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PREPARATIVE SYNTHESIS OF VERATRALDEHYDEOXIME ESTERS

N. A. Zhukovskaya,[1] E. A. Dikusar,[1*]
and O. G. Vyglazov[2]

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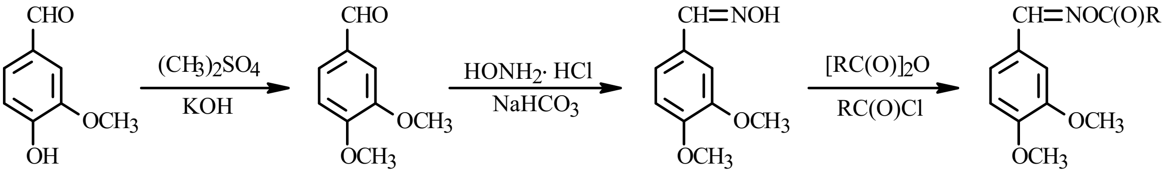
*Preparative syntheses of veratraldehydeoxime esters **6-24**, available fragrances produced from vanillin (**1**), in 82-92% yield from veratraldehydeoxime (**3**) were developed.*

Key words: vanillin, veratraldehyde, oxime, carboxylic acids, anhydrides, acid chlorides, esters, aroma analysis.

Veratraldehyde (3,4-dimethoxybenzaldehyde, **2**) occurs in small quantities in essential oil of *Cymbopogon javanensis* and has a persistent pleasant woody aroma with hints of vanilla and heliotrope. Veratraldehyde is used in several perfumes, deodorants, and food additives and is employed as an intermediate in the synthesis of certain drugs [1].

The goal of our work was to develop a preparative synthesis of esters of veratraldehydeoxime **6-24** based on the available industrial starting material vanillin (**1**) [2, 3]. Veratraldehyde (**2**) was prepared by methylation of vanillin by Me_2SO_4 in the presence of KOH by the Schotten—Baumann reaction. We developed a more convenient and simple synthetic method than that described in the literature [4]. It produced **2** in high purity and 90% yield. Reaction of **2** with hydroxylamine produced veratraldehydeoxime (**3**) in 92% yield by a method analogous to the published one [5].



1 **2** **3** **6 - 24**

R = Me (**6**), Et (**7**), Pr (**8**), MeCH (**9**), Bu (**10**), $MeCHCH_2$ (**11**), $Me(CH_2)_4$ (**12**), $Me(CH_2)_5$ (**13**), $Me(CH_2)_6$ (**14**), $Me(CH_2)_7$ (**15**), $Me(CH_2)_8$ (**16**), $Me(CH_2)_{11}$) (**17**), *cyclo*-C_6H_{11} (**18**), C_6H_5 (**19**), $C_6H_5(CH_2)_2$ (**20**), $C_6H_5MeCHCH_2$ (**21**), *trans*-$C_6H_5CH=CH$ (**22**), MeO (**23**), EtO (**24**)

Esters of veratraldehydeoxime **6-24** were prepared by reaction of **3** with alkylcarboxylic acid anhydrides **4a-d** in anhydrous benzene in the presence of catalytic amounts of $HClO_4$ or with alkyl- and arylcarboxylic acid chlorides **5a-o** in the presence of pyridine by our method for synthesizing analogous compounds [6]. The synthesis was carried out at 20-23°C for 24-36 h, consisted of simple mixing of the appropriate reagents, and occurred without special cooling or stirring. Esters of veratraldehydeoxime **6-24** were obtained in 82-92% yield and were colorless viscous oils or crystalline compounds (crystallizing from a benzene:hexane mixture). The esters did not required additional purification; did not contain impurities of starting compounds, benzene, and pyridine; and were suitable for direct use in the perfumery and food industries [7]. The purity of the products according to PMR spectroscopy was 97-98%. Esters **6-24** were stable on storage at +5°C in the absence of air and light.

The structures of **6-24** were confirmed by elemental analysis, cryoscopic molecular-weight determination, PMR spectra, and IR spectra. Analytical results and molecular-weight determinations of all synthesized compounds agreed with those

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1) Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, 220072, Minsk, ul. Surganova, 13, e-mail: evgen_58@mail.ru; 2) OOO Tereza-Inter, Russia, 129110, Moscow, Olimpiiskii prosp., 22, e-mail: ilb_chuiko@mail.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 558-560, November-December, 2008. Original article submitted February 12, 2008.

calculated. The molecular weight could not be determined from the molecular ion in mass spectra because of the low thermal stability of **6-24**, which was consistent with previous results [8].

IR spectra of **6-24** contained absorption bands (CH_{Ar}) at 3100-3000 cm^{-1}; (CH_{Alk}), 3000-2800; (C=O), 1770-1730; (C=N), 1675-1665; (Ar), 1600-1360; (C–O), 1300-1000; and (CH_{Ar}), 880-620.

PMR spectra of **6-24** showed resonances for methoxyl protons that appeared as two singlets at 3.90-4.10 ppm; for aromatic protons as a multiplet at 6.70-7.50; and for the HC=N proton as a singlet at 8.20-8.30. The PMR spectra of **6-24** contained resonances characteristic of the ester groups [2, 3, 6].

The organoleptic properties of the synthesized veratraldehydeoxime (**3**) and its esters **6-24** were evaluated by the Taste Committee of the Accredited Monitoring Analytical Laboratory OOO Teresa-Inter (Moscow). The statistical average taste aromas of the pure products are given below:

Product	*Aroma*	*Product*	*Aroma*
3	vanilla-berry, woody hint	**15**	creamy-vanilla with dust hint
6	vanilla-woody with berry-flower hint	**16**	creamy-vanilla with spicy hint
7	vanilla-creamy	**17**	vanilla-spice with woody hint
8	buttery with vanilla-woody hint	**18**	clove-woody
9	berry with sweet cranberry hint	**19**	clove-creamy
10	berry with citrus and powdery hints	**20**	clove-creamy with berry hint
11	berry with sweet hint of viburnum	**21**	clove-woody with grapefruit hint
12	berry-buttery with cheese hint	**22**	clove-flowery with vanilla hint
13	milk with vanilla-berry hint	**23**	clove-vanilla
14	milk-vanilla with freshness hint	**24**	vanilla-clove with creamy-berry hint.

The synthesized compounds had unique aromas with various hints and could be used to create berry, milk-creamy, vanilla, and woody-spice fragrances. It was interesting that the fragrance depended on the ester structure. Increasing the aliphatic radical in esters **6-17** changed the aroma from vanilla-woody to milk-creamy with berry hints. Changing the aliphatic acid moiety to a cyclic one in esters **18-21** produced a pronounced clove aroma with various hints.

EXPERIMENTAL

IR spectra of the synthesized compounds in a thin layer or KBr were recorded on a Protege-460 Nicolet IR-Fourier spectrometer. PMR spectra in $CDCl_3$ solutions (5%) were obtained on a BS-587A spectrometer (100 MHz, Tesla). Chemical shifts were determined relative to TMS internal standard. Molecular weight (MW) was determined by cryoscopy in benzene. The physicochemical properties of the synthesized veratraldehyde (**2**) and veratraldehydeoxime (**3**) agreed with those published [1, 4, 5, 9].

Veratraldehyde (2). KOH (14 g, 90%) was dissolved in water (210 mL), cooled to 20-23°C, stirred vigorously, and treated with vanillin (**1**, 0.2 mol). After the vanillin was completely dissolved, the solution was treated in one portion with Me_2SO_4 (22 mL), stirred for 6 h at 20-23°C, cooled to 5°C without stirring, and left for 10-12 h. The resulting crystalline precipitate of veratraldehyde (**2**) was filtered on a porous glass filter, washed with a small amount of water, and dried in air. Yield, 90%.

Veratraldehydeoxime (3). Veratraldehyde (**2**, 0.21 mol), hydroxylamine hydrochloride (0.27 mol), $NaHCO_3$ (0.28 mol), and ethanol (75 mL, 96%) were refluxed for 1 h, poured into a beaker with water (300 mL), cooled to 5°C, and left for 10-12 h. The resulting crystalline precipitate of veratraldehydeoxime (**3**) was filtered on a porous glass filter, washed with a small amount of water, and dried in air. Yield, 92%.

Esters of Veratraldehydeoxime 6-9. Veratraldehydeoxime (**3**, 0.01 mol) and the anhydride of the appropriate acid (**4a-d**, 0.011 mol) were dissolved in anhydrous benzene (20 mL), treated with $HClO_4$ (1 drop, 47%), shaken, left at 20-23°C for 24-36 h, diluted with water, and extracted with benzene. The organic layer was separated, washed with water and $NaHCO_3$

solution (5%), and dried over $CaCl_2$. Solvent was removed at reduced pressure (p = 10-15 mm Hg) keeping the temperature below 25-30°C.

The following compounds were prepared by this method:

***N*-Acetyloximino-3,4-dimethoxyphenylmethane (6).** Yield 88%, mp 43-44°C, $C_{11}H_{13}NO_4$, found MW 218.6, calcd 223.

***N*-Propionyloximino-3,4-dimethoxyphenylmethane (7).** Yield 85%, mp 61-62°C, $C_{12}H_{15}NO_4$, found MW 226.0, calcd 237.

***N*-Butyryloximino-3,4-dimethoxyphenylmethane (8).** Yield 87%, mp 63-64°C, $C_{13}H_{17}NO_4$, found MW 240.8, calcd 251.

***N*-*iso*-Butyryloximino-3,4-dimethoxyphenylmethane (9).** Yield 86%, mp 50-51°C, $C_{13}H_{17}NO_4$, found MW 242.3, calcd 251.

Esters of Veratraldehydeoxime 10-24. Veratraldehydeoxime (**3**, 0.01 mol) was dissolved in anhydrous benzene (50 mL), treated with anhydrous pyridine (0.01 mol), cooled to 15°C, mixed by careful shaking, treated with the appropriate acid chloride (**5a**-**o**, 0.01 mol), left at 20-23°C for 24-36 h, and treated with water. The product was extracted by benzene. The organic layer was separated, washed with water and $NaHCO_3$ solution (5%), and dried over $CaCl_2$. Solvent was removed at reduced pressure (10-15 mm Hg) keeping the temperature below 25-30°C.

The following compounds were prepared by this method:

***N*-Valeroyloxyimino-3,4-dimethoxyphenylmethane (10).** Yield 82%, mp 62-63°C, $C_{14}H_{19}NO_4$, found MW 253.7, calcd 265.

***N*-*iso*-Valeroyloxyimino-3,4-dimethoxyphenylmethane (11).** Yield 84%, d_{20}^{20} 1.0813, n_D^{20} 1.5480, $C_{14}H_{19}NO_4$, found MW 255.1, calcd 265.

***N*-Caproyloxyimino-3,4-dimethoxyphenylmethane (12).** Yield 88%, mp 41-42°C, $C_{15}H_{21}NO_4$, found MW 266.2, calcd 279.

***N*-Enanthyloxyimino-3,4-dimethoxyphenylmethane (13).** Yield 86%, mp 44-45°C, $C_{16}H_{23}NO_4$, found MW 281.4, calcd 293.

***N*-Caprylyloxyimino-3,4-dimethoxyphenylmethane (14).** Yield 84%, mp 47-48°C, $C_{17}H_{25}NO_4$, found MW 290.5, calcd 307.

***N*-Pelargonyloxyimino-3,4-dimethoxyphenylmethane (15).** Yield 85%, mp 40-41°C, $C_{18}H_{27}NO_4$, found MW 309.6, calcd 321.

***N*-Capryloxyimino-3,4-dimethoxyphenylmethane (16).** Yield 85%, mp 42-43°C, $C_{19}H_{29}NO_4$, found MW 329.4, calcd 335.

***N*-Tridecanoyloxyimino-3,4-dimethoxyphenylmethane (17).** Yield 87%, mp 56-57°C, $C_{22}H_{35}NO_4$, found MW 360.8, calcd 377.

***N*-Cyclohexylmethanoyloxyimino-3,4-dimethoxyphenylmethane (18).** Yield 88%, mp 50-51°C, $C_{16}H_{21}NO_4$, found MW 283.4, calcd 291.

***N*-Benzoyloxyimino-3,4-dimethoxyphenylmethane (19).** Yield 86%, mp 110-111°C, $C_{16}H_{15}NO_4$, found MW 280.0, calcd 285.

***N*-(3-Phenylpropionyloxyimino)-3,4-dimethoxyphenylmethane (20).** Yield 88%, mp 55-56°C, $C_{18}H_{19}NO_4$, found MW 302.7, calcd 313.

***N*-(3-Phenylbutyryloxyimino)-3,4-dimethoxyphenylmethane (21).** Yield 87%, d_{20}^{20} 1.1692, n_D^{20} 1.5795, $C_{19}H_{21}NO_4$, found MW 318.3, calcd 327.

***N*-*trans*-Cinnamoyloxyimino-3,4-dimethoxyphenylmethane (22).** Yield 87%, d_{20}^{20} 1.0484, n_D^{20} 1.6110, $C_{18}H_{17}NO_4$, found MW 303.8, calcd 311.

***N*-3,4-Dimethoxyphenylmethaneiminomethylcarbonate (23).** Yield 84%, mp 49-50°C, $C_{11}H_{13}NO_5$, found MW 230.9, calcd 239.

***N*-3,4-Dimethoxyphenylmethaneiminoethylcarbonate (24).** Yield 85%, mp 54-55°C, $C_{12}H_{15}NO_5$, found MW 246.2, calcd 253.

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