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A CONVENIENT SYNTHESIS OF DILL APIOLE

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Summary

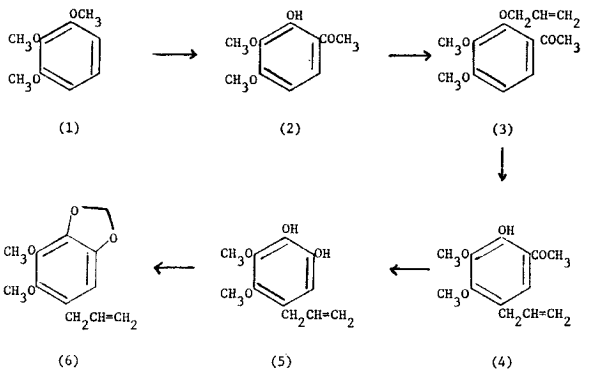
A convenient synthesis of 1-allyl-2,3-dimethoxy-4,5-methylene-dioxybenzene (dill apiole) (6) has been developed.

Dill apiole (6), which occurs in several essential oils, was first synthesized by Baker *et al.*[1] Although their method cannot be considered unambiguous and none of the intermediates was purified, the final product was converted into a solid tribromide which proved to be identical with that obtained from the natural product. Dallacker[2] has since synthesized dill apiole (6) by an unambiguous route but it seemed to us that the reactions set out in Scheme 1 might also provide an unambiguous and practical synthesis of this substance (6).

Treatment of 1,2,3-trimethoxybenzene (1) (which is conveniently prepared on a large scale by the method of Baker[3]) with acetyl chloride and aluminium chloride in carbon disulphide, after the method of Perkin and Weizmann[4] gave 3,4-dimethoxy-2-hydroxyacetophenone (2). When this substance (2) was treated with allyl bromide and potassium carbonate in acetone a good yield of the ether (3) was obtained. This substance (3) was characterized as its crystalline 2,4-dinitrophenylhydrazone.

On heating the allyl ether (3) it underwent a *para* Claisen rearrangement and gave a satisfactory yield of the phenolic ketone (4), which also gave a crystalline 2,4-dinitrophenylhydrazone. When the phenolic ketone (4) was subjected to the Dakin oxidation a mixture of the desired dihydroxy compound (5) and starting material was obtained. Attempts to separate this mixture were not rewarding and as a result the reaction mixture was treated directly with dibromomethane and potassium fluoride in N,N-dimethylformamide.[5] Dill apiole (6) was then easily separated from the reaction mixture by chromatography. The synthetic dill apiole (6) had the expected spectroscopic properties.

Scheme 1



Microanalyses were carried out by the Australian Microanalytical Service, Melbourne. Melting points were determined on a Kofler hot stage. Low resolution mass spectra were measured on a Varian MAT-CH7 instrument using the conditions stated in each case; only values for m/e greater than 100 and with a relative intensity greater than 10% of the base peak are usually quoted. Nuclear magnetic resonance (n.m.r.) spectra were obtained with a Varian A60A or Hitachi Perkin-Elmer R-24B instrument operating at 60MHz. Light petroleum refers to a fraction of boiling range 55–65°.

3,4-Dimethoxy-2-hydroxyacetophenone (2)

After the method of Perkin and Weizmann[4] 1,2,3-trimethoxybenzene[3] (1)(168g) and acetyl chloride (86.4g) were dissolved in CS_2 (1100ml) and the solution was cooled to −3°. Powdered anhydrous $AlCl_3$ (200g) was added in one portion with swirling. After 10 min the mixture became red and HCl was evolved. The mixture was allowed to stand overnight then refluxed for 1h. After cooling, the CS_2 was decanted and the remaining red tar was decomposed with cold 1 : 1 aq. HCl (1700ml). The mixture was extracted with ether then the ether solution was shaken exhaustively with 5% aq. NaOH. The alkaline extract was acidified and the product was recovered with ether. The resulting oil (153.7g) was distilled at 155-159°/4mm and the distillate (138.8g) was crystallized from methanol to yield 3,4-dimethoxy-2-hydroxyacetophenone (2) as cream prisms (106.5g) m.p. 74-76° (lit[4] 77°). N.m.r. spectrum ($CDCl_3$) δ: 2.50, s, 3, $COCH_3$; 3.80, s, 3, OCH_3; 3.83, s, 3, OCH_3; 6.37, 7.33 ABq (J = 8Hz), 2, ArH; 12.50, s, 1, OH. Mass spectrum (25°/70eV) m/e: 196 (81%), 181 (100), 153 (18).

2-Allyloxy-3,4-dimethoxyacetophenone (3) and its 2,4-Dinitrophenylhydrazone

A mixture of 3,4-dimethoxy-2-hydroxyacetophenone (2) (100g), freshly distilled allyl bromide (68g), anhydrous K_2CO_3 (80g) and acetone (1 l) was boiled for 24h then filtered and evaporated. The oily product was taken up in ether and the solution was washed exhaustively with 5% aq. NaOH and water then dried and evaporated.

Chromatography of the resulting pale brown oil on alumina (200g) with benzene gave a pale yellow oil (103.5g). A small portion of this product distilled at 90-110° (bath) / 0.2mm to give *2-allyloxy-3,4-dimethoxyacetophenone* (3) as a pale yellow oil (Found: C, 66.0; H, 6.7. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%). N.m.r. spectrum (CCl_4) δ: 2.43, s, 3, $COCH_3$; 3.70, s, 3, OCH_3; 3.79, s, 3, OCH_3; 4.52, d (b), 2, CH_2; 5.30, m, 2, $CH=CH_2$; 5.90, m, 1, $CH=CH_2$; 6.54, 7.23 ABq (J = 7Hz) 2, ArH. Mass spectrum (25° / 70eV) m/e: 236 (92%), 221 (46), 218 (18), 195 (42), 194 (50), 193 (55). 181 (100), 179 (55), 167 (28), 165 (23), 152 (55), 137 (75), 135 (50).

The *2,4-dinitrophenylhydrazone of 2-allyloxy-3,4-dimethoxyacetophenone* was prepared by the usual method[6] and crystallized from ethanol as red plates m.p. 147-148.5° (Found: C, 54.8; H, 4.8. $C_{19}H_{20}N_4O_7$ requires C, 54.8; H, 4.8%).

5-Allyl-3,4-dimethoxy-2-hydroxyacetophenone (4) and its 2,4-Dinitrophenylhydrazone

The allyl ether (3) (100g) was heated at 190-200° under N_2 for 2.5h then at 210-220° for 0.5h. The oil was cooled to room temperature, dissolved in ether and shaken with 5% aq. NaOH. The alkaline extract was acidified and the resulting brown oil (91g) was recovered by extraction with ether. Distillation of this product afforded *5-allyl-3,4-dimethoxy-2-hydroxyacetophenone* (4) as a pale yellow oil (62.2g) b.p. 125-128° / 0.6mm (Found: C, 66.2; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%). N.m.r spectrum (CCl_4) δ: 2.48, s, 3, $COCH_3$; 3.17, d (b), 2, CH_2; 3.80, s, 3, OCH_3; 3.91, s, 3, OCH_3; 4.90, m, 2, $CH=CH_2$; 5.70, m, 1, $CH=CH_2$; 7.03, s, 1, ArH; 12.40, s, 1, OH. Mass spectrum (25° / 70eV) m/e: 236 (100%), 221 (63), 203 (11), 193 (26), 161 (15), 133 (18).

The *2,4-dinitrophenylhydrazone of 5-allyl-3, 4-dimethoxy-2-hydroxyacetophenone* was prepared by the usual method[6] and crystallized from ethanol as orange needles m.p. 154.5-156.0°. (Found: C, 54.6; H, 4.9. $C_{19}H_{20}N_4O_7$ requires C, 54.8; H, 4.8%).

1-Allyl-2,3-dimethoxy-4,5-methylenedioxybenzene (Dill Apiole) (6)

A mixture of the phenol (4) (50g) and 5% aq. NaOH (186.4ml) was stirred under N_2 for 20 min to remove air; a yellow salt separated during this time. 3% Aqueous H_2O_2 (312.3ml) was then added to the mixture all at once whereupon the temperature rose and a clear brown solution was formed. The mixture was stirred for 2h, then acidified with 10% aq. HCl (111ml) and extracted with ether. The extract was washed with 5% aq. $NaHCO_3$ to remove a dark impurity then washed with water, dried (Na_2SO_4) and evaporated. Distillation of the resulting brown residue gave a mixture of 1-allyl-4,5-dihydroxy-2,3-dimethoxy-benzene (5) and unchanged (4) as a yellow oil (38.5g) b.p. 130-138° / 1mm. N.m.r. spectrum ($CDCl_3$) δ: 2.52, s, $COCH_3$; 3.23, d (b), CH_2; 3.70. s, OCH_3; 3.83, s, OCH_3; 3.92, s, OCH_3; 4.90, m, $CH=CH_2$; 5.60, m, $CH=CH_2$; 6.39, s, ArH; 7.19, s, ArH; 12.52, s, OH. Ratio of integrals of signals at δ 6.39 [ArH of (5)] and 7.19 [ArH of (4)]=3:2.

Attempts to separate the phenols (5) and (4) via their acetates were unsuccessful and prolonged chromatography of the mixture resulted in decomposition.

After the method of Clark *et al*[5] a solution of the mixture of (4) and (5) (8g) in dry N,N-dimethylformamide (50ml) was treated with anhydrous KF (4.64g) and

dibromomethane (10.40g) then stirred under N_2 for 2h at 110-120° (bath). After cooling, the mixture was poured into water and extracted with ether. The ethereal extract was washed repeatedly with 5% aq. NaOH then dried and evaporated. Chromatography of the resulting brown oil on alumina (Act 1; 80g) with benzene yielded dill apiole (6) as a colourless oil (1.7g) b.p. 119-120°/2mm. N.m.r. spectrum (CCl_4) δ: 3.20, d (b), 2, CH_2; 3.61, s, 3, OCH_3; 3.84, s, 3, OCH_3; 4.90, m, 2, $CH=CH_2$; 5.62, m, 1, $CH=CH_2$; 5.70, s, 2, CH_2O_2; 6.12, s, 1, ArH. Mass spectrum (25°/70eV) m/e: 222 (100%), 207 (25), 177 (44), 149 (19), 121 (13).

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References

1. Baker, W., Jukes, E.H.T., and Subrahmanyam, C.A. (1934) *J. Chem. Soc.* 1681.
2. Dallacker, F. (1969) *Chem Ber.* **102,** 2663.
3. Baker, W. (1941) *J. Chem. Soc.* 662
4. Perkin, W.H. Jr, and Weizmann, C. (1906) *J. Chem. Soc.* **89,** 1649.
5. Clark, J.H., Holland, H.L., and Miller, J.M. (1976) *Tetrahedron Lett.* 3361.
6. Vogel, A.I. (1956) *Practical Organic Chemistry*, 3rd edn., Longmans, London.

บทคัดย่อ

1-Allyl-2,3-dimethoxy-4,5-methylenedioxybenzene สามารถสังเคราะห์ได้อย่างสะดวกโดยใช้ 1,2,3-trimethoxybenzene ดังปรากฏในรายงานนี้