[Contribution from the Noyes Chemical Laboratory, University of Illinois]

DIHYDRO-1,4-PYRANS. VI.[1] OPENING AND CLOSING THE RING

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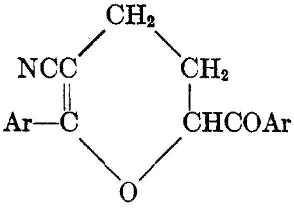
Dihydro-1,4-pyrans (I) are cyclic enol ethers of aldehydes or ketones. In view of their somewhat peculiar structure these substances might be expected to behave as vinyl ethers. In particular the opening of the ring by acidic reagents should offer no difficulty. Although this expectation was fully realized in the simple types studied by Perkin,[2] by Fargher and Perkin[3], and by Lipp[4], the more complex derivatives encountered in this laboratory[1] have proved refractory. The latter are of type I in which Ar = phenyl, *p*-tolyl or *p*-anisyl.



I

However, by the introduction of suitable groups into the molecule we have succeeded in synthesizing a dihydro-1,4-pyran of a more tractable type. It is 2-mesityl-5,6-dihydro-1,4-pyran-6-carboxylic acid (II) as shown on p. 402. This dihydro-1,4-pyran has properties very similar to those of type I but can also undergo ring opening. When it is treated with sulfuric acid in the presence of methyl alcohol the methyl ester of α-hydroxy-(2,4,6-trimethylbenzoyl) valeric acid (III) is formed. Heat reconverts the open-chain acid to the cyclic compound with the loss of water.

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[1] For the preceding paper in this series see Hully, Brock, and Fuson, *J. Am. Chem. Soc.*, **58**, 2634 (1936).

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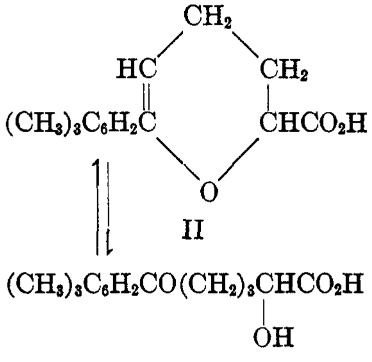
** Röhm and Haas Post-Doctorate Fellow, 1937–1938; du Pont Post-Doctorate Fellow, 1938–1939.

[2] Perkin, *J. Chem. Soc.*, **51**, 702 (1887).

[3] Fargher and Perkin, *ibid.*, **105**, 1353 (1914).

[4] Lipp, *Ann.*, **289**, 173 (1896).

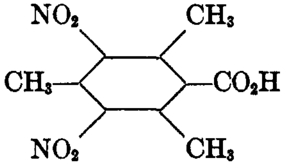


II

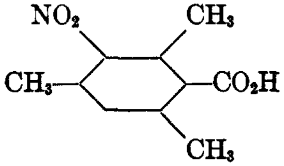
III

The hydroxy acid (III) was obtained by an interesting reaction. Ethyl α-hydroxy-γ-(2,4,6-trimethylbenzoyl) sorbate (VII), prepared by the method of Fuson, Christ, and Whitman,[5] was hydrogenated in the presence of Raney nickel.† The presence of the hydroxy acid (III) in the crude reaction mixture was demonstrated by treating the impure material with α-naphthyl isocyanate and isolating the corresponding urethan. Purification of the hydroxy acid by distillation was impossible; this process gave instead the cyclic acid (II).

The hydroxy acid (III) was best obtained by hydrolysis of the methyl ester, which was obtained from the cyclic acid by ring opening. Permanganate oxidation of the hydroxy acid gave an oil, which, upon nitration, yielded 3,5-dinitro-2,4,6-trimethylbenzoic acid. Treatment of the methyl ester with fuming nitric acid gave 3-nitro-2,4,6-trimethylbenzoic acid (VI).



V



VI

The use of a mixture of concentrated nitric and sulfuric acids produced the methyl ester of the trinitro acid (IV) to be discussed later.

Mention should be made of two other compounds which were found among the hydrogenation products. These were obtained in considerable

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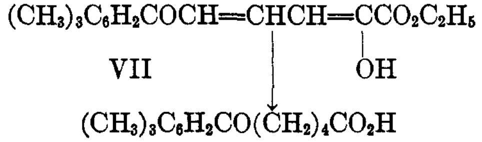
[5] Fuson, Christ, and Whitman, *J. Am. Chem. Soc.*, **58**, 2450 (1936).

† Attempts to hydrogenate the benzoate of the sorbic ester did not give promising results and were abandoned.

quantities when the hydrogenation was carried out with Adams' catalyst[6] in acidic absolute alcohol.



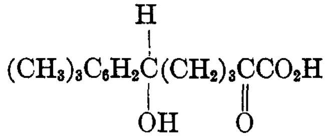
$$(CH_3)_3C_6H_2COCH{=}CHCH{=}\underset{\displaystyle |\atop OH}{C}CO_2C_2H_5$$

VII

$$\downarrow$$

$$(CH_3)_3C_6H_2CO(CH_2)_4CO_2H$$

VIII



$$(CH_3)_3C_6H_2\overset{\displaystyle H \atop |}{\underset{\displaystyle | \atop OH}{C}}(CH_2)_3\underset{\displaystyle \| \atop O}{C}CO_2H$$

IX

One of the acids, δ-trimethylbenzoylvaleric acid (VIII), was isolated as the *p*-phenylphenacyl ester. The structure assigned was established by synthesis. An authentic specimen of the acid was obtained by condensation of mesitylene with adipic anhydride. Its *p*-phenylphenacyl ester was shown by the mixture melting point method to be identical with that from the hydrogenation product (VIII). The keto acid gave a monobromo derivative which was converted by permanganate oxidation into a mixture of 2,4,6-trimethylbenzoic acid and succinic acid.

By fractional distillation of the liquid mixture of esters and saponification of the highest-boiling fraction there was obtained a third hydrogenation product, melting at 81°. It yielded a phenylhydrazone, and therefore is a keto acid. Since the ε-keto group cannot yield a phenylhydrazone on account of steric hindrance, this substance must be an α-keto acid. It may have the structure IX or that of the corresponding diketo acid. Its analysis corresponds to that expected on the basis of formula IX.

The new dihydro-1,4-pyran (II) reacted with a variety of reagents. Hydrogenation, however, could not be effected catalytically or with sodium amalgam. Treatment with hydrogen iodide and red phosphorus apparently failed also to reduce the ethylenic linkage. However, it cleaved the molecule to give adipic acid.‡

Bromination converted the cyclic acid into a monobromo derivative. Oxidation with ozone or dilute nitric acid gave 2,4,6-trimethylbenzoic acid, as would be expected. The most interesting result was obtained by

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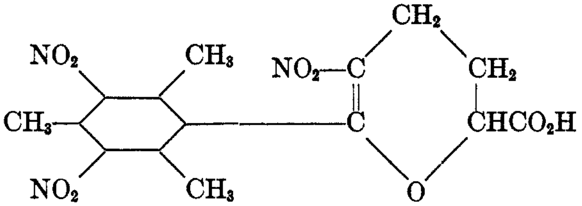
[6] ADAMS, VORHEES, AND SHRINER, *Organic Syntheses*, Coll. Vol. I, 452 John Wiley and Sons, Inc., New York, **1932**.

‡ This type of cleavage is characteristic of mesityl ketones [KLAGES AND LICKROTH, *Ber.*, **32**, 1549 (1899)].

nitration. A trinitro derivative was formed which very probably has the structure represented by IV.



IV

The dihydro-1,4-pyran ring evidently undergoes nitration after the fashion of true aromatic compounds.

EXPERIMENTAL

Reactions of Ethyl α-Hydroxy-δ-(2,4,6-trimethylbenzoyl)sorbate

1. Benzoylation.—To a solution of 0.23 g. of sodium in 10 cc. of absolute alcohol was added 50 cc. of dry ether. To the resulting solution were added 3.26 g. of the ester and 1.7 g. of benzoyl chloride. The mixture was allowed to stand overnight. Water was added, and the ethereal solution, after being washed several times with 2.5% potassium hydroxide solution, and then with water, was dried and concentrated. Addition of petroleum ether caused the benzoate to separate in the form of lemon yellow prisms; m.p. 109°; yield, 2.7 g.

Anal. Calc'd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16.
Found: C, 73.46; H, 5.97.

2. Hydrogenation.—In a typical experiment 69 g. of the ester was hydrogenated in three equal portions. The portions were each suspended in 100 cc. of ethanol, about one gram of Raney nickel catalyst was added, and the mixture was hydrogenated at a pressure of approximately 40 lbs. per sq. in. At the end of about five hours all the yellow solid had dissolved and the solution had absorbed nearly two moles of hydrogen. The three solutions were combined, evaporated to a small volume, and the residual oil was suspended in 700 cc. of a 10% solution of sodium carbonate, and refluxed for twelve hours. At the conclusion of this period the solution was cooled, and unchanged ester was extracted with ether. Upon acidification of the water layer the free hydroxy acid was obtained as a yellow oil, which was extracted with ether, dried, concentrated, and the residue was distilled under a pressure of 20 mm. The resulting crystalline mass was recrystallized from benzene-ligroïn as white prisms; m.p. 147–149°; yield 25 g. By addition of more ligroïn to the solution another gram of material may be obtained, making the total yield 44% of the theoretical. The 2-mesityl-5,6-dihydro-1,4-pyran-6-carboxylic acid obtained in this way was pure enough for most reactions; however, upon recrystallization it melted at 149–150°.

Anal. Calc'd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37; neutr. equiv., 246.1; mol. wt. 246.1.
Found: C, 73.42, 73.21; H, 7.30, 7.36; neutr. equiv., 245.7, 249.7, 246.4; mol. wt. (in boiling acetone), 251, 254.

The acid is readily soluble in a solution of sodium bicarbonate.

Reaction of the Cyclic Acid with Reducing Agents

1. Catalytic hydrogenation.—The acid (4.5 g.) was dissolved in absolute alcohol (50 cc.) and hydrochloric acid (0.5 cc.), and platinum oxide (0.2 g.) was added. After three days' treatment with hydrogen the starting material was recovered. Other unsuccessful attempts were made using as catalysts nickel, palladium, and platinum oxide at 70°.

2. Sodium amalgam.—One-half gram of the acid was dissolved in 0.5*N* sodium hydroxide solution, and 40 g. of 2% sodium amalgam added. After fourteen hours the solution was decanted from the mercury and acidified. The recovered product melted at 149°, and was shown by a mixture melting-point determination to be the starting material.

3. Red phosphorus and hydriodic acid.—One-half gram of the acid was refluxed for four hours with a mixture of 0.5 g. of red phosphorus and 10 cc. of constant-boiling hydriodic acid. At the end of this period the mixture was diluted with water, and filtered through a sintered glass funnel. The phosphorus was washed thoroughly with ether. The filtrate was extracted with ether, the extract was washed with water and with a solution of sodium thiosulfate, dried, and concentrated. Upon addition of petroleum ether white crystals were obtained; m.p. 150° (previous softening); melting-point of mixture with starting material, 130–137°. The yield was 0.1 g. It was shown by a mixture melting-point determination to be adipic acid.

Anal. Calc'd for $C_6H_{10}O_4$: C, 49.32; H, 6.90.
Found: C, 49.73; H, 6.60.

Reaction of the Cyclic Acid with Oxidizing Agents

1. Alkaline hydrogen peroxide.—The acid (0.2 g.) was dissolved in 5 cc. of 2*N* sodium hydroxide solution and 1 cc. of 30% hydrogen peroxide was added. After standing overnight, the solution was acidified with acetic acid, and the solid was collected; m.p. 148°. It was shown by a mixture melting point determination to be the starting material.

2. Ozone.—One gram of pure crystalline acid was dissolved in 50 cc. of dry carbon tetrachloride. Ozone was led through the solution for a period of four hours. The ozonized product was insoluble and separated on the surface of the solution as a viscous mass. It was decomposed by adding water directly to the carbon tetrachloride solution and warmed slightly on the steam bath to insure complete decomposition. The solvent was then evaporated. The viscous residue was distilled at low pressure and solidified after standing for a short period. Recrystallization from benzene gave 0.3 g. of colorless crystals; m.p. 152°. The melting point of a mixture with 2,4,6-trimethylbenzoic acid showed no depression.

3. Dilute nitric acid.—One-half gram of the cyclic acid was suspended in 20 cc. of water containing 5 cc. of concentrated nitric acid. The mixture was refluxed for about thirty minutes; the oil which formed at first gradually solidified. The mixture was cooled, and the product was collected; yield, 0.3 g.; m.p. 151°. A mixture melting-point determination showed the compound to be 2,4,6-trimethylbenzoic acid.

Bromination of the cyclic acid.—The acid (0.35 g.) was dissolved in carbon tetrachloride (10 cc.) and cooled in ice water while a solution of bromine (0.23 g.) in carbon tetrachloride (5 cc.) was added with shaking. A copious evolution of hydrogen bromide was observed. When about nine-tenths of the calculated quantity of bromine had been added the rate of bromination appeared to slow up appreciably and the reaction was stopped. The solution was concentrated to a small volume, and petroleum ether was added. The slightly pink crystals of the bromo acid were collected; yield, 0.30 g. The compound melted at 139°. Recrystallization from chloroform-petroleum ether gave colorless needles; m.p. 139°. The Beilstein test for halogen was positive.

Anal. Calc'd for $C_{15}H_{17}BrO_3$: C, 55.41; H, 5.27.
Found: C, 55.58; H, 5.07.

Nitration of the cyclic acid.—One-half gram of the acid was dissolved in 5 cc. of concentrated sulfuric acid, and concentrated nitric acid was added dropwise until the further addition of acid seemed to produce no change in the color. The mixture was poured on ice, and the yellow product was collected and washed with water. Upon crystallization from dilute alcohol the 2-(3,5-dinitromesityl)-3-nitro-5,6-dihydro-1,4-pyran-6-carboxylic acid was obtained as yellow needles; m.p. 250°, with decomposition; yield, 0.5 g. These crystals contained water of hydration which could be removed from the product only by repeated crystallization from benzene. The product so purified melted at 255°.

Anal. Calc'd for $C_{15}H_{15}N_3O_9$: C, 47.26; H, 3.96; N, 11.01.
Found: C, 47.60; H, 4.10; N, 10.81.

The *methyl ester* of the nitro acid was prepared by refluxing with a mixture of methyl alcohol and concentrated sulfuric acid. The product was obtained from methyl alcohol as stout yellow prisms; m.p. 162–163°.

Anal. Calc'd for $C_{16}H_{17}N_3O_9$: C, 48.62; H, 4.33; N, 10.62.
Found: C, 48.66; H, 4.20; N, 10.70.

Esterification and ring-opening of the acid.—Ten grams of the cyclic acid was dissolved in 200 cc. of methyl alcohol, and 7 cc. of concentrated sulfuric acid was added. The mixture was refluxed for four hours, after which the solution was concentrated at room temperature under reduced pressure. When the volume had been reduced to about one-fifth, the mixture was poured into water, and the product was taken up in ether. The ethereal extract was washed with bicarbonate solution and with calcium chloride solution and dried over calcium chloride. Upon concentration of the solution and the addition of petroleum ether the methyl α-hydroxy-δ-(2,4,6-trimethylbenzoyl)valerate separated as an oil, but crystallized upon standing in the ice-chest; yield, 6.5 g.; m.p. 43–44°. A further quantity of ester (1.3 g.) can be recovered by further concentration of the solution. The ester can be distilled unchanged under reduced pressure.

Anal. Calc'd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97.
Found: C, 69.24; H, 7.75.

Reactions of α-Hydroxy Ester

1. Saponification.—The crude uncrystallized ester obtained from 0.5 g. of the cyclic acid was saponified by boiling for three hours with 10 cc. of 10% sodium hydroxide. Upon acidification of the alkaline solution, a yellow oil was obtained. This was taken up in ether, dried, and the ether was evaporated. The resulting oil was placed in a test-tube with 1 cc. of α-naphthyl isocyanate and heated at 100° for fifteen minutes. The resulting solid was taken up in ether and extracted with sodium bicarbonate. The bicarbonate solution was acidified, and the acid liberated was taken up in ether, dried, and concentrated. After addition of petroleum ether the solution was allowed to stand; 0.15 g. of white crystals was obtained. After repeated crystallization from ether-petroleum ether the urethan melted at 145–146°.

Anal. Calc'd for $C_{26}H_{27}NO_5$: C, 72.04; H, 6.13; N, 3.23.
Found: C, 72.00; H, 6.23; N, 3.40.

The liquid acid obtained by the saponification of the α-hydroxy ester can be distilled under reduced pressure practically without residue. Under these conditions it is converted to the cyclic acid; m.p. 149–150°.

2. Oxidation.—(a) Alkaline permanganate.—One gram of pure crystalline ester was saponified by boiling for two hours with 10 cc. of 10% sodium hydroxide solution. The solution was diluted to 100 cc., cooled in ice, and 0.76 g. of potassium permanganate was added in 50 cc. of water. After twelve hours sulfur dioxide was passed in to dissolve the manganese dioxide. The acidified solution was extracted with ether, and the ethereal extract was dried, concentrated, and the residue was distilled under reduced pressure. The yellow oil obtained could not be crystallized, so it was dissolved in 3 cc. of concentrated sulfuric acid and nitrated by the addition of about 0.5 cc. of concentrated nitric acid. After standing for three hours the mixture was poured on ice, and the product was twice crystallized from benzene. The 3,5-dinitro-2,4,6-trimethylbenzoic acid melted at 230–231° and was identified by a mixture melting-point determination.

(*b*) *Fuming nitric acid.*—One gram of the ester was powdered and added to 50 cc. of fuming nitric acid, and the mixture was stirred for twenty-four hours. The mixture was poured on ice, the product collected, and recrystallized from benzene-ligroïn; m.p. 181–182°. This was shown by a mixture melting-point determination to be 3-nitro-2,4,6-trimethylbenzoic acid.

3. Nitration.—One-half gram of crude crystalline ester was dissolved in 5 cc. of concentrated sulfuric acid and concentrated nitric acid added to constant color. The solution was poured on ice; the yellow, crystalline product was collected, and recrystallized from methyl alcohol; m.p. 162–163°. By a mixture melting-point determination this was shown to be identical with the methyl ester of the trinitro cyclic acid.

4. Reaction with phenylmagnesium bromide.—A solution of phenylmagnesium bromide prepared from 7.9 g. of bromobenzene and 1.33 g. of magnesium turnings in 100 cc. of dry ether was concentrated by distillation of 75 cc. of the ether. Then 75 cc. of dry benzene was added. The resulting mixture was refluxed on a hot plate while 2.8 g. of the ester in 25 cc. of dry benzene was added; the mixture was then refluxed for three hours and poured on 200 g. of ice containing 2 cc. of concentrated sulfuric acid. The mixture was separated, and the benzene layer was washed with water, dried, and concentrated to a small volume. Upon addition of ligroïn 1.3 g. of needles was obtained, which upon repeated crystallization melted at 134–135°. Evaporation of the mother liquor left an oil which was not identified.

Anal. Calc'd for $C_{27}H_{30}O_3$: C, 80.54; H, 7.53.
Found: C, 80.61; H, 7.72.

5. *Reaction with liquid ammonia.*—One gram of the pure solid ester was dissolved in 10–15 cc. of liquid ammonia in a stout Pyrex tube, and the tube was sealed. After being allowed to stand at room temperature for four days the tube was opened, the contents were poured out, and the excess ammonia was allowed to evaporate. Upon addition of a small quantity of ether the amide crystallized, and was collected. It

melted at 111.5–112.5°, and the melting point was not raised by repeated recrystallizations from toluene. The yield was nearly quantitative.

Anal. Calc'd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.02; N, 5.32.
Found: C, 68.54; H, 8.10; N, 5.39.

Hydrogenation of ethyl α-hydroxy-δ-(2,4,6-trimethylbenzoyl)sorbate by the Adams method.[6]—When the hydrogenation was carried out with Adams' catalyst in acidic absolute alcohol there resulted a yield of 10–15% of the cyclic acid and an oil.

Four grams of this oil was dissolved in a solution of 0.8 g. of sodium carbonate in 15 cc. of water. The solution was made faintly acidic with hydrochloric acid, 4.4 g. of *p*-phenylphenacyl bromide in 30 cc. of ethyl alcohol was added, and the mixture was refluxed for one hour. The oil precipitated by the addition of water was taken up in ether and dried. The solution was concentrated, and petroleum ether was added; 0.5 g. of slightly colored crystals were obtained. These were twice recrystallized from ethyl alcohol; m.p. 79°. By a mixture melting-point determination the compound was identified as the *p*-phenylphenacyl ester of δ-(2,4,6-trimethylbenzoyl)valeric acid.

Anal. Calc'd for $C_{29}H_{30}O_4$: C, 78.71; H, 6.83.
Found: C, 78.51; H, 6.95.

In another experiment the reduced ester was fractionally distilled and the highest boiling fraction saponified separately with 10% potassium hydroxide solution. The mixture was acidified, extracted with ether, and the ethereal extract was dried and distilled. The distillate upon crystallization from ether-petroleum ether gave white crystals; m.p. 74–78°; yield, 0.6 g. When pure the keto acid melted at 81°.

Anal. Calc'd for $C_{16}H_{20}O_4$: C, 68.18; H, 7.63.
Found: C, 68.30; H, 7.77.

The *phenylhydrazone*, once recrystallized from benzene, melted at 103–104°.

δ-(2,4,6-Trimethylbenzoyl)valeric acid.—This acid was prepared by a modification of the method used by Hill[4] for the preparation of δ-benzoylvaleric acid.[7]

Seventy-three grams of adipic acid was refluxed for six hours with 200 cc. of acetic anhydride. The excess acetic anhydride and the acetic acid formed in the reaction were removed by distilling the mixture under a pressure of 18 mm. until the temperature of the heating bath reached 120°. The residual adipic anhydride was dissolved in 200 cc. of nitrobenzene.

Aluminum chloride (150 g.) was dissolved in a mixture of nitrobenzene (350 cc.), carbon disulfide (200 cc.) and mesitylene (140 cc.). This mixture was cooled to 10°, and the solution of anhydride was added slowly. The mixture was stirred mechanically for fourteen hours without further addition of ice to the cooling bath. After addition of ice and hydrochloric acid to the mixture the solvents were removed by steam distillation. The brown residual oil was taken up in ether, washed with hydrochloric acid and finally extracted with 5% potassium hydroxide solution. The alkaline solution was acidified and extracted with ether. Upon concentration of the ethereal solution and addition of petroleum ether the trimethylbenzoylvaleric acid was obtained as needles melting at 59°; yield, 35 g. Recrystallization gave colorless needles; m.p. 60°.§

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[7] HILL, *J. Am. Chem. Soc.*, **54**, 4105 (1932).

§ This compound was prepared previously by Borsche [*Ber.*, **52**, 2080 (1919)] who failed to report either the melting point or analysis.

Anal. Calc'd for $C_{15}H_{20}O_3$: C, 72.6; H, 8.07.
Found: C, 72.4; H, 8.13.

Evaporation of the ether solution containing the alkali-insoluble material gave a solid which when recrystallized from alcohol gave 18 g. of *1,4-di-(2,4,6-trimethylbenzoyl)butane*[8]; m.p. 106°.

p-*Phenylphenacyl ester of δ-(2,4,6-trimethylbenzoyl)valeric acid.*—The ester was prepared in the usual manner by the action of *p*-phenylphenacyl bromide on the sodium salt of δ-(2,4,6-trimethylbenzoyl)valeric acid. The product after repeated crystallization from ethyl or methyl alcohol melted at 79°.

Anal. Calc'd for $C_{29}H_{30}O_4$: C, 78.71; H, 6.83.
Found: C, 79.61; H, 6.87.

Bromination of δ-(2,4,6-trimethylbenzoyl)valeric acid.—The acid (2.48 g.; 0.01 mole) was dissolved in carbon tetrachloride and bromine (1.60 g.; 0.01 mole) was added to the solution at 0°. A lowering in the reaction rate was observed when about nine-tenths of the bromine had been added, and the addition was discontinued. The solution was evaporated to a small volume, and ligroïn was added. Upon cooling crystals melting at 90–92° were obtained. Upon recrystallization from chloroform-petroleum ether the compound was obtained as colorless needles; m.p. 90–92°.

Anal. Calc'd for $C_{15}H_{19}BrO_3$: C, 55.07; H, 5.86.
Found: C, 55.34; H, 6.07.

Oxidation of δ-bromo-δ-(2,4,6-trimethylbenzoyl)valeric acid.—One gram of the brominated acid was dissolved in 100 cc. of 1% potassium hydroxide solution and potassium permanganate solution added at room temperature until a permanent purple color was reached. Sulfur dioxide was passed in to dissolve the precipitated manganese dioxide and the organic acids were separated from water solution by continuous extraction with ether. Upon concentration of the ethereal solution and fractional crystallization of the solid obtained, both succinic acid (m.p. 182°) and mesitylglyoxylic acid (m.p. 117°) were obtained; both were identified by mixture melting-point determinations.

SUMMARY

A new dihydro-1,4-pyran has been isolated from the hydrogenation products of ethyl α-hydroxy-δ-(2,4,6-trimethylbenzoyl)-sorbate (II). This compound, 2-mesityl-5,6-dihydro-1,4-pyran-6-carboxylic acid (IV), undergoes ring opening to yield the corresponding open-chain acid. Dehydration of the latter regenerates the dihydro-1,4-pyran.

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[8] Kao, *J. Chinese Chem. Soc.*, **3**, 355 (1935); See also BORSCHE, *loc. cit.*