Syntheses of Polymerizable Acetals. II. Readily Hydrolyzable Acetals from Citronellol and Vitamins

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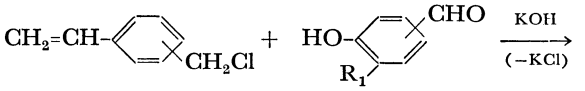
Three perfume acetals and four vitamin acetals have been synthesized by the acid-catalyzed reactions of vinylbenzyloxy- and methoxy-substituted benzaldehydes with citronellol and the reactions of vinylbenzaldehyde with vitamins B_6, C, B_1, and B_2, respectively. The acid hydrolyses of these novel acetals readily released citronellol and vitamins under mild conditions, some accelerations of the hydrolysis rate by the electron-donating para substituents being observed in the case of the perfume acetals.

The controlled release of functional compounds by means of the hydrolytic cleavage of chemical bonds is interesting since the susceptibility to cleavage is dependent upon chemical structure, thereby assuring a variety of release rates.

Some instances of the controlled release taking advantage of the ready hydrolysis of an ester linkage are known.[1,2] In a previous paper,[3] the syntheses of the polymerizable vinylbenzaldehyde acetals with perfume alcohols, which provided, by polymerization, the pendant polymers possessing the ability of the ready release of pendant portion (perfume) by acid hydrolysis, were reported.

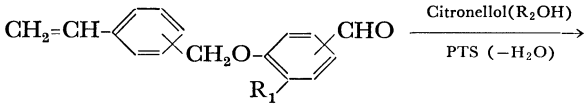
The present paper is intended to cover three perfume acetals synthesized from the benzaldehyde substituted with electron-donating groups and citronellol as well as four vinylbenzaldehyde acetals with vitamin alcohols, all acetals synthesized being novel.

Acetals of substituted benzaldehyde with citronellol have been synthesized *via* the following route.

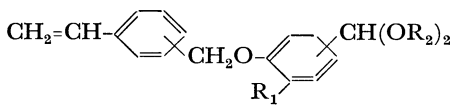


I: *m*/*p*=60/40

IIa: R_1=H (CHO, para to OH)
IIb: R_1=OCH_3 (CHO, meta to OH and para to R_1)
IIc: R_1=OCH_3 (CHO, para to OH)

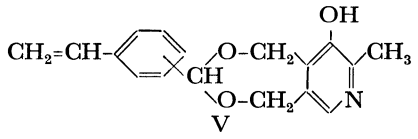


IIIa: R_1=H (CHO, para to OCH_2)
IIIb: R_1=OCH_3 (CHO, meta to OCH_2)
IIIc: R_1=OCH_3 (CHO, para to OCH_2)

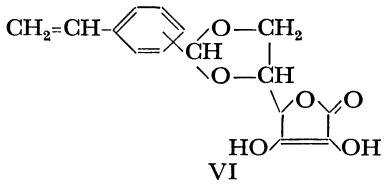


IVa: R_1=H ($CH(OR_2)_2$, para to OCH_2)
IVb: R_1=OCH_3 ($CH(OR_2)_2$, meta to OCH_2)
IVc: R_1=OCH_3 ($CH(OR_2)_2$, para to OCH_2)

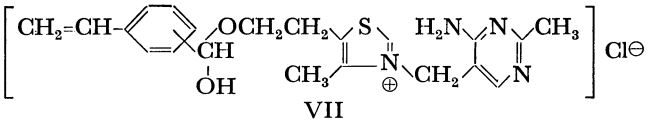
Vinylbenzaldehyde acetals with vitamin alcohols have been prepared from vinylbenzaldehyde (*m*/*p*=60/40) and the corresponding vitamin alcohols in the same manner as that for IVa—c. The structures of the acetals conforming to the experimental data are as follows.



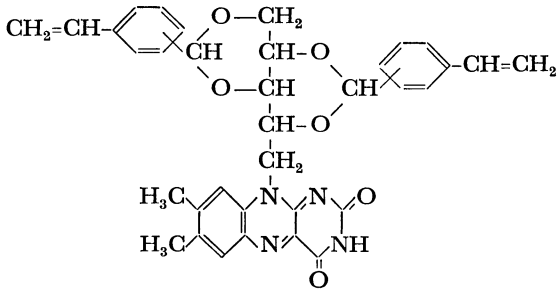
V
Acetal with vitamin B_6



VI
Acetal with vitamin C



VII
Hemiacetal with vitamin B_1



VIII
Acetal with vitamin B_2

The ring structure of acetal VIII is uncertain, due to insufficient analytical data sufficient to exactly determine the structures of the dioxa rings. Vinylbenzyl chloride (I) and vinylbenzaldehyde,[3] both of which were 60/40 mixtures of the meta and para isomers, were chosen as starting materials from the stand-point of availability, such that the acetals made should also be mixtures of the meta and para isomers. The isomers, however, could not be separated by chromatographic means; all attempts to determine the *m*/*p* ratios in the acetals isolated also failed. These problems, however, are not thought to pose any practical troubles.

Benzaldehyde acetals with citronellol, bearing two electron-donating alkoxyl substituents at both the para and meta positions (IVa—c), were synthesized smoothly. Despite the poor stabilities and limited solubilities of the vitamins employed, the vitamin acetals and a hemiacetal were isolated in low yields. Vitamin B_1

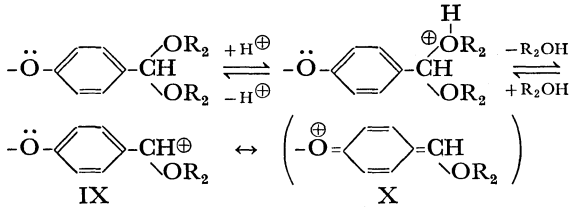
provided only a hemiacetal (VII), presumably due to the steric hindrance exerted by the bulky vitamin B_1 molecule and the electrostatic repulsion of the VII cation produced against the attack of another vitamin B_1 cation.

The ring structure of the acetal V involving a seven-membered dioxa ring appears to be correct, since a phenolic hydroxyl singlet (δ=5.9 ppm) exists in the NMR. The poor reactivity of the phenolic hydroxyl group in the acetalization also supports this structure.

The ring structure of acetal VIII with two six-membered dioxa rings, as presented here, is thought to represent the most strain-free structure. However, five-membered and seven-membered dioxa rings may also be possible, since it appears that little differences exist in the reactivity of acetalization among the three secondary hydroxyl groups in riboflavin and that the main factor determining the ring structure is a steric one.

In vitamin acetal syntheses, the poor solubilities of the vitamins employed in solvents appear to be the principal causes of the low yields found for VI, VII, and VIII. In the case of acetal V, the basicity of the ring nitrogen lowered the acidity of the reaction medium, thereby causing a low yield. However, a large amount of unreacted vitamin was recovered making recycling possible.

The hydrolytic behavior of the acetals has also been investigated. Thus, when subjected to acid hydrolysis with *p*-toluenesulfonic acid in water–tetrahydrofuran (1:2 vol/vol) at 20 °C, monomers IVa—c with electron-donating para substituents hydrolyzed more rapidly than vinylbenzaldehyde dicitronellyl acetal, indicating the resonance stabilization of the intermediate carbocation (IX) and the resulting acceleration of hydrolysis.



It appears reasonable that a more electron-donating *p*-methoxyl substituent (IVb) provides a higher rate than the *p*-benzyloxyl substituent (IVa and IVc).

Since the hydrolysis of acetals from aromatic aldehydes is generally rapid,[4] the differences observed in the rate of hydrolysis were small and all acetals synthesized underwent complete hydrolysis under mild acidic conditions, thereby assuring the controlled release of the functional portions (perfumes and vitamins).

The acetals and the hemiacetal synthesized possess polymerizable styrenic double bonds which, on polymerization, afford the vinyl polymers containing functional portions as pendant.

Experimental

IR, ^{1}H-NMR, and mass spectra were obtained with a Hitachi EPI-G spectrophotometer, a JNM-PMX 60 spectrometer, and a Hitachi RMU-6 MG spectrometer, respectively. Elemental analyses were conducted using a Perkin-Elmer 240.

4-(Vinylbenzyloxy)benzaldehyde (IIIa). A solution of 4-hydroxybenzaldehyde (IIa) (12.2 g, 100 mmol) in methanol (60 ml) containing potassium hydroxide (6.6 g, 100 mmol) was evaporated *in vacuo* at 50 °C to dryness. The residue was dissolved in *N,N*-dimethylformamide (60 ml). vinylbenzyl chloride (15.3 g, 100 mmol)(I ; Seibi Chem. Co., 60/40 mixture of meta and para isomers) and phenothiazine (0.1 g) added, and the solution kept at 90 °C for 2 h under nitrogen. The reaction mixture was then poured into a large quantity of water and the resulting oily mass extracted with ether. The extract was washed with dilute aqueous sodium hydroxide, then with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo* at 50 °C. The oily mass was washed with a large amount of petroleum ether and dried *in vacuo* to give a yellowish compound in 60% yield. Oxime: mp 95—96 °C (colorless crystals). This product was pure by TLC and all attempts to separate the meta and para isomers failed.

Found: C, 80.53; H, 6.00%. Calcd for $C_{16}H_{14}O_2$: C, 80.68; H, 5.88%. IR (CCl_4) 2840, 2740 (CHO), 1695 (C=O), 1600 (aryl), 990, 910 (vinyl) cm^{-1}. NMR (CCl_4) δ 5.1 (s, 2H, CH_2), 5.2 (d, 1H, $C\underline{H}_2$=CH–), 5.7 (d, 1H, $C\underline{H}_2$=CH–), 6.6 (q, 1H, CH_2=C$\underline{H}$–), 7—8 (m, 8H, ArH), 9.9 (s, 1H, CHO) ppm. Mass (*m/e*) 283 (M^+, 3), 117 (100).

3-Vinylbenzyloxy-4-methoxybenzaldehyde (IIIb). Following the same procedure as for IIIa, a light brown viscous liquid was obtained in 50% yield. Oxime: oily.

Found: C, 76.04; H, 6.08%. Calcd for $C_{17}H_{16}O_3$: C, 76.12; H, 5.97%. IR (CCl_4) 2840, 2720 (CHO), 1690 (C=O), 1600 (aryl), 990, 910 (vinyl) cm^{-1}. NMR (CCl_4) δ 3.8 (s, 3H, OCH_3), 5.0 (s, 2H, CH_2), 5.2 (d, 1H, $C\underline{H}_2$=CH–), 5.7 (d, 1H, $C\underline{H}_2$=CH–), 6.6 (q, 1H, CH_2=C$\underline{H}$–), 6.7—7.4 (m, 7H, ArH), 9.8 (s, 1H, CHO) ppm. Mass (*m/e*) 268 (M^+, 54), 117 (100).

4-Vinylbenzyloxy-3-methoxybenzaldehyde (IIIc). Following the same procedure as that for IIIa, a light brown solid was obtained in 40% yield. Oxime: mp 82—83 °C (white powder).

Found: C, 76.04; H, 6.06%. Calcd for $C_{17}H_{16}O_3$: C, 76.12; H, 5.97%. IR (CCl_4) 2830, 2720 (CHO), 1680 (C=O), 1590 (aryl), 990, 910 (vinyl) cm^{-1}. NMR (CCl_4) δ 3.8 (s, 3H, OCH_3), 5.1 (s, 2H, CH_2), 5.2 (d, 1H, $C\underline{H}_2$=CH–), 5.7, (d 1H, $C\underline{H}_2$=CH–), 6.6 (q, 1H, CH_2=C$\underline{H}$–), 6.5—7.3 (m, 7H, ArH), 9.7 (s, 1H, CHO) ppm. Mass (*m/e*) 268 (M^+, 3), 117 (100).

4-(Vinylbenzyloxy)benzaldehyde Dicitronellyl Acetal (IVa). A solution of IIIa (3.0 g, 13 mmol), citronellol (3.9 g, 25 mmol), *p*-toluenesulfonic acid (PTS) (0.4 g), and phenothiazine (0.1 g) in chloroform (100 ml) was refluxed for 6 h in a flask fitted with a Soxhlet extractor charged with 3 A molecular sieves (1/16). The chloroform solution was then washed with aqueous sodium carbonate, dried over anhydrous sodium sulfate, and evaporated *in vacuo* at 50 °C to leave an oil. The oil was subjected to alumina column chromatography to collect petroleum ether eluates. Upon evaporation of the solvent, a pale yellow liquid, pure by VPC, was obtained. This could not be separated into the meta and para isomers (31% yield).

Found: C, 81.65; H, 9.24%. Calcd for $C_{36}H_{52}O_3$: C, 81.20; H, 9.77%. IR(CCl_4) 2960—2850 (alkyl), 1600 (aryl), 990, 910 (vinyl) cm^{-1}. NMR(CCl_4) δ 0.8—3.6 (m, 38 H, citronellyl), 5.1 (s, 2H, $ArCH_2O$), 5.1—5.6 (m, 2 H, $C\underline{H}_2$=CH–+–CH$\begin{matrix}\diagup O- \\ \diagdown O-\end{matrix}$), 5.7 (d, 1H, $C\underline{H}_2$=CH–), 6.5—7.6 (m, 9H, CH_2=C$\underline{H}$–+ArH) ppm. Mass (*m/e*) 377 ($M^+ - OC_{10}H_{19}$).

3-Vinylbenzyloxy-4-methoxybenzaldehyde Dicitronellyl Acetal (IVb). Following the same procedure as that for IVa, a pale yellow liquid was obtained in 27% yield.

Found: C, 79.16; H, 9.24%. Calcd for $C_{37}H_{54}O_4$: C, 79.00; H, 9.61%. IR(CCl_4) 2960—2860 (alkyl), 1600 (aryl), 990, 910 (vinyl) cm^{-1}. NMR(CCl_4) δ 0.8—3.5 (m, 38 H, citronellyl), 3.8 (s, 3 H, OCH_3), 5.0 (s, 2 H, Ar-CH_2O), 5.3 (s, 1H, $-CH(O-)(O-)$), 5.2 (d, 1H, CH_2=CH-), 5.7 (d, 1H, CH_2=CH-), 6.3—7.5 (m, 8H, CH_2=CH-+ArH) ppm. Mass (*m/e*) 407 ($M^+-OC_{10}H_{19}$).

4-Vinylbenzyloxy-3-methoxybenzaldehyde Dicitronellyl Acetal (IVc). Following the same procedure as that for IVb, a pale yellow liquid was obtained in 28% yield.

Found: C, 79.17; H, 9.35%. Calcd for $C_{37}H_{54}O_4$: C, 79.00; H, 9.61%. IR(CCl_4) 2970—2850 (alkyl), 1600 (aryl), 990, 910 (vinyl) cm^{-1}. NMR(CCl_4) δ 0.8—3.5 (m, 38H, citronellyl), 3.8 (s, 3H, OCH_3), 5.0 (s, 2H, $ArCH_2O$), 5.1 (d, 1H, CH_2=CH-), 5.3 (s, 1H, $-CH(O-)(O-)$), 5.7 (d, 1H, CH_2=CH-), 6.5—7.6 (m, 8H, CH_2=CH-+ArH) ppm. Mass (*m/e*) 563 (M^+, 6), 286 (100).

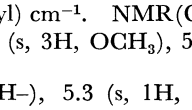
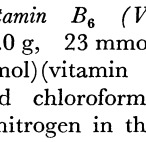
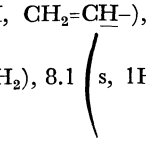
Vinylbenzaldehyde Acetal with Vitamin B_6 (V). A mixture of vinylbenzaldehyde (3.0 g, 23 mmol) (*m/p*=60/40),[3] pyridoxine (9.3 g, 45 mmol)(vitamin B_6), PTS (0.5 g), phenothiazine (0.1 g), and chloroform (100 ml) was stirred at 70 °C for 6 h under nitrogen in the presence of 3A molecular sieves (1/16). The reaction mixture was washed with aqueous sodium carbonate, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness *in vacuo* at 50 °C. The brown mass was purified by alumina column chromatography and the methanol eluates collected. Upon evaporation of the solvent, a brownish oily mass, which was pure by TLC, was obtained in 4% yield.

Found: C, 72.16; H, 6.28; N, 4.51%. Calcd for $C_{17}H_{16}NO_3$: C, 72.08; H, 6.01; N, 4.95%. IR(CCl_4) 3600 (OH), 1600 (aryl), 1120 (ether), 990, 910 (vinyl) cm^{-1}. NMR(CCl_4+DMSO-d_6) δ 2.4 (s, 3H, CH_3), 4.5(s, 1H, $-CH(O-)(O-)$), 4.6—5.1 (m, 4H, CH_2), 5.2 (d, 1H, CH_2=CH-), 5.8 (d, 1H, CH_2=CH-), 5.9 (s, ArOH), 6.5—6.8 (b, 1H, $-CH(O-)(O-)$), 7.0—8.0 (m, ArH) ppm. Mass (*m/e*) 283 (M^+, 4), 43 (100).

Vinylbenzaldehyde Acetal with Vitamin C (VI). A mixture of vinylbenzaldehyde (3.0 g, 23 mmol), L-ascorbic acid (4.0 g, 23 mmol)(vitamin C), PTS (0.4 g), phenothiazine (0.1 g), and dioxane (50 ml) was stirred at room temperature for 24 h under nitrogen in the presence of 3A molecular sieves with the exclusion of light. Dioxane was then removed by freeze-drying, the residue extracted with ether, and the extract evaporated *in vacuo* at 50 °C. The oily mass, which was washed with petroleum ether, afforded a colorless sticky mass, which was pure by TLC, in 13% yield.

Found: C, 61.27; H, 5.60%. Calcd for $C_{15}H_{14}O_6$: C, 62.07; H, 4.83%. IR ($CHCl_3$) 3580 (OH), 1680 (C=O), 1120 (C-O-), 990, 910 (vinyl) cm^{-1}. NMR(CCl_4+DMSO-d_6) δ 3.4—3.5 (t, 2H, CH_2), 4.1 (b, 1H, $-OCHCH_2-$), 4.8—4.9 (s, 1H, $-CHCHO-$), 5.3 (s, 1H, $-CH(O-)(O-)$), 5.2 (d, 1H, CH_2=CH-), 5.8 (d, 1H, CH_2=CH-), 6.7 (b, 1H, CH_2=CH-), 7.0—7.8 (m, 4H, ArH) ppm.

Vinylbenzaldehyde Hemiacetal with Vitamin B_1 (VII). A mixture of vinylbenzaldehyde (1.5 g, 11 mmol), thiamine hydrochloride (3.8 g, 11 mmol), PTS (0.5 g), phenothiazine (0.1 g), and acetonitrile (50 ml) was stirred at room temperature for 72 h under nitrogen in the presence of 3A molecular sieves (1/16). The reaction mixture was evaporated in vacuo at 50 °C to dryness and washed with petroleum ether and ether. The residue was thoroughly shaken with a mixture of aqueous sodium carbonate and sodium chloride and chloroform and the chloroform layer dried over anhydrous sodium sulfate. The sodium sulfate was filtered and extracted with acetonitrile to afford a white powder (mp 138—140 °C) in 10% yield upon evaporation of solvent.

Found : C, 56.77; H, 5.95; N, 12.99%. Calcd for $C_{20}H_{24}N_4O_2SCl$: C, 57.14; H, 5.73; N, 13.33%. IR(KBr) 3300 (OH+NH_2), 1650 (C=$\overset{+}{N}$<), 1000, 920 (vinyl) cm^{-1}. NMR ($CDCl_3$+DMSO-d_6) δ 2.3—2.6 (d, 6H, $2CH_3$), 2.9—3.2 (t, 2H, ), 3.4 (s, 1H, OH), 3.6—3.8 (t, 2H, OCH_2CH_2), 5.2 (d, 1H, CH_2=CH-), 5.5 (s, 3H, $-CHO-+-\overset{\oplus}{N}-CH_2$), 5.8 (d, 1H, CH_2=CH-), 6.6—7.0 (b, 1H, CH_2=CH-), 7.0—7.6 (m, 4H, ArH), 7.6—7.8 (b, 2H, NH_2), 8.1 (s, 1H, ), 9.8 (s, 1H, ) ppm.

Vinylbenzaldehyde Acetal with Vitamin B_2 (VIII). A mixture of vinylbenzaldehyde (2.0 g, 15 mmol), riboflavin (2.9 g, 7.6 mmol)(vitamin B_2), PTS (0.4 g), phenothiazine (0.1 g), and dioxane (50 ml) was stirred at 50 °C for 5 h under nitrogen in the presence of 3A molecular sieves (1/16), followed by stirring at room temperature for 20 h. The dioxane was then removed by freeze-drying and the residue washed with petroleum ether and aqueous sodium hydrogen carbonate and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, evaporated *in vacuo* at 50 °C to leave a reddish brown powder (mp 110—113 °C) in 8% yield.

Found: C, 70.62; H, 5.33 ; N, 8.09%. Calcd for $C_{35}H_{32}N_4O_6$: C, 69.54; H, 5.30; N, 9.27%. IR($CHCl_3$) 3380 (NH), 1680 (C=O), 990, 910 (vinyl) cm^{-1}. NMR($CDCl_3$+DMSO-d_6)δ 2.2—2.5 (s, 6H, $2CH_3$), 3.0—5.0 (m, 7H, $3CH+2CH_2$), 5.1—5.3 (d, 3H, CH_2=CH-+-$CH(O-)(O-)$), 5.8 (d, 2H, CH_2=CH-), 6.5—7.7 (m, 12H, ArH), 8.3 (b, 1H, NH) ppm. Mass (*m/e*) 604 (M^+, 2), 18 (100).

Hydrolyses of Acetals. A solution of the acetal (1 mmol), PTS (0.05 g), and *t*-butylcatechol (0.001 g) in 30 ml of H_2O–THF (1 : 2 v/v) was stirred at 20 °C under nitrogen. The reaction mixture was neutralized with solid sodium carbonate and evaporated *in vacuo* at 50 °C to remove THF, followed by extraction with a mixture of aqueous sodium carbonate and chloroform. The chloroform layer was dried over anhydrous sodium sulfate and evaporation *in vacuo* at 50 °C afforded the sample for analysis. NMR-determinations using either methoxyl or aryl signals provided the degree of hydrolysis. Typical data are as follows.

IVa: 72.8% in 2 h and 100% in 10 h; IVb: 82.9% in 2 h and 100% in 10 h; IVc: 74.6% in 2 h and 100% in 10 h; V; 62.8% in 2 h and 100% in 10 h; vinylbenzaldehyde dicitronellyl acetal:[3] 64.0% in 2 h and 100% in 10 h.

References

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