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Usnic Acid. X.[1] The Pyrolysis of Tetrahydrodesoxyusnic- and Dihydrousnic-Acids. (2)[1]

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The pyrolysis of tetrahydrodesoxyusnic- and dihydrousnic acids and their acetates was studied and the reaction mechanisms were proposed.

It was reported in a previous paper[1] of this series that tetrahydrodesoxyusnic acid (I) gave, on dry distillation with $CaCl_2$, 7-acetyl-3-ethyl-5-methyl-6-hydroxycoumaran-2-one (II) of mp 70°, 7-acetyl-3,5-dimethyl-6-hydroxycoumaran-2-one (III) of mp 131°, methyl ethyl ketone and methyl *n*-propyl ketone, and the mechanism of the pyrolysis was discussed. This paper deals with the pyrolysis of tetrahydrodesoxyusnic-, dihydrousnic-acids and their acetates without $CaCl_2$ and its mechanism. Tetrahydrodesoxyusnic acid (I) was heated at 220—230° without $CaCl_2$ for 40 min under ordinary pressure to give a colorless distillate, in which acetone, methyl ethyl ketone and methyl *n*-propyl ketone were detected by gas chromatography, and a non-volatile residue. The residue was then distilled at 220—230° under reduced pressure (1 mmHg) to give II of mp 83.5—84.5°, $C_{13}H_{14}O_4$, and III of mp 131°, $C_{12}H_{12}O_4$, which was proved to be identical with 7-acetyl-3,5-dimethyl-6-hydroxycoumaran-2-one, and a yellow needles (IV) of mp 93—94°, $C_{17}H_{20}O_4$. The seeding of crystals of mp 83.5—84.5° into a saturated methanolic solution of II of mp 70° converted the latter into the former.

The *Rf* values of both compounds proved to be identical. The ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra of both compounds were virtually identical. These evidences indicate that II of mp 83.5—84.5° and II of mp 70° are 7-acetyl-3-ethyl-5-methyl-6-hydroxycoumaran-2-one and dimorphic.

The compound (IV), which gives green coloration with $FeCl_3$, shows UV maxima (mμ, log ε) at 240.5 (4.39), 290.5 (3.95), 373 (3.65), and exhibits infrared (IR) bands (cm^{-1}) at 1720 (C=O), 1630 (chelated aromatic C=O), 1220, 1070 (-C-O-C- of benzofuran) and 895 (isolated aromatic proton), and exhibits NMR signals (τ-value) which could be assigned to the respective groups in Table I. The NMR spectrum suggests that IV has an isolated $-CH_2-$ group and a *n*-propyl group which is also confirmed by the presence of species *m/e* 217.080 ($M^+-COC_3H_7$) on the mass (MS) spectrum. These data indicate that this compound (IV) could be formulated as shown in Chart 1.

The formation of II and III from I could be easily explained by the mechanism proposed previously.[1] The formation of IV from I could be explained by the following mechanism. Intermediate A, derived from I by cleavage of the ether linkage followed by dehydration and by the Jacobson rearrangement of the angular methyl group, as in the case of the pyrolysis of methyldihydrousnic acid,[3] is protonated by the acids present in the reaction mixture to give intermediate B and the methyl group of B undergoes the Jacobson rearrangement in a reverse manner to give intermediate C, as in the case of the pyrolysis of I with $CaCl_2$.[1] The conversion of I to intermediate C could also be explained by the 1,5-sigmatropic supra-

1) Part IX: K. Takahashi and M. Takani, *Chem. Pharm. Bull.* (Tokyo), **19**, 2079 (1971).
2) Location: *Takaramachi, Kanazawa.*
3) K. Takahashi and M. Takani, *Chem. Pharm. Bull.* (Tokyo), **18**, 1831 (1970).

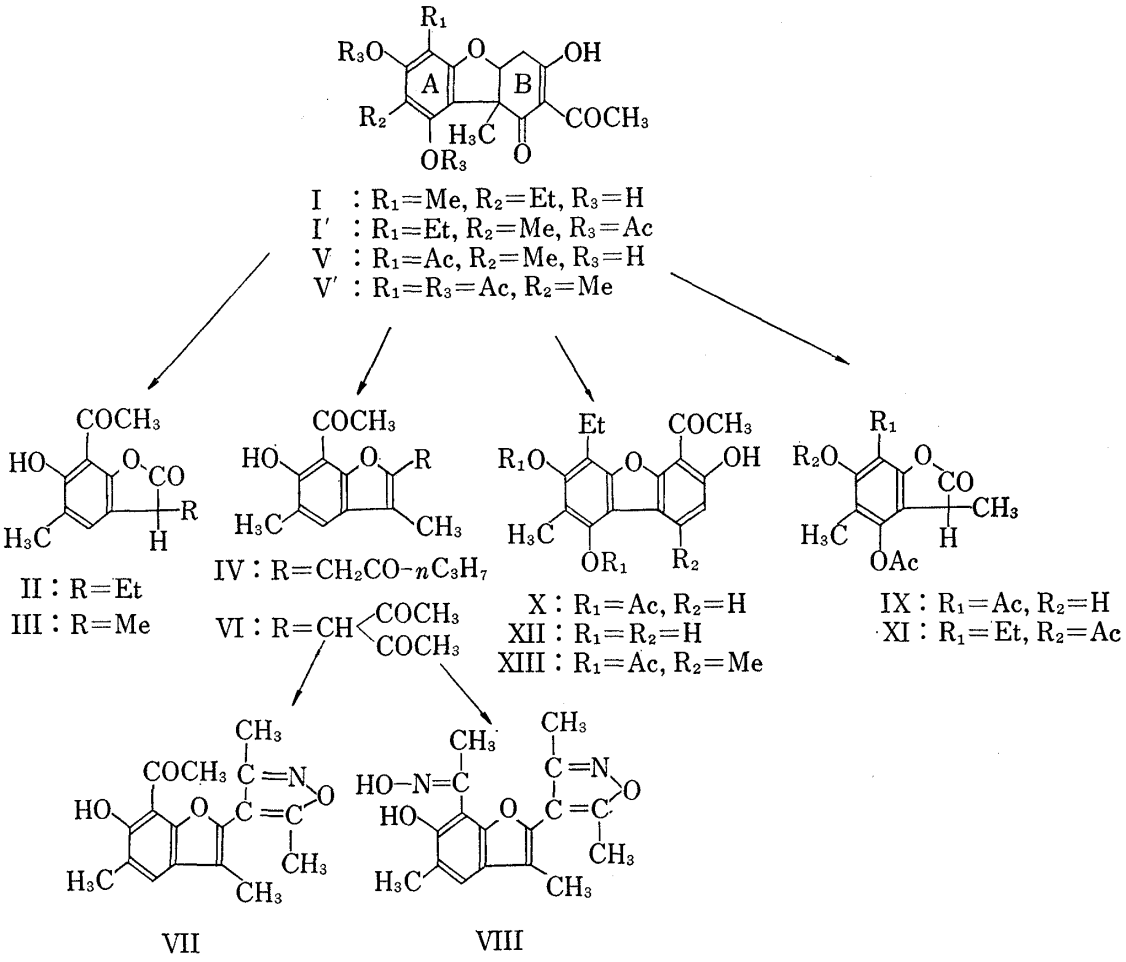


Chart 1

TABLE I. The NMR Data (τ-Value in $CDCl_3$,60 Mc, J in cps)

	IV	VI
$CH_2CH_2CH_3$	9.09 (t) 3H (J=7.8)	
$CH_2CH_2CH_3$	8.43 (m) 2H	
$CH_2CH_2CH_3$	7.54 (t) 2H (J=7.2)	
$COCH_3$		7.97 (s) 6H
C-CH_3	7.86 (s) 3H	7.87 (s) 3H
C-CH_3	7.72 (s) 3H	7.68 (s) 3H
$COCH_3$	7.20 (s) 3H	7.16 (s) 3H
-CH_2-	6.22 (s) 2H	
Ar-H	2.64 (s) 1H	2.58 (s) 1H
OH chelated	−3.08 (s) 1H	−3.08 (s) 1H
chelated enol		−6.74 (s) 1H

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

facial transformation.[1] The single ketonic fission of intermediate C, followed by decarboxylation and dehydration, produces IV, a benzofuran derivative, while the double ketonic fissions at two bonds[1] followed by lactonisation produce coumaran-2-ones such as II and III, at the last stage of the reaction. Compounds such as IV′, IV″, and IV‴ which might be produced by this mechanism have not been detected in the reaction mixture (Chart 2).

By the same mechanism, dihydrousnic acid (V) is expected to give a benzofuran deriva-

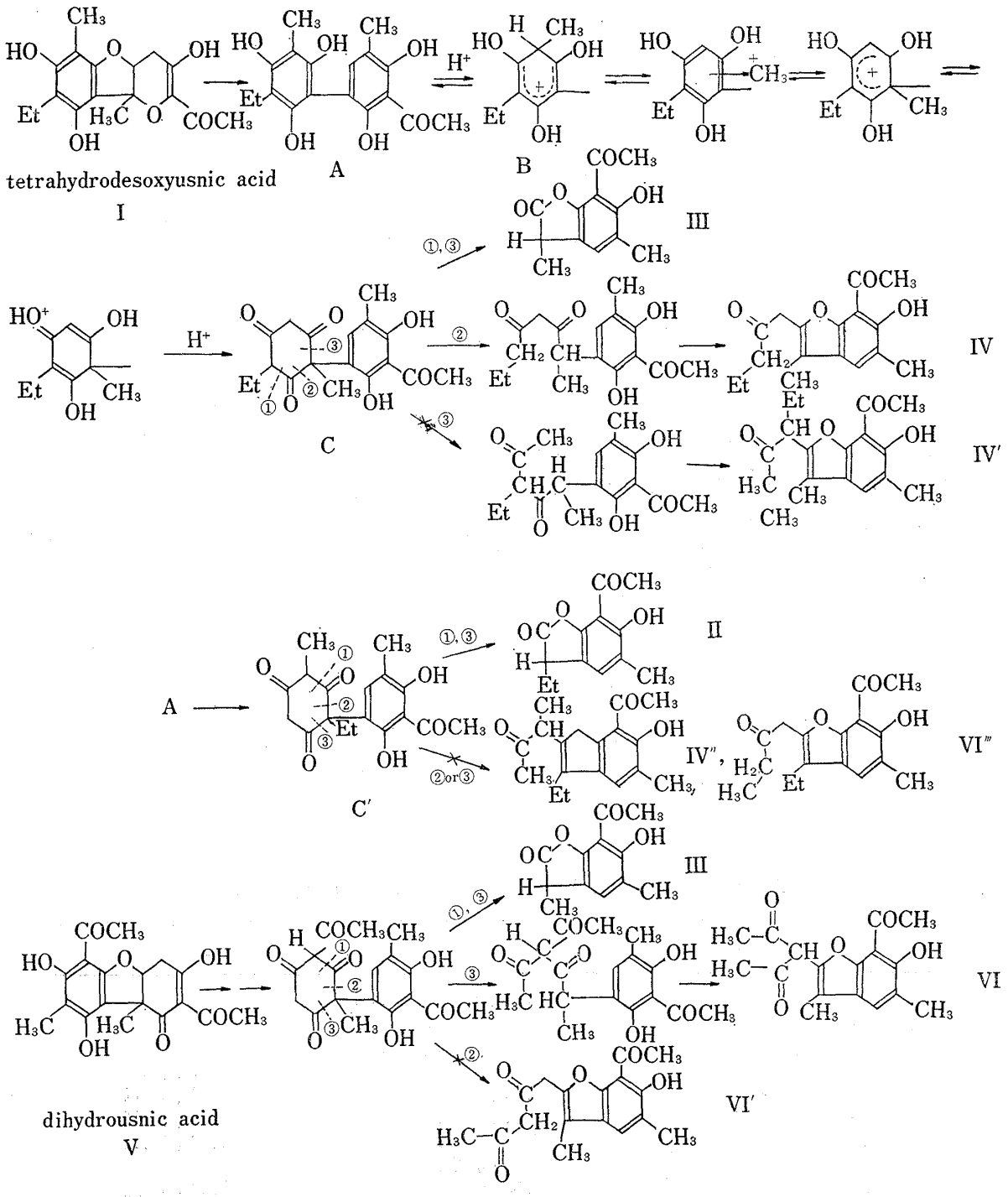


Chart 2

tive by the single ketonic fission at the last stage of the reaction. Dihydrousnic acid[4] (V) was heated at 240—250° without $CaCl_2$ for 30 min under ordinary pressure to give a colorless distillate and a non-volatile residue. The residue was then distilled at 240—250° under reduced pressure (1 mmHg) to give VI of mp 137—138°, $C_{17}H_{18}O_5$ and III. The compound (VI) gave red coloration with $FeCl_3$, and monooxime anhydride (VII) of mp 198°, $C_{17}H_{17}O_4N$ and bisoxime monoanhydride (VIII) of mp 208°, $C_{17}H_{18}O_4N_2$. The compound (VII) shows a strong IR band at 1630 cm^{-1} assignable to a chelated aromatic C=O, but VIII do not show

4) S. Shibata, K. Arakawa and K. Takahashi, *Yakugaku Zasshi*, **72**, 255 (1952).

such a band. The UV spectrum of VI with maxima (mμ, log ε) at 244 (4.42), 286.5 (4.16), 368 (3.65), approximately resembles that of IV, and VI shows IR bands (cm^{-1}) at 1635 (broad, chelated C=O), 1250, 1075 (-C-O-C- of benzofuran), 910 (isolated aromatic proton). The NMR signals of VI could be assigned to respective groups as shown in Table I. The presence of the signal at 7.97 τ (s, 6H) and the absence of the signal of a methine group suggest that VI might be β-substituted acetylacetone and in an enol form. The signal at −6.74 τ which could be assigned to a chelated enol OH group, is very sharp, probably suggesting that VI might be a β-diketone such as β-phenyl-acetylacetone. R.L. Lintvedt and H.F. Holtzclaw, Jr. have reported that a β-diketone exhibits a sharp enolic OH peak, when substituted with electron-withdrawing group and/or group which enhance the resonance in the enolic ring.[5] These data indicate that this compound (VI) could be formulated as shown in Chart 1.

The formation of VI from V could be explained by the same mechanism as that of the formation of IV from I, as shown in Chart 2. The compound (VI') has not been detected in the reaction mixture.

Shibata, Arakawa, and Takahashi[4] reported that diacetyldihydrousnic acid (V') gave, on dry distillation without $CaCl_2$, 7-acetyl-3,5-dimethyl-4-acetoxy-6-hydroxycoumaran-2-one (IX). To study the reaction mechanism, diacetyltetrahydrodesoxyusnic acid (I')[6] was pyrolysed. Diacetyltetrahydrodesoxyusnic acid (I') was heated at 220—230° for 30 min without $CaCl_2$ under ordinary pressure and was then distilled at 220—230° under reduced pressure (1 mmHg) to give yellow needles (X) of mp 210°, $C_{21}H_{20}O_7$ and colorless crystals (XI) of mp 121—122°, $C_{16}H_{18}O_6$. The faint yellow needles (X) were deacetylated to give XII of mp 273°, $C_{17}H_{16}O_5$. The UV spectrum of X with maxima (mμ, log ε) at 237 (4.60), 257 (4.39, sh), 269 (4.58), 301 (3.71, sh), 358 (3.67) resembles that of diacetyldibenzofuran derivative (XIII),[6] which was obtained from 9-O-acetyltetrahydrodesoxyusnic acid[6] by the Dienone-Phenol rearrangement. The UV spectrum of XII with maxima (mμ, log ε), at 225 (4.43, sh), 229.5 (4.58), 266.5 (4.51), 280 (4.32, sh), 310 (3.47) resembles that of deacetylated derivative[6] of XIII, suggesting that X is structurally related to dibenzofuran derivative, XIII. The compound (X) exhibits IR bands (cm^{-1}) at 1750 (OAc), 1640 (chelated C=O), 1105, 1060 (-C-O-C-), 860 (two aromatic protons at *ortho* position). The NMR signals of X and XIII could be assigned to the respective groups as shown in Table II. These spectral data indicate that X could be formulated as shown in Chart 1.

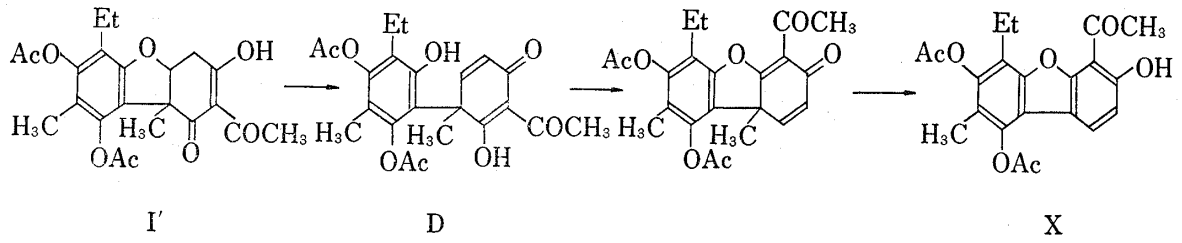
Table II. The NMR Data (τ-Value in $CDCl_3$, 60 Mc, J in cps)

	$CH_3C\underline{H}_2$-	Ar-CH_3	OAc	$COCH_3$	$CH_3C\underline{H}_2$-	Ar-H	Chelated OH
X	8.69 (t) 3H J=7.8	7.92 (s) 3H	7.58 (s) 3H 7.50 (s) 3H	7.04 (s) 3H	7.15 (q) 2H J=7.8	3.18, 3.04 (d) 1H 2.40, 2.25 (d) 1H	−2.90 (s) 1H
XIII	8.71 (t) 3H J=7.2	7.97 (s) 3H 7.30 (s) 3H	7.58 (s) 6H	7.06 (s) 3H	7.22 (q) 2H J=7.2	3.30 (s) 1H	−3.02 (s) 1H

The compound (XI) shows UV maxima (mμ, log ε) at 210 (4.37, an end absorption), 272 (3.11), 278 (3.14), and IR bands (cm^{-1}) at 1815 (γ-lactone), 1770, 1760 (two acetates) and NMR signals (τ-value) at 8.85 (t, 3H, $C\underline{H}_3$-CH_2-, J=7.8 cps), 8.495 (d, 3H, $C\underline{H}_3$-CH<, J=8.4 cps), 8.06 (s, 3H, aromatic-CH_3), 7.66 (s, 3H, OAc), 7.64 (s, 3H, OAc), 7.44 (q, 2H, CH_3-$C\underline{H}_2$-, J=7.8 cps), 6.255 (q, 1H, CH_3-$C\underline{H}$<, J=8.4 cps). Indeed, the compound (XI) was proved to be identical with 3,5-dimethyl-4,6-diacetoxy-7-ethylcoumaran-2-one which was obtained from 7-acetyl-3,5-dimethyl-4,6-diacetoxycoumaran-2-one[7] by reduction with zinc

5) R.L. Lintvedt and H.F. Holtzclaw, Jr., *Inorg. Chem.*, **5**, 239 (1966).
6) M. Takani and K. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2072 (1971).
7) C. Schöpf and F. Ross, *Ann.*, **546**, 1 (1941).

amalgam.[8] The formation of X from I′ might be explained as follows: Intermediate D, derived from I′ by cleavage of the ether linkage followed by dehydration, might give X by a mechanism such as the aromatisation reaction of androsta-1,4-dien-3-one,[9] but further investigation should be performed (Chart 3).

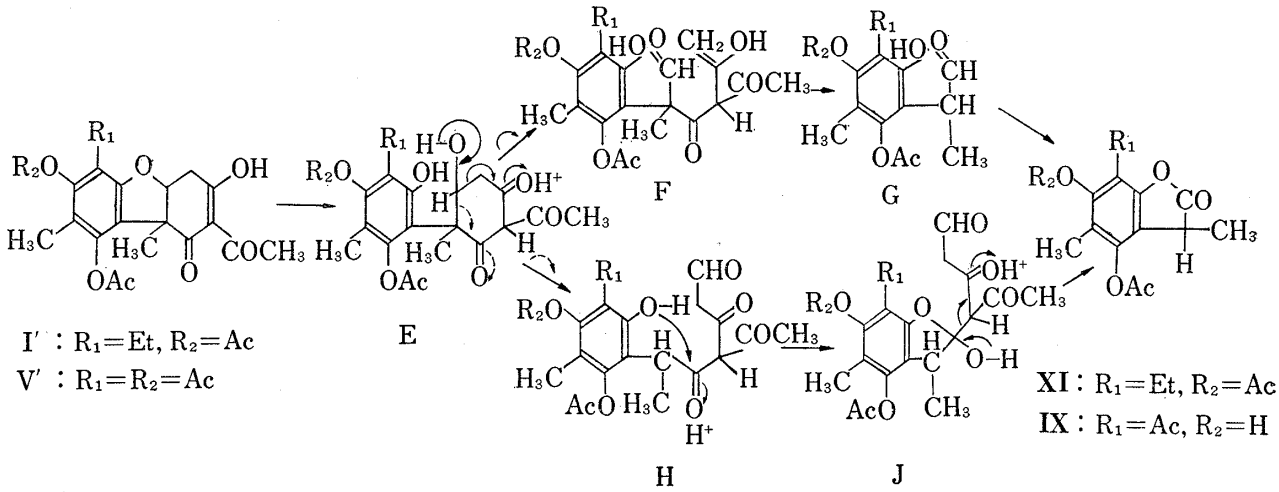


I′ D X

Chart 3

The reaction mechanism of the formation of XI from I′ could be explained as follows: Intermediate E might give intermediate G through intermediate F by the retro-Aldol reaction followed by the ketonic fission, and intermediate G might give XI by the air oxidation followed by the lactonisation. An alternative mechanism involving the retro-Aldol reaction might be possible as shown in Chart 4. Thus the pyrolysis of diacetyldihydrousnic acid (V′) could be understood analogously.

The acetylation of I and V would make the migration of the methyl or ethyl groups of the ring A difficult and would change the reaction course to give coumaran-2-one such as IX and XI, not II and III.



I′ : R_1=Et, R_2=Ac
V′ : R_1=R_2=Ac

E F G H J

XI : R_1=Et, R_2=Ac
IX : R_1=Ac, R_2=H

Chart 4

Experimental

The IR spectra were taken in KBr pellet with a Nippon Bunko DS-402G spectrometer, the UV in EtOH with a Hitachi EPS-2U recording spectrometer, the NMR in $CDCl_3$ with a JNM-C-60-H high resolution NMR spectrometer at 60Mc with $(CH_3)_4$ Si as internal reference, the gas chromatogram with a Shimazu GC-4BPF equipped with hydrogen flame ionisation detector and the MS with a JNM-01SG mass spectrometer, the ionizing current kept at 200 μA, while the ionisation energy being maintained at 75 eV and source temperature at 70°.

Dry-Distillation of I without $CaCl_2$——One g and half of I was heated at 220—230° for 40 min under ordinary pressure to give a colorless distillate, 4 ml of which was extracted with ether (5 ml) and the ether

8) Y. Asahina and M. Yanagita, *Yakugaku Zasshi*, **59**, 688 (1939).
9) K. Tsuda, E. Ohki and S. Nozoe, *J. Org. Chem.*, **28**, 783 (1963).

layer (1 μl) was injected directly to the gas chromatograph. The gas chromatogram showed three peaks at t_R 2.35 min, t_R 3.5 min and t_R 5.2 min. These values were virturally identical with those of acetone (t_R 2.4 min), methyl ethyl ketone (t_R 3.5 min) and methyl *n*-propyl ketone (t_R 5.3 min), measured under the same condition (10% polyethyleneglycol 1540 on a support of celite 545 (30—60 mesh), 2.0 m×4 mm, temp. 70°, N_2 gas, 30 ml/min (FID). After removing the colorless distillate, the non-volatile residue was distilled *in vacuo* under 1 mmHg to give an orange yellow distillate, which solidified by treatment with methanol to give a yellow powder. From 16.3 g of I, 9.6 g of the yellow powder was obtained. The powder (9.6 g) was chromatographed over 350 g of Kiesel gel with benzene–ethyl acetate (80:1). The fractions (13 g each) from No. 28 to 30 gave pale yellow needles (II) of mp 83.5—84.5° from methanol. 6 mg. *Rf*: 0.73 (benzene: ethyl acetate=20:1). UV λ_{max} mμ (log ε): 247 (4.03, sh), 260.5 (4.05), 354 (3.55). IR ν_{max} cm^{-1}: 1810, 1635, 1445, 1430—1420, 1320, 1180, 1105, 1040, 1030, 895, 830, 795. *Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.42; H, 6.11. The fractions from No. 35 to 45 gave yellow needles (III) of mp 131° from methanol. This compound was proved to be identical with 7-acetyl-3,5-dimethyl-6-hydroxycoumaran-2-one[1] by the mixed fusion and UV, IR spectra. The fractions from No. 100 to 125 gave 775 mg of a powder, which was rechromatographed over 40 g of Kiesel gel with benzene–ethyl acetate (80:1). The fractions (10 g each) from No. 14 to 20 (614 mg) were again chromatographed over 40 g of Kiesel gel with benzene–ethyl acetate (80:1). The fractions (7 g each) from No. 23 to 30 gave yellow needles (IV) of mp 93—94° from methanol. 300 mg. $FeCl_3$: green. Mass Spectrum (*m/e*, relative intensity, formula): M$^+$ 288.140, 12, $C_{17}H_{20}O_4$; 273.113, 0.2, $C_{16}H_{17}O_4$ (M$^+$ -CH_3); 245.121, 1, $C_{15}H_{17}O_3$ (M$^+$ -$COCH_3$); 217.080, 100, $C_{13}H_{13}O_3$ (M$^+$ -COC_3H_7); 199.071, 17, $C_{13}H_{11}O_2$ ($C_{13}H_{13}O_3$-H_2O, m* 182.5); 175.079, 2, $C_{11}H_{11}O_2$ ($C_{13}H_{13}O_3$ -C_2H_2O); 71.051, 9, COC_3H_7. *Anal.* Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.79; H, 7.02.

The Conversion of II[1] of mp 70° to II of mp 83.5—84.5°——i) A saturated methanolic solution of II of mp 70° (optically inactive, *Rf*=0.73 (benzene: ethyl acetate=20:1), IR ν_{max} cm^{-1}: 1810, 1635, 1450, 1430, 1325, 1180, 1100, 1050, 1025, 910, 850, 795) was seeded with the crystals of II of mp 83.5—84.5° to give yellow crystals of mp 83.5—84.5° in good yield, which were proved to be identical with II of mp 83.5—84.5° by the mixed fusion and IR. ii) Seventy mg of II of mp 70° was melted in a test tube and after being cooled, it was crystallised from methanol to give II of mp 83.5—84.5° (mixed fusion and UV, IR and NMR comparisons). UV λ_{max} mμ (log ε): 246 (4.03, sh), 261 (4.06), 355 (3.55). IR ν_{max} cm^{-1}: 1810, 1635, 1445, 1435—1420, 1320, 1180, 1105, 1040, 1030, 895, 835, 795. NMR (τ-value): 9.06 (t, 3H), 7.90 (m, 2H), 7.77 (s, 3H), 7.26 (s, 3H), 6.36 (t, 1H), 2.82 (s, 1H), −2.98 (s, 1H). *Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.63; H, 6.49.

Dry-Distillation of V without $CaCl_2$——Three g of V was heated at 240—250° for 30 min under ordinary pressure to give a colorless distillate and non-volatile residue. The residue was then distilled *in vacuo* (1 mmHg) to give an orange yellow solid, which was treated with methanol. The methanol-insoluble fraction gave III of mp 131°. The methanol-soluble fraction, after methanol being evaporated, was treated with benzene and the benzene-soluble fraction (220 mg) was obtained. The benzene-soluble fractions (2.2 g) from 10 runs were chromatographed over 110 g of Kiesel gel with benzene-ethyl acetate (100:1). The fractions (10 g each) from No. 47 to 52 gave yellow crystals (VI) of mp 137—138° from methanol. Mass Spectrum (*m/e*, relative intensity, formula) M$^+$ 302.113, 100, $C_{17}H_{18}O_5$: 287.089, 6, $C_{16}H_{15}O_5$ (M$^+$-CH_3); 284.105, 18, $C_{17}H_{16}O_4$ (M$^+$-H_2O, m* 267.1); 269.082, 4, $C_{16}H_{13}O_4$ ($C_{17}H_{16}O_4$-CH_3); 259.095, 92, $C_{15}H_{15}O_4$ (M$^+$-$COCH_3$, m* 222.1); 245.080, 10, $C_{14}H_{13}O_3$ ($C_{16}H_{15}O_5$-C_2H_2O); 241.088, 50, $C_{15}H_{13}O_3$ ($C_{15}H_{15}O_4$-H_2O, m* 224.3); 231.103, 5, $C_{14}H_{15}O_3$ ($C_{15}H_{15}O_4$-CO); 223.075, 3, $C_{15}H_{11}O_2$ ($C_{15}H_{13}O_3$-H_2O); 217.084, 25, $C_{13}H_{13}O_3$ ($C_{15}H_{15}O_4$-C_2H_2O); 213.091, 9, $C_{14}H_{13}O_2$ ($C_{14}H_{15}O_3$-H_2O); 199.075, 22, $C_{13}H_{11}O_2$ ($C_{13}H_{13}O_3$-H_2O). *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.53; H, 5.96. From 30 g of V, 200 mg of VI and 300 mg of III were obtained.

Oximation of VI——A mixture of VI (100 mg), hydroxylamine-HCl (60 mg), pyridine (100 mg) and ethanol (1 ml) was refluxed on a steam bath for 4 hr. The mixture was evaporated to dryness *in vacuo* to give a yellow powder, which was washed with 3% HCl and then water, and the powder was chromatographed over Kiesel gel (14 g) with benzene-ethyl acetate (50:1) to give oxime anhydride (VII) of mp 198° and bisoxime monoanhydride (VIII) of mp 208°. *Anal.* Calcd. for $C_{17}H_{17}O_4N$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.36; H, 5.85; N, 4.93. *Anal.* Calcd. for $C_{17}H_{18}O_4N_2$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.49; H, 6.06; N, 8.81.

Dry-Distilation of I′ without $CaCl_2$——Diacetyltetrahydrodesoxyusnic acid (I′) of mp 131°[6] was heated at 220—240° for 30 min under ordinary pressure and the non-volatile residue was then distilled *in vacuo* (1 mmHg) to give a yellow distillate, which solidified to a powder by treatment with methanol. The powder (2.7 g), obtained from 4 g of I′, was chromatographed over 136 g of Kiesel gel with benzene–ethyl acetate (10:1). The fractions (10 g each) from No. 33 to 39 gave faint yellow crystals (X) of mp 210° from metanol. 30 mg. $FeCl_3$: green. *Anal.* Calcd. for $C_{21}H_{20}O_7$: C, 65.61; H, 5.24. Found: C, 65.97; H, 5.26. M.W. 384 (mass spectrometry). The fractions from No. 40 to 80 were rechromatographed under the same condition to give colorless crystals (XI) of mp 121—122° from methanol. 50 mg. *Anal.* Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.53; H, 5.86.

Deacetylation of X——The compound (X) was deacetylated with conc. H_2SO_4 in cold to give XII of mp 273° from methanol-benzene. *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.36. Found: C, 67.54; H, 5.44.

Reduction of 7-Acetyl-3,5-dimethyl-4,6-diacetoxycoumaran-2-one[7]——A mixture of coumaran-2-one (0.8 g), zinc amalgam (3 g), toluene (5 ml), dil. HCl (conc. HCl:H_2O=1:1) (50 ml) and acetic acid (2 drops) was refluxed for one hr and 10 ml. of dil. HCl was added to the mixture every one hr. The mixture was refluxed for 7 hr, totally. Then the mixture was extracted with ether and the ether extract gave a resinous substance, which was acetylated with acetic anhydride (8 ml) and conc. H_2SO_4 (one drop) at 60° for 30 min. The solution was poured into ice water and extracted with ether. The ether layer gave a resinous substance (650 mg), which was chromatographed over Kiesel gel (80 g) with benzene-ethyl acetate (10:1). The fractions (10 g each) from No. 25 to 31 gave colorless plates of 3,5-dimethyl-4,6-diacetoxy-7-ethylcoumaran-2-one of mp 120°. 20 mg. It was proved to be identical with XI by the mixed fusion and IR. *Anal* Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.61; H, 5.96.

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