[Contribution from the Department of Chemistry, Massachusetts Institute of Technology]

Preparation of Glutaraldehyde and Pseudopelletierine[1,2]

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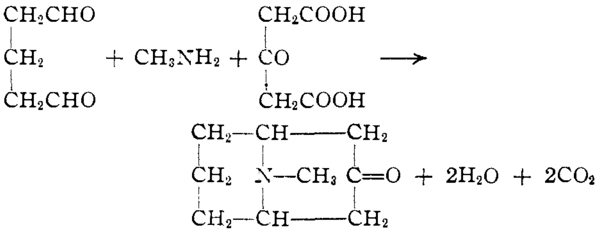
An improved preparation of glutaraldehyde has been developed based on a porcedure described by Shaw: pyridine → dihydropyridine → glutaraldehyde dioxime (40–46%) → glutaraldehyde in aqueous solution (90%). The condensation of glutaraldehyde with methylamine and acetonedicarboxylic acid has been found to be more sensitive to *p*H and faster than indicated by the work of Schöpf and Lehmann. Maximum yields of pseudopelletierine of 45–57% were obtained at *p*H 2.5–4 and were reached after reaction periods of about 4 hours.

The preparation of pseudopelletierine on a very small scale by a Mannich-type condensation of glutaraldehyde, methylamine and acetonedicarboxylic acid has been reported by Menzies and Robinson[5] and by Schöpf and Lehmann.[6] We have reinvestigated the condensation in the process of preparing moderately large quantities of pseudopelletierine, and were led to redetermine the influence of *p*H and reaction time upon the yield because of discrepancies between our results and those reported previously.[6]



pseudopelletierine

Previous investigators have prepared the glutaraldehyde required for synthesis of pseudopelletierine by reduction of cyclopentene ozonide or by oxidation of 1,2-cyclopentanediol with lead tetraacetate. Neither method appeared to be suitable for the preparation of molar or larger quantities of glutaraldehyde. In the present work, glutaraldehyde was prepared on a small scale by oxidation with lead tetraacetate of the mixture of stereoisomeric 1,2,3-cyclohexanetriols obtained by hydrogenation of pyrogallol. A modification of a procedure described by Shaw[7] (described in the Experimental part) was used for larger scale preparations of glutaraldehyde from pyridine. Since this work was completed Longley and Emerson[8] have described the preparation of glutaraldehyde by another useful method; the hydrolysis of 2-ethoxy-3,4-dihydro-1,2-pyran, obtained by 1,4-addition of ethyl vinyl ether to acrolein.

A number of preparations of pseudopelletierine which were conducted at *p*H 5.5 and 25° in a phosphate buffer gave yields of 12–29%, compared to reported yields[6] of 71–95%. Under these conditions the yield reached a maximum after 6 hours. At 0° the yield of pseudopelletierine was not changed significantly, but complete spontaneous decarboxylation of the condensation product did not occur, and the decarboxylation was completed by heating in acid solution.

On reinvestigation of the condensation of glutaraldehyde with methylamine and acetonedicarboxylic acid at 25° and *p*H values of 1 to 7, the following yields of pseudopelletierine (based on glutaraldehyde) were obtained after reaction periods of 90 hours: *p*H, 1, 2%; *p*H 2, 29%; *p*H 3, 49%; *p*H 4, 52%; *p*H 5, 23%; *p*H 6, 7%; *p*H 7, 1%. These data are not in agreement with the results obtained by Schöpf and Lehmann, who reported the following yields (the first figure is the yield after 3 days and the second after an 8-day reaction period): *p*H 3, 60, 62%; *p*H 5, 69, 71%; *p*H 7, 50, 72%; *p*H 9, 30, 36%; *p*H 11, 30, 36%; *p*H 13, 20, 53%. The reason for the discrepancy is not apparent.

The following yields of pseudopelletierine were obtained at 25° from a mixture initially buffered to *p*H 3 with acetic acid after the reaction times indicated: 0.25 hour, final *p*H 3.0, yield 9%; 0.5 hour, *p*H 3.0, 14%; 1.0 hour, *p*H 3.1, 27%; 2.0 hours, *p*H 3.5, 37%; 4.0 hours, *p*H 3.9, 42%; 8.0 hours, *p*H 4.0, 40%.

Two preparations of pseudopelletierine on a one molar scale at a *p*H of 3–4 maintained by a citric acid–disodium hydrogen phosphate buffer gave yields of 44 and 55%; with an acetic acid–hydrochloric acid buffer at a *p*H of 2.7–4.0 the yield was 45%. Without a buffer the *p*H rose from 2.9 to 6.4 during the reaction and the yield was 43%. It is of interest that the largest yields of pseudopelletierine were obtained at *p*H values (2.5–4) near the *p*H at which another Mannich condensation recently was found to have a maximum rate.[9] It seems probable that the reaction does not proceed at low *p*H because the methylamine is present to a large extent as a salt, while at high *p*H glutaraldehyde is unstable and can undergo self-condensation or condensation with methylamine leading to resinous products.

After most of this work was completed a preparation of pseudopelletierine was described by Ziegler and Wilms[10] from glutaraldehyde prepared from cyclopentene ozonide, methylamine hydrochloride and acetonedicarboxylic acid in a phosphate buffer. The reaction time was 5 days. Repetition of their procedure with glutaraldehyde prepared from the dioxime showed that the initial *p*H was 2.5 and gave 57% yields of pseudopelletierine with a reaction time of either 1 or 5 days.

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(3) Abbott Laboratories Fellow, 1948–1949.

(4) du Pont Postdoctorate Fellow, 1946–1947.

(5) R. C. Menzies and R. Robinson, *J. Chem. Soc.*, **125**, 2163 (1924).

(6) C. Schöpf and G. Lehmann, *Ann.*, **518**, 1 (1935).

(7) (a) B. D. Shaw, *J. Chem. Soc.*, **127**, 215 (1925); (b) *ibid.*, 300 (1937).

(8) R. L. Longley, Jr., and W. S. Emerson, This Journal, **72**, 3079 (1950).

(9) E. R. Alexander and E. J. Underhill, *ibid.*, **71**, 4014 (1949).

(10) K. Ziegler and H. Wilms, *Ann.*, **567**, 31 (1950).

A number of alkaloids have been prepared by the condensation of dialdehydes or other dicarbonyl compounds with amines and acetonedicarboxylic acid, in reactions somewhat analogous to those used for the synthesis of pseudopelletierine and tropinone.[11] If the results of the present work apply to some extent to related condensation reactions, initial *p*H values near 3 should be most suitable, the *p*H should not be allowed to rise above 4, and shorter reaction times than are commonly used might prove to be sufficient.

Pseudopelletierine has been reported to melt at 46°,[12] in the range 48–49°[5,6,10,13] and at 53–54°.[14] Analyses have been reported[12,13] corresponding to the formula $C_9H_{15}NO$, indicating that the form melting at 48° is anhydrous. In the present work it was observed that pseudopelletierine purified by sublimation under reduced pressure and recrystallization from petroleum ether under anhydrous conditions formed white, very hygroscopic crystals melting at 64–65° with the proper analysis and neutral equivalent for the anhydrous base, $C_9H_{15}NO$. On exposure to moist air a hemihydrate was formed melting at 48–49°, and it is probable that the form of pseudopelletierine previously described melting at 48–49° is the hemihydrate.

Experimental[15]

Glutaraldehyde Dioxime.—A mixture of 316 g. (4 moles) of dry pyridine and 1800 ml. of commercial anhydrous methanol was placed in a 5-l. three-necked flask fitted with an efficient reflux condenser protected from atmospheric moisture. The mixture was heated to the reflux temperature with an electric mantle and 92 g. (4 gram atoms) of sodium was added in freshly cut 4–5-g. pieces. The sodium was added at a rate which kept the mixture at the reflux temperature, with the aid of external heating near the end of the reaction period (1 to 1.5 hours). When all the sodium had dissolved, the flask was cooled momentarily and a slurry of 280 g. (4 moles) of technical hydroxylamine hydrochloride in 250 ml. of water and 250 ml. of 95% ethanol was added. A solution of 255 ml. of concentrated hydrochloric acid in 500 ml. of 95% ethanol was added immediately afterward, producing considerable heat of neutralization and precipitation of sodium chloride. The mixture was heated at the reflux temperature for 1.5 hours and filtered to remove sodium chloride while it was still warm. The sodium chloride was washed with small portions of ethanol, the filtrate was concentrated to a volume of 500–800 ml. by distillation at atmospheric pressure, and cooled. The white solid which separated was dissolved by the addition of a solution of 280 g. of sodium hydroxide in 800 ml. of water. The solution was extracted with 400 ml. of ether (discarded) and the aqueous layer was separated and acidified with 1100 ml. of 1:1 hydrochloric acid. The mixture was cooled to 10° and the glutaraldehyde dioxime was collected on a Büchner funnel, washed on the funnel with five 300-ml. portions of cold water (the optimum amount for removal of inorganic salts without excessive loss of the product), pressed as dry as possible by use of a rubber dam, and dried to constant weight in an oven at 80–90°. The yield of crude glutaraldehyde dioxime containing less than 1% of inorganic ash, m.p. 165–169°, was 103–120 g. (40–46% based on sodium) in a series of 25 preparations. The yields obtained by a similar procedure in which sodium and absolute ethanol (rather than methanol) were used were 27–29% based on the weight of sodium. Yields are calculated on that basis since it appears to be most practical to use pyridine and hydroxylamine hydrochloride in excess.

Glutaraldehyde.—A 10% aqueous hydrochloric acid solution (815 ml., 2.34 moles) was cooled to 0° and placed in a 2-l. three-necked flask equipped with a mechanical stirrer and a dropping funnel, and 150 g. (1.17 moles) of crude glutaraldehyde dioxime was added. The mixture was cooled to -10° with a bath containing Dry Ice and trichloroethylene and a solution of 161.5 g. (2.34 moles) of sodium nitrite in 200 ml. of water was added with stirring in a period of 3 to 5 hours.[16] During the addition the temperature of the reaction mixture was kept between −10° and −5° and foaming was controlled by the occasional addition of small portions of ether. The orange-yellow solution was neutralized by the addition of an excess of reprecipitated calcium carbonate, and the portion which did not dissolve was removed by filtration through a Büchner funnel containing a mat of filter-aid. The clear aqueous solution was used immediately for the preparation of pseudopelletierine. Aliquots from four preparations were treated with 2,4-dinitrophenylhydrazine reagent, and the weights of the bis-2,4-dinitrophenylhydrazone precipitates, washed and dried but not recrystallized (m.p. 184–186°), corresponded to 85.7–95.6% yields of glutaraldehyde with an average yield of 90%. An analytical sample of glutaraldehyde bis-2,4-dinitrophenylhydrazone purified by recrystallization from nitromethane[17] melted at 192.5–193.3° (ref. 7b reports m.p. 169–172°).

Anal. Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.35; H, 3.50; N, 24.34. Found: C, 44.41; H, 3.58; N, 24.22.

Since both glutaraldehyde dioxime and glutaraldehyde react with 2,4-dinitrophenylhydrazine reagent to precipitate the bis-2,4-dinitrophenylhydrazone, the glutaraldehyde solution was steam distilled in one instance and the derivative was prepared from the dilute steam distillate in 85% yield (based on the dioxime), indicating that conversion of the dioxime to glutaraldehyde by reaction with nitrous acid is essentially complete. Although pure glutaraldehyde polymerizes readily, the aqueous solution obtained by steam distillation proved to be quite stable and was kept at 5° for 2 weeks with a decrease in glutaraldehyde content of only 5%.

Conversion of an aqueous suspension of glutaraldehyde dioxime to glutaraldehyde by treatment with oxides of nitrogen[7a,18] (prepared from nitric acid and arsenic trioxide) or with commercial nitrogen dioxide was less convenient and gave poorer yields.

Glutaraldehyde also was prepared on a small scale by the cleavage of 1,2,3-cyclohexanetriol with lead tetraacetate. Pyrogallol was hydrogenated in absolute ethanol in the presence of Raney nickel at 165° and 3000 lb. pressure and the crude product was fractionated to separate the mixture of stereoisomeric 1,2,3-cyclohexanetriols formed[19] from cyclohexanediols produced by partial hydrogenolysis. The mixture of 1,2,3-cyclohexanetriols (13.0 g., b.p. 150–155° at 7 mm.) was dissolved in 130 g. of glacial acetic acid and 81 g. of lead tetraacetate was added in a period of 3 hours in small portions with stirring and cooling to keep the mixture at room temperature. After the mixture was stirred for an additional 0.5 hour 3 ml. of ethylene glycol was added to reduce any excess lead tetraacetate, followed after 15 minutes by 150 ml. of a saturated solution of sodium sulfate in 3% sodium hydroxide solution. Lead sulfate was separated by centrifuging, and the solution of glutaraldehyde was used for the preparation of pseudopelletierine (in 34% yield) by procedure (a) described below.

Pseudopelletierine (a) Preparation at *p*H 5.5 and 25°.—In a 5-l. flask were placed in the order named a solution of 40 g. of sodium dihydrogen phosphate monohydrate in 2.5 l. of water, the aqueous glutaraldehyde solution freshly prepared from 150 g. of glutaraldehyde dioxime, 160 g. (1.08 moles) of acetonedicarboxylic acid[20] and 140 ml. of a 31.4%

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[11] T. A. Henry, "The Plant Alkaloids," J. and A. Churchill Ltd., London, 1949, pp. 61–62, 79–81.

[12] C. Tanret, *Compt. rend.*, **88**, 718 (1879).

[13] G. Ciamician and P. Silber, *Ber.*, **25**, 1602 (1892).

[14] K. Hess and A. Eichel, *ibid.*, **50**, 381 (1917).

[15] Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy and his associates for analyses.

[16] L. C. Keagle and W. H. Hartung, This Journal, **68**, 1609 (1946), have used a similar procedure for conversion of succinaldehyde dioxime to succinaldehyde.

[17] We are indebted to William J. Keller for data concerning the pure sample.

[18] A method used for conversion of succinaldehyde dioxime to succinaldehyde by C. Harries, *Ber.*, **34**, 1494 (1901); *ibid.*, **35**, 1183 (1902).

[19] H. Lindemann and H. Baumann, *Ann.*, **477**, 97 (1930); H. Lindemann and A. deLange, *ibid.*, **483**, 31 (1930).

[20] "Organic Syntheses," Coll. Vol. 1, second edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 10; C. K. Ingold and L. C. Nickolls, *J. Chem. Soc.*, **121**, 1642 (1922).

aqueous methylamine solution (containing 43.6 g. or 1.41 moles of methylamine). The *p*H of the mixture initially was 3.5–3.7 and was raised to 5.5 by the addition of 10% aqueous sodium hydroxide solution (approximately 200 ml.). After the mixture had stood for 7 days at room temperature it was made basic (*p*H 9–10) by the addition of 500 ml. of 2 *N* sodium hydroxide solution and filtered through a mat of filter-aid. The filtrate was extracted with eight 200-ml. portions of methylene chloride[21] and the combined extracts were dried over magnesium sulfate and concentrated by distillation. Pseudopelletierine was isolated from the dark brown residue either by rapid distillation at about 1 mm., a short path distillation or sublimation at 60–100° and 0.2–0.3 mm., or preferably by the following procedure. The residue from the methylene chloride extracts was extracted with 100-ml. portions of boiling hexane until no more material went into solution. This procedure separated the product from an insoluble resin which otherwise interfered with the distillation. The combined hexane extracts were concentrated and the residue was either distilled through a short, large-diameter column at 1 mm. or sublimed at 0.2–0.3 mm. Pseudopelletierine obtained by any of these procedures formed white crystals containing a small amount of an impurity that caused it to darken on standing. Material which had darkened could be purified by redistillation, b.p. 101–104° (6 mm.). Ten preparations of pseudopelletierine by this procedure gave yields from 19.2 to 46.5 g. (12–29% assuming a 90% yield of glutaraldehyde from the dioxime).

(b) **Preparation at *p*H 5.5 and 0°.**—Preparations at 0° followed procedure (a) except that 1200 ml. of the water was replaced with 1200 g. of ice and the reaction mixtures were cooled with ice for 40 hours. At the end of that time the reaction mixtures were acidified to *p*H 2 with concentrated hydrochloric acid, warmed to 50° on a steam-bath for 1 hour, and cooled. Pseudopelletierine was isolated as in procedure (a), including the hexane extraction procedure and distillation of the product at 1 mm. In four preparations the yield was 15.3–42.0 g. (10–26%). In one case in which the reaction mixture was not acidified and heated the yield of pseudopelletierine was 10.5 g., but an additional 31.5 g. was obtained by acidifying the aqueous alkaline solution, heating it to 50°, again making it alkaline and extracting and distilling the product.

(c) **Yield as a Function of *p*H at 25°.**—Buffered aqueous solutions (250 ml. in volume) were prepared from the following quantities of reagents:

*p*H	Citric acid, g.	$Na_2HPO_4 \cdot 12H_2O$, g.
3.0	30.0	30.0
4.0	23.6	55.2
5.0	18.6	73.7
6.0	14.2	90.5
7.0	6.8	118.0

Acetonedicarboxylic acid (17 g., 0.116 mole) and 31.4% methylamine solution (11 ml., 0.11 mole) were added, followed by sufficient 2 *N* sodium hydroxide solution to bring the *p*H (measured with a Beckman *p*H meter) to the values listed. Glutaraldehyde dioxime (80 g.) was converted to an aqueous solution of glutaraldehyde by the procedure described above. Assay of two aliquots with 2,4-dinitrophenylhydrazine reagent showed that the yield was 89%. Aliquots of the aldehyde solution containing 0.0992 mole of glutaraldehyde were added to the buffers and the solutions were diluted to 500 ml. Measurement of *p*H showed that the desired values were obtained, within 0.1 *p*H unit. The mixtures were allowed to stand at room temperature for 90 hours, and the *p*H was readjusted to the desired value several times during the reaction period by adding citric acid. The solutions with *p*H 3, 4 and 5 increased in *p*H by a maximum of 0.5 unit. Each of the solutions was made alkaline (*p*H 9–10) by addition of 6 *N* sodium hydroxide and filtered. The filtrates were extracted with three 100-ml. and four 50-ml. portions of methylene chloride, and the combined extracts were dried over sodium sulfate and concentrated. The pseudopelletierine was isolated in each case by hexane extraction of the residue and sublimation of the hexane-soluble material at 0.1–0.2 mm. with a maximum heating block temperature of 120°. Similar condensations were carried out at *p*H 1 and 2. The solution with *p*H 1 was buffered with 34 g. of potassium acid sulfate and that with *p*H 2 with 20 g. of citric acid. The yields of pseudopelletierine obtained are stated in the Introductory part.

Two preparations by this procedure at *p*H 3 with ten times the quantities of reagents specified gave yields of pseudopelletierine of 45 and 55%, b.p. 108–110° (7 mm.).

(d) **Preparation in Acetic Acid Buffer.**—Acetonedicarboxylic acid (170 g., 1.16 moles), glacial acetic acid (132 ml., 2.3 moles) and 31.4% aqueous methylamine solution (110 ml., 1.1 moles) were added to 2 l. of water. The *p*H of the resulting solution was adjusted to 2.7 by the addition of 1:1 aqueous hydrochloric acid (50 ml.). The aqueous glutaraldehyde solution freshly prepared from 150 g. of glutaraldehyde dioxime was added and the solution was diluted to a volume of 4.5 l. The *p*H of the solution was 2.7. Evolution of carbon dioxide began soon and the *p*H of the solution rose to 3.7 within 4 hours. After a reaction time of 16 hours the solution (*p*H 3.8) was made alkaline and the product was isolated as in procedure (c). Distillation of the hexane-soluble material gave 73.1 g. (46%) of pseudopelletierine, b.p. 100–101.5° (5–6 mm.).

(e) **Yield as a Function of Time at *p*H 3.**—The aqueous glutaraldehyde solution prepared from 87 g. (0.666 mole) of the dioxime was mixed with proportionate quantities of the reagents specified in (d). One-sixth aliquots of the mixture were withdrawn periodically and treated at once with sufficient concentrated hydrochloric acid to lower the *p*H to 0.55–0.66. The solutions were heated on a steam-bath at a maximum temperature of 70° for 30 minutes, at which time gas evolution had ceased. The solutions were cooled and the pseudopelletierine was isolated as in procedure (c), with purification of the hexane-soluble material by sublimation at 0.1 mm. and a heating block temperature of 60–100°. The yields of pseudopelletierine obtained are listed in the Introductory part.

(f) **Procedure of Ziegler and Wilms.**—The procedure described by Ziegler and Wilms[10] was repeated using aqueous glutaraldehyde prepared from glutaraldehyde dioxime. The initial *p*H of the reaction mixture was 2.5. The product was isolated from half of the reaction mixture after 1 day by the procedure described under (c), and from the other half after the specified reaction time of 5 days. The yield of pseudopelletierine in each case was 57%.

(g) **Properties of Pseudopelletierine.**—Pseudopelletierine purified by distillation formed a white solid which could be sublimed readily at 0.1 mm. as large, white hygroscopic crystals. Recrystallization from petroleum ether gave the anhydrous base as very hygroscopic, white crystals provided care was taken to exclude atmospheric moisture; m.p. 64–65°. An analytical sample with the same melting point was prepared by sublimation at 0.1 mm.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.13; neut. equiv., 153.2. Found: C, 70.17; H, 9.80; N, 9.12; neut. equiv., 152.

On exposure to atmospheric moisture anhydrous pseudopelletierine rapidly absorbed water and formed a hemihydrate which melted at 48–49° and gave a mixed melting point with the anhydrous form of 54–59°.

Anal. Calcd. for $C_9H_{15}NO \cdot {}^1/_2H_2O$: C, 66.65; H, 9.94; N, 8.63; neut. equiv., 162.2. Found: C, 66.69; H, 9.76; N, 8.56; neut. equiv., 160.

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[21] Extraction with ether required use of a continuous extractor for a period of 2 days.[6,10]