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SYNTHESIS AND STRUCTURE—AROMA CORRELATION OF ANISALDEHYDE OXIME ESTERS

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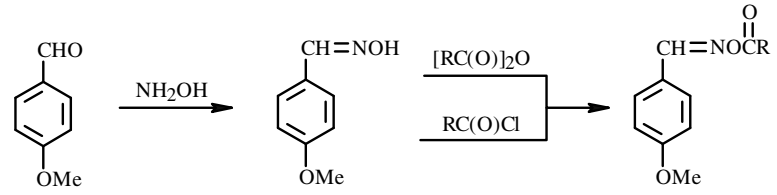
*Preparative syntheses from anisaldehyde **1** of the anti-isomer of anisaldehyde oxime **2** and anisaldehyde oxime esters **3a-q** in 84-93% yields were developed. The structure—aroma correlation of **2** and **3a-q** was studied.*

Key words: anisaldehyde, oxime, carboxylic acids, anhydrides, acid chlorides, esters, aroma analysis, aromas.

The study of aroma—structure relationships of fragments and constituents of natural compounds used in synthesis is a promising area of fragrance chemistry [1-3]. Oximes of several available natural aldehydes and ketones can act as convenient synthons for preparing perfumes, aromatic compounds, and biologically active compounds [4-7]. It has been found that just the presence in fragrances based on oximes of menthone, camphor, jasmorange, veratraldehyde, or citral can cause interaction with olfactory and gustatory receptors and create the sensation of aroma or taste [3].

The goal of our work was to prepare a homologous series of new esters from the anti-isomer of anisaldehyde oxime (**2**). Anisaldehyde oxime esters **3a**-**q** were synthesized by reacting **2** with anhydrides of alkylcarboxylic acids in the presence of catalystic amounts of $HClO_4$ (**3a**-**d**) or acid chlorides of alkyl-, cycloalkyl-, and arylcarboxylic acids in the presence of pyridine (**3e**-**q**). The yields of **3a**-**q** were 84-93%.



1 **2** **3a - q**

CH_3 (**a**), C_2H_5 (**b**), $CH_3(CH_2)_2$ (**c**), $(CH_3)_2CH$ (**d**), $CH_3(CH_2)_3$ (**e**), $(CH_3)_2CHCH_2$ (**f**), $(CH_3)_3C$ (**g**), $CH_3(CH_2)_4$ (**h**), $CH_3(CH_2)_5$ (**i**), $CH_3(CH_2)_6$ (**j**), $CH_3(CH_2)_7$ (**k**), $CH_3(CH_2)_8$ (**l**), *cyclo*-C_6H_{11} (**m**), 1-Ad (**n**), C_6H_5 (**o**), CH_3O (**p**), C_2H_5O (**q**)

The structures of **2** and **3a**-**q** were confirmed by elemental analysis, cryoscopic molecular-weight determination, and IR and PMR spectra. The purity of the products was 97 ± 1% according to PMR spectroscopy. Elemental analyses and molecular weights of all synthesized compounds agreed with those calculated.

The Gustation Committee of the Accredited Control-Analytical Laboratory of OOO Tereza-Inter (Moscow) carried out an organoleptic assessment of the aromas of **2** and **3a**-**q**. Table 1 lists the mean-statistical data for the aromas of the pure compounds.

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TABLE 1. Organoleptic Assessment of Aromas of **2** and **3a–q**

Compound	Aroma
2	Weak, flowery-berry. Hints of jasmine, narcissus, cranberry, viburnum
3a	Flowery, sweet. Hints of lilac with shades of vanilla-powder
3b	Flowery-fruity. Hints of lilac and rose with shades of red apple
3c	Fruity-berry. Hints of red apple and plum with shades of cranberry and viburnum
3d	Berry. Hints of cranberry and mountain cranberry with shades of flower-vanilla
3e	Berry. Hints of cranberry with shades of vanilla-cream
3f	Berry. Hint of sugary cranberry
3g	Berry. Hint of sugary mountain cranberry
3h	Berry. Aroma of sour viburnum with hint of white wine
3i	Berry. Aroma of ripe viburnum with shades of sweetness
3j	Berry-fruity. Hints of cranberry and blueberry with shades of apple-vanilla
3k	Berry-cream. Hints of blueberry and bilberry with shades of cream-wood
3l	Fruity-creamy. Hints of red apple and plum with shades of vanilla-cream
3m	Fruity-flowery, perfume. Hints of kiwi and cherry with shades of jasmine and gummy rose
3n	Flowery, perfume with light fruity hint. Hints of jasmine, ylang-ylang, and rose with shades of plum-powder
3o	Flowery, perfume. Hints of lilac and jasmine with shades of musk
3p	Flowery. Hints of lilac and flower-of-the-valley with shades of powder
3q	Flowery. Hints of lilac and rose with shades of vanilla-powder

All products were very interesting for possible use in the production of perfumes and food aromas and for use in the candy and alcohol industries. Compounds **3e**-**3g**, **3j**, and **3k** were especiallly interesting and promising because they had distinct and characteristic aromas of berries such as cranberry, blueberry, and bilberry, which are popular and constantly requested on the food aroma market. Compounds **3e**-**3g**, **3j**, and **3k** can solve the problem of creating distinct berry aromas for the food industry becase it is problematical to create aromas similar to the natural aroma of the aforementioned fruits from the existing assortment of fragrances.

The structure—aroma relationships of the synthesized compounds are interesting. Increasing the alkyl substituent in **3a**-**3f** and **3h**-**3l** converted from flowery to fruity and then to berry aroma with a subsequent intensification of hints of berry-cream. Substituting alkyl radicals in **3m**-**3o** by cyclic ones produced and strengthened the flowery aroma.

EXPERIMENTAL

IR spectra of the synthesized compounds in thin layers or KBr were recorded on a Protege-460 (Nicolet) IR—Fourier spectrophotometer. PMR spectra in $CDCl_3$ solutions (5%) were obtained on a BS-587A (100 MHz, Tesla) spectrometer. Chemical shifts were determined relative to TMS internal standard; molecular weights (MW), by cryoscopy in benzene. The physicochemical properties of the pure anti-isomer of **2**, mp 64-65°C and synthesized from anisaldehyde (**1**) by the standard method [6], agree with the literature [8].

Anisaldehyde Oxime Esters 3a-d (general method). The anti-isomer of **2** (0.01 mol) and the anhydride of the appropriate acid (0.011 mol) were dissolved in anhydrous benzene (30 mL), treated with $HClO_4$ (47%, 1 drop), stirred, 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 $CaCl_2$. The solvent was evaporated at reduced pressure (p = 10-15 mm Hg) keeping the temperature below 25-30°C. The final purification was carried out by column chromatography over silica gel L 5/40 μm with hexane eluent.

The following compounds were prepared by this method.

***anti*-4-Methoxyphenylmethanal-*O*-acetyloxime (3a).** Yield 89%, d_{20}^{20} 1.2277, n_D^{20} 1.5500. $C_{10}H_{11}NO_3$. IR spectrum (ν, cm^{-1}): 3102, 3080, 3040, 3008 (=CH and CH_{Ar}); 2964, 2938, 2916, 2841 (CH_{Alk}); 1763 (C=O); 1606 (C=N); 1600, 1573, 1513, 1463, 1367 (Ar); 1305, 1259, 1205, 1172, 1112, 1028 (C–O); 835 (CH_{Ar}).

PMR spectrum (δ, ppm): 2.10 (s, CH_3), 3.72 (s, CH_3O), 6.65-7.70 (m, C_6H_4), 8.18 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-propionyloxime (3b).** Yield 84%, mp 43-44°C. $C_{11}H_{13}NO_3$. IR spectrum (ν, cm^{-1}): 3098, 3080, 3070, 3055, 3009 (=CH and CH_{Ar}); 2968, 2970, 2936, 2905, 2880, 2840 (CH_{Alk}); 1762 (C=O); 1609 (C=N); 1600, 1569, 1513, 1460, 1422, 1352 (Ar); 1314, 1257, 1218, 1180, 1073 (C–O); 880, 844, 824 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.13 (t, CH_3), 2.48 (q, CH_2), 3.82 (s, CH_3O), 6.75-7.75 (m, C_6H_4), 8.27 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-butyroyloxime (3c).** Yield 80%, mp 38-40°C. $C_{12}H_{15}NO_3$. IR spectrum (ν, cm^{-1}): 3100, 3070, 3055, 3009 (=CH and CH_{Ar}); 2963, 2940, 2900, 2875, 2840 (CH_{Alk}); 1763 (C=O); 1605 (C=N); 1600, 1569, 1512, 1460, 1421, 1360 (Ar); 1305, 1255, 1172, 1136, 1080, 1026 (C–O); 880, 834 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.90 (t, CH_3), 1.74 (m, CH_2), 2.42 (q, CH_2), 3.81 (s, CH_3O), 6.75-7.75 (m, C_6H_4), 8.26 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-isobutyroyloxime (3d).** Yield 84%, d_{20}^{20} 1.0374, n_D^{20} 1.5348. $C_{12}H_{15}NO_3$. IR spectrum (ν, cm^{-1}): 3100, 3070, 3045, 3009 (=CH and CH_{Ar}); 2976, 2937, 2915, 2877, 2840 (CH_{Alk}); 1759 (C=O); 1605 (C=N); 1600, 1571, 1515, 1469, 1422, 1387 (Ar); 1312, 1256, 1173, 1128, 1098, 1029 (C–O); 858, 834, 745 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.23 [d, $(CH_3)_2C$], 2.66 (m, CH), 3.77 (s, CH_3O), 6.70-7.75 (m, C_6H_4), 8.25 (s, HC=N).

Anisaldehyde Oxime Esters 3e-q (general method). Compound **2** (0.01 mol) was dissolved in anhydrous benzene (50 mL), treated with anhydrous pyridine (0.01 mol), cooled to 15°C, stirred by carefully shaking, treated with the acid chloride of the appropriate acid, 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 evaporated at reduced pressure (p = 10-15 mm Hg) keeping the temperature below 25-30°C. The final purification was carried out by purification over silica gel L 5/40 μm with hexane eluent.

The following compounds were prepared by this method.

***anti*-4-Methoxyphenylmethanal-*O*-valeroyloxime (3e).** Yield 89%, d_{20}^{20} 1.0026, n_D^{20} 1.5432. $C_{13}H_{17}NO_3$. IR spectrum (ν, cm^{-1}): 3100, 3080, 3070, 3040, 3010 (=CH and CH_{Ar}); 2960, 2934, 2873, 2840 (CH_{Alk}); 1763 (C=O); 1606 (C=N); 1600, 1571, 1514, 1465, 1421, 1346 (Ar); 1311, 1256, 1172, 1144, 1093, 1029 (C–O); 834 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.87 (t, CH_3), 1.15-1.90 [m, $(CH_2)_2$], 2.29 (t, CH_2), 3.74 (s, CH_3O), 6.70-7.65 (m, C_6H_4), 8.20 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-isovaleroyloxime (3f).** Yield 87%, d_{20}^{20} 1.0734, n_D^{20} 1.5315. $C_{13}H_{17}NO_3$. IR spectrum (ν, cm^{-1}): 3100, 3080, 3045, 3004 (=CH and CH_{Ar}); 2962, 2936, 2918, 2873, 2841 (CH_{Alk}); 1762 (C=O); 1606 (C=N); 1600, 1572, 1514, 1465, 1422, 1363 (Ar); 1305, 1285, 1258, 1216, 1172, 1157, 1090, 1029 (C–O); 835 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.92 [d, $(CH_3)_2C$], 1.20-2.60 (m, CH), 2.17 (s, CH_2), 3.67 (s, CH_3O), 6.60-7.65 (m, C_6H_4); 8.16 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-pivaloyloxime (3g).** Yield 85%, mp 40-41°C. $C_{13}H_{17}NO_3$. IR spectrum (ν, cm^{-1}): 3100, 3080, 3070, 3055, 3040, 3020, 3009 (=CH and CH_{Ar}); 2977, 2963, 2934, 2870, 2842 (CH_{Alk}); 1746 (C=O); 1607 (C=N); 1600, 1568, 1513, 1460, 1430, 1360 (Ar); 1312, 1259, 1176, 1123, 1109, 1027 (C–O); 889, 832, 835 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.29 [s, $(CH_3)_3C$], 3.81 (s, CH_3O), 6.75-7.75 (m, C_6H_4), 8.29 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-caproyloxime (3h).** Yield 82%, d_{20}^{20} 0.9842, n_D^{20} 1.5350. $C_{14}H_{19}NO_3$. IR spectrum (ν, cm^{-1}): 3100, 3080, 3040, 3007 (=CH and CH_{Ar}); 2957, 2933, 2871, 2861, 2840 (CH_{Alk}); 1764 (C=O); 1606 (C=N); 1600, 1572, 1514, 1465, 1420, 1350 (Ar); 1306, 1257, 1216, 1172, 1144, 1094, 1030 (C–O); 885, 834 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.90 (t, CH_3), 1.20-1.95 [m, $(CH_2)_3$], 2.44 (t, CH_2), 3.82 (s, CH_3O), 6.75-7.75 (m, C_6H_4), 8.27 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-enanthyloxime (3i).** Yield 80%, mp 49-50°C. $C_{15}H_{21}NO_3$. IR spectrum (ν, cm^{-1}): 3100, 3080, 3045, 3015 (=CH and CH_{Ar}); 2955, 2945, 2927, 2870, 2857 (CH_{Alk}); 1763 (C=O); 1610 (C=N); 1600, 1572, 1515, 1465, 1418, 1360 (Ar); 1313, 1292, 1254, 1234, 1179, 1137, 1106, 1025 (C–O); 881, 839, 820 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.90 (t, CH_3), 1.10-2.00 [m $(CH_2)_4$], 2.45 (t, CH_2), 3.83 (s, CH_3O), 6.75-7.80 (m, C_6H_4), 8.28 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-caprylyloxime (3j).** Yield 86%, mp 34-35°C. $C_{16}H_{23}NO_3$. IR spectrum (ν, cm^{-1}): 3099, 3070, 3010 (=CH and CH_{Ar}); 2953, 2924, 2870, 2856 (CH_{Alk}); 1763 (C=O); 1606 (C=N); 1600, 1580, 1512, 1460, 1420, 1370 (Ar); 1304, 1256, 1172, 1133, 1099, 1026 (C–O); 895, 835 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.85 (t, CH_3), 1.05-1.97 [m, $(CH_2)_5$], 2.41 (t, CH_2), 3.79 (s, CH_3O), 6.75-7.75 (m, C_6H_4), 8.24 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-pelargonyloxime (3k).** Yield 85%, mp 39-40°C. $C_{17}H_{25}NO_3$. IR spectrum (ν, cm^{-1}): 3100, 3080, 3070, 3060, 3040, 3011 (=CH and CH_{Ar}); 2954, 2926, 2869, 2853 (CH_{Alk}); 1752 (C=O); 1607 (C=N); 1600, 1570, 1511, 1465, 1423, 1380 (Ar); 1310, 1300, 1257, 1224, 1180, 1135, 1114, 1030 (C–O); 897, 832 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.88 (t, CH_3), 1.12-1.95 [m $(CH_2)_6$], 2.45 (t, CH_2), 3.84 (s, CH_3O), 6.65-7.75 (m, C_6H_4), 8.28 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-capryloxime (3l).** Yield 88%, mp 39-40°C. $C_{18}H_{27}NO_3$. IR spectrum (ν, cm^{-1}): 3100, 3085, 3075, 3060, 3040, 3011, 3011 (=CH and CH_{Ar}); 2955, 2919, 2869, 2850, 2840 (CH_{Alk}); 1754 (C=O); 1609 (C=N); 1600, 1571, 1514, 1471, 1417, 1379, 1355 (Ar); 1315, 1288, 1256, 1211, 1180, 1135, 1116, 1070, 1057, 1030 (C–O); 897, 845, 832 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.86 (t, CH_3), 1.20-1.30 [m, $(CH_2)_6$], 1.70 (q, CH_2), 2.43 (t, CH_2), 3.81 (s, CH_3O), 6.90-7.66 (m, C_6H_4), 8.27 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-cyclohexanemethanoyloxime (3m).** Yield 90%, mp 83-84°C. $C_{15}H_{19}NO_3$. IR spectrum (ν, cm^{-1}): 3099, 3085, 3070, 3040, 3027, 3009 (=CH and CH_{Ar}); 2929, 2900, 2853 (CH_{Alk}); 1737 (C=O); 1607 (C=N); 1600, 1570, 1513, 1465, 1449, 1420, 1365 (Ar); 1258, 1202, 1176, 1153, 1119, 1026 (C–O); 831 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.20-2.05 (m, C_6H_{10}), 2.44 (m, CH); 3.82 (s, CH_3O), 6.90-7.70 (m, C_6H_4), 8.29 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-(1-adamantane)methanoyloxime (3n).** Yield 90%, mp 116-117°C. $C_{19}H_{23}NO_3$. IR spectrum (ν, cm^{-1}): 3097, 3080, 3070, 3055, 3045, 3020, 3006 (=CH and CH_{Ar}); 2934, 2905, 2885, 2850, 2824 (CH_{Alk}); 1736 (C=O); 1606 (C=N); 1600, 1567, 1512, 1453, 1425, 1344 (Ar); 1254, 1207, 1175, 1101, 1057, 1045, 1023 (C–O); 895, 833 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.50-2.20 (m, $C_{10}H_{15}$), 3.83 (s, CH_3O), 6.80-7.75 (m, C_6H_4), 8.30 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-benzoyloxime (3o).** Yield 90%, mp 95-96°C. $C_{15}H_{13}NO_3$. IR spectrum (ν, cm^{-1}): 3097, 3075, 3065, 3045, 3035, 3011 (=CH and CH_{Ar}); 2970, 2934, 2855, 2840 (CH_{Alk}); 1735 (C=O); 1607 (C=N); 1600, 1571, 1514, 1452, 1422, 1355 (Ar); 1253, 1220, 1173, 1082, 1064, 1025 (C–O); 870, 833, 701, 682 (CH_{Ar}).

PMR spectrum (δ, ppm): 3.87 (s, CH_3O), 6.85-8.25 (m, C_6H_4 and C_6H_5), 8.49 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-(methylcarbonate)oxime (3p).** Yield 81%, mp 84-85°C. $C_{10}H_{11}NO_4$. IR spectrum (ν, cm^{-1}): 3100, 3088, 3070, 3060, 3040, 3011 (=CH and CH_{Ar}); 2970, 2958, 2910, 2844 (CH_{Alk}); 1764 (C=O); 1607 (C=N); 1600, 1573, 1514, 1442, 1350 (Ar); 1256, 1180, 1113, 1029 (C–O); 899, 866, 833, 774 (CH_{Ar}).

PMR spectrum (δ, ppm): 3.83 (s, CH_3O), 3.90 (s, CH_3O), 6.80-7.80 (m, C_6H_4), 8.27 (s, HC=N).

***anti*-4-Methoxyphenylmethanal-*O*-(ethylcarbonate)oxime (3q).** Yield 84%, d_{20}^{20} 1.1099, n_D^{20} 1.5440. $C_{11}H_{13}NO_4$. IR spectrum (ν, cm^{-1}): 3100, 3075, 3060, 3040, 3010 (=CH and CH_{Ar}); 2983, 2938, 2912, 2841 (CH_{Alk}); 1774 (C=O); 1606 (C=N); 1600, 1573, 1514, 1444, 1422, 1398, 1369, 1347 (Ar); 1304, 1258, 1235, 1173, 1112, 1028 (C–O); 854, 835, 778 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.30 (t, CH_3), 3.76 (s, CH_3O), 4.26 (q, CH_2), 6.70-7.75 (m, C_6H_4), 8.19 (s, HC=N).

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