NOTE: This is a shorter, adapted version of the published procedure

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Rheosmin ("Raspberry Ketone") and Zingerone, and Their Preparation by Crossed Aldol-Catalytic Hydrogenation Sequences[1]

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The article includes background information on the target compounds and the synthetic methods used…

Preparations of the two closely-related natural products rheosmin ("raspberry ketone", 4-(4'-hydroxyphenyl)-2-butanone) and zingerone (4-(4'-hydroxy-3'-methoxyphenyl)-2-butanone), are well-suited for the introductory organic laboratory. The crossed-aldol condensation of 4-hydroxybenzaldehyde with acetone gives an adduct (4-(4'-hydroxyphenyl)-3-buten-2-one), which is hydrogenated cleanly over rhodium on alumina to form rheosmin. Condensation of vanillin with acetone gives 4-(4'-hydroxy-3'-methoxyphenyl)-3-buten-2-one, which is hydrogenated to zingerone. The article includes background information on the target compounds and the synthetic methods used, along with experimental procedures and IR and NMR data on the compounds encountered.

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Introduction

The wide occurrence and many variants of aldol-type processes have long made them a prominent part of organic chemistry [1–3], and thus of the chemical education literature [4–11]. Various laboratory texts include crossed-aldol reactions, usually preparations of benzalacetone and benzalacetophenone derivatives, starting from such compounds as benzaldehyde, piperonal, nitrobenzaldehyde, or anisaldehyde. These go smoothly, and they easily allow students to isolate pure crystalline products in a single laboratory period, although the main use of the adducts obtained may be purely academic. Experiments that demonstrate catalytic hydrogenation, also important, have received extensive coverage over the years [12–15]. To make organic laboratories more appealing, more preparations involving natural products might be attractive additions to the repertoire, even if the experimental procedures do not always lend themselves so readily to finishing within one laboratory period. This paper discusses crossed-aldol/catalytic-hydrogenation sequences leading to the closely-related natural products zingerone and rheosmin, both of which work well as organic laboratory targets.

Background to the Synthetic Sequences and the Target Compounds

Vanillin, a pleasant compound for laboratory exercises [16–19], has long been known to undergo a facile crossed-aldol reaction with acetone to give 4-(4'-hydroxy-3'-methoxyphenyl)-3-buten-2-one, which can be hydrogenated to zingerone (4-(4'-hydroxy-3'-methoxyphenyl)-2-butanone), a substance originally identified as a major flavor of ginger [20, 21]. Although zingerone was later indicated mainly to be an apparent result of a retro-aldol decomposition of a precursor in the plant [22], the compound has maintained a modest phytochemical and medicinal interest [23–28]. Another phenolic aldehyde, 4-hydroxybenzaldehyde (itself a natural product), condenses with acetone to give 4-(4'-hydroxyphenyl)-3-buten-2-one, a precursor to rheosmin (4-(4'-hydroxyphenyl)-2-butanone) [29, 30], a substance colloquially called the "raspberry ketone" [31]. Although rheosmin has been known as a flavor substance since the 1920s and is on the U.S. FDA's "GRAS" (generally regarded as safe) food additives list [32], its characterization in raspberries and other natural sources [31, 33–37], as well as wider commercial use as a fragrance additive, came in more recent decades. The toxicology of rheosmin has been investigated [38, 39], as has its insect attractant [40, 41] and olfactory qualities [42, 43]. The structural similarity between rheosmin and zingerone suggests a similar biogenesis [31], and studies have shown similar metabolic fates for

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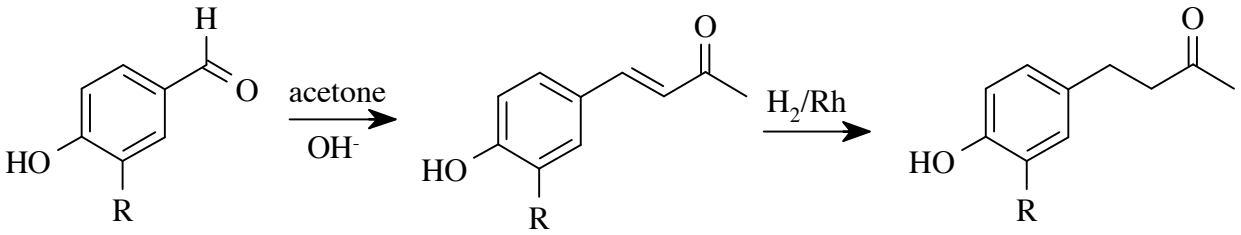

Vanillin, R = OCH_3
4-Hydroxybenzaldehyde, R = H

Zingerone, R = OCH_3
Rheosmin, R = H

the two compounds [44, 45]. It should be noted that the synthetic precursors, the crossed-aldol adducts ("dehydrorheosmin" and "dehydrozingerone"), are obscure natural products in their own right, having been identified as minor plant metabolites [23, 46].

Discussion of the Preparative Crossed-Aldol and Hydrogenation Reactions

Vanillin and 4-hydroxybenzaldehyde react fairly readily with acetone at room temperature, but (unlike benzaldehyde and other nonphenolic aromatic aldehydes) too slowly to finish in one laboratory period. Presumably, anions of phenolic aldehydes are less readily attacked by the acetone enolate ion than neutral molecules would be; suggestions for a related molecular modeling exercise appear in the Experimental Section. Literature reports of the condensation of vanillin with acetone typically involve a 24-hour reaction time. Leaving the blood-red homogeneous mixture more than two or three days results in a lower-quality product. The literature procedure can be modified to proceed cleanly over the course of one week, by changing the solvent ratio and using a higher concentration of aqueous hydroxide, to give a slurry which reacts more slowly. The reaction can quickly and easily be set up by students one week, then continued the next. Similar differences in condensation conditions for 4-hydroxybenzaldehyde make a qualitatively similar, but more modest, difference in the results. To allow flexibility in setting up, both 24-hour and one-week procedures are given for each crossed-aldol reaction, on two different scales. The 0.25-g-scale procedures (indicated as "semimicroscale") were fully class-tested; the 60-mg-scale procedures (indicated as "microscale") were checked (duplicate runs) by the author. With either starting material, the product obtained appears pure spectroscopically, although the crude 4-hydroxybenzaldehyde/acetone adduct is typically somewhat discolored. The vanillin/acetone adduct is easily recrystallized from ethanol/water. With a little more

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effort the 4-hydroxybenzaldehyde/acetone adduct can be recrystallized from water alone; although a single recrystallization does not give a melting range that matches the 112 °C reported by Mannich and Merz [30], purity nonetheless appears excellent, and satisfactory for the subsequent hydrogenation.

Catalytic hydrogenation of the α,β-unsaturated ketones, to give zingerone and rheosmin, can give more difficulty than the condensation. Literature reports appear of palladium and Raney nickel giving significant over-hydrogenation to give alcohols as byproducts, in 15–20% yield, which complicates cleanup and isolation of pure ketone products [30, 36, 47]. Platinum has also been used, but vacuum distillation was required before crystallization [20]. Mannich and Merz pointed out [30] that the ketone products were stable to the hydrogenation conditions they used, so the alcohol was perhaps generated via an initial 1,4-hydrogenation, followed by saturation of the resulting enol. Purifications are, of course, appropriate exercises for students of organic chemistry, but the difficulty of obtaining pure products in high yield made these particular hydrogenation-purification approaches unattractive for the introductory organic course. Previous experience [48] in which rhodium had given cleaner reactions than palladium or platinum, led to trying rhodium in this case with excellent results. Hydrogenation is rapid using 0.5% rhodium on alumina (commercial pellets were ground in a porcelain mortar); crude products are obtained in high yield and high spectroscopic purity (based on comparison of IR and 60-MHz proton NMR with those of commercial material) with no evidence of overhydrogenation. Different texts present varied apparatus for hydrogenations [49-51];

Rheosmin can be purified further by recrystallization from water; zingerone's low melting point (ca. 40 °C) makes crystallization difficult [30, 52], but ether and petroleum ether have been used for this purpose [20, 30]. While rhodium is a little more expensive than platinum or palladium, a 25-gram bottle of 0.5% catalyst will suffice for hundreds of hydrogenations. The 0.5% rhodium on alumina also offers the advantage of being pale enough that the disappearance of the starting material's yellow color is clearly visible as the hydrogenation approaches completion. As with the crossed-aldol reactions, hydrogenation procedures are included on two different scales. An alternative to suction filtration, using a Celite-packed column made from a pipet, appears in the microscale hydrogenation procedure; for variety, one may wish to have

the students prepare aldol adducts by the semimicroscale procedure, then perform hydrogenations on microscale. Before the laboratory (preferably!), or while the hydrogenation is in progress, students should be asked to calculate the expected uptake of hydrogen.

Alternative Preparations of Rheosmin and Zingerone

Based on yields and convenience, the reactions selected and adapted for this laboratory exercise appear to be the methods of choice for rheosmin and zingerone. There are however, other methods reported for both compounds. Rheosmin has also been synthesized from phenol by Amberlyst-15-catalyzed addition of 3-buten-2-one [53]. Zingerone has been prepared several additional ways. These include reduction and decarboxylation of ethyl vanillylideneacetoacetate [52]; reaction of 4-benzyloxy-3-methoxybromomethylbenzene with the the anion of acetone dimethylhydrazone, followed by oxidative hydrolysis, then hydrogenolysis to remove the benzyl group [54]; by reaction of methyllithium with 3-(4'-hydroxy-3'-methoxyphenyl)-*N*-methoxy-*N*-methylpropanamide [55]; and by Amberlyst-15-catalyzed addition of 3-buten-2-one to 2-methoxyphenol [53]. If structural variants were desired, some of the alternatives might offer advantages. Students in an advanced organic laboratory might find a comparison of the alternate methods to be an interesting and challenging exercise; however, we have not pursued this option.

Experimental Section

Preliminary remarks

The experimental procedures that follow are based on the expectation that students will previously have had a laboratory-based general chemistry course, that they will have encountered a variety of basic organic laboratory operations before this exercise, and that they will be familiar with the standard precautions that go with the use of acids, bases, common solvents, and other laboratory reagents. A further expectation is that instructors using these procedures will be experienced in the standard organic teaching laboratory setting, and that instructors will check out laboratory procedures before using them in their classes. Commonly-accepted laboratory safety precautions, including but not limited to the use of appropriate safety goggles or safety glasses, are to be followed throughout.

Semimicroscale condensation of 4-hydroxybenzaldehyde with acetone

A 13 × 100-mm Pyrex screw-cap culture tube is charged with 0.25 g (2.05 mmol) of 4-hydroxybenzaldehyde and 1.0 mL (14 mmol) of acetone. After the solid has dissolved, 1.0 mL of 10% (w/v) (2.5 M) aqueous NaOH (*caution: caustic!*) is added, the tube is capped and shaken to get a clear dark amber solution; the solution is left to stand for 24–48 hours. Within 24 hours, the mixture turns to an orange-red semisolid mass. For workup, the mixture is treated with 5.0 mL of 3 M aqueous HCl, recapped, and shaken vigorously (one to several minutes) until the initially oily suspension yields a slurry of crystals. If the suspended oil does not crystallize within five minutes, addition of a small seed crystal and further shaking should be effective. The mixture is suction filtered, and the filter cake is washed with a few mL of cold water. *Waste disposal note: The acidic aqueous filtrate contains acetone and reaction byproducts and must, therefore, be placed in the organic solvent waste container. If requested by the instructor, the filtrate should be neutralized with sodium bicarbonate prior to pouring it into the waste container*. Air drying of the product gives fine brown crystals, generally with m.p. 97–101 °C, whose IR and NMR spectra typically indicate high purity. Recrystallization from boiling water (ca. 100 mL per gram) gives material that is light yellow in color, with melting ranges up to ca. 108 °C. Spectroscopic data: IR (KBr): 3150 (br, s), 1660 (w), 1625 (s), 1600 (vs), 1575 (s), 1510 (m), 1435 (m/s), 1370 (m), 1330 (w), 1290 (m), 1250 (vs), 1200 (m), 1170 (s), 1100 (w), 1000 (m), 1075 (m), 860 (vw), 840 (w), 820 (w), 740 (w) cm^{-1}. ^{1}H NMR (300-MHz, $CDCl_3$): 8.1 (br, 1 H); 7.5 (d, *J*=16, 1 H); 7.4 (d, *J*=8, 2 H); 6.9 (d, *J*=8, 2 H); 6.6 (d, *J*=16, 1 H); and 2.4 (s, 3 H) ppm. ^{13}C NMR (75-MHz, $CDCl_3$): 201, 159, 145, 131, 126, 124, 116, and 27 ppm.

Semimicroscale hydrogenation

Caution: Hydrogen gas is extremely flammable! Use only in a well-ventilated room, and do not use flames or other sources of ignition in the laboratory during the experiment. Gas cylinders must be properly secured and transported, and equipped with appropriate pressure regulators. Particularly, if more than one source of hydrogen is in use, it may be prudent to have students set up their apparatus in the fume hoods. Also note: methanol is toxic and can be absorbed through the skin; avoid skin contact and breathing of methanol vapor.

NOTE: For the preparation below, use a round-bottomed flask, magnetic stirrer, and takeoff adapter to which you will attach a rubber balloon filled with H_2. Refer to the details of the experiment below the following first paragraph:

Microscale hydrogenation of 4-(4'-hydroxyphenyl)-3-buten-2-one to rheosmin

The apparatus (Figure 2), hydrogenation procedure, and filtration are the same as for the above microscale hydrogenation to zingerone, except that 60 mg (0.37 mmol) of 4-(4'-hydroxyphenyl)-3-buten-2-one is used as the starting material. Evaporation, characterization of product, and waste disposal are as noted in the semimicroscale hydrogenation to rheosmin.

Details of the hydrogenation of 4-(4'-hydroxy-3'-methoxyphenyl)-3-buten-2-one to zingerone (provided as a supplement for the rheosmin synthesis experiment above).

Clamp a 10-mL round-bottomed flask above a magnetic stirrer, and charge it with a magnetic stirbar, 0.25 g (1.30 mmol) of 4-(4'-hydroxy-3'-methoxyphenyl)-3-buten-2-one, 50 mg of powdered 0.5% rhodium on alumina, and 4 mL of methanol. Next fit the flask with a Claisen adapter, the vertical tube of which is closed with a rubber septum, and the sidearm of which is connected to a ca. 60-cm length of polyvinylchloride (pvc, Tygon™ or equivalent) tubing. The other end of the tubing is stiffened by insertion of a ca.10-cm glass tube. In an adjacent water bath (a standard pneumatic trough works well) is suspended a 100-mL graduated cylinder, filled with water and with the open end down in the bath. The end of the tube is immersed in the water bath, but not under the graduated cylinder. Via a syringe needle through the septum, with stirring, the apparatus is flushed gently with nitrogen for 1–2 minutes. Stirring is stopped, then the apparatus is flushed gently with hydrogen for 1–2 minutes, and then the end of the outlet tube is pushed up into the graduated cylinder. When the cylinder is nearly full of hydrogen, the gas flow is stopped and the inlet needle is removed. The starting volume is noted, and rapid stirring is started. Hydrogen uptake typically is complete within 40 minutes; complete reaction is indicated by cessation of hydrogen uptake and by disappearance of the solution's initial yellow color. After uptake ceases, the mixture is suction filtered through diatomaceous earth (Celite) in a small Büchner funnel or fritted filter using several mL of methanol to rinse the flask and the filter cake. The filtrate is evaporated to a viscous oil by heating gently on a hot plate (in the fume hood) in a small tared beaker to which boiling chips have been added. IR and NMR spectra of the material thus obtained match those of commercial zingerone, although it may be difficult to induce the oil to crystallize. Addition of a tiny seed crystal and stirring with a spatula gives a waxy solid.

REFERENCES

1. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 3rd ed., Plenum: New York and London, 1990; pp 55–79.
2. March, J. *Advanced Organic Chemistry*, 4th ed., Wiley: New York, 1992; pp 937–951.
3. Mann, J. *Chemical Aspects of Biosynthesis*; Oxford University Press: Oxford, 1994; pp 7, 19, 32.
4. Howells, H. P. *J. Chem. Educ.* **1930**, *7*, 597.
5. Angres, I.; Zeiger, H. E. *J. Chem. Educ.* **1974**, *51*, 64.
6. Hawbecker, B. L.; Kurtz, D. W.; Putnam, T. D.; Ahlers, P. A.; Gerber, G. D. *J. Chem. Educ.* **1978**, *55*, 540.
7. Rowland, A. T.; Brechbiel, M. W.; Gerelus, A. S. *J. Chem. Educ.* **1985**, *62*, 908.
8. García-Raso, A.; García-Raso, J.; Sinisterra, J. V.; Mestres, R. *J. Chem. Educ.* **1986**, *63*, 443.
9. Hathaway, B. A. *J. Chem. Educ.* **1987**, *64*, 367.

10. Nwaukwal, S. O. *J. Chem. Educ*. **1993**, *70*, 626.
11. Clausen, T. P.; Johnson, B.; Wood, J. *J. Chem. Educ*. **1996**, *73*, 266.
12. Landgrebe, J. A. *J. Chem. Educ*. **1995**, *72*, A220.
13. De,S.;Gambhir,G.;Krishnamurthy,H.G.*J.Chem.Educ*.**1994**,*71*,992.
14. Wilen,S.H.;Kremer,C.B.*J.Chem.Educ.***1962**,*39*,209.
15. Tucker, S. H. *J. Chem. Educ*. **1950**, *27*, 489.
16. Lee, M. *J. Chem. Educ*. **1993**, *70*, A155.
17. Fowler, R. G. *J. Chem. Educ*. **1992**, *69*, A43.
18. Ainscough,E.W.;Brodie,A.M.*J.Chem.Educ*.**1990**,*67*,1070.
19. Lampman, G. M.; Sharpe, S. D. *J. Chem. Educ*. **1983**, *60*, 503.
20. Nomura, H. *J. Chem. Soc*. **1917**, *111*, 769.
21. Lapworth, A.; Pearson, L. K.; Royle, F. A. *J. Chem. Soc*. **1917**, *111*, 777.
22. Connell, D. W.; Sutherland, M. D. *Aust. J. Chem*. **1969**, *22*, 1033. 23. Ayer, W.A.; Singer, P.P. *Phytochemistry* **1980**, *19*, 2717.
24. Hirvi, T.; Honkanen, E.; Pyysalo, T. *Z. Lebens. Unters. Forsch*. **1981**, *172*, 365. 25. Sanz, J. F.; Barbera, O.; Marco, J. A. *Phytochemistry* **1989**, 28, 2163.
26. Suekawa, M.; Yuasa, K.; Isono, M.; Nishida, S. Japanese patent Jpn. Kokai Tokkyo Koho JP 62,283,922 [87,283,922] (Cl. A61K31/12), 09 Dec. 1987, Appl. 86/123,589, 30 May 1986; *Chem. Abstr*. **1988**, *109*, 176342w.
27. Oloke, J. K.; Kolawole, D. O.; Erhun, W. O. *J. Ethnopharmacology* **1989**, *25*, 109.
28. Biondi, D.; Cianci, P.; Geraci, C.; Ruberto, G. *Flavour Fragrance J*. **1993**, 8, 331; *Chem. Abstr*. **1994**, *120*, 330907v.
29. Nomura, H.; Nozawa, F. *Chemisches Zentralblatt* **1921(I)**, 1017.
30. Mannich, C.; Merz, K. W. *Archiv d. Pharm*. **1927**, *265*, 15.
31. Deifel, A. *Z. Lebensm. Unters. Forsch*. **1989**, *188*, 330.
32. Arctander, S. *Perfume and Flavor Chemicals (Aroma Chemicals),* Vol. I, Arctander: Montclair N. J., 1969; entry 1760.
33. Schinz, H.; Seidel, C. F. *Helv. Chim. Acta* **1957**, *40*, 1839.
34. Schinz, H.; Seidel, C. F. *Helv. Chim. Acta* **1961**, *44*, 278.
35. Honkanen, E.; Pyysalo, T.; Hirvi, T. *Z. Lebensm. Unters. Forsch*. **1980**, *171*, 180.
36. Pabst, A.; Barron, D.; Adda, J.; Schreiber, P. *Phytochemistry* **1990**, *29*, 3853.
37. Perez, R. L. *J. Chromatogr*. **1983**, *259*, 176.
38. Gaunt, I. F.; Sharrat, M.; Colley, J.; Lansdown, A. B. G.; Grasso, P. *Fd. Cosmet. Toxicol*. **1970**, *8*, 349.

39. Opdyke, D. L. J. *Fd. Cosmet. Toxicol*. **1978**, *16*, 781.

40. Keiser, I.; Nakagawa, S.; Kobayashi, R. M.; Chambers, D. L.; Urago, T.; Doolittle, R. E. *J. Econ. Ent.* **1973**, *66*, 112.

41. Tan, K. H.; Nishida, R. *Appl. Entomol. Zool*. **1995**, *30*, 494.

42. Kikuchi, T. *Nature* **1973**, *243*, 36.

43. Metcalf, R. L.; Mitchell, W. C.; Metcalf, E. R. *Proc. Nat. Acad. Sci. USA* **1983**, *80*, 3143. 44. Monge, P.; Scheline, R.; Solheim, E. *Xenobiotica* **1976**, *6*, 411.

45. Sporstφl,S.;Scheline,R.R.*Xenobiotica***1982**,*12*,249.

46. deBernardi,M.;Vidari,G.;Vita-Finzi,P.*Phytochemistry***1976**,*15*,1785.

47. Banno, K.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **1976**, *49*, 1453.

48. Jacobson, R.; Taylor, R. J.; Williams, H. J.; Smith, L. R. *J. Org. Chem*. **1982**, *47*, 3140; and references 7a and 8 therein.

49. Mayo, D. W.; Pike, R. M.; Trumper, P. K. *Microscale Organic Laboratory*, 3rd ed.; Wiley: New York, 1994; pp 246–252.

50. Pavia, D. L.; Lampman, G. M.; Kriz, G. S.; Engel, R. G. *Organic Laboratory Techniques—A Microscale Approach*, 2nd ed.; Saunders: Orlando, FL, 1995; pp 191–195.

51. Williamson, K. L. *Macroscale and Microscale Organic Experiments*, 2nd ed.; Heath: Lexington, MA, 1994; pp 284–293.

52. Lapworth, A.; Wykes, F. H. *J. Chem. Soc*. **1917**, *111*, 791.

53. Bunce, R. A.; Reeves, H. D. *Syn. Comm*. **1989**, *19*, 1109.

54. Enders, D.; Eichenauer, H.; Pieter, R. *Chem. Ber*. **1979**, *112*, 3703.

55. Sanders, W. J.; Seidel, J. L. *J. Agr. Food Chem*. **1992**, *40*, 263.