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38. **Kōtaro Takahashi and Shuichi Miyashita :** Usnic Acid. III.[*1] Anhydromethyldihydrousnic Acid.

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It was shown in the preceding papers that methylation of dihydrousnic1) and usnic acids2) with dimethylsulfate and sodium hydroxide took place at the 3-position of A rings in both molecules to form a gem-dimethyl group and the resulted methyldihydrousnic acid should be formulated as I. Acetylation of I liberated one mole of water to give anhydromethyldihydrousnic acid monoacetate, $C_{21}H_{20}O_7$ (Ⅱa), m.p. 173°. Ⅱa was deacetylated to anhydromethyldihydrousnic acid, $C_{19}H_{18}O_6$ (Ⅱb), m.p. 245~246°, which, on reacetylation, returned to Ⅱa. The present communication deals with the constitution of Ⅱ and the reaction mechanism of the acetylation of I.

Ⅱb has infrared absorption bands at 1670 ($\alpha\beta,\gamma\delta$-unsatd. ring C=O in A ring), 1635 (chelated C=O), 1603, 1585, 1500 (C=C of phenyl and furan), 1395, 1375, and 1195 (gem-dimethyl) cm^{-1}.

The nuclear magnetic resonance spectrum[*3] of Ⅱa (Fig. 1) exhibits several signals, from which the following conclusion can be derived. The signal at 0.43 p.p.m. (aromatic >C-H) is not split, which indicates that there is no proton in its *ortho*-position. The 4.45 and 4.52 p.p.m. signals are assigned to -$COCH_3$, and the 4.62 p.p.m. signal to -$OCOCH_3$, respectively. The 4.96 p.p.m. signal which appears as a singlet is due to an aromatic >C-CH_3, and the 5.79 p.p.m. signal is assigned to a gem-dimethyl as it has an absorption intensity twice as high as the 4.96 p.p.m. signal.

Ⅱb yielded bisoxime monoanhydride, $C_{19}H_{18}O_5N_2$, m.p. 255° (decomp.), which was oxidized by hydrogen peroxide to a derivative of isoxazol dicarboxylic acid,1) m.p. 216°. This fact indicates that the same A ring is present in both molecules of I and Ⅱb.

Upon ozonolysis of Ⅱa, $C_{18}H_{18}O_7$ (Ⅲa) was obtained as white crystals, m.p. 193~195°. It was soluble in $NaHCO_3$ solution with bubbling and negative to the ferric chloride reaction. The infrared spectrum of Ⅲa has absorption bands at 2680, 2620 and 2560 (broad, OH of COOH), 1770 (phenol acetate), 1705 ($\alpha\beta$-unsatd. COOH), 1700 (Ar-$COCH_3$), 1685 ($\alpha\beta$-unsatd. C=O), 1605, 1585, 1575 and 1490 (phenyl and furan), 1390, 1370, 1170 and 1135 (isopropyl) cm^{-1}. By methylation with diazomethane, Ⅲa gave a mono methylester $C_{19}H_{20}O_7$ (Ⅲb), m.p. 122~123°.

The infrared spectrum of Ⅲb has absorption maxima at 1760 (phenol acetate), 1710 ($\alpha\beta$-unsatd. $COOCH_3$), 1690 (Ar-$COCH_3$), 1680 ($\alpha\beta$-unsatd. C=O), 1600, 1590, 1570 and 1490 (phenyl and furan) cm^{-1}.

The nuclear magnetic resonance spectrum of Ⅲb (Fig. 2) exhibits signals at 0.37 p.p.m. (aromatic >C-H, no proton to its *ortho*-position), 3.30 p.p.m. (-CH_3 in ester), 4.47 p.p.m. (-$COCH_3$), 4.83 p.p.m. (-$OCOCH_3$), 4.88 p.p.m. (aromatic >C-CH_3), 5.89 and 6.05 p.p.m. (isopropyl). The 5.79 p.p.m. signal (gem-dimethyl) of Ⅱa is divided into two signals at 5.89 and 6.05 p.p.m. (J=6.5 c.p.s.) and the two signals, 4.45 and 4.52 p.p.m. (-$COCH_3$) decrease to one signal at 4.47 p.p.m. in Ⅲb. This differences in nuclear magnetic resonance spectra of Ⅱa and Ⅲb indicates that in the ozonolysis of Ⅱa, decomposition took place in the A

[*1] Part Ⅱ : This Bulletin, **10**, 607 (1962).

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[*3] Spectra were run in $CHCl_3$ solution with a Varian spectrometer opearting at 40 m.c., and calibrated by the sideband technique against internal chloroform standard.

1) K. Takahashi, S. Miyashita : This Bulletin, **10**, 603 (1962).

2) Part Ⅱ : Cited above.

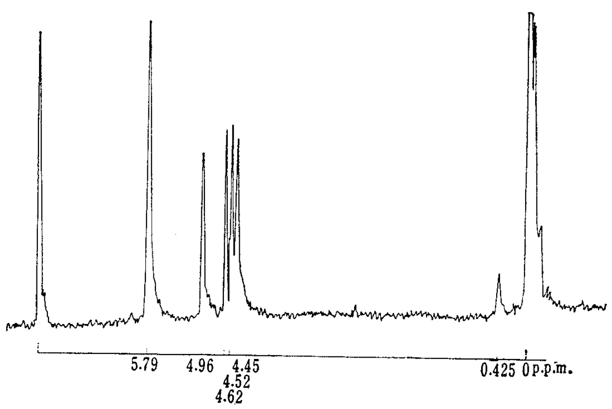

Fig. 1. Nuclear Magnetic Resonance Spectrum of Anhydromethyldihydrousnic Acid Monoacetate Ⅱa in $CHCl_3$ (p.p.m. from chloroform, at 40 m.c.)

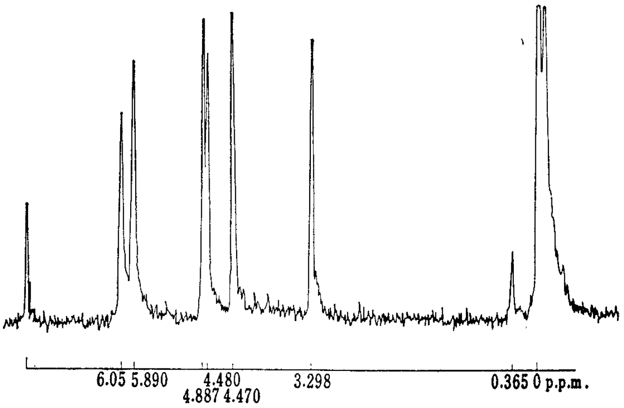

Fig. 2. Nuclear Magnetic Resonance Spectrum of Ⅲb in $CHCl_3$ (p.p.m. from chloroform, at 40 m.c.)

ring of Ⅱa which had a gem-dimethyl and a $-COCH_3$ group. Hydrolysis of Ⅲa gave rise to $C_{16}H_{16}O_6$ (Ⅲc), m.p. 235~237°, which was also obtained from Ⅲb by hydrolysis.

Ⅲc gave a violet coloration with ferric chloride, and formed by diazomethane a methyl ester, $C_{17}H_{18}O_6$ (Ⅲd), m.p. 123~124° (red-violet coloration with ferric chloride) and also a monoxime $C_{16}H_{17}O_6N$, m.p. 233° (decomp.) (black-green coloration with ferric chloride). The infrared spectra of Ⅲc has absorption maxima at 1700 ($\alpha\beta$-unsatd. COOH), 1670 ($\alpha\beta$-unsatd. C=O) and 1640 (chelated C=O) cm^{-1}.

Ⅲc was decarboxylated on heating with quinoline and copper powder at 260~270° for 30 minutes to give $C_{15}H_{16}O_4$ (Ⅳ) as white crystals, m.p. 113.5°, which formed a bisoxime $C_{15}H_{18}O_4N_2$, m.p. 179~181° (blue green coloration with ferric chloride). The infrared spectrum of Ⅳ has absorption bands at 1670 ($\alpha\beta$-unsatd. C=O), 1630 (chelated $-COCH_3$ in aromatic ring) cm^{-1} and a new band at 3090 cm^{-1}. (=CH in furan ring).

Ⅳ was oxidized with ozone in chloroform solution to give $C_{10}H_{10}O_5$ (Ⅴa) as a white crystalline powder, m.p. 180° (decomp.), which was difficult to crystallise. By methylation with diazomethane, Ⅴa gave a methyl ester $C_{11}H_{12}O_5$ (Ⅴb), m.p. 98~99° which produced a red-violet coloration with ferric chloride. On heating at 180°, Ⅴa yielded $C_9H_{10}O_3$ (Ⅵ) as faintly yellowish crystal, m.p. 146°. This compound was proved by the mixed melting point determination and infrared spectra to be identical with a authentic sample of 4'-methyl-2',6'-dihydroxyacetophenone,$^{3)}$ synthesised from orcinol. The constitutions of Ⅱ, Ⅲ, Ⅳ, Ⅴ and Ⅵ are shown in chart 1.

The reaction mechanism of the formation of anhydromethyldihydrousnic acid monoacetate (Ⅱa) from methyldihydrousnic acid (I) may be as follows (Chart 2). The first stage of this reaction is the fission of a -C-O-C- bond in the furan ring, which produces two hydroxyl groups, and the hydroxyl in B ring is then dehydrated to produce a double bond. At the next stage, a newly genarated hydroxyl in A ring and an enol hydroxyl in B ring combine with each other to give a -C-O-C- bond and finally the newly formed dienone ring undergoes the Dienone-phenol type rearrangement to give Ⅱa.

Experimental*4

Acetylation of I. Formation of IIa——Methyldihydrousnic acid (I) was acetylated and from the MeOH or EtOH-insoluble fraction, anhydromethyldihydrousnic acid monoacetate $C_{21}H_{20}O_7$ (Ⅱa), m.p.

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*4 The IR spectra were taken in KBr pellet by Nippon Bunko I.R.S. infra code, the UV spectra were measured in EtOH solution by Hitachi EPU-2A photo-electric spectrophotometer and the NMR spectra were taken by Varian 40 Mc. NMR spectrometer by using $CHCl_3$ as internal reference at 40 Mc. Some weak bands of the IR spectra were excluded in the description.

3) P.R. Saraiya, R.C. Shah : Proc. Indian Acad. Sci., **31**, 213~223 (1950).

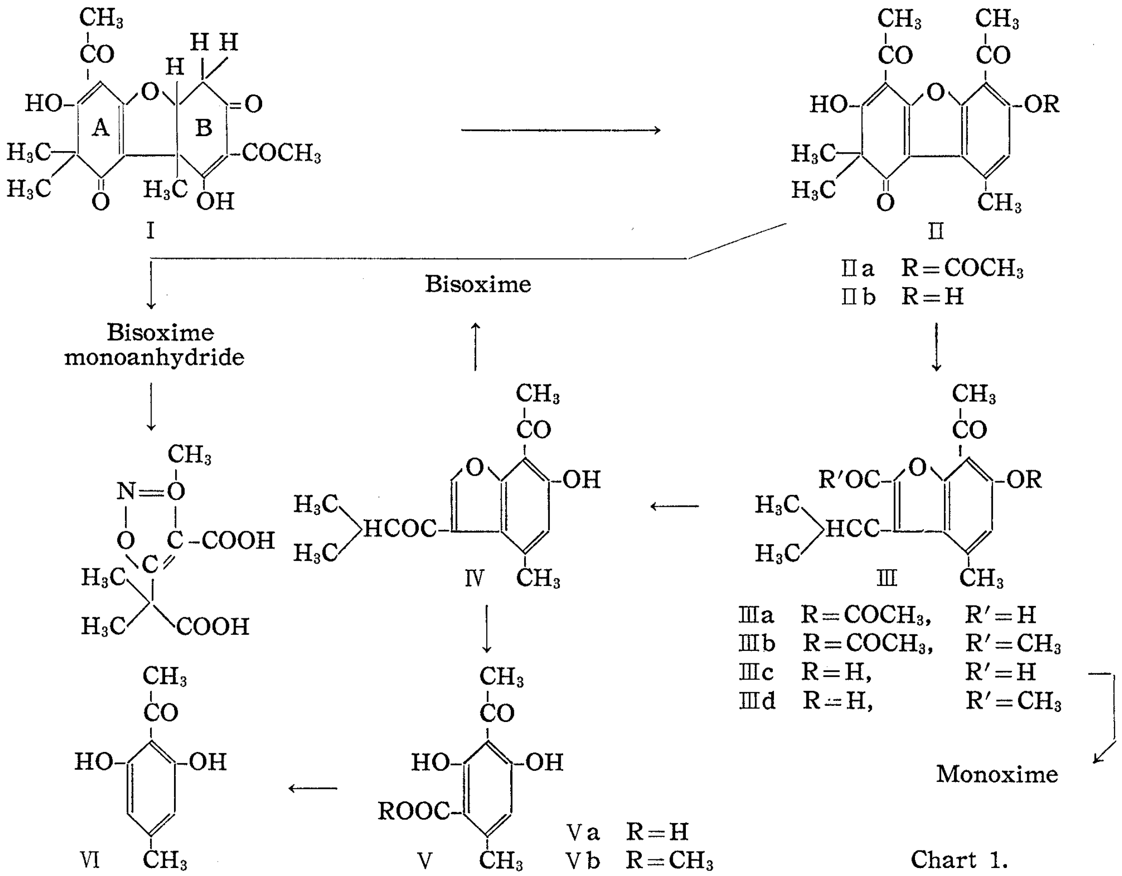

Chart 1.

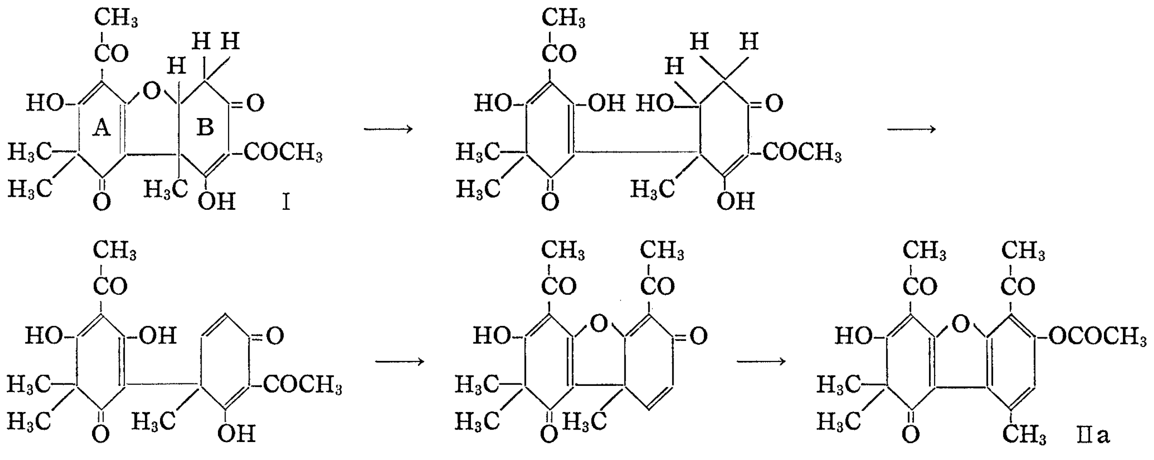

Chart 2.

172~173° was obtained.[1] IR ν_{max} cm^{-1} : 1760 (s), 1690 (s), 1605 (s), 1565 (shoulder), 1485 (w), 1460 (w), 1440 (m), 1380 (m), 1372 (m), 1365 (m), 1260 (m), 1215 (s), 1190 (m), 1085 (m), 1055 (m), 1010 (w), 975 (w), 920 (w), 885 (w), 850 (w).

IR spectra of IIb[1] ν_{max} cm^{-1} : 1670 (s), 1635 (s), 1603 (m), 1585 (s), 1565 (shoulder), 1500 (m), 1455 (m), 1395 (w), 1380 (m), 1375 (m), 1350 (m), 1320 (w), 1245 (m), 1225 (m), 1195 (m), 1160 (w), 1085 (s), 1025 (w), 845 (s).

Acetylation of IIb[1] to IIa——A half gram of IIb was acetylated with Ac_2O (5.0 cc.) and two drops of conc. H_2SO_4 on a water bath at 80° for 3 hr. to give IIa, m.p. 172°, which was proved to be identical with IIa by the IR spectrum and admixture with anhydromethyldihydrousnic acid monoacetate (IIa).

Bisoxime monoanhydride of IIb——A mixture of 0.5 g. of IIb, 0.5 g. of $NH_2OH \cdot HCl$ and 0.5 g. of anyhd. NaOAc in 40 cc. of EtOH was warmed at 80~90° for 3 hr. White crystals, separated out under cooling, were recrystallized from benzene-ethanol (1:1) to give $C_{19}H_{18}O_5N_2$ as white needle, m.p.

255°(decomp.). Yield, 0.33 g. $FeCl_3$ reaction : dark green. *Anal.* Calcd. for $C_{19}H_{18}O_5N_2$: C, 64.40; H, 5.12; N, 7.91. Found : C, 64.45; H, 5.21; N, 7.36.

Oxidation of bisoxime monoanhydride of IIb with H_2O_2——To a solution of 0.5 g. of bisoxime monoanhydride of Ⅱb in 20 cc. of 5% KOH solution, 10 cc. of 3% H_2O_2 was added twice and 1 cc. of 30% H_2O_2, five times at intervals of 0.5 hr., and then 5 cc. of 30% H_2O_2 was added three times at intervals of 1 hr., at 70~75°. The yellow reaction solution was acidfied with dil. HCl, salted out with NaCl, and extracted with Et_2O. After drying with anhyd. Na_2SO_4, the Et_2O was distilled off to give $C_9H_{11}O_5N$ as white crystals, m.p. 216°, which was identical with the isoxazole dicarboxylic acid derivative[3] by the mixed melting point determination and IR spectrum. *Anal.* Calcd. for $C_9H_{11}O_5N$: C, 50.70; H, 5.20; N, 6.57. Found : C, 50.48; H, 5.07, N, 6.60. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1720 (s), 1710 (s), 1600 (s), 1500 (w), 1420 (m), 1310 (m), 1290 (m), 1260 (m), 1170 (m), 1120 (s), 1025(m), 1020(m), 920(m. broad), 850 (m. broad), 750 (m), 735 (m).

Ozonolysis of IIa. Formation of IIIa——Five grams of Ⅱa were dissolved in $CHCl_3$ (50 cc.) and ozonized O_2 was passed through under ice cooling for 4~5 hr. Then water (2 cc.) and EtOH (18 cc.) were added to the $CHCl_3$ solution and the mixture was warmed on a water bath for 30 min. most of the solvent was distilled off, and the residue was rerystallized from dil. EtOH, giving $C_{18}H_{18}O_7$ (Ⅲa) as white crystals, m.p. 193~195°(decomp.). $FeCl_3$ reaction : negative. *Anal.* Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found : C, 62.30; H, 5.14. UV $\lambda_{\max}$ mμ (log ε) : 236 (4.29), 285.5 (4.16)· IR $\nu_{\max}$ cm^{-1} : 2680 (w), 2620 (w), 2560 (w), 1770 (w), 1705 (s), 1700 (s), 1685 (s), 1605(w), 1585(s), 1575 (s), 1490(w), 1440 (s), 1390 (w), 1370 (m), 1290 (s), 1240 (m), 1200 (s), 1190 (s), 1170 (s), 1135 (m), 1080 (m), 1050 (m), 965(m), 930(w), 890 (m), 840 (w), 805 (w), 725 (w).

Methylation of IIIa. Formation of IIIb——One gram of Ⅲa was dissolved in a mixture of tetrahydrofuran and Et_2O (1:1) and methylated with CH_2N_2 to give $C_{19}H_{20}O_7$ (Ⅲb) as white crystals, m. p. 122~123°. $FeCl_3$ reaction : negative. *Anal.* Calcd. for $C_{19}H_{20}O_7$: C, 63.33; H, 5.99. Found : C, 63.36; H, 5.69. UV $\lambda_{\max}$ mμ (log ε) : 225 (4.35), 290 (4.13). IR $\nu_{\max}$ cm^{-1} : 1760 (s), 1710(s), 1690(s), 1680(s), 1600 (m), 1590 (m), 1570 (m), 1450 (m), 1380 (m), 1360 (s), 1340(s), 1300(s), 1250(s), 1200(s), 1190(s), 1160 (w), 1130 (m), 1080 (m), 1055 (m), 1000 (m), 960 (m), 950 (m), 925 (m), 905 (m), 775 (m).

Hydrolysis of IIIa. Formation of IIIc——Two and a half grams of Ⅲa were treated with 15 cc. of 5% NaOH solution at room temperature for 1 hr. After acidification with dil. HCl, the resulting precipitate was recrystallized from dil. EtOH to give $C_{16}H_{16}O_6$ (Ⅲc) as yellow crystals m.p. 235~237°. $FeCl_3$ reaction : dark violet. *Anal.* Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found : C, 63.29; H, 5.28. This compound was also obtained from Ⅲb by hydrolysis with 5% alcoholic NaOH. UV $\lambda_{\max}$ mμ (log ε) : 239 (4.23), 284 (4.26), 347 (3.77). IR $\nu_{\max}$ cm^{-1} : 2560 (w), 1700 (s), 1670 (m), 1640 (s), 1570 (s), 1510 (m), 1430 (m), 1380 (m), 1350 (m), 1320 (m), 1280 (m), 1240 (s), 1165 (s), 1130 (m), 1090 (m), 960 (s), 920 (w), 870 (m), 840 (w), 810 (m).

Methylation of IIIc. Formation of IIId——On methylation with CH_2N_2 in tetrahydrofuran and Et_2O (1:1) solution, Ⅲc gave a methyl ester, $C_{17}H_{18}O_6$ (Ⅲd) as white crystals, m.p. 123~124°. $FeCl_3$ reaction : red-violet. *Anal.* Calcd. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found : C, 64.29; H, 5.70. UV $\lambda_{\max}$ mμ (log ε) : 227 (4.24), 283 (4.40), 338 (4.05).

Oximation of IIIc. Formation of Monoxime——To a solution of 0.5 g. of Ⅲc in 15 cc. of EtOH, a mixture of 0.29 g. of $NH_2OH \cdot HCl$ and 0.34 g. of anhyd. NaOAc in 10 cc. of EtOH and a little volume of water was added and the solution warmed on a water bath for 2 hr. After evaporation of most of EtOH, water was added to give an oil, which solidified after standing overnight in an ice box. Recrystallised from dil. EtOH gave $C_{16}H_{17}O_6N$ as yellow crystals m.p. 233°(decomp.). $FeCl_3$: green black. *Anal.* Calcd. for $C_{16}H_{17}O_6N$: C, 60.18; H, 5.37; N, 4.39. Found : C, 60.57; H, 5.57; N, 4.35. IR $\nu_{\max}$ cm^{-1}: 1710 (s), 1680 (s), 1630 (m), 1580 (s), 1410 (m), 1380 (m), 1240 (s), 1170 (s), 1140 (m), 1030 (m), 960 (m), 800 (m), 740 (m).

This oxime gave a methyl ester $C_{17}H_{19}O_6N$, m.p. 162~164°, by CH_2N_2. *Anal.* Calcd. for $C_{17}H_{19}O_6N$: C, 61.25; H, 5.75; N, 4.20. Found : C, 61.80; H, 5.70; N, 4.07.

Decarboxylation of IIIc. Formation of IV——A mixture of 2.0 g. of Ⅲc, 0.6 g. of copper powder and 6 cc. of quinoline was refluxed at 260~270° for 30 min. Then, to this mixture, Et_2O was added and copper powder was removed by filtration. After evaporation of the solvent, a black resinous substance, containing some crystalline material, was distilled at 180~200° under 1 mm. Hg pressure. The distillate crystallized readily and was recrystallized from 50% AcOH to give $C_{15}H_{16}O_4$ (Ⅳ) as white crystals, m.p. 113.5°. $FeCl_3$ reaction : red-violet. *Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.26; H, 6.25. UV $\lambda_{\max}$ mμ (log ε) : 229.5 (4.50), 282 (4.26), 340 (3.82). IR $\nu_{\max}$ cm^{-1} : 3090 (w), 1670 (s), 1630 (s), 1575 (m), 1550 (s), 1500 (s), 1450 (m), 1430 (m), 1390 (s), 1370 (s), 1340 (w), 1300(s), 1240 (s), 1200 (w), 1150 (m), 1120 (s), 1100 (m), 1060 (m), 1030 (w), 950 (s), 860 (m), 830 (m), 780 (w), 750 (w).

Oximation of IV. Formation of Bisoxime——To a solution of 0.5 g. of Ⅳ in 10 cc. of EtOH, a mixture of 0.55 g. of $NH_2OH \cdot HCl$ and 0.65 g. of anhyd. NaOAc in 10 cc. of EtOH and a little volume of water was added and the solution warmed on a water bath for 2 hr. and treated as in the oximation of Ⅲc to give $C_{15}H_{18}O_4N_2$ as white crystals, m.p. 179~181°. $FeCl_3$ reaction : blue-green. *Anal.* Calcd. for $C_{15}H_{18}O_4N_2$: C, 62.05; H, 6.25; N, 9.65. Found : C, 62.25; H, 6.42; N, 9.64.

Ozonolysis of IV. Formation of Va——One and a half grams of IV was dissolved in $CHCl_3$ (30 cc.) and ozonized O_2 was passed through for 1.5 hr. under ice cooling. The $CHCl_3$ solution was distilled off and water (50 cc.) was added and the solution warmed on a water bath at 40∼50° for 5 hr. The ozonide was decomposed gradually and became a crystalline powder, containing some resinous material. This was extracted with Et_2O, the Et_2O was evaporated, and the resulting material was treated with benzene, whereby a benzene-insoluble white crystalline powder was obtained. It was unstable and difficult to crystallize, so it was dissolved in MeOH and treated with water to give $C_{10}H_{10}O_5$ (Va) as a white crystalline powder. After two repetitions of this purification procedure it melted at 180° (decomp.). Yield, 0.5 g. $FeCl_3$: red-violet. *Anal.* Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found : C, 57.17; H, 4.82. UV λ_{max} mμ (log ε) : 212 (4.33), 232 (4.29), 256 (4.20), 276 (shoulder, 4.12), 350 (3.76). IR ν_{max} cm^{-1} : 1640 (s), 1610 (s), 1570 and 1560 (shoulder), 1480 (m), 1440 (w), 1400 (w), 1380 (s), 1300 (s), 1260 (s), 1220 (w), 1190 (s), 1135 (w), 1090 (w), 1030 (w), 970 (m), 885 (m), 840 (m), 730 (w).

Methylation of Va. Formation of Vb——With CH_2N_2 in the usual way, Va (0.1 g.) was methylated to $C_{11}H_{12}O_5$ (Vb), m.p. 98∼99°. $FeCl_3$ reaction : red-violet. *Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found : C, 58.92; H, 5.46. UV λ_{max} mμ (log ε) : 207.5 (4.12), 241 (4.37), 261 (4.29), 330 (3.62). IR ν_{max} cm^{-1} : 1640 (s), 1620 (s), 1590 (shoulder), 1570 (s), 1480 (m), 1450 (m), 1440 (w), 1420 (w), 1390 (w), 1360 (w), 1330 (s), 1250 (s), 1190 (s), 1130 (s), 1085 (m), 1035 (m), 1020 (m), 970 (s), 900 (m, broad), 850 (m), 825 (m), 755 (w), 745 (w).

Decarboxylation of Va. Formation of 4′-Methyl-2′,6′-dihydroxyacetophenone (VI)——A quarter gram of Va was heated at 180°. Decarboxylation took place under vigorous bubbling. After the end of bubbling, the product was distilled at 180∼200° under 1 mm. Hg pressure to give $C_9H_{10}O_3$ (VI) m.p. 146°. $FeCl_3$ reaction : dark green. This compound was undepressed by admixture with a sample of 4′-methyl-2′,6′-dihydroxy acetophenone and both IR spectra were identical. *Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found : C, 65.01; H, 6.21. UV λ_{max} mμ (log ε) : 208 (4.11), 225 (4.07), 275.5 (4.11), 340 (3.38). IR ν_{max} cm^{-1} : 1640 (s), 1590 (shoulder, s), 1580 (s), 1520 (w), 1440 (m), 1390 (m), 1370 (m), 1360 (m), 1280 (m), 1250 (s), 1200 (m), 1080 (m), 1065 (m), 1030 (w), 1005 (w), 960 (m), 825 (m), 790 (w), 750 (m).

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Summary

Anhydromethyldihydrousnic acid, acetylation product of methyldihydrousnic acid, was proved to have structure (II). It was assumed that the reaction mechanism was not a simple acetylation reaction but it involved the fission and reformation of a -C-O-C- bond in the furan ring and the Dienone-Phenol rearrangement.

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