The Oxidation of 2,3-Dihydro-4*H*-pyran-4-ones[1]

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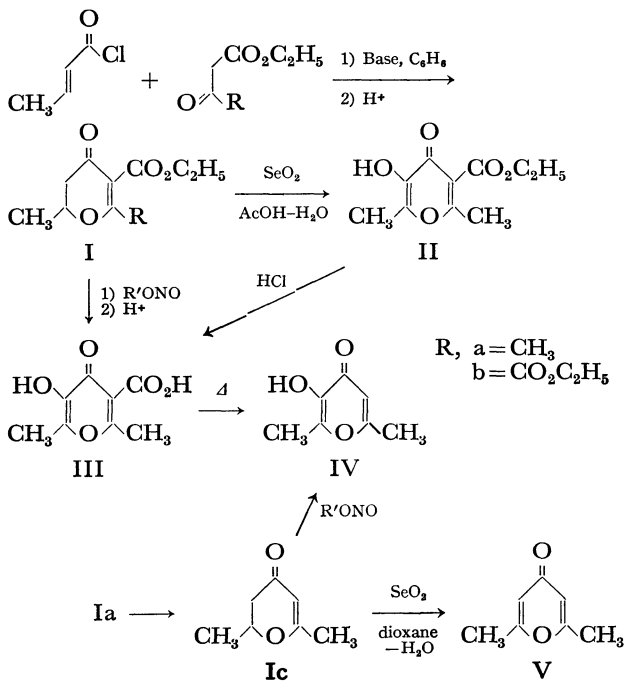
The synthesis and oxidation of substituted 2,3-dihydro-4*H*-pyran-4-ones are described. The reaction of crotonoyl chloride with β-ketoester gave dihydro-4*H*-pyran-4-ones (I). Dihydro-γ-pyrone (Ia) is oxidized, hydrolyzed, and subsequently decarboxylated to give 6-methyl maltol (IV).

3-Hydroxy-4*H*-pyran-4-ones, especially 3-hydroxy-2-methyl-4*H*-pyran-4-one, *i.e.*, maltol, have long been known and have been widely used as food flavors. Maltol has been synthesized from kojic acid or pyromeconic acid as the starting material.[2] Recently, these compounds have also been obtained[3] from inaccessible dihydro-γ-pyrones in low yields.

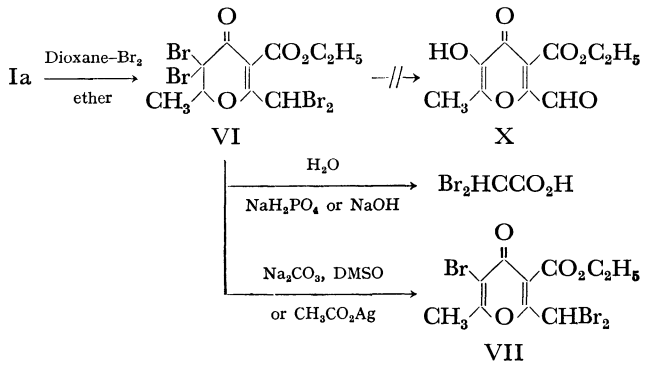
In this investigation, we aimed to get dihydro-γ-pyrones (I) and succeeded in preparing α-diketones by oxidation. We have previously reported on the oxidation of 2-carbethoxy-2-methylcyclopentanone to give 5-carbethoxy-2-hydroxy-5-methylcyclopent-2-en-1-one.[4] These studies have now been extended to dihydro-γ-pyrones (I). I was synthesized directly by the condensation of β-ketoesters with crotonoyl chloride.



5-Carbethoxy-2,3-dihydro-2,6-dimethyl-4*H*-pyran-4-one (Ia)[5] and 2,3-dihydro-2,6-dimethyl-4*H*-pyran-4-one (Ic)[6] has already been synthesized. 5,6-Dicarbethoxy-2,3-dihydro-2-methyl-4*H*-pyran-4-one (Ib) was obtained by the condensation of sodium ethyl oxalacetate[7] with crotonoyl chloride. The oxidation of Ia with selenium dioxide gave 5-carbethoxy-3-hydroxy-2,6-dimethyl-4*H*-pyran-4-one (II) in a low yield. The hydrolysis of II in hydrochloric acid afforded 5-hydroxy-2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxylic acid (III) in a 75% yield, and subsequent decarboxylation of III in diphenyl ether at 250°C yielded 3-hydroxy-2,6-dimethyl-4*H*-pyran-4-one (IV) in a 30% yield. These compounds, II, III, and IV, had a characteristic odor like maltol and gave an intense violet color with ferric chloride.

However, α-diketone was not isolated from Ib. Dihydro-γ-pyrone (Ic) gave a dehydrogenated compound, 2,6-dimethyl-4*H*-pyran-4-one (V). Furthermore, the nitrosation of Ia followed by acid hydrolysis afforded III. However, Ib gave only a tarry material, and IV was obtained from Ic.

The bromination of Ia with an excess of dioxane dibromide in ether gave 3,3-dibromo-6-dibromomethyl-5-carbethoxy-2,3-dihydro-2-methyl-4*H*-pyran-4-one (VI) in a 72.4% yield. The structure of VI was assigned on the basis of its IR, and NMR spectra and the results of an elemental analysis.



The hydrolysis of VI with sodium biphosphate in dioxane–water at 85°C for 10 hr afforded dibromoacetic acid in an 80% yield. A similar compound was also prepared by the hydrolysis of a dilute sodium hydroxide solution at 0°C for 24 hr. The hydrolysis of 5-carbethoxy-2,3-dihydro-6-methyl-γ-pyrones has been shown to give

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3) K. Nakanishi, M. Nagao, and K. Okada, *Yakugaku Zasshi* **88**, 1044 (1968), Jap. Pat. 17905 (1967); M. Higuchi *et al.*, Jap. Pat. 21106 (1970); A.A. Schleppnik, U.S. 3474113 (1969); A.A. Schleppnik and M.L. Oftedahl, U. S. 3491122 (1970); *Chem. Abstr.*, **72**, 78880t; A. A. Schleppnik and M. L. Oftedahl, Jap. Pat. 6813 (1970).

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5) E. Graf and K. C. Liu, *Arch. Pharm.*, **300**, 348 (1967).

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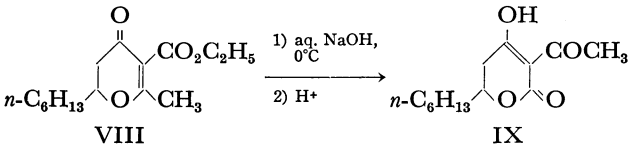
3-acetyl-5,6-dihydro-4-hydroxy-α-pyrones, together with δ-acetoxy-β-ketoesters.[5] Similarly, the treatment of aqueous sodium hydroxide with 5-carbethoxy-2-hexyl-2,3-dihydro-6-methyl-4*H*-pyran-4-one (VIII), which has been easily obtained by the condensation of ethyl acetoacetate with 2-nonenoyl chloride, afforded the corresponding α-pyrone (IX) in a 77.9% yield.



VIII IX

It may be supposed that compound VI is first hydrated to a double bond instead of to its two nucleophilic carbons, and that a subsequent ring cleavage produces dibromoacetic acid. On the other hand, the treatment of VI with equimolar amounts of sodium carbonate in DMSO provided 3-bromo-6-dibromomethyl-5-carbethoxy-2-methyl-4*H*-pyran-4-one (VII) in a 54.6% yield. When silver acetate and VI were refluxed in acetic acid, dehydrobromination also occurred to yield VII. Under various conditions, none of the expected hydrolysis product (X) could be isolated from the reaction mixture.

Accordingly, it may be supposed that the lack of success in introducing the α-carbonyl group into dihydro-γ-pyrones (I) is due to the low stability of the ring, as will be discussed above.

Experimental

All the melting points and boiling points are uncorrected. The infrared spectra were recorded with a Hitachi Model EPI-S2 spectrophotometer, and the ultraviolet spectra, with a Hitachi Model EPS-3T spectrophotometer. The NMR spectra were obtained on a JEOL Model C-60H spectrometer, with tetramethylsilane as the internal reference.

Materials. 5-Carbethoxy-2,3-dihydro-2,6-dimethyl-4*H*-pyran-4-one,[5] 2,3-dihydro-2,6-dimethyl-4*H*-pyran-4-one,[6] sodium ethyl oxalacetate,[7] *n*-butyl nitrite,[8] and crotonoyl chloride[9] were prepared by the method described in the literature. The other chemicals were commercially available and well purified by the usual procedures before use.

*5,6-Dicarbethoxy-2,3-dihydro-2-methyl-4*H*-pyran-4-one (Ib).* To a suspension of sodium ethyl oxalacetate (20 g) (0.095 mol) in 90 ml of dry benzene, 5.3 g (0.05 mol) of crotonoyl chloride diluted with 10 ml of benzene was added, drop by drop, at 15—20 °C for 30 min. The mixture was then refluxed at 70 °C for 1 hr with stirring. After cooling, 50 ml of cold water was added, and the mixture was made slightly acidic with 10% sulfuric acid. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with water and dried over magnesium sulfate. Fractional distillation under nitrogen gave ethyl oxalacetate and 6.2 g of an oil (bp 150—170 °C/0.7 mmHg). The redistillation of the latter oil gave 4.7 g (36.6%) of pure Ib; bp 142—147 °C/0.3 mmHg; n_D^{20} 1.4872; IR (neat) 1725, 1655 (C=O), 1568 (C=C), 1370, 1300—1030 cm^{-1} (C–O–C); NMR (CCl_4) 1.20 (3H, d, J=8.0), 1.29 (3H, t, J=7.0), 1.36 (3H, t, J=7.0), 2.3—3.1 (2H, m), 4.13 (2H, q, J=7.0), 4.20 (2H, q, J=7.0), 3.9—4.4 (1H, m). Found: C, 56.24; H, 6.66%. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29%. 2,4-Dinitrophenylhydrazone; mp 113—115 °C. Found: C, 49.05; H, 4.97%. Calcd for $C_{18}H_{20}N_4O_9$: C, 49.54; H, 4.62%.

*5-Carbethoxy-3-hydroxy-2,6-dimethyl-4*H*-pyran-4-one (II).* To a hot (80 °C) solution of 11.1 g (0.1 mol) of selenium dioxide in 100 ml of acetic acid and 4 ml of water, was added 10 g (0.05 mol) of Ia all at once. The mixture was refluxed with stirring for 24 hr, and then the precipitated selenium was filtered out. The filtrate was concentrated and distilled to give a yellow oil (bp 105—110 °C/0.2 mmHg); when this oil was allowed to stand overnight, it gave a crystalline material together with 4 g of recovered Ia. Filtration, followed by recrystallization from aqueous ethanol, afforded 410 mg (4.0%) of II as colorless needles; mp 155 °C; IR (KBr): 3260 (O–H), 1736, 1665 (C–O), 1605 (C=C), 1225, 1190, 1105 cm^{-1} (C–O–C); UV (EtOH) 222 mμ (ε 13560), 275 mμ (ε 7400); NMR ($CDCl_3$) 1.36 (3H, t, J=7.0), 2.30 (3H, s), 2.40 (3H, s), 4.43 (2H, q, J=7.0), 6.45 (1H, s); Found: C, 56.87; H, 5.94%. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%.

*5-Hydroxy-2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxylic Acid (III). a)*: A mixture of 170 mg of II and 3 ml of 6M hydrochloric acid was heated at 100 °C for 2 hr. The cooled mixture was extracted with chloroform and washed with water. The subsequent evaporation of the solvent gave a crude product; this was recrystallized from water to give pure III (112 mg, 75%) as colorless needles; mp 161 °C. IR (KBr): 3300, 3060—2640 (O–H), 1730, 1663 (C=O), 1620, 1570 (C=C) 1220, 1098 cm^{-1} (C–O–C); UV (EtOH), 223 mμ (ε 14000), 279 mμ (ε 6590); NMR ($CDCl_3$) 2.45 (3H, s), 2.86 (3H, s), 6.54 (1H, broad s). Found: C, 52.18; H, 4.72%. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38%.

b): Dry hydrogen chloride was introduced into a cold, stirred solution of 6.0 g (0.03 mol) of Ia in 40 ml of dry ether at 0 °C for 25 min. Then, 5.0 g (0.05 mol) of *n*-butyl nitrite in 5 ml of ether was added over a period of 30 min at 0—5 °C. The mixture was then heated at 35 °C for 4.5 hr. After cooling, the solvent was removed by distillation and the residue was hydrolyzed with 70 ml of 3M hydrochloric acid by refluxing for 5 hr. The removal of the hydrochloric acid, filtration, and subsequent recrystallization from water provided the product, III (1.0 g, 18.1%), as colorless needles; mp 160—161 °C. The infrared spectrum and the other chemical properties were identified with those of the III presented above.

*3-Hydroxy-2,6-dimethyl-4*H*-pyran-4-one (IV). a)*: A solution of 200 mg of III in 4.0 g of diphenyl ether was heated at 250—260 °C for 1 hr. After cooling, the reaction mixture was poured into 0.25M aqueous sodium hydroxide (8 ml) and the aqueous layer was separated. To remove the diphenyl ether, the aqueous layer was extracted with ether and acidified with hydrochloric acid. Extraction with ether, followed by evaporation, gave crude IV; this was recrystallized from water to provide IV (46 mg, 30%) as colorless needles; mp 159—160 °C (lit,[10] mp 162.5 °C). A mixed-melting-point determination with an authentic sample[10] indicated no depression. IR (KBr): 3230 (O–H), 1660 (C=O), 1617, 1580 (C=C), 1215 cm^{-1} (C–O–C); NMR ($CDCl_3$) 2.28 (3H, s), 2.34 (3H, s), 6.25 (1H, s), 7.32 (1H, s). Found: C, 59.97; H, 5.77%. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75%.

b): To a stirred solution of 1.26 g (0.01 mol) of Ic, 0.8 ml of hydrochloric acid, and 30 ml of ethanol, 3.2 g (0.031 mol)

8) W. A. Noyes, "Organic Syntheses," Coll. Vol. II, p. 546 (1943).

9) R. C. Fuson, R. E. Christ, and G. M. Whitman, *J. Amer. Chem. Soc.*, **58**, 2450 (1936).

10) J. N. Gollie and T. Tickle, *J. Chem. Soc.*, **81**, 1005 (1902).

of *n*-butyl nitrite diluted with 10 ml of ethanol was added at gentle refluxing for 5 min, and then the mixture was kept for 10 hr. The solvent was evaporated and the residue was recrystallized from water to yield 50 mg (3.6%) of IV; mp 159—160 °C.

2,6-Dimethyl-4H-pyran-4-one (V). A mixture of 1.26 g (0.01 mol) of Ic, 1.10 g (0.01 mol) of selenium dioxide, 25 ml of dioxane, and 2.5 ml of water was refluxed with stirring for 40 hr. After cooling the selenium was filtered out and the solvent was removed. The residue was extracted with chloroform, and the subsequent evaporation of the chloroform gave a black oil, which was then sublimed at 150 °C under reduced pressure (15—20 mmHg). The sublimed crystals were recrystallized from chloroform to give 154 mg (12.2%) of V as colorless needles; mp 129—130 °C (lit,[11] mp 132 °C); IR (KBr) 3040 (C–H), 1660 (C=O), 1610, 1590 (C=C), 1396, 1160 (C–O–C), 900 cm^{-1}. The infrared spectrum and the other chemical properties were identical with those of an authentic sample.[11]

3,3-Dibromo-6-dibromomethyl-5-carbethoxy-2,3-dihydro-2-methyl-4H-pyran-4-one (VI). Bromine (39.2 g, 0.248 mol) was stirred into 70 ml of dioxane with cooling over a period of 15 min. The mixture was then diluted with 35 ml of ether, and 7.0 g (0.035 mol) of Ia in 35 ml of ether was dropped in at room temperature over 15 min period. Then the mixture was refluxed for 7 hr and allowed to stand overnight at room temperature. The resulting mixture was poured into ice water. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with water and dried over magnesium sulfate. The evaporation of the solvent and recrystallization from ethanol afforded colorless plates (13.1 g, 72.4%); mp 88—89 °C IR (KBr): 1710, 1700 (C=O), 1600 cm^{-1} (C=C); NMR (CCl_4) 1.40 (3H, t, J=7.0), 1.95 (3H, d, J=6.0), 4.40 (2H, q, J=7.0), 4.67 (1H, m), 7.05 (1H, s). Found: C, 23.43; H, 2.11%. Calcd for $C_{10}H_{10}Br_4O_4$: C, 23.38; H, 1.96%.

Reaction of VI with Sodium Biphosphate. A mixture of 6.3 g (0.04 mol) of sodium biphosphate, 5.1 g (0.01 mol) of VI, 25 ml of water, and 25 ml of dioxane was stirred at 84—85 °C for 10 hr. After cooling, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with water and dried over magnesium sulfate. After the removal of the ether, the distillation of the residual oil gave 1.8 g (80%) of dibromoacetic acid; bp 110—112 °C/5 mmHg (lit,[12] bp 195—197 °C/250 mmHg). IR (neat): 3020, 2630—2510 (O–H), 1720 (C=O), 910 cm^{-1}; NMR (CCl_4) 5.63 (1H, s), 10.05 (1H, s); mol. wt. 217 (alkali titration), $C_2H_2Br_2O_2$ require 218.

Reaction of VI with Sodium Hydroxide. A mixture of 5.0 g (0.01 mol) of VI, 4.0 g (0.1 mol) of sodium hydroxide, and 100 ml of water was stirred at 0 °C for 24 hr. The resulting mixture was acidified with hydrochloric acid and extracted with ether. After drying, the ether was evaporated and the residual oil was distilled to give 0.8 g (38%) of dibromoacetic acid; bp 90—98 °C/1.0 mmHg.

3-Bromo-6-dibromomethyl-5-carbethoxy-2-methyl-4H-pyran-4-one (VII). *a)*: A mixture of 20.4 g (0.04 mol) of VI and 4.3 g (0.04 mol) of sodium carbonate in 75 ml of DMSO was stirred at 20 °C for 3 hr. The resulting mixture was poured into ice water and extracted with chloroform. After drying, the solvent was evaporated and the residual solid was crystallized from aqueous ethanol to give 9.45 g (54.6%) of VII; mp 149—151 °C. IR (KBr): 1732, 1638 (C=O and C=C), 1395, 1010, 720 cm^{-1}; NMR ($CDCl_3$) 1.36 (3H, t, J=6.8), 2.56 (3H, s), 4.31 (2H, q, J=6.8), 6.59 (1H, s). Found: C, 27.95; H, 2.36%. Calcd for $C_{10}H_9Br_3O_4$: C, 27.74; H, 2.10%.

b): A mixture of 2.6 g (0.005 mol) of VI and 3.3 g (0.02 mol) of silver acetate in 40 ml of acetic acid was refluxed, with stirring, for 4 hr. To the mixture was then added 3 ml of water, after which the hot mixture was refluxed for an additional 2 hr. The subsequent filtration of the silver bromide and evaporation of the solvent gave a crude product. Recrystallization from aqueous ethanol afforded 0.8 g (38%) of VII as fine needles; mp 149—150 °C.

5-Carbethoxy-2-hexyl-2,3-dihydro-6-methyl-4H-pyran-4-one (VIII). A mixture of 5.0 g (0.21 mol) of magnesium turnings, 40 ml of absolute ethanol, 0.5 ml of carbon tetrachloride, and 50 ml of dry benzene was heated under reflux for 3 hr. The solvent was then distilled off, and 100 ml of benzene was added to the magnesium ethoxide. To this suspension, 26 g (0.2 mol) of ethyl acetoacetate was added below 30 °C, and then 36.6 g (0.21 mol) of 2-nonenoyl chloride[13] was slowly added over a period of 30 min at room temperature. The mixture was heated at 70 °C for 20 min with stirring. After cooling, the reaction mixture was acidified with 10% sulfuric acid. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with water, dried over sodium sulfate, and concentrated. The residue was distilled, thus giving VIII (15.3 g, 57%); bp 137—139 °C/0.3 mmHg, n_D^{20} 1.4825; IR (neat): 1710, 1680 (C=O), 1600 cm^{-1} (C=C); NMR (CCl_4) 0.88 (3H, t, J=7.0), 1.15 (3H, t, J=7.0), 1.30 (10H, broad s), 2.06 (3H, s), 2.28 (2H, d, J=8.2), 4.04 (2H, q, J=7.0), 4.18 (1H, m). Found: C, 66.80; H, 8.95%. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01%. 2,4-Dinitrophenylhydrazone; mp 110—113 °C.

3-Acetyl-6-hexyl-5,6-dihydro-4-hydroxy-2H-pyran-2-one (IX). A cold solution of 10.7 g (0.04 mol) of VIII and 3.2 g (0.08 mol) of sodium hydroxide in 160 ml of water was stirred at 0—2 °C for 24 hr. The resulting mixture was acidified with hydrochloric acid, and then the crystalline material was precipitated. Filtration and recrystallization from aqueous ethanol afforded IX (7.5 g, 77.9%) as colorless crystals; mp 69.5—70 °C; IR (KBr): 1690 (C=O), 1565 cm^{-1} (C=C); NMR ($CDCl_3$) 0.88 (3H, t, J=7.0), 1.30 (10H, broad s), 2.53 (3H, s) 2.62 (2H, d, J=1.8), 4.25 (1H, m), 17.4 (1H, s). Found: C, 64.77; H, 8.40%. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39%.

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12) W. H. Perkin, *J. Chem. Soc.*, **65**, 425 (1894).
13) E. Otto and K. Zimmerman, *Ann. Chem.*, **425**, 330 (1921).