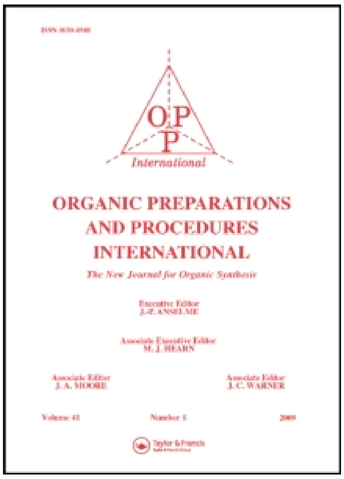


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF 4*H*-PYRAN-2,6-DICARBOXYLIC ACID AND 4-METHYL-4*H*-PYRAN-2,6-DICARBOXYLIC ACID

J. C. Lewis[a]; R. M. Seifert[a]
[a] Western Regional Research Laboratory, Agricultural Research Service, U.S. Department of Agriculture, Berkeley, California

To cite this Article Lewis, J. C. and Seifert, R. M.(1971) 'PREPARATION OF 4*H*-PYRAN-2,6-DICARBOXYLIC ACID AND 4-METHYL-4*H*-PYRAN-2,6-DICARBOXYLIC ACID', Organic Preparations and Procedures International, 3: 5, 243 — 248
To link to this Article: DOI: 10.1080/00304947109356783
URL: http://dx.doi.org/10.1080/00304947109356783

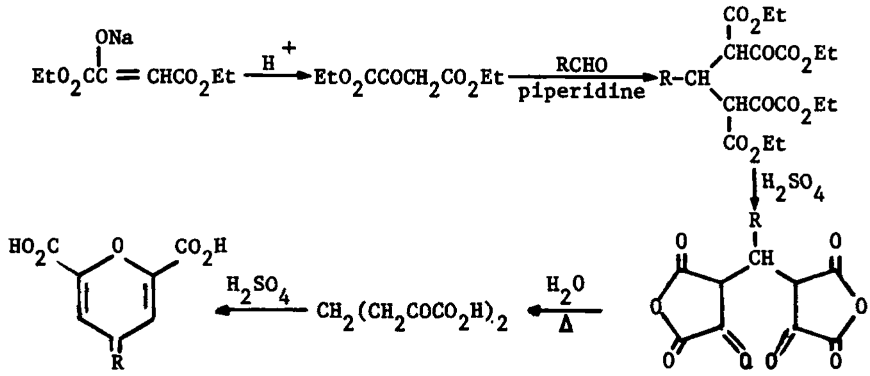
ORGANIC PREPARATIONS AND PROCEDURES INT. 3(5), 243-248 (1971)

PREPARATION OF 4H-PYRAN-2,6-DICARBOXYLIC ACID AND 4-METHYL-4H-PYRAN-2,6-DICARBOXYLIC ACID

J. C. Lewis and R. M. Seifert

Western Regional Research Laboratory
Agricultural Research Service, U.S. Department of Agriculture
Berkeley, California 94710

4H-Pyran-2,6-dicarboxylic acid has recently attracted interest as the only analogue of pyridine-2,6-dicarboxylic acid (dipicolinic acid = DPA) which is fully active as a substitute for DPA in sporulation of a DPA-less mutant of Bacillus megaterium;[1] the pyrandicarboxylic acid has also been used in other investigations[2] of DPA in bacterial spores. Although synthesized many years ago, details are scattered. Herein are reported our best procedures based on six separate preparations. The analogue 4-methyl-4H-pyran-2,6-dicarboxylic acid also was prepared. The method, based on the procedures of Blaise and Gault[3] and of Gault,[4,5] is illustrated in the scheme. Some modification[6,7] came to our attention later. The overall yield was 20% of theory (or 8% by weight of the sodium enolate); Gault's overall yield could not be calculated.



R = H, CH_3

EXPERIMENTAL

Starting materials.-- Practical grades diethyl oxalacetate sodium salt and formaldehyde (35-40%) were used. Practical grade piperidine was redistilled.

Diethyl oxalacetate.-- This intermediate must be of good quality.[4a,5b] The sodium enolate (630 g, 3 moles) is mixed into 2 liters of chilled 1.5 N HCl; caking must be avoided. The subsequent operations must be performed quickly. Diethyl oxalacetate is extracted with three 450-g portions of diethyl ether, and the combined ethereal extracts are washed with four 300-ml. portions of distilled water. The ether is distilled under a water aspirator, and then the diethyl oxalacetate is recovered by a rough fractional distillation using a Vigreaux column under a good vacuum, bp. 52°/0.05 mm Hg, or 76°/0.4 mm, to give 280-420 g (50-75%) of product with refractive index n_D = 1.449. The major by-product in the ethereal extract is the high-boiling lactone of triethyl oxalocitrate;[5a] if the crude extract is processed quickly, the residue after distillation of diethyl oxalacetate should amount to less than 10%.

The colorless ester is stable for at least a few weeks refrigerated or for a few days at 25°, but preferably it is used promptly to avoid poor crystallization of the next intermediate from the viscous reaction mixture.

Tetraethyl 1,5-dioxo-1,2,4,5-pentanetetracarboxylate.-- To 94 g (0.50 mole) of diethyl oxalacetate at 20-25° is added with stirring 20 g of 37% formalin, followed by 0.2 ml. of piperidine. The mixture thickens and should set to a solid cake within a few hours although a semi-solid slush is sometimes formed more slowly. After crystallization seems complete, the cake is crushed with 125 ml. of 95% ethanol and filtered to give the crystalline tetraester. With patience additional crops may be recovered by refrigeration of the filtrate and by dilution with an equal volume of water. Friable material is suitable for the next step without further purification, whereas sticky material gives poor yields of the next intermediate. The total yield is 64 g. (63%), mp. 86-92°, after recrystallization from aq. ethanol (1:1), water, ether or benzene. The reported yields are 75-80% (mp. ∼ 112°),[4a] 74% (mp. 74.7-76.2°),[6] 65% (mp. 100-116°).[7] The discordant mps. probably indicate the presence of varied proportions of tautomers and a hydrate in the crystallized product; three of these forms, mp. 81, 83 and 110-116°, have been purified.[4a,8]

1,5-Dioxo-1,2:4,5-pentanetetracarboxylic dianhydride.--The tetraester (102 g, 0.25 mole) is dispersed in 110 ml. of conc. H_2SO_4; the mixture is then stirred thoroughly after the ester has dissolved; it is allowed to stand at 25° for several days until crystallization is complete.[4a] The dianhydride is filtered on sintered glass funnel, washed free of color by the cautious addition (gas evolution!) of 110 ml. of conc. HCl,[9] then freed of HCl by washing with 165 ml. of anhydrous benzene to give 40-50 g (67-83%) of unstable product which is preferably decomposed at once to 2,6-dioxoheptanedioic acid.

2,6-Dioxoheptanedioic acid.--The dianhydride is dissolved in 4 times its weight of water and warmed cautiously to near boiling (gas evolution!).[3a] The resulting crude 2,6-dioxoheptanedioic acid is obtained in near quantitative yield by drying *in vacuo*, and may be used directly in the next step. Purification is accomplished by crystallization from a minimum volume of acetic acid, mp. 127° (dec.), lit.[3a,6,7] 127 (dec.) 127.8-129.6, 127-128°.

4*H*-Pyran-2,6-dicarboxylic acid.--2,6-Dioxoheptanedioic acid (7.5 g, 0.04 mole) is dissolved in 20 ml. of conc. H_2SO_4, kept at room temperature for 3 hours, and then poured onto shaved ice.[3b] The precipitate is filtered on sintered glass and then washed with cold water. The crude pyrandicarboxyiic acid is dissolved in a minimum amount of 1N NH_4OH and crystallized on the addition of a slight excess of 1N HCl. Yield 6.4 g (94%), lit.[6] 93%. A final recrystallization is accomplished from 400 parts of water at 80-90 C. The fine white needles decompose without melting at about 250°. An analytical sample was dried at 100° *in vacuo*.

Anal. Calcd for $C_7H_6O_5$: C, 49.5; H, 3.72; mol. wt. 170.1. Found: C, 49.4; H, 3.56; mol. wt. (titration with NaOH), 170.1.

NMR (DMSO-d_6, 90°) δ 7.0 (v. br., 2H, -COOH),6.97 (t, J = 4Hz, 2H, protons on carbons -3 and -5), 3.00 (t, J = 4Hz, 2H, methylene protons on carbon-4).[10]

The calcium chelate, $CaC_7H_4O_5 \cdot 3H_2O$, is isomorphous with Ca dipicolinate trihydrate by X-ray crystallography.[11] The anhydrous Ca chelate turns orange slowly in air.

Tetraethyl 1,5-dioxo-3-methyl-1,2,4,5-pentanetetracarboxylate.-- To 94 g (0.50 mole) of diethyl oxalacetate at 15-20° is added with stirring 11 g (0.25 mole) of acetaldehyde and 15 g of water, followed by 0.2 g of piperidine introduced cautiously with stirring while the temperature is kept below 25°. Unlike the reaction with formaldehyde, heat is evolved vigorously (presumably because the acetaldehyde is monomeric). The syrups obtained at higher temperatures gave poor yields or failed to crystallize even when seeded. After several days at 25°, the reaction mixture forms a nearly solid cake which is triturated with 95% ethanol, refrigerated and filtered. Further crops of product are obtained by dilution of the filtrate with an equal volume of water. Total yield 57-67 g (54-64%); lit.[4b,7] 85, 50%; after recrystallization from aqueous ethanol (1:1), benzene/petroleum ether (1:1), or carbon tetrachloride/petroleum either (1:1), mp. 82-90°, lit.[4b,7] ~112, 100-117°. The poor melting point probably arises from the presence of tautomers in the crystallized product, but this does not interfere with its use in the next step.

1,5-Dioxo-3-methyl-1,2:4,5-pentanetetracarboxylic dianhydride.-- Friable crystals (sticky crystals gave much poorer yields) of the tetraester (40.6 g, 0.1 mole) stirred into 44 ml. of conc. H_2SO_4 are allowed to stand for several days. Crystals are recovered as with the homologous compound; yield 20 g (74%), lit.[4b] 70%. The unstable crystals are used at once in the next step.

4-Methyl-2,6-dioxoheptanedioic acid.-- Freshly prepared crystals of the dianhydride are decomposed in 3 times their weight of hot water as with the homologue. Decarboxylation becomes vigorous at about 65°. Since this compound is hard to crystallize,the nearly colorless reaction mixture is dried *in vacuo* for use at the next step. The yield is nearly quantitative. Purified material was obtained by sublimation and by crystallization from water, diethyl ether, and 2-butanone, mp. 126°, lit.[3a,7] 140 (dec.), 135-141° (dec.).

4-Methyl-4H-pyran-2,6-dicarboxylic acid.-- Crude 4-methyl-2,6-dioxoheptanedioc acid (50 g, 0.25 mole) is triturated with 135 ml. of conc. H_2SO_4 at 25°. After several hours, the red reaction mixture is poured onto crushed ice and the rust-colored precipitate is collected on sintered glass, then washed exhaustively with cold water and finally with dry ether to remove uncyclized or reverted methyldioxoheptanedioic acid. Yield of dull-pink product 62%;lit.[3b] nearly 100%. The trace impurity is hard to remove by crystallization from water but white crystals are obtained by sublimation. At about 0.025 mm methyldioxoheptanedioic acid sublimes between 80 and 100° and methylpyrandicarboxylic acid sublimes between 110 and 140°. An impure light tan product is obtained above 145°.

An analytical sample was prepared by sublimation, mp. ∿265° dec., lit.[3b] ∿260° dec.

Anal. Calcd for $C_8H_8O_5$: C, 52.2; H, 4.38. Found: C, 52.1; H, 4.41. NMR (D_2O, 80°, referenced to t-butyl alcohol at δ 1.23) δ 6.10 (d, J=4Hz, 2H, olefenic protons on carbons -3 and -5), 3.25 (m, 1H, proton on carbon -4), 1.20 (d, J = 7Hz, methyl protons).

REFERENCES

1. A. Fukuda, C. Gilvarg, and J. C. Lewis, J. Biol. Chem., 244, 5636 (1969).
2. J. C. Lewis, Chapter 9, Dormancy, in G. W. Gould and A. Hurst, "The Bacterial Spore," Academic Press, London and New York, 1969.
3. (a) E. E. Blaise and H. Gault, Bull. Soc. chim. France, Ser. 4, 1, 75 (1907).
   (b) E. E. Blaise and H. Gault, Ibid., 1, 129 (1907).
4. (a) H. Gault, Ibid., 1, 21 (1907).
   (b) H. Gault, Ibid., 1, 40 (1907).
5. (a) H. Gault, Compt. rend. Acad. Sci., 158, 632 (1914).
   (b) H. Gault, Ibid., 158, 711 (1914).
6. A. C. Cope and A. Fournier, J. Amer. Chem. Soc., 79, 3896 (1957).
7. R. Onno, J. Rech. Centre Natl. Rech. Sci., Lab. Bellevue (Paris), 11, 205 (1960).
8. H. Gault and E. Elkik, Compt. rend. Acad. Sci., 242, 2958 (1956).
9. Conc. HCl gives vigorous gas evolution from diethyl oxaloacete, but conc. H_2SO_4 does not.
10. We are indebted to R. E. Lundin for NMR constants, and to L. M. White for elemental analyses.
11. K. J. Palmer and K. S. Lee, Acta Crystallogr., B25, 2412 (1969).

(Received September 3, 1971)