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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Preparative Synthesis of Veratraldehyde and Citral Oxime Esters

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Abstract—Procedures were developed for preparing veratraldehyde, oximes of veratraldehyde and citral, and esters of these oximes, which are readily accessible fragrance compounds that can be synthesized from commercially available raw materials.

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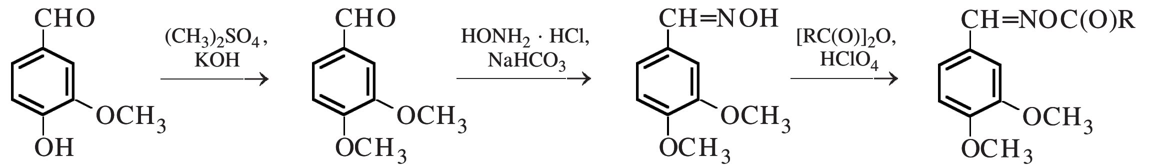
Veratraldehyde (3,4-dimethoxybenzaldehyde) is present in small amounts in *Cymbopogon javanensis* essential oil. It is used in relatively few perfume compounds, odorants, and food aromatizers, and also as intermediate in synthesis of certain drugs [1]. Citral (3,7-dimethyl-2,6-octadienal) is present in lemongrass, cubeb, citrus, and some other essential oils. It is a 7 : 3 mixture of *E* and *Z* isomers. Citral is widely used in many perfume compounds, odorants, and food aromatizers [1–3].

The goal of this study was to develop of procedures for preparative synthesis of veratraldehyde and citral oxime esters from commercially available raw materials: vanillin and citral. Veratraldehyde **II** was prepared by Schotten–Baumann methylation of vanillin **I** with Me_2SO_4 in the presence of KOH. We developed a synthesis procedure that is simpler and more convenient than the procedure described previously [4] and allows preparation of veratraldehyde **II** of high purity in 90% yield. Veratraldehyde oxime **III** was prepared in 92% yield by the reaction of **II** with hydroxylamine; the procedure was similar to that described in [5].

Veratraldehyde and citral oxime esters were prepared by reactions of oximes of veratraldehyde (**III**) and citral (**IV**) with alkanecarboxylic acid anhydrides in absolute benzene in the presence of catalytic amounts of $HClO_4$ or with alkane- and arenecarboxylic acid chlorides in the presence of pyridine by the procedure developed for synthesis of related compounds [6–8]. The reactants were mixed, and the mixture was allowed to stand at 20–23°C for 24–36 h. Intense cooling and stirring were not required. Oxime esters derived from veratraldehyde (**Va**–**Vs**) and citral (**VIa**–**VIt**) were prepared in 82–92% yields:



I **II** **III** **Va–Vt**

where R = Me (**Va**), Et (**Vb**), Pr (**Vc**), Me_2CH (**Vd**), Bu (**Ve**), Me_2CHCH_2 (**Vf**), $Me(CH_2)_4$ (**Vg**), $Me(CH_2)_5$ **(Vh), $Me(CH_2)_6$** (**Vi**), $Me(CH_2)_7$ (**Vj**), $Me(CH_2)_8$ (**Vk**), $Me(CH_2)_{11}$ (**Vl**), *cyclo*-C_6H_{11} (**Vm**), C_6H_5 (**Vn**), $C_6H_5(CH_2)_2$ **(Vo), $C_6H_5MeCHCH_2$** (**Vp**), *trans*-$C_6H_5CH=CH$ (**Vq**), MeO (**Vr**), EtO (**Vs**).

Properties of oxime esters derived from veratraldehyde (**Va–Vs**) and citral (**VIa–VIt**)

Ester	Yield, %	T_m, °C	d_{20}^{20}	n_D^{20}	Found			Formula	Calculated, %			*M*	
					C	H	N		C	H	N	found	calculated
Va	88	43–44			59.77	6.13	6.47	$C_{11}H_{13}NO_4$	59.19	5.87	6.27	218.6	223.2
Vb	85	61–62			61.01	6.76	5.60	$C_{12}H_{15}NO_4$	60.75	6.37	5.90	226.0	237.2
Vc	87	63–64			62.58	7.04	5.26	$C_{13}H_{17}NO_4$	62.14	6.82	5.57	240.8	251.3
Vd	86	50–51			62.37	6.97	5.41	$C_{13}H_{17}NO_4$	62.14	6.82	5.57	242.3	251.3
Ve	82	62–63			63.56	7.35	5.02	$C_{14}H_{19}NO_4$	63.38	7.22	5.28	253.7	265.3
Vf	84		1.0813	1.5480	63.51	7.25	5.10	$C_{14}H_{19}NO_4$	63.38	7.22	5.28	255.1	265.3
Vg	88	41–42			64.72	7.78	4.86	$C_{15}H_{21}NO_4$	64.50	7.58	5.01	266.2	279.3
Vh	86	44–45			65.70	8.06	4.49	$C_{16}H_{23}NO_4$	65.51	7.90	4.77	281.4	293.4
Vi	84	47–48			66.58	8.29	4.20	$C_{17}H_{25}NO_4$	66.43	8.20	4.56	290.5	307.4
Vj	85	40–41			67.45	8.52	4.12	$C_{18}H_{27}NO_4$	67.26	8.47	4.36	309.6	321.4
Vk	85	42–43			68.31	8.90	3.91	$C_{19}H_{29}NO_4$	68.03	8.71	4.18	329.4	335.4
Vl	87	56–57			70.13	9.38	3.53	$C_{22}H_{35}NO_4$	69.99	9.34	3.71	360.8	377.5
Vm	88	50–51			66.19	7.44	4.52	$C_{16}H_{21}NO_4$	65.96	7.26	4.81	283.4	291.3
Vn	86	110–111			67.90	5.72	4.55	$C_{16}H_{15}NO_4$	67.36	5.30	4.91	280.0	285.3
Vo	88	55–56			69.22	6.34	4.25	$C_{18}H_{19}NO_4$	69.00	6.11	4.47	302.7	313.4
Vp	87		1.1692	1.5795	69.94	6.58	4.06	$C_{19}H_{21}NO_4$	69.71	6.47	4.28	318.3	327.4
Vq	87		1.0484	1.6110	69.68	5.57	4.32	$C_{18}H_{17}NO_4$	69.44	5.50	4.50	303.8	311.3
Vr	84	49–50			55.61	5.60	5.53	$C_{11}H_{13}NO_5$	55.23	5.48	5.85	230.9	239.2
Vs	85	54–55			57.14	6.11	5.30	$C_{12}H_{15}NO_5$	56.91	5.97	5.53	246.2	253.3
VIa	86		1.0589	1.4968	69.62	9.17	6.67	$C_{12}H_{19}NO_2$	68.87	9.15	6.69	202.2	209.3
VIb	90		0.9758	1.4920	69.88	9.36	6.29	$C_{13}H_{21}NO_2$	69.92	9.48	6.27	211.6	223.3
VIc	83		0.9859	1.4794	70.90	9.78	6.07	$C_{14}H_{23}NO_2$	70.85	9.77	5.90	226.9	237.3
VId	85		1.0035	1.4750	70.82	9.86	5.86	$C_{14}H_{23}NO_2$	70.85	9.77	5.90	228.7	237.3
VIe	92		0.9785	1.4876	71.56	10.13	5.77	$C_{15}H_{25}NO_2$	71.67	10.03	5.57	240.1	251.4
VIf	88		0.8114	1.4798	72.36	10.51	5.06	$C_{16}H_{27}NO_2$	72.41	10.25	5.28	256.1	265.4
VIg	93		0.8901	1.4808	73.33	10.75	5.03	$C_{17}H_{29}NO_2$	73.07	10.46	5.01	269.5	279.4
VIh	84		1.9974	1.4839	73.72	10.90	4.67	$C_{18}H_{31}NO_2$	73.67	10.61	4.77	279.9	293.5
VIi	85		0.9785	1.4842	74.36	10.98	4.44	$C_{19}H_{33}NO_2$	74.22	10.82	4.55	292.8	307.5
VIj	86		0.9130	1.4798	76.40	11.55	3.81	$C_{23}H_{41}NO_2$	75.98	11.37	3.85	340.9	363.6
VIk	85		1.0580	1.4798	77.28	11.90	3.64	$C_{28}H_{51}NO_2$	77.54	11.85	3.23	415.3	433.7
VIl	80		1.0501	1.5025	74.13	10.23	4.99	$C_{17}H_{27}NO_2$	73.60	9.80	5.05	264.7	277.4
VIm	84		1.0224	1.5208	75.32	7.80	4.92	$C_{17}H_{21}NO_2$	75.25	7.80	5.16	260.3	271.4
VIn	87		0.9530	1.5268	76.58	8.48	4.70	$C_{19}H_{25}NO_2$	76.22	8.42	4.68	284.9	299.4
VIo	81		1.0752	1.5724	76.85	8.13	4.70	$C_{19}H_{23}NO_2$	76.73	7.79	4.71	287.5	297.4
VIp	80	38–39			74.70	7.34	9.12	$C_{20}H_{22}N_2O_2$	74.49	6.88	8.69	308.5	322.2
VIq	83		1.1376	1.5424	65.20	6.90	8.86	$C_{17}H_{20}N_2O_4$	64.54	6.37	8.85	306.1	316.4
VIr	82		0.9310	1.4856	63.72	8.36	6.33	$C_{12}H_{19}NO_3$	63.98	8.50	6.22	216.6	225.3
VIs	84		0.9836	1.4860	65.90	9.20	6.18	$C_{13}H_{21}NO_3$	65.25	8.85	5.85	223.0	239.3
VIt	86		0.8945	1.4848	64.49	8.75	4.82	$C_{15}H_{23}NO_4$	64.03	8.25	4.98	264.9	281.4

$Me_2C{=}CH(CH_2)_2C(Me){=}CHCH{=}O$

$\rightarrow Me_2C{=}CH(CH_2)_2C(Me){=}CHCH{=}NOH$
IV
$\rightarrow Me_2C{=}CH(CH_2)_2C(Me){=}CHCH{=}NOC(O)R,$
VIa–VIt

where R = Me (**VIa**), Et (**VIb**), Pr (**VIc**), Me_2CH (**VId**), Me_2CHCH_2 (**VIe**), $Me(CH_2)_4$ (**VIf**), $Me(CH_2)_5$ **(VIg), $Me(CH_2)_6$ (VIh)**, $Me(CH_2)_7$ (**VIi**), $Me(CH_2)_{11}$ (**VIj**), $Me(CH_2)_{16}$ (**VIk**), *cyclo*-C_6H_{11} (**VIl**), C_6H_5 (**VIm**), $C_6H_5(CH_2)_2$ (**VIn**), *cis*-$C_6H_5CH{=}CH$ (**VIo**), $C_6H_5CH{=}C(C{\equiv}N)$ (**VIp**), 3-$O_2NC_6H_4$ (**VIq**), MeO (**VIr**), EtO (**VIs**), $MeOC(O)(CH_2)_2C$ (**VIt**).

Oxime esters **Va**–**Vs** and **VIa**–**VIt** are colorless viscous liquids or crystalline compounds crystallizing from benzene–hexane (see table). The esters do not require additional purification, contain no admixtures of the starting compounds, benzene, and pyridine, and can be directly used in fragrance and food industry [3]. According to the ^{1}H NMR spectra, the compounds were 97–98% pure. Oxime esters **Va**–**Vs** and **VIa**–**VIt** can be well stored at a temperature below +5°C in the dark under anaerobic conditions. Unsaturated compounds **VI**–**VIt** were stabilized by adding 0.5% hydroquinone to prevent polymerization.

The compositions and structures of oxime esters **Va**–**Vs** and **VIa**–**VIt** were confirmed by elemental analysis, cryoscopic determination of the molecular weight (see table), and ^{1}H NMR and IR spectroscopy.

The IR spectra of veratraldehyde oxime esters **Va**–**Vs** contain the following absorption bands, cm^{-1}: CH_{Ar} in the range 3100–3000, CH_{Alk} at 3000–2800, C=O at 1770–1730, C=N at 1675–1665, Ar at 1600–1360, C–O at 1300–1000, CH_{Ar} at 880–620. In the ^{1}H NMR spectra of veratraldehyde oxime esters **Va**–**Vs**, the MeO protons give two singlets at 3.90–4.10 ppm. The aromatic protons appear as a multiplet at 6.70–7.50 ppm. The HC=N proton signal is a singlet at 8.20–8.30 ppm.

The IR spectra of citral oxime esters **VIa**–**VIt** contain the following absorption bands, cm^{-1}: CH_{Alk} in the range 3000–2800, =CH at 3050–3020, C=O at 1770–1740, C=C at 1670–1665, C=N at 1645–1635, CH_2 at 1667–1663, C–O at 1250–1180. The IR spectra of aromatic carboxylic acid esters **VIm**–**VIq** also contain the CH_{Ar} absorption bands at 3100–3000 and 707–690, and the Ar absorption bands at 1600–1595, 1455–1450, and 1380–1370 cm^{-1}. The C≡N group in the IR spectrum of **VIp** gives a band at 2219 cm^{-1}, and the NO_2 group in the spectrum of **VIq** gives two characteristic bands at 1535 and 1350 cm^{-1}. In the ^{1}H NMR spectra of **VIa**–**VIt**, the $Me_2C{=}C$ protons are manifested as two broadened singlets at 1.60 ± 0.05 and 1.66 ± 0.04 ppm, and the MeC=C protons, as a broadened singlet at 2.05 ± 0.05 ppm. The HC=C protons appear as signals at 4.90–6.40 ppm. The signals of aromatic protons in **VIm**–**VIq** are observed as a multiplet at 7.10–9.00 ppm.

The ^{1}H NMR spectra of **Va**–**Vs** and **VIa**–**VIt** also contain the characteristic signals of the ester fragments.

EXPERIMENTAL

The IR spectra were recorded on a Protege-460 IR Fourier spectrometer (Nicolet) from thin films or KBr pellets. The ^{1}H NMR spectra were measured on a BS-587A spectrometer (100 MHz, Tesla) from 5% solutions in $CDCl_3$; the chemical shifts were determined relative to internal tetramethylsilane. The molecular weight *M* was determined cryoscopically in benzene. The physicochemcial characteristics of veratraldehyde **II** and of oximes of veratraldehyde (**III**) and citral (**IV**) were in agreement with reference data [1, 9, 10].

Veratraldehyde II. A 14-g portion of 90% KOH was dissolved in 210 ml of water. The solution was cooled to 20–23°C, and 0.2 mol of vanillin was added with vigorous stirring. After vanillin fully dissolved, 22 ml of Me_2SO_4 was added in a single portion. The mixture was stirred for 6 h at 20–23°C, after which the stirring was stopped, and the mixture was cooled to 5°C and left for 10–12 h. The crystalline precipitate of veratraldehyde **II** formed in the process was filtered off on a glass frit, washed with a small amount of water, and dried in air. Yield 90%.

Veratraldehyde oxime III. A mixture of veratraldehyde **II** (0.21 mol), hydroxylamine hydrochloride (0.27 mol), sodium hydrogen carbonate (0.28 mol), and 96% ethanol (75 ml) was refluxed for 1 h. Then the mixture was poured into a beaker with 300 ml of water, cooled to 5°C, and left for 10–12 h. The crystalline precipitate of veratraldehyde oxime **III** formed in the process was filtered off on a glass frit, washed with a small amount of water, and dried in air. Yield 92%.

Veratraldehyde and citral oxime esters Va–Vd and VIa–VId (general procedure). Veratraldehyde oxime **III** or citral oxime **IV** (0.01 mol) and appropriate acid anhydride (0.011 mol) were dissolved in 20 ml of absolute benzene, and a drop of 47% $HClO_4$ was added. The mixture was shaken and allowed to stand at 20–23°C for 24–36 h. Then the mixture was diluted with water, and the product was extracted with benzene. The organic layer was separated, washed with water and 5% aqueous $NaHCO_3$, and dried over $CaCl_2$. The solvent was removed at reduced pressure (13–20 kPa), avoiding heating above 25–30°C.

Veratraldehyde and citral oxime esters Ve–Vs and VIe–VIt (general procedure). Veratraldehyde oxime **III** or citral oxime **IV** (0.01 mol) was dissolved in 50 ml of absolute benzene, and 0.01 mol of absolute pyridine was added. Appropriate acid chloride (0.01 mol) was added to the resulting solution with cooling to 15°C and careful shaking. The mixture was allowed to stand at 20–23°C for 24–36 h, after which it was diluted with water, and the product was extracted with benzene. The organic layer was separated, washed with water and 5% $NaHCO_3$ solution, and dried over $CaCl_2$. The solvent was removed at reduced pressure (13–20 kPa), avoiding heating above 25–30°C.

CONCLUSIONS

(1) A procedure was developed for preparing veratraldehyde and citral oxime esters in high yields by reactions of the corresponding oximes with carboxylic acid anhydrides and chlorides.

(2) A series of previously unknown veratraldehyde and citral oxime esters were synthesized and characterized. The compounds are highly pure and can be directly used in fragrance and food industry.

REFERENCES

1. Voitkevich, S.A., *865 Dushistykh veshchestv dlya parfyumerii i bytovoi khimii* (865 Fragrance Compounds for Perfumery and Household Chemistry), Moscow: Pishchevaya Prom–st., 1994, pp. 140–142.
2. Kraft, P. and Swift, K.A.D., *Perspectives in Flavor and Fragrance Research*, Weinheim: Wiley–VCH, 2005.
3. Sarafanova, L.A., *Pishchevye dobavki: Entsiklopediya* (Food Additives: Encyclopedia), St. Petersburg: GIRD, 2003.
4. Johnson, S., *J. Chem. Soc.*, 1928, vol. 133, no. 12, pp. 2924–2930.
5. Beckman, T., *Chem. Ber.*, 1882, vol. 15, no. 8, pp. 2782–2790.
6. Zhukovskaya, N.A., Dikusar, E.A., Moiseichuk, K.L., et al., *Zh. Prikl. Khim.*, 2006, vol. 79, no. 4, pp. 642–644.
7. Dikusar, E.A., *Zh. Prikl. Khim.*, 2006, vol. 79, no. 6, pp. 1043–1045.
8. Dikusar, E.A., Vyglazov, O.G., Moiseichuk, K.L., et al., *Zh. Prikl. Khim.*, 2005, vol. 78, no. 1, pp. 122–126.
9. Nedel, F. and Huldschinski, I., *Chem. Ber.*, 1953, vol. 86, pp. 1005–1010.
10. *Dictionary of Organic Compounds*, New York: Eyre and Spottiswoode, 1934. Translated under the title *Slovar' organicheskikh soedinenii*, Moscow: Inostrannaya Literatura, 1949, vol. 1, pp. 555–556, 914–915.