Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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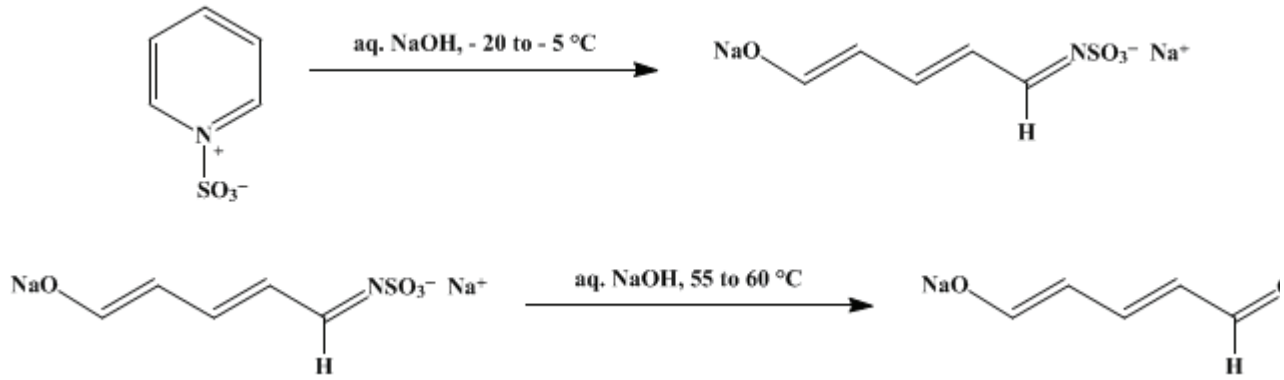
Organic Syntheses, Coll. Vol. 6, p.640 (1988); Vol. 59, p.79 (1979).

GLUTACONALDEHYDE SODIUM SALT FROM HYDROLYSIS OF PYRIDINIUM-1-SULFONATE

[2-Pentenedial, ion (1^-), sodium]



Submitted by Jan Becher[1]
Checked by J. P. O'Brien, S. Teitel, and G. Saucy.

1. Procedure

A 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer is charged with 42 g. (1.1. moles) of sodium hydroxide dissolved in 168 ml. of water. The contents of the flask are cooled to −20° and stirred vigorously as 48 g. (0.30 mole) of pyridinium-1-sulfonate (Note 1), which has been previously chilled to −20°, is added in one portion. The mixture is stirred for 20 minutes while the temperature is kept below −5° (Note 2). The cooling bath is removed, and the stirred mixture is warmed gradually to 20° over 20 minutes. The temperature of the dark orange mixture is then raised to 55–60°, but after 1 hour lowered again to −5°. The brown crystals that separate are filtered by suction, pressed into a compact filter cake, and washed with three 100-ml. portions of acetone (Note 3), yielding 46–52 g. of crude product after drying on filter paper overnight or at 50° (1 mm.) for 1 hour (Note 4).

If further purification is desired, the crude product is added to 1 l. of methanol in a 2-l., three-necked, round-bottomed flask equipped with a reflux condenser and a mechanical stirrer. The mixture is stirred and heated under reflux for 30 minutes. A 10-g. portion of activated carbon is added, and after 5 minutes the hot mixture is filtered. The light yellow-red filtrate is concentrated to a volume of 50 ml. under reduced pressure and cooled to 0°. The resulting orange crystals are filtered, washed with two 25-ml. portions of acetone, and dried for 1 hour at 50° (1 mm.), affording 24–27 g. (50–58%) of glutaconaldehyde sodium salt dihydrate (Note 5) and (Note 6).

2. Notes

1. Pyridinium-1-sulfonate was prepared according to the procedure of Sisler and Audrieth.[2] The submitter reports that this procedure may be conveniently carried out at 5 times the specified scale. The reagent should be dry and used soon after its preparation. The checkers found that a technical grade of pyridinium-1-sulfonate (sulfur trioxide pyridine complex) purchased from Aldrich Chemical Company, Inc., gave substantially lower yields of product.
2. The initial exothermic reaction that occurs at this point produces the intermediate glutaconaldehyde iminesulfonate disodium salt shown in the scheme. It separates as a yellow, unstable precipitate that may be isolated by filtering, washing with ice-cold isopropyl alcohol, and drying. The yield of the disodium salt is 64 g. (96%).
3. The acetone washes serve to remove colored by-products.
4. The crude product is relatively stable and sufficiently pure for most purposes.

5. The submitter advises that the product be dried at room temperature for 17 hours prior to analysis. An analysis including a Karl Fischer titration for water content was reported by the checkers. Analysis calculated for $C_5H_5O_2Na\cdot(H_2O)_2$: C, 38.46; H, 5.82; H_2O, 23.08. Found: C, 38.67; H, 5.91; H_2O, 23.40. The m.p. of the product is higher than 350° and its spectral characteristics are as follows: IR (KBr) $cm.^{-1}$: 3320 (H_2O), 1723, 1715 (C=O), 1530 (C-O); ^1H NMR (DMSO-d_6), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 5.07 (d of d, $J = 9$ and 13, 2H, H_2 and H_4), 7.03 (t, $J = 13$, 1H, H_3), 8.58 (d, $J = 9$, 2H, H_1 and H_5); UV (aqueous 0.1 *M* sodium hydroxide) nm. max. (log ε): 363 (4.75).
6. The water of hydration that accompanies the glutaconaldehyde sodium salt described in this procedure may interfere with applications requiring anhydrous conditions. Consequently the submitter has provided the following alternative procedure for preparing the anhydrous potassium salt. Pyridinium-1-sulfonate (108 g., 0.679 mole) is added to a solution of 155 g. (3.88 moles) of potassium hydroxide in 378 ml. of water in a 1-l. flask; the solution is stirred and cooled to −20°. After 1 hour, the temperature is slowly raised to 20° over 4 hours. The mixture is heated at 30–40° for 30 minutes and cooled to 5°. The crude product that precipitates is filtered, washed with two 100-ml. portions of acetone, and dried in the air, giving 120 g. of yellow-brown crystals. This material is heated at reflux in 2.5 l. of methanol, 5 g. of activated carbon is added, the carbon is filtered, and the filtrate is concentrated under reduced pressure to a volume of 100 ml. The pale yellow crystals of glutaconaldehyde potassium salt are collected, washed with acetone, and dried, yielding 53–57 g. (57–62%). Analysis of the potassium salt indicates the empirical formula $C_5H_5O_2K$, and the salt melts above 350°. The ^1H NMR spectrum is identical to that of the sodium salt, and the UV spectrum in aqueous 0.1 *M* potassium hydroxide solution exhibits a maximum at 362 nm. (log ε, 4.84).
The sodium and potassium salts of glutaconaldehyde are soluble only in polar solvents such as water, dimethyl sulfoxide, *N,N*-dimethylformamide, pyridine, and methanol. However, the stable tetrabutylammonium salt is soluble in relatively nonpolar solvents such as chloroform and ethyl acetate. It may be prepared from the potassium salt in the following manner. A 1-l. Erlenmeyer flask equipped with a magnetic stirring bar is charged with a solution of 13.6 g. (0.100 mole) of crude glutaconaldehyde potassium salt in 200 ml. of water and a solution of 33.9 g. (0.100 mole) of tetrabutylammonium hydrogen sulfate in 200 ml. of ice-cold water, the pH of which was adjusted to 10 by adding aqueous 2 *M* sodium hydroxide. The resulting mixture is stirred for 5 minutes in an ice bath and extracted with three 400-ml. portions of dichloromethane, previously dried by filtration through anhydrous potassium carbonate. The combined dichloromethane extracts are dried over 20 g. of anhydrous potassium carbonate and evaporated under reduced pressure. A 100-ml. portion of toluene is added, and the mixture is again evaporated under reduced pressure, removing residual water. The yield of dry, nearly colorless crystals of glutaconaldehyde tetrabutylammonium salt monohydrate is 23–25.1 g. (64–70%), m.p. 105–108°. Analysis corresponds to the empirical formula $C_{21}H_{41}NO_2\cdot H_2O$, and the salt may be recrystallized from ethyl acetate.

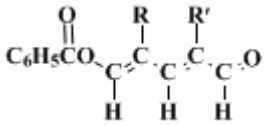
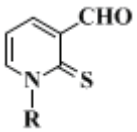
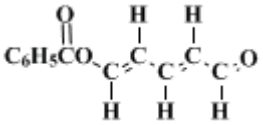
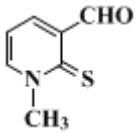
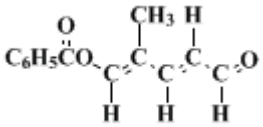
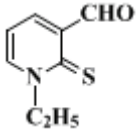
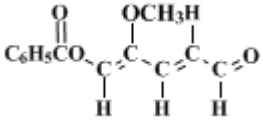
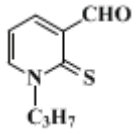
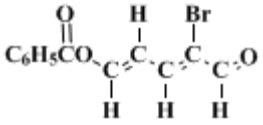
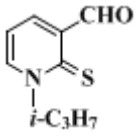
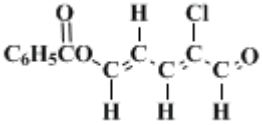
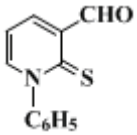
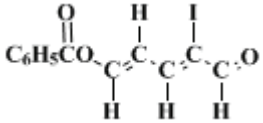
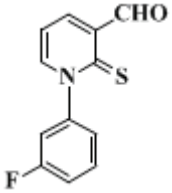
3. Discussion

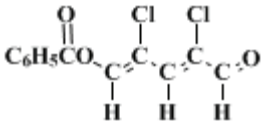
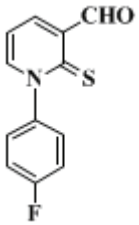
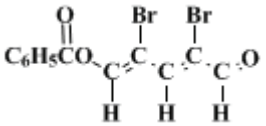
The sodium salt of glutaconaldehyde, first described by Baumgarten[3] in 1924, has been mentioned several times in the literature subsequently, but without full details of its preparation. The present procedure involves base-catalyzed hydrolysis of pyridinium-1-sulfonate at low temperature to glutaconaldehyde iminesulfonate dianion, followed by a second hydrolysis of the iminesulfonate at 55–60°, affording glutaconaldehyde sodium salt as a dihydrate.[4] The anhydrous potassium salt[5] and the monohydrated tetrabutylammonium salt may be prepared by similar procedures (see (Note 6)). In addition to being anhydrous, the potassium salt is more stable than the sodium salt; however, the sodium salt has the advantage of being more soluble in dimethyl sulfoxide and *N,N*-dimethylformamide. Analogous glutaconaldehyde iminesulfonate dianions with methyl and methoxy substituents at the 4-position are obtained by regiospecific ring opening of 3-methyl and 3-methoxy pyridinium-1-sulfonates.[6]

The reaction of glutaconaldehyde anion with benzoyl chloride and acetic anhydride gives the corresponding enol esters.[3,7] 4-Methyl- and 4-methoxyglutaconaldehyde enol benzoates are available by benzoylation of the corresponding iminesulfonate dianions and subsequent hydrolysis (Table I).[6] Halogenation of glutaconaldehyde anion or its enol benzoate gives a series of 2-halo and 2,4-dihalo

derivatives (Table I).[6,8]

TABLE I
GLUTACONALDEHYDE ENOL BENZOATES[6,7,8] AND 1-SUBSTITUTED 3-FORMYL-2(1*H*)-PYRIDINETHIONES[9] PREPARED FROM GLUTACONALDEHYDE ANION AND ITS DERIVATIVES

						
R	R'	M.p. (°)	Yield (%)	R	M.p. (°)	Yield (%)[d]
H				CH_3		
	H	119–121	87		126–128	58
CH_3				C_2H_5		
	H	138–139	61[a]		109–110	61
CH_3O				C_3H_7		
	H	123–124	27[a]		88–90	65
H				*i*-C_3H_7		
	Br	128–129	72[b]		113–115	75
H				C_6H_5		
	Cl	126–128	55[c]		180–182	95
H				3-FC_6H_4		
	I	131–141	58[c]		171–173	97
Cl				4-FC_6H_4		

	Cl	114–116	66[c]		191–193	82
	Br	98–100	65[c]			

[a]This ester was prepared by benzoylation of the corresponding glutaconaldehyde iminesulfonate dianion and subsequent hydrolysis.
[b]This ester was prepared by bromination of glutaconaldehyde enol benzoate.
[c]This ester was prepared by halogenation of glutaconaldehyde anion followed by benzoylation.
[d]The 3-formyl-2(1*H*)-pyridinethiones were prepared by reaction of glutaconaldehyde anion with the corresponding isothiocyanates (RN=C=S).

Glutaconaldehyde anion serves as an interesting intermediate for the synthesis of heterocyclic compounds. Pyrylium perchlorate has been prepared from glutaconaldehyde and 70% perchloric acid in ether at −55°.[10] The reactions of glutaconaldehyde anion with alkyl and aryl isothiocyanates and isoselenocyanates evidently occur initially at the 2-position of the former, leading to a variety of *N*-substituted 3-formyl-2(1*H*)pyridinethiones and the corresponding selenones (Table I).[9] A five-membered heterocycle, 2-isoxazolin-5-yl acetaldehyde oxime, is formed from reaction with hydroxylamine.[11] The chemistry of glutaconaldehyde is closely related to the chemistry of 5-amino-2,4-pentadienal, derivatives of which are interesting sources for a variety of polyenes. A review on glutaconaldehyde and 5-amino-2,4-pentadienal has recently been published.[12]

References and Notes

1. Department of Chemistry, Odense University, DK 5230, Odense M. Denmark.
2. H. H. Sisler and J. F. Audrieth, *Inorg. Synth.*, **2**, 173 (1946).
3. P. Baumgarten, *Ber. Dtsch. Chem. Ges.*, **57**, 1622 (1924).
4. P. Baumgarten, *Ber. Dtsch. Chem. Ges.*, **59**, 1166 (1926).
5. S. S. Malhotra and M. C. Whiting, *J. Chem. Soc.*, 3812 (1960).
6. J. Becher, N. Haunsø, and T. Pedersen, *Acta Chem. Scand., Ser. B.*, **29**, 124 (1975).
7. J. Becher, *Acta Chem. Scand.*, **26**, 3627 (1972).
8. J. Becher and M. C. Christensen, *Tetrahedron*, **35**, 1523 (1979).
9. J. Becher and E. G. Frandsen, *Acta Chem. Scand., Ser. B*, **30**, 863 (1976); J. Becher and E. G. Frandsen, *Tetrahedron*, **33**, 341 (1977); J. Becher, E. G. Frandsen, C. Dreier, and L. Henriksen, *Acta Chem. Scand., Ser. B*, **31**, 843 (1977).
10. F. Klages and H. Träger, *Chem. Ber.*, **86**, 1327 (1953).
11. J. Becher and J. P. Jacobsen, *Acta Chem. Scand., Ser. B*, **31**, 184 (1977).
12. J. Becher, *Synthesis*, 589 (1980).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

H_2O

Glutaconaldehyde sodium salt

2-Pentenedial, ion (1^-), sodium

glutaconaldehyde potassium salt

sodium and potassium salts of glutaconaldehyde

sodium salt of glutaconaldehyde

glutaconaldehyde sodium salt as a dihydrate

4-Methyl- and 4-methoxyglutaconaldehyde enol benzoates

3-formyl-2(1H)pyridinethiones

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

sulfur trioxide (7446-11-9)

chloroform (67-66-3)

acetone (67-64-1)

carbon,
activated carbon (7782-42-5)

benzoyl chloride (98-88-4)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

hydroxylamine (7803-49-8)

dichloromethane (75-09-2)

N,N-dimethylformamide (68-12-2)

dimethyl sulfoxide (67-68-5)

perchloric acid (7601-90-3)

glutaconaldehyde

PYRIDINIUM-1-SULFONATE

glutaconaldehyde sodium salt dihydrate

glutaconaldehyde iminesulfonate disodium salt

tetrabutylammonium hydrogen sulfate (32503-27-8)

glutaconaldehyde tetrabutylammonium salt monohydrate

glutaconaldehyde iminesulfonate

glutaconaldehyde anion

Pyrylium perchlorate

glutaconaldehyde enol benzoate

2-isoxazolin-5-yl acetaldehyde oxime

5-amino-2,4-pentadienal