



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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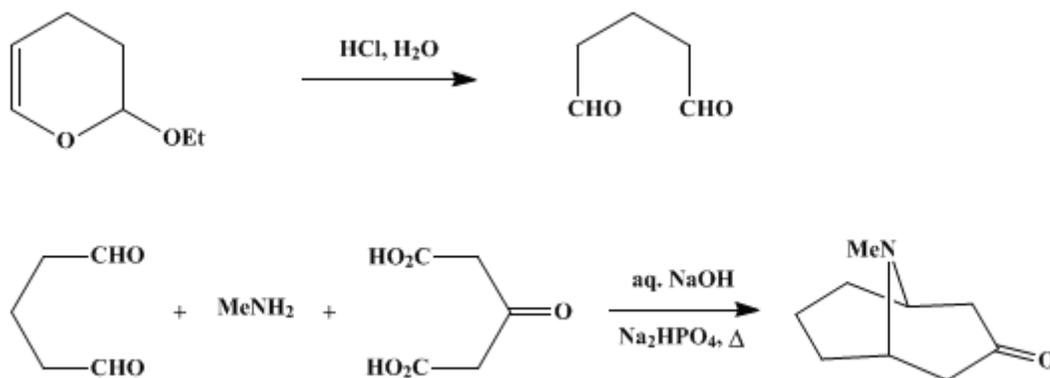
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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PSEUDOPELLETTIERINE



Submitted by Arthur C. Cope, Hugh L. Dryden, Jr., and Charles F. Howell¹.
Checked by N. J. Leonard, D. F. Morrow, and W. D. Smart.

1. Procedure

In a 3-l. round-bottomed flask equipped with a mechanical stirrer and flushed with a slow stream of **nitrogen** are placed 22 ml. (0.26 mole) of concentrated **hydrochloric acid** (sp. gr. 1.18), 165 ml. of "deoxygenated" water (**Note 1**), and 64 g. (0.5 mole) of **2-ethoxy-3,4-dihydro-2H-pyran** (b.p. 62–65°/50 mm., n_D^{25} 1.4378) (**Note 2**). The mixture is stirred vigorously for 20 minutes and then allowed to stand for 1 hour.

To the resulting colorless solution of **glutaraldehyde** are added, in order, 350 ml. of water, 50 g. (0.74 mole) of commercial **methylamine hydrochloride** dissolved in 500 ml. of water, 83 g. (0.57 mole) of **acetonedicarboxylic acid** (**Note 3**) dissolved in 830 ml. of water, and a solution of 88 g. (0.25 mole) of **disodium hydrogen phosphate dodecahydrate** and 7.3 g. (0.18 mole) of **sodium hydroxide** dissolved in 200 ml. of water by heating. **Carbon dioxide** is evolved, and the pH of the solution, initially 2.5, increases to 4.5 after the mixture has been stirred under **nitrogen** for 24 hours. Concentrated **hydrochloric acid** (33 ml.) is added, and the solution is heated on the steam bath for 1 hour to complete the decarboxylation (**Note 4**). After the solution has been cooled to room temperature, 75 g. of **sodium hydroxide** in 100 ml. of water is added (**Note 5**), and the basic mixture is extracted with eight 250-ml. portions of **methylene chloride** (**Note 6**). The combined **methylene chloride** extracts are dried over **sodium sulfate**, concentrated to about 500 ml. (**Note 7**), and filtered through a layer of 400 g. of **alumina** (**Note 8**) packed in a 50-mm. column. The column is eluted with **methylene chloride** until about 1.5 l. of eluate has been collected. The eluate is concentrated under reduced pressure to yield crystalline but yellow pseudopelletierine. The solid is sublimed at 40° and 0.3 mm. to yield 47–55.5 g. (61–73%) of crude, nearly colorless pseudopelletierine (**Note 9**). The product is dissolved in 100 ml. of boiling **pentane**, 3 ml. of water is added, and the mixture is boiled until the aqueous layer disappears. After thorough chilling in a refrigerator, the crystals which separate are collected on a filter and washed well with ice-cold **pentane**. Evaporation of the combined filtrate and washings to 20 ml., followed by filtration and washing, yields a second crop of almost equally pure material. The combined pseudopelletierine hemihydrate weighs 47–55 g. and melts at 47–48.5°. Sublimation of the hemihydrate as described above removes the water of hydration and yields 44–52 g. (58–68%) of pure, colorless pseudopelletierine, m.p. 63–64° (sealed tube). Anhydrous material which has been prepared in this manner does not decompose on storage under dry conditions.

2. Notes

1. "Deoxygenated" water is prepared by passing a stream of **nitrogen** through ordinary distilled water and is used throughout the preparation until the condensation has been completed. The use of ordinary distilled water may lower the yield by no more than a few per cent.

2. This compound is prepared by the addition of ethyl vinyl ether to acrolein, under conditions similar to those described for a similar addition of methyl vinyl ether to crotonaldehyde (p. 311); see Longley and Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950). Glutaraldehyde is available currently as a 30% aqueous solution from Carbide and Carbon Chemicals Company, 30 East 42nd Street, New York.
3. The preparation of acetonedicarboxylic acid is described in *Org. Syntheses Coll. Vol. 1*, 10 (1941). The acid may also be obtained from Chas. Pfizer & Company, 630 Flushing Avenue, Brooklyn 6, New York.
4. Omission of the decarboxylation step decreases the yield of crude material to 57%. The temperature should reach about 80°.
5. The pH rises to about 12. A lower pH allows extraction of more of the dark-brown resin. The extraction must be performed promptly since the product can undergo self-condensation at this pH.
6. The employment of ether instead of methylene chloride requires the use of a continuous extractor for 2 days.
7. The checkers found that the purification of the pseudopelletierine could be simplified, at least in those preparations in which commercial acetonedicarboxylic acid was used. Thus, the crude product obtained by evaporation to dryness of the methylene chloride extracts can be sublimed directly. Two sublimations give pseudopelletierine of m.p. 62–64°, in 58–62% yield, comparable to the product obtained after the more extended purification procedure described in the text.
8. Chromatographic alumina (400 g.) is treated with 500 ml. of ethyl acetate at room temperature. After 48 hours, the alumina is collected on a filter and washed first with 1 l. of distilled water and then with 1 l. of methanol. After drying in air, the alumina is activated by heating at 120° for 3 hours at 50–100 mm.
9. Resublimation directly may serve for the final purification (Note 7). Distillation is inconvenient because of the tendency of pseudopelletierine to crystallize in the condenser. The distilled product darkens rather rapidly even in the cold and melts at 47–53°. The once sublimed product also darkens slowly even when kept under dry nitrogen in a refrigerator. If anhydrous pseudopelletierine is exposed to moist air, the hemihydrate is formed, m.p. about 48°.

3. Discussion

Pseudopelletierine has been obtained from the bark of the pomegranate tree (*Punica granatum* L.).^{2,3,4,5} The synthesis of the alkaloid from glutaraldehyde, methylamine, and calcium acetonedicarboxylate was first achieved by Menzies and Robinson.⁶ The synthetic method subsequently was improved by Schöpf and Lehmann,⁷ and others.^{8,9} The condensation of a dialdehyde with an amine and acetonedicarboxylic acid to form a heterobicyclic compound (an alkaloid or alkaloid analog, usually employing mild or so-called "physiological" conditions) is sometimes referred to as a Robinson-Schöpf synthesis.

The experimental procedure described is essentially one reported by Ziegler and Wilms⁸ as subsequently modified,⁹ except that the glutaraldehyde is prepared from 2-ethoxy-3,4-dihydro-2H-pyran instead of cyclopentene ozonide⁸ or pyridine via dihydropyridine and glutaraldehyde dioxime.⁹ Essentially these procedures have been reported briefly by other investigators.¹⁰ Pseudopelletierine also has been prepared by the Dieckmann condensation of 1-methyl-2,6-piperidinediacetic acid diethyl ester with sodium.¹¹

References and Notes

1. Massachusetts Institute of Technology, Cambridge 39, Massachusetts.
2. Tanret, *Compt. rend.*, **88**, 716 (1879); **90**, 696 (1880).
3. Piccinini, *Gazz. chim. ital.*, **29**, II, 311 (1899).
4. Hess and Eichel, *Ber.*, **50**, 1386 (1917); **52**, 1005 (1919).
5. Chaze, *Compt. rend. soc. biol.*, **118**, 1065 (1935).
6. Menzies and Robinson, *J. Chem. Soc.*, **125**, 2163 (1924).
7. Schöpf and Lehmann, *Ann.*, **518**, 1 (1935).
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9. Cope, Dryden, Overberger, and D'Addieco, *J. Am. Chem. Soc.*, **73**, 3416 (1951).
10. Alder and Dortmann, *Ber.*, **86**, 1544 (1953).

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

Pseudopelletierine

pseudopelletierine hemihydrate

cyclopentene ozonide

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Acetonedicarboxylic acid

Acrolein (107-02-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

pyridine (110-86-1)

sodium (13966-32-0)

Pentane (109-66-0)

Methylamine hydrochloride (593-51-1)

methylamine (74-89-5)

methylene chloride (75-09-2)

crotonaldehyde (123-73-9)

methyl vinyl ether (9003-09-2)

ethyl vinyl ether (109-92-2)

glutaraldehyde (111-30-8)

disodium hydrogen phosphate dodecahydrate (10039-32-4)

2-ethoxy-3,4-dihydro-2H-pyran

calcium acetonedicarboxylate

dihydropyridine

glutaraldehyde dioxime

1-methyl-2,6-piperidinediacetic acid diethyl ester