Cholest-5-ene-3β,7α-diol (3b). A. From the 7α-Hydroperoxide 3a.—A solution of 1 mg of **3a** in methanol was reduced with an excess of sodium borohydride. Thin layer chromatographic analysis of the reduction mixture established that only **3b** was present and that no **4b** had been formed. Pure **3b** was recovered by preparative thin layer chromatography and identified by thin layer and gas chromatographic means.

B. From 5α-Cholest-6-ene-3β,5-diol.—Pure **2b**, mp 148–149° (lit. mp 147–150°,[4c] 170–175, 166–171, and 134–135°,[5] 181°[22]), prepared by sodium borohydride reduction of **2a**, free from **3a** and all other detectable sterols, was dissolved in acetone (10 mg/5 ml) and warmed at 50° on a water bath. Aliquots (80 μg) were removed at intervals for thin layer chromatographic analysis. The intensity of the **3b** spot on chromatograms increased over the period 24–72 hr. After 72 hr the sample was chromatographed using benzene–ethyl acetate (3:7) with triple ascending irrigation. The **3b** zone was eluted and the pure product was crystallized from diethyl ether–hexane, thus yielding pure **3b**: mp 185–186° (lit.[9] mp 158–161 and 176–187°); $\bar{\nu}_{\max}^{\mathrm{KBr}}$ 3350, 1630 cm^{-1}, identical with spectra of an authentic sample. The **3b** preparation was also identical in thin layer and gas chromatographic properties with an authentic sample of **3b**.

C. From Cholesterol Acetate (1b).—Fraction D, 2.994 g, obtained from autoxidation of **1b**, characterized by thin-layer chromatographic mobility R_c 1.11 with an intense blue color with sulfuric acid spray, was composed of **3c** and **4c** in the proportion 3:2. Hydrolysis of the material with 5% sodium methoxide in methanol followed by chromatography on Sephadex LH-20 and crystallization several times from methanol gave pure **3b**: mp 182–184° (lit.[9] mp 158–161 and 176–187°); $[\alpha]_D$ −75.8° (lit.[9] $[\alpha]_D$ −89°); R_c 0.28 (blue color with sulfuric acid); t_R 2.2 (3% QF-1), 1.6 (3% SE-30); R_v 1.5; nmr δ 0.68 (s, 3 H, C-18 protons), 0.86 (d, J = 5 Hz, 6 H, C-26, C-27 protons), 0.92 (d, J = 5 Hz, C-21 protons), 0.99 (s, 3 H, C-19 protons), 3.50 (m, $W_{1/2}$ = 12 Hz, 1 H, 3α proton), 3.85 (q, $J_{6,7}$ = 5.5, $J_{7,8}$ = 1.5 Hz, 1 H, 7β proton), 5.60 ppm (d, J = 5.5 Hz, 1 H, C-6 vinyl proton); mass spectrum identical with that of the 3β,7β-diol **4b**. In addition to **3b** thus recovered there was obtained from the Sephadex LH-20 column a pure sample of **4b**, identified by melting point, chromatographic, and spectral properties with an authentic sample.

Registry No.—**4a**, 36871-91-7; **4c**, 36871-92-8; 3β-acetoxycholest-5-ene 20α-hydroperoxide, 36871-93-9; 3β-acetoxycholest-5-ene 25-hydroperoxide, 36871-94-0.

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[22] H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1792 (1948). It appears that **2b** may exist in different crystalline modifications depending on conditions of recrystallization and drying.

Syntheses of 2,5-Dimethyl-4-hydroxy-2,3-dihydrofuran-3-one (Furaneol), a Flavor Principle of Pineapple and Strawberry

GEORGE BÜCHI*[1] AND EDOUARD DEMOLE

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

ALAN F. THOMAS

Firmenich et Cie, Laboratoire de Recherche, Geneva

Received August 8, 1972

Three syntheses of furaneol, a flavor component of strawberry and pineapple, are described. Oxidation of the known 2,5-dimethyl-2,5-dimethoxy-2,5-dihydrofuran with potassium chlorate in the presence of catalytic amounts of osmium tetroxide in aqueous solution gave *erythro*-3,4-dihydroxyhexane-2,5-dione, while hydrodimerization of methylglyoxal with zinc yielded the threo isomer. Both dihydroxy diketones on exposure to mildly basic reagents were converted to furaneol. Acidic reagents did not lead to furaneol but its aliphatic isomer 3-hydroxy-3-hexene-2,5-dione and 3-acetyl-2,5-dimethyl-4,5-dihydrofuran-4-one, the latter originating from cleavage to pyruvic acid followed by condensation with starting material. In a third synthesis hexane-3,4-dione was transformed to the symmetrical dibromide and then to furaneol by hydrolysis.

Among the many hundreds of compounds isolated from the volatile portions of fruit aromas,[2] furaneol [2,5-dimethyl-4-hydroxy-2,3-dihydrofuran-3-one (**5**)] occupies a central position. It was isolated at the same time from the organoleptic principle of pineapple[3] and from strawberry flavor.[4] Since this flavor principle with a powerful caramel-like odor has found many applications in the food and beverage industry, its chemical synthesis has become of some interest. Furaneol was first prepared accidentally, in unspecified yield, from rhamnose and piperidine acetate in hot ethanol solution.[5] Two rational syntheses[6,7] of furaneol have been described, but both seem unpractical for production purposes. In this paper we describe syntheses of furaneol from three different, readily available starting materials. Oxidation of 2,5-dimethyl-2,5-dimethoxy-2,5-dihydrofuran (**2**) prepared by bromination of 2,5-dimethylfuran (**1**) in methanol solution,[8] with potassium chlorate and a catalytic amount of osmium tetroxide[9] in aqueous tetrahydrofuran containing sodium bicarbonate, gave the diol **3** in 10% yield. Since we suspected that most of the diol **3** was lost by hydrolysis the oxidation was performed in a more aqueous reaction medium and in the absence of bicarbonate. The dihydroxy diketone **4** was thus obtained in nearly quantitative yield. The diol **3** is formed also upon oxidation of the olefin with potassium permanganate and we concluded that it has cis stereochemistry and the resulting dihydroxy diketone **4** the erythro configuration. Parenthetically, infrared measurements indicate the presence of only one intramolecular hydrogen bond in the erythro isomer, suggesting the preferred conformation **4**. Efforts to convert the cis diol **3** to furaneol by elimina-

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[1] To whom correspondence should be addressed.

[2] H. G. Maier, *Angew. Chem.*, **82**, 965 (1970) (review article).

[3] J. O. Rodin, C. M. Himel, R. M. Silverstein, R. W. Leeper, and W. A. Gortner, *J. Food Sci.*, **30**, 280 (1965).

[4] B. Willhalm, M. Stoll, and A. F. Thomas, *Chem. Ind. (London)*, 1629 (1965). The physical properties of furenidones were described by A. Hofmann, W. v. Philipsborn, and C. H. Eugster, *Helv. Chim. Acta*, **48**, 1322 (1965).

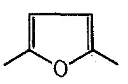
[5] J. E. Hodge, B. E. Fisher, and E. C. Nelson, *Amer. Soc. Brew. Chem. Proc.*, 84 (1963).

[6] A. Hofmann and C. H. Eugster, *Helv. Chim. Acta*, **49**, 53 (1966).

[7] D. W. Henry and R. M. Silverstein, *J. Org. Chem.*, **31**, 2391 (1966).

[8] J. Levisalles, *Bull. Soc. Chim. Fr.*, 997 (1957).

[9] *Cf.* H. Muxfeldt and G. Hardtmann, *Justus Liebigs Ann. Chem.*, **669**, 113 (1963).



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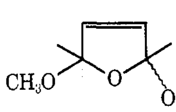

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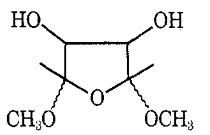

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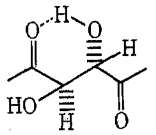
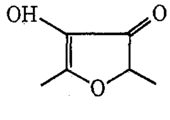


4 erythro isomer



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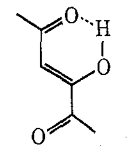


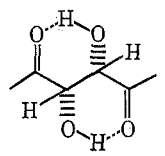
6

tion of two molecules of methanol under the agency of *p*-toluenesulfonic acid, sulfanilic acid, and other acidic reagents failed, although a faint odor of furaneol was noticed frequently during these experiments. Dehydration of the erythro dihydroxy diketone **4** in the presence of acidic catalyst or by thermolysis, again, did not yield furaneol (**5**), but its aliphatic isomer 3-hydroxy-3-hexene-2,5-dione (**6**). Attempts to effect cyclization under basic conditions were more encouraging. Eventually, both sodium hydrogen carbonate and disodium hydrogen phosphate were found to be useful catalysts, yielding furaneol in over 50% yield.

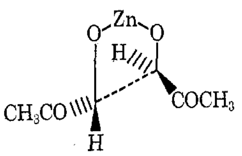
We next turned to exploring alternate methods for the preparation of the aliphatic precursor **4**. Hydrodimerization of methylglyoxal (**7**) with zinc in aqueous acetic acid solution furnished a new dihydroxy diketone which turned out to be the threo isomer **8** with two intramolecular hydrogen bonds. Predominant formation of the threo isomer can be attributed to dimerization within conformation **9** or **10** with minimum steric interference between large substituents. Condensation of the threo epimer **8** with acetone gave two products separable by chromatography. The major compound was the 1,3-dioxolane **11**, whose nmr spectrum exhibited a single signal[10] for the geminal dimethyl grouping confirming the stereochemistry already assigned. Elemental composition and mass spectrum of the minor compound demonstrated that it resulted from combination of the threo dihydroxy diketone **8** with two molecules of acetone, and the nmr spectrum is in agreement with structure **12**. Since the enol forms of the erythro and threo dihydroxy diketones **4** and **8** are identical, base-catalyzed cyclization of the threo isomer **8** should also lead to furaneol (**5**), and this was confirmed by experiment.

CH_3COCHO

7



8 threo isomer



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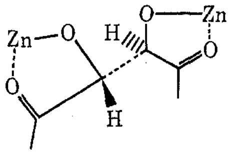

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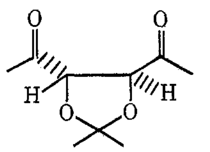

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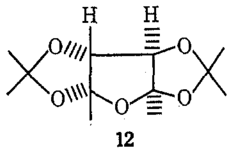

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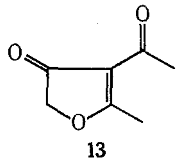

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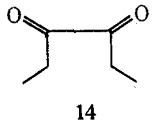

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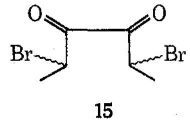
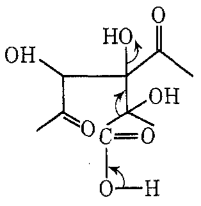
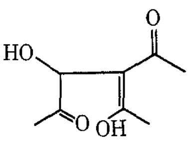


15

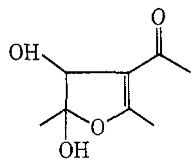
In view of our experience with the erythro isomer **4** we had doubts about the ability of acids to catalyze the transformation of the threo dihydroxy ketone **8** to furaneol (**5**), and these were confirmed by experiments. The threo isomer on treatment with acids is transformed to a mixture of 3-hydroxy-3-hexene-2,5-dione (**6**) and a new compound in varying amounts depending on conditions used. Based on spectral properties (see Experimental Section) the unknown was assigned the furenidone structure **13**. The appearance of this product seemed puzzling until it was realized that the triketone **6** could hydrolyze to pyruvic acid, which in turn could condense with the starting material to give the β-hydroxycarboxylic acid A.



A



B



C

Decarboxylation with concomitant elimination of water could yield B. Cyclization to C followed by loss of water could give the furenidone **13**. In support of this hypothesis condensation of pyruvic acid with the dihydroxy diketone **8** does indeed furnish the furenidone **13**.

Finally, the conversion of hexane-3,4-dione (**14**) to furaneol (**5**) was studied. The symmetrical dibromide **15** as a mixture of threo and erythro forms was available in nearly quantitative yield by straightforward bromination in ether–dioxane solution. Hydrolysis of the dibromide **15** at reflux gave furaneol (**5**) in 46% yield based on hexane-3,4-dione (**14**). After this last synthesis of furaneol (**5**) had been completed we became aware of a German patent application describing the same sequence of chemical operations.[11]

Experimental Section

Microanalyses were performed in the laboratory of Dr. E. Palluy, Firmenich et Cie, Geneva. Boiling points and melting points are uncorrected. Nmr spectra were measured in CCl_4 solution.

2,5-Dimethyl-2,5-dimethoxy-3,4-*cis*-dihydroxytetrahydrofuran (3). A.—A heterogeneous mixture of 2,5-dimethyl-2,5-dimethoxy-2,5-dihydrofuran (**2**)[8] (2.5 g, 15.8 mmol), potassium chlorate (2.8 g, 22.8 mmol), osmium tetroxide (0.09 g, 0.3 mmol), sodium bicarbonate (1.9 g, 22.6 mmol), tetrahydrofuran (25 ml), and water (35 ml) was stirred at 30° for 63 hr and concentrated to approximately one quarter of its volume under reduced pressure, and the residue was extracted twice with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under vacuum, leaving 0.32 g (10%) of **3** as colorless crystals, mp 95–99°.

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[10] *Cf.* F. I. Carroll, *J. Org. Chem.*, **31**, 366 (1966).

[11] W. J. Evers, German Offenlegungsschrift 2,105,014 (1971); Belgian Patent 762,686 (1971); U. S. Patent 3,629,292 (1971).

B.—A solution of 47.4 g (0.3 mol) of **2** in 300 ml of butanol was cooled to −8°, and a solution of 31.6 g (0.2 mol) of potassium permanganate and 45 g (0.183 mol) of magnesium sulfate (hydrate) in 750 ml of water was added over a period of 40 min, during which the temperature was maintained below −2°. After storage at room temperature for 4 hr the mixture was filtered and concentrated to 100 ml. The concentrate was extracted with butanol, dried ($MgSO_4$), and evaporated to give 9 g of product. Two crystallizations from hexane gave a product, mp 95–99° which was raised to 104–106° on sublimation, nmr ($CCl_4 + CD_3COCD_3$) δ 1.29 (6 H, s), 3.22 (6 H, s), 4.00 (4 H, m).

Anal. Calcd for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 50.10; H, 8.18.

***erythro*-3,4-Dihydroxyhexane-2,5-dione (4).**—A mixture of **2** (7.16 g, 45.2 mmol), potassium chlorate (7.9 g, 64.5 mmol), osmium tetroxide (0.25 g, 1.0 mmol), tetrahydrofuran (50 ml), and water (100 ml) was heated for 18 hr to 45–50° in an oil bath. The resulting yellow solution was evaporated to dryness under reduced pressure and the residue was taken up in successive portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated, giving 6.9 g (~100%) of crude dihydroxy diketone **4** which was recrystallized from $CCl_4/CHCl_3$: mp 59–61°; R_f 0.73 (silica gel G, ethyl acetate); ir (KBr) 3320 cm^{-1}; ($CHCl_3$, dilute) 3450–3550, 1705–1710 cm^{-1}; mass spectrum (70 eV) *m/e* 128, 43; nmr ($CDCl_3$, CCl_4) δ 2.32 (6 H, s), 3.85 (2 H, s), 4.34 (2 H, s).

Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.68; H, 6.84.

Furaneol (5). A.—Erythro dihydroxy diketone **4** (5.4 g, 36.9 mmol) was dissolved in 100 ml of a freshly prepared saturated solution of $NaHCO_3$ in H_2O (pH ~8.0) and extracted at room temperature with pentane in a continuous extractor. After 1 week the extract contained 0.61 g of crystalline furaneol (**5**). The extraction process was continued for a second week using ethyl ether containing 10–15% of pentane. Evaporation gave a second crop of furaneol (**5**) (1.81 g), total yield 51%. The furaneol obtained was recrystallized at low temperature from a saturated solution in petroleum ether (bp 30–50°) and identified with authentic furaneol[4] by melting point (78–80° dec) and ir and nmr spectra. The latter showed signals ($CDCl_3$) at δ 1.45 (3 H, d, J = 7 Hz), 2.30 (3 H, s), 4.55 (1 H, q, J = 7 Hz), 7.65 (1 H, broad).

B.—A solution of erythro dihydroxy diketone **4** (10.0 g, 68.5 mmol) in 200 ml of 1 *M* Na_2HPO_4 (pH 8.12) was sealed in an ampoule at 10 mm and then maintained at 75° for 24 hr. Continuous extraction with a mixture of ether–petroleum ether, 1:1 (v/v), during 24 hr followed by drying and evaporation gave 4.545 g (52%) of furaneol (**5**) judged to be pure by nmr spectroscopy. The threo isomer **8** when treated under identical conditions yielded furaneol (**5**) in identical yield.

***threo*-3,4-Dihydroxyhexane-2,5-dione (8).**—A solution of 25 g of methylglyoxal (**7**) (50% aqueous solution, commercially available) was further diluted with water (25 ml) and stirred under nitrogen while 11 g of zinc dust was added in one lot. The temperature rose to 50° within 3 min and as it began to fall (6 min) 100 ml of acetic acid (10% aqueous) was added dropwise over 1 hr. Three extractions with ethyl acetate gave, after concentration, 7.0 g of crude material that crystallized at 0° from ethyl acetate–petroleum ether. Two recrystallizations from the same solvent mixture gave the threo compound **8**: mp 89–90°;[12] R_f 0.77 (silica gel G, ethyl acetate); ir (KBr) 3470 (unchanged in $CHCl_3$), 1705–1715 cm^{-1}; mass spectrum (70 eV) *m/e* 128, 43; nmr ($CDCl_3$, CCl_4) δ 2.33 (6 H, s), 3.72 (2 H, d, J = 6.5 Hz), 4.56 (2 H, d, J = 6.5 Hz).

Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.35; H, 7.05.

Reaction of *threo*-3,4-Dihydroxyhexane-2,5-dione (8) with Acetone.—A solution of the threo compound **8** (10 g) in 50 ml of dry acetone and 0.6 ml of concentrated sulfuric acid was shaken at room temperature for 4 hr, 10 g of dry potassium carbonate was added, and after stirring for 15 min the mixture was filtered and concentrated. The residue (11 g) showing two peaks in glc (Carbowax column), was chromatographed on silica gel. The less polar compound **12** (40% of the mixture) had mp 54–55°; ir, neither OH nor C═O absorptions; mass spectrum (70 eV) (rel intensity) 43 (100), 87 (23), 229 ($M^+ - 15$) (13), 101 (12), 107, and 171 (9); nmr δ 1.29 (6 H, s), 1.43 (6 H, s), 1.57 (6 H, s), 4.18 (2 H, s).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.20; H, 8.08.

The more polar compound **11** (60% of the mixture) was obtained as a liquid: mass spectrum (70 eV) *m/e* (rel intensity) 43 (100), 143 (23), 171 ($M^+ - 15$) (1); nmr (CCl_4) δ 1.38 (6 H, s), 2.23 (6 H, s), 4.47 (2 H, s).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.02; H, 7.66.

Reaction of Threo Dihydroxy Ketone 8 with Acids.—When heated with acids or water, compound **8** is transformed to two new compounds whose relative proportions depend on the reaction conditions. In a typical experiment the solution obtained after heating 10 g of **8** with 10 g of oxalic acid in 100 ml of water for 22 hr at reflux was extracted with ethyl acetate. The organic layer was dried and concentrated to yield 8 g of residue, bp 60–61° (10 mm). A sample of **6** was purified further by semipreparative vpc (silicone rubber column, 6 ft, 150°): nmr (CCl_4) δ 2.20 (3 H, s), 2.35 (3 H, s), 6.1 (1 H, s) and a low-field enol proton; mass spectrum (70 eV) *m/e* (rel intensity) 43 (100), 85 (53).

Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.22; H, 6.15.

The yield of **6** is estimated to have been 85%. Heating 5 g of the dihydro diketone **8** in 50 ml of water containing 0.5 ml of concentrated HCl (resulting pH ~3) at reflux for 48 hr gave 66% of **6**, 16% of **13**, and 17% of starting material **8**.

Condensation of the Dihydroxy Diketone 8 with Pyruvic Acid.—A solution of **8** (15 g) and pyruvic acid (15 g) in 150 ml of water was heated at reflux for 10 hr and the product was isolated by extraction with ethyl acetate. Evaporation gave a crude product (15 g). Distillation, bp 42–45° (0.1 mm), yielded **13** judged to be 95% pure by glc: ir (neat) 1702, 1673, 1568 cm^{-1}; uv (hexane) 223 nm (ϵ 9350), 266 (10,000); mass spectrum (70 eV) *m/e* (rel intensity) 43 (100), 67 (76), 139 (52), 154 (47); nmr (CCl_4) δ 1.47 (3 H, d, J = 7 Hz), 2.33 (3 H, s), 2.58 (3 H, s), 4.60 (1 H, q, J = 7 Hz).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.10; H, 6.60.

Bromination of Hexane-3,4-dione (14).—To a solution of hexane-3,4-dione (**14**) (25 g, 0.219 mol) in 100 ml of dioxane and 100 ml of ether was added with stirring during 90 min 72 g (0.45 mol) of bromine at 15–20°. After storage at 20° during 15 hr the reaction mixture was evaporated at 40° and finally attached to a vacuum system at 0.001 mm. The residue (57.3 g, 96%) consists of the dibromide **15**, nmr (CCl_4) δ 1.81 (6 H, d, J = 7 Hz), 5.20 (2 H, q, J = 7 Hz).

Hydrolysis of the Dibromide 15 to Furaneol (5).—A mixture of the dibromide **15** (57.3 g, 0.211 mol) and 500 ml of water was heated under reflux during 2 hr with stirring. After cooling to room temperature the reaction mixture was adjusted to pH ~4 by addition of solid Na_2CO_3. After addition of sufficient sodium acetate to buffer the solution (to pH ~5) it was extracted twice with petroleum ether. Evaporation of the organic layer gave 3.2 g of uncharacterized material. The aqueous phase was saturated with NaCl and extracted three times with ethyl acetate. After drying and evaporating 23.8 g of crude furaneol (**5**) were obtained. Glc indicated a purity of 55%. Purification by distillation at 0.001 mm gave 12.4 g of pure furaneol (**5**).

Registry No.—**3**, 36871-75-7; **4**, 36871-95-1; **5**, 3658-77-3; **6**, 36871-77-9; **8**, 36871-96-2; **11**, 36871-97-3; **12**, 36871-98-4; **13**, 36871-78-0.

Acknowledgment.—The work at MIT was generously supported by Firmenich et Cie, Geneva.

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[12] A 3,4-dihydroxyhexane-2,5-dione, mp 74°, of unknown configuration was described by F. Micheel, *Justus Liebigs Ann. Chem.*, **496**, 77 (1932).