VI to VII——VI (1.8 g) in 10% alc. KOH was refluxed on a steam bath for 2 hr and the solvent was evaporated *in vacuo* and water was added to the residue and filtered. The aqueous solution was acidified with dil. HCl under cooling to give colorless needles, $C_{16}H_{16}O_7$ (VII), mp 211—212° (from dil. EtOH). The crystal form changed at 180—190° to a larger needle and melted at 211—212° under the micromelting point determination, probably due to lactonisation. $FeCl_3$ reaction: dark-violet. This is soluble in 5% $NaHCO_3$ solution under bubbling. *Anal.* Calcd. for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 60.24; H, 4.86. UV λ_{max} mμ (log ε): 239 (4.22), 285 (4.32), 342 (3.92). IR ν_{max} cm^{-1}: 3260 (w, chelated OH); 2700 (w), 2630 (w), 2560 (w) (OH of COOH); 1705 (s, COOH); 1685 (s, α,β-unsatd. C=O); 1635 (s, chelated C=O); 1575 (s), 1550 (sh.), 1510 (w) (C=C of phenyl and furan); 1470 (s); 1380 (s), 1350 (w) (gem-dimethyl); 1320 (w); 1304 (w); 1250 (s, C-O-C); 1152 (s); 1140 (w); 1095 (w, C-O-C); 1030 (w); 988 (m); 964 (w); 950 (m); 875 (w); 846 (w); 820 (w); 786 (w); 755 (w).

Formation of VI from VII——To 2 ml of conc. H_2SO_4, 50 mg of VII was added at room temp. and the mixture was allowed to stand for 1 hr and then poured into ice water to give VI, mp 211—212°. *Anal.* Found: C, 64.07; H, 4.78. By vaccum distillation at 200—240° (bath temp.) under 1 mmHg, VII was converted to VI. *Anal.* Found: C, 63.57; H, 4.78.

Ozonolysis of VII——VII (0.85 g) was dissolved in ethylacetate (200 ml) and the ozonized O_2 was passed through it under acetone-dryice cooling at −15° for 9 hr and then MeOH (10 ml) was added and the solution was boiled gently on a water bath for 30 min and was distilled off *in vacuo* to give a resinous substance which was dissolved in a small amount of benzene. The benzene solution, after drying with Na_2SO_4, was chromatographed on silica gel with benzene. The eluate was distilled to give a crystalline substance which was sublimated *in vacuo* to give colorless needles, $C_{11}H_{12}O_5$ (IVb), mp 98—99°. $FeCl_3$ reaction: red-violet. It was proved to be identical with methyl 2,4-dihydroxy-3-acetyl-6-methylbenzoate[3] by the mixed melting

10) The IR spectra were taken in KBr pellet by Nippon Bunko IRS infracode, the UV spectra were measured in EtOH by Hitachi EPS-2U recording spectrophotometer, the NMR spectra were taken by JNM-C-60-H high resolution NMR instrument in $CDCl_3$ at 60 Mc, $(CH_3)_4Si$ as internal reference. Some of weak bands of IR spectra were omitted in description.

point determination and the UV and the IR spectra. *Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 59.11; H, 5.63.

Bromination of XI[3] (Methylester of III) with N-Bromosuccinimide——To a suspension of N-bromosuccinimide (140 mg) in CCl_4 (2 ml) was added XI (250 mg) in CCl_4 (1 ml) and the mixture was gently boiled on a steam bath for 1 hr. After cooling and filtering of the succinimide, the filtrate was distilled *in vacuo* to give a crystalline substance, which was treated with a small amount of hot water to remove succinimide and was recrystallized from EtOH to give pale yellow crystals, $C_{17}H_{17}O_6Br$ (XII), mp 140—142°. Yield 190 mg. $FeCl_3$ reaction: red-violet. *Anal.* Calcd. for $C_{17}H_{17}O_6Br$: C, 51.39; H, 4.53. Found: C, 51.31; H, 4.45. UV λ_{max} mμ (log ε): 229.5 (4.11), 289.5 (4.33), 350 (3.97). IR ν_{max} cm^{-1}: 1713 (s), 1700 (s), 1635 (s), 1595 (sh.), 1588 (s), 1570 (sh.), 1465 (m), 1448 (m), 1370 (s), 1343 (m), 1308 (s), 1272 (m), 1215 (s), 1195 (m), 1156 (s), 1137 (m), 1106 (m), 1030 (w), 1000 (w), 958 (m), 923 (w), 867 (m), 820 (w), 780 (w), 720 (w), 700 (w). NMR data (Table I) indicate that the phenyl proton was brominated.

Bromination of VI. Formation of X——A suspension of VI (60 mg) and N-bromosuccinimide (40 mg, 1.1 mol) in 10 ml of CCl_4 was warmed on a steam bath for 2 hr and after cooling, removing of the succinimide by filtration, the filtrate was distilled off to give a crystalline substance, which was, after treatment with hot water, recrystallized from EtOH to give bromo-derivative $C_{16}H_{13}O_6Br$ (X), mp 244—245°. Yield 35 mg. $FeCl_3$ reaction: red-brown. *Anal.* Calcd. for $C_{16}H_{13}O_6Br$: C, 50.40; H, 3.41. Found: C, 50.68; H, 3.73. UV λ_{max} mμ (log ε): 237 (4.47), 297 (4.08), 355 (4.09). IR ν_{max} cm^{-1}: 1740 (s, α,β-unsatd. δ-lactone); 1698 (s, α,β-unsatd. C=O); 1640 (s, chelated C=O); 1590 (s), 1565 (sh.) (C=C of phenyl and furan); 1478 (m); 1385 (m), 1370 (m) (gem-dimethyl); 1310 (m); 1265 (w), 1233 (s, C-O-C); 1192 (sh.); 1184 (s); 1132 (s); 1092 (w); 1064 (w, C-O-C); 1030 (w); 1002 (w); 978 (w); 965 (w); 928 (m); 878 (m); 790 (w); 775 (w); 742 (w).

Synthesis of X from 3-Isobutyryl-4-methyl-6-hydroxy-7-acetyl-coumarone-2-carboxylic Acid (III)——A suspension of 1.4 g of III and 3.7 g of dioxane-dibromide in 10 ml of dioxane was stirred vigorously at room temp. for 3 hr. The suspension became almost colorless at the end of the reaction, which was then evaporated to give a pale yellow crystalline mass. As it was difficult to purify this mass, it was treated as follows. The yellow mass, after washing with benzene, was pyrolysed in a reagent tube at 240° for 10 min under liberating of HBr gas. Then, it was chromatographed by the TLC method, using silica gel as adsorbant and benzene:ethyl acetate (9:1) as solvent. A yellow part (*Rf* value *ca.* 0.66) was cut off and extracted with $CHCl_3$. The $CHCl_3$ solution gave, on evaporation, a pale yellow needles, $C_{16}H_{13}O_6Br$ (X), mp 244—245° (from EtOH). $FeCl_3$ reaction: red-brown. *Anal.* Calcd. for $C_{16}H_{13}O_6Br$: C, 50.40; H, 3.41; Br, 20.97. Found: C, 50.55; H, 3.42; Br, 20.81. This was proved to be identical with bromo-derivative of VI by the mixed melting point determination and the UV and the IR spectra.

Acetylation of Va——A mixture of 0.2 g of Va, 2 ml of Ac_2O and one drop of conc. H_2SO_4 was warmed on a steam bath for 10 min. After cooling, the mixture was poured into ice water and allowed to stand in a refrigerator to give a precipitate. It was chromatographed on Al_2O_3 with $CHCl_3$ and the eluate was evaporated to give crystals, $C_{20}H_{20}O_7$ (Vb), mp 196° (from dil. EtOH). $FeCl_3$ reaction: violet-brown. *Anal.* Calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.76; H, 5.39. UV λ_{max} mμ (log ε): 242 (4.38), 292 (3.99), 354 (4.13). IR ν_{max} cm^{-1}: 1750 (s), 1730 (s), 1695 (s), 1640 (s), 1600 (w), 1570 (s), 1550 (sh.), 1507 (w), 1455 (m), 1398 (m), 1378 (s), 1320 (m), 1255 (s), 1242 (s), 1184 (w), 1152 (w), 1136 (w), 1095 (sh.), 1085 (s), 1032 (s), 1013 (w), 1005 (m), 965 (w), 945 (w), 902 (w), 862 (w), 845 (w), 762 (w), 746 (w), 695 (w).

Methylation of Va——To a solution of 0.2 g of Va in EtOH (40 ml) was added 3.03 ml of 0.2 N NaOH and the orange-red solution was evaporated *in vacuo* to dryness to give orange yellow powder. The powder, after drying in a desicator overnight, was suspended in 50 ml of anhyd. acetone and after addition of 0.12 g of dimethylsulfate, was refluxed on a steam bath. After warming for 11 hr, the powder was dissolved and then white powder separated out. It was refluxed for 15 hr altogether. The solution, obtained by filtration of white powder while hot, was concentrated *in vacuo* below 40° to give a crystalline substance, which was washed with water and was separated into 5% NaOH-insoluble and soluble portions and from the NaOH-insoluble portion 0.15 g of crystalline substance was obtained, which was recrystallized from 60% EtOH to give crystals, $C_{19}H_{20}O_6$ (Vc), mp 225—227°. $FeCl_3$ reaction: negative. *Anal.* Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 65.97; H, 5.87. UV λ_{max} mμ (log ε): 239 (4.40), 287.5 (3.76), 345 (4.15). IR ν_{max} cm^{-1}: 1695 (s), 1683 (s), 1612 (s), 1570 (s), 1550 (sh.), 1505 (m), 1465 (m), 1455 (w), 1400 (w), 1383 (m), 1360 (sh.), 1330 (w), 1288 (m), 1264 (m), 1247 (m), 1228 (m), 1184 (w), 1163 (w), 1134 (m), 1110 (s), 1067 (m), 1022 (s), 1008 (m), 986 (w), 970 (w), 946 (w), 898 (w), 852 (w), 765 (w). From the 5% NaOH soluble portion, Va (45 mg) was recovered.

Methylether-acetate of Va——Methylether of Va (0.103 g) and *p*-toluenesulfonic acid monohydrate (0.054 g) in acetic anhydride (2 ml) were stirred at room temp. for 20 hr and then 50 g of ice was added to the orange-yellow solution to give a crystalline mass, which was then filtered and on drying, was chromatographed by the thin-layer chromatography, using silica gel as adsorbant and benzene-ethyl acetate (4:1) as eluant. The portion of *Rf* value of about 0.44 was cut off and extracted with ether. The ether was evaporated to give methylether-acetate, $C_{21}H_{22}O_7$ (Vd), mp 109—111° (from MeOH). *Anal.* Calcd. for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 64.90; H, 5.63. UV λ_{max} mμ (log ε): 241 (4.36), 286.5 (3.77), 345 (4.12). IR ν_{max} cm^{-1}: 1740 (s), 1705 (s), 1690 (s), 1670 (m), 1601 (m), 1565 (s), 1500 (w), 1470 (w), 1450 (w),

1400 (w), 1385 (m), 1290 (m), 1260 (sh.), 1240 (s), 1182 (w), 1150 (w), 1125 (w), 1100 (s), 1065 (w), 1035 (m), 985 (w), 970 (w), 945 (w), 920 (w), 846 (w), 840 (w), 765 (w).

Monoxime of Va——A mixture of 200 mg of Va, 170 mg of hydroxylamine hydrochloride and 210 mg of anhyd. CH_3COONa in EtOH (20 ml) was refluxed on a steam bath for 3 hr. The solution was distilled off *in vacuo* to give a pale yellow substance, which gave $C_{18}H_{19}O_6N$, mp 235—236° (decomp.) by recrystallization from dil. EtOH. $FeCl_3$ reaction: green-brown. *Anal.* Calcd. for $C_{18}H_{19}O_6N$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.60; H, 5.72; N, 4.02. UV λ_{max} mμ (log ε): 244.5 (4.50), 296.5 (3.88), 358 (4.00). IR ν_{max} cm^{-1}: 3450 (m), 3340 (m), 1704 (sh.), 1692 (s), 1678 (s), 1668 (s), 1622 (s), 1562 (s), 1540 (sh.), 1513 (w), 1445 (m), 1402 (m), 1378 (s), 1352 (w), 1318 (w), 1278 (w), 1257 (s), 1210 (m), 1130 (m), 1087 (s), 1060 (w), 1032 (s), 1005 (w), 956 (w), 945 (w), 916 (w), 862 (w), 830 (w), 755 (w), 732 (w).

Attempts of Dehydration of Va——1) Two tenth g of Va was heated at 220° for 10 min and distilled at 200—240° under 1 mmHg without dehydration or any chemical change. 2) Two tenth g of Va and conc. H_2SO_4 (3 ml) was allowed to stand at room temp. for 1 hr and poured into ice water to give the starting material. 3) One tenth g of Va and 0.5 g of P_2O_5 in toluene (20 ml) was warmed on a steam bath for 1 hr or refluxed on an oil bath for 3 hr and poured into ice water to give the starting material. 4) A mixture of 140 mg of Va, 2 ml of pyridine and 0.6 ml of $POCl_3$ was allowed to satnd at room temp. for 48 hr. After decomposition of $POCl_3$ with icewater, the reaction mixture was extracted with ether to give the starting material.

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