THE SYNTHESIS AND SPECTRAL PROPERTIES OF *N*-(3,4,5-TRIMETHOXYBENZOYL)-3,6-DIHYDRO-1,2-OXAZINES AND *N*-(3,4,5-TRIMETHOXYBENZOYL)TETRAHYDRO-1,2-OXAZINES

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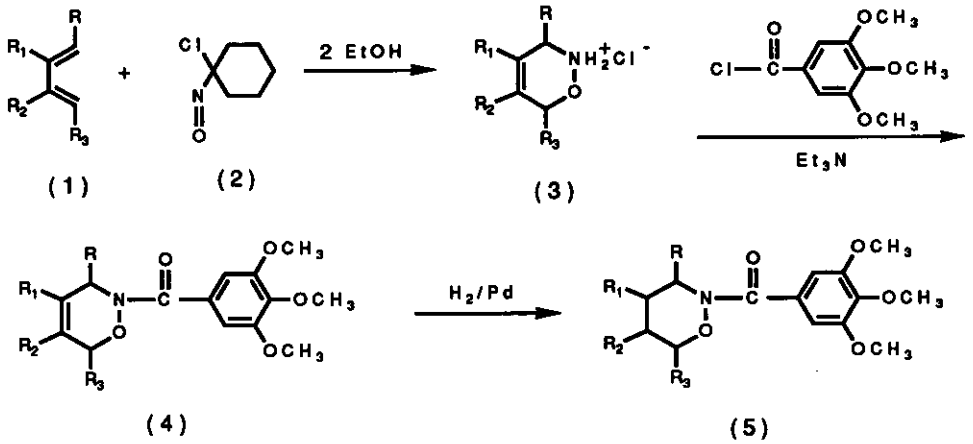
Abstract - In an attempt to develop neurosedatives of enhanced pharmacological activity and lower side-effect toxicity than those currently available, a series of novel 3,4,5-trimethoxybenzamides derived from either 3,6-dihydro-1,2-oxazine or tetrahydro-1,2-oxazine has been synthesized and fully characterized spectroscopically.

INTRODUCTION

A considerable number of 3,4,5-trimethoxybenzamides has been reported to possess central nervous system depressant or tranquilizing activity.[1] One of these compounds, *N*-(3,4,5-trimethoxybenzoyl) tetrahydro-1,4-oxazine, which displayed tranquilizing properties free from any muscle-relaxant effect,[2,3] has been adopted for therapeutical use. Neurodepressant and analgetic actions of alkoxybenzamides depend, to a certain extent, upon the number and position of the methoxy groups present. As a matter of fact, the 3,4,5-trimethoxy substitution pattern in the aromatic system has been assumed to be a necessary structural element for retaining maximum neurodepressant activity.[1e] Partial or complete removal of the methoxy groups decreases neurodepressant activity, and the lengthening of the ethereal alkyl chain increases toxicity. The degree of toxicity also depends on the nature of the heterocyclic amine moiety incorporated into the benzamide structure. Replacement of the morpholine unit by pyrrolidine, piperidine or thiomorpholine increases toxicity conciderably.[2] The variations in the amine function may also alter the depressant activity.[4] The pharmacological importance of the internal ether linkage present in the morpholine group has been emphasized.[2,3] The absence of the ether linkage in the amine moiety suspends sedative properties.[2] Finally, an increase in the distance between the trimethoxyphenyl and the carbonyl amine nucleus, in general, diminishes the neuroplegic activity of the compound.[1e]

DISCUSSION

In an attempt to enhance pharmacological activity while concomitantly to depress less desirable side effects of neurosedatives, a series of novel 3,4,5-trimethoxybenzamides, in which the amine function was either 3,6-dihydro-1,2-oxazine or tetrahydro-1,2-oxazine, was synthesized. In the 1,2-oxazines, analogs of morpholine (1,4-oxazine), the ethereal oxygen is in position 2 with respect to the nitrogen atom. The replacement of the morpholine unit by the 1,2-oxazine system will provide useful information about the effect of the presence of an ethylenic function or alkyl substitution as well as the change in the position of ethereal oxygen in the heterocyclic amine unit, on the pharmacological properties of 3,4,5-trimethoxybenzamides. The preparation and structural features of the synthesized benzamides are presented below. All new oxaza trimethoxybenzamides will be subjected to biological screening. The pharmacological results will be reported elsewhere. The 3,6-dihydro-1,2-oxazines used for the synthesis of *N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine were prepared from the corresponding 1,3-butadienes (1) and 1-chloro-1-nitrosocyclohexane(2), by methods described previously,[5] to yield the 3,6-dihydro-1,2-oxazinium chlorides (3), which were purified by trituration with ether. The 3,4,5-trimethoxybenzamides were prepared by refluxing benzene solutions of equimolar amounts of 1,2-oxazinium chlorides and 3,4,5-trimethoxybenzoyl chloride in the presence of two equivalents of triethylamine. The crude products, *N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazines (4) were subjected to chromatography on alumina (activated 80-200 mesh Fisher type F-20), with the solvent system hexane-chloroform (5:95). Most of the benzamides were crystalline compounds and were purified by recrystallization from isopropanol. Some products, however, were very viscous liquids and had to be purified using the fractional column chromatography technique. Pure benzamides (4) were subjected to hydrogenation at atmospheric pressure using 5% palladium on carbon as a catalyst and ethyl acetate as solvent. The products, *N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazines (5) were purified by recrystallization from pentane-ether. The structures of all benzamides (4 and 5) were determined by spectroscopic techniques (principally ^{1}H and ^{13}C nmr) and elemental composition was determined by combustion analysis.



(1) (2) (3) (4) (5)

I, Ia.	R, R_2, R_3 = H; R_1 = Ph
II, IIa.	R = CH_3; R_1, R_2 = H; R_3 = Ph
III.	R, R_1 = H; R_2 = C_2H_5; R_3 = Ph
IV, IVa.	R = CH_3; R_1 = H; R_2 = C_5H_{11}; R_3 = Ph
V, Va.	R, R_1 = H; R_2 = CH_3; R_3 = p-$C_6H_4OCH_3$
VI.	R, R_1 = H; R_2 = C_2H_5; R_3 = p-$C_6H_4OCH_3$
VII, VIIa.	R, R_2 = CH_3; R_1 = H; R_3 = p-$C_6H_4OCH_3$
VIII, VIIIa.	R = CH_3; R_1 = H; R_2 = C_2H_5; R_3 = p-$C_6H_4OCH_3$
IX.	R, R_1 = H; R_2 = C_2H_5; R_3 = p-$C_6H_4OC_2H_5$
X, Xa.	R, R_2 = CH_3; R_1 = H; R_3 = p-$C_6H_4OC_2H_5$

The proton nmr spectra of all benzamides (4) which show expected resonances due to protons of the 3,6-dihydro-1,2-oxazine system, also contain resonances at δ 3.73 - 3.90 which are consistent with the presence of the protons of the methoxy groups contained in the benzoyl moiety. The resonances due to aromatic protons of the benzoyl group appear at δ 6.59 - 7.14. The resonances of the aromatic protons of the para alkoxy (methoxy or ethoxy) substituted phenyl group at position 6 of the oxazine appear as pseudo AB patterns at δ 6.82-7.03. The amyl protons were not resolved exept for the terminal methyl group. The carbon-13 resonances of benzamides containing the 3,6-dihydro-1,2-oxazine system, were assigned on the basis of the shifts of the oxazine carbon atoms previously reported,[7] as well as standard chemical shift values.[8] The assignment of proton and carbon-13 resonances of the tetrahydro-1,2-oxazine moiety present in benzamides (Ia, IIa, IVa, Va, VIIa, VIIIa, Xa) was based on 2D-COSY experiments, and heteronuclear correlation spectroscopy (HETCORR).[9] The assignment of proton resonances of the 4-phenyltetrahydro-1,2-oxazine group present in Ia has been accomplished using 2D-COSY, HETCORR and decoupling techniques. Similar results were obtained using either technique. The axial-equatorial assignments were made on the basis of the intensities of the COSY cross peaks assuming that the aromatic group was in an equatorial position. It was necessary to use 2D techniques because the shifts

of the protons at the 3 and 6-positions of the tetrahydrooxazines were sometimes markedly different (up to 1.5 ppm) from those observed for the corresponding dihydro compounds. This is demonstrated below for 5-methyl-6-(4-methoxyphenyl)-3,6-dihydro-1,2-oxazine and the corresponding tetrahydro compound.

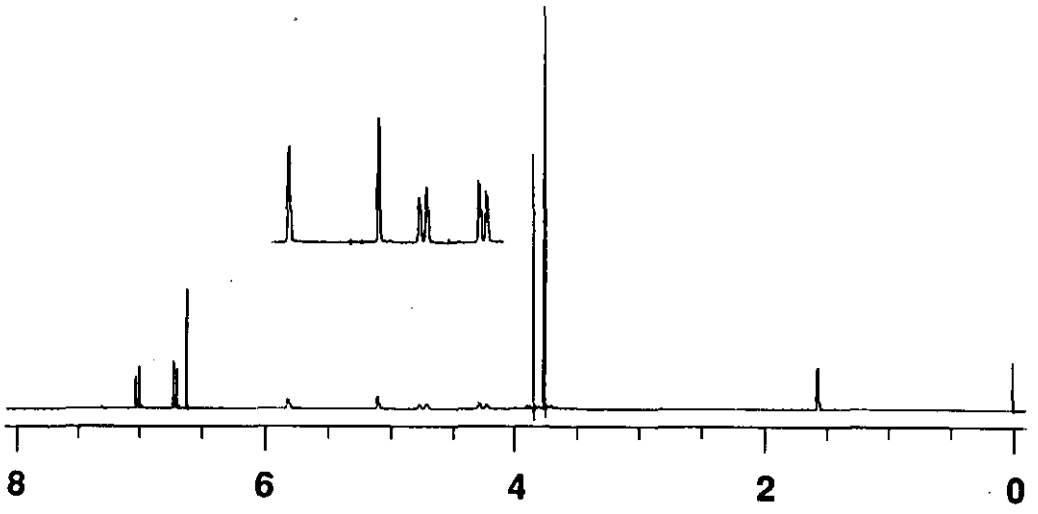


Figure 1. Proton Nmr spectrum of 5-methyl-6-(4-methoxyphenyl)-3,6-dihydro-1,2-oxazine

The proton spectrum for the dihydro compound (Figure 1) contains a resonance for the C-6 proton at 5.10 ppm while the chemical shift for the same proton (at C-6) is 4.18 ppm, for the corresponding tetrahydro compound (Figure 2). The resonances due to the protons at C-3 of the dihydro compound appear centered at 4.50 ppm, but the corresponding absorption for the tetrahydro compound appears as two signals at 3.41 and 4.72 ppm (axial and equatorial protons respectively).

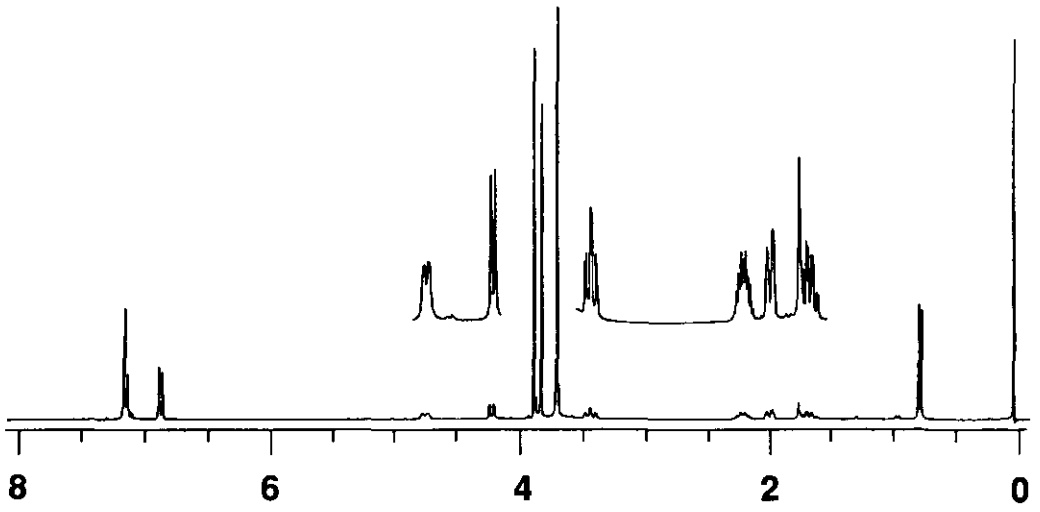


Figure 2. Proton Nmr spectrum of 5-methyl-6-(4-methoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazine.

Intuitively, the chemical shifts for the protons at C-3 and C-6 of the tetrahydro compound would seem to be reversed. However, the proton - carbon correlation spectrum shown in Figure 3 permits the unequivocal assignment of the proton chemical shifts. Clearly, the chemical shift for one of the protons at C-3 is larger than that for the proton at C-6. The weak ^{13}C peak at 44.5 ppm is correlated with the ^{1}H peaks at 3.41 ppm and 4.72 ppm (protons at C-3 due to -CH_2N-).

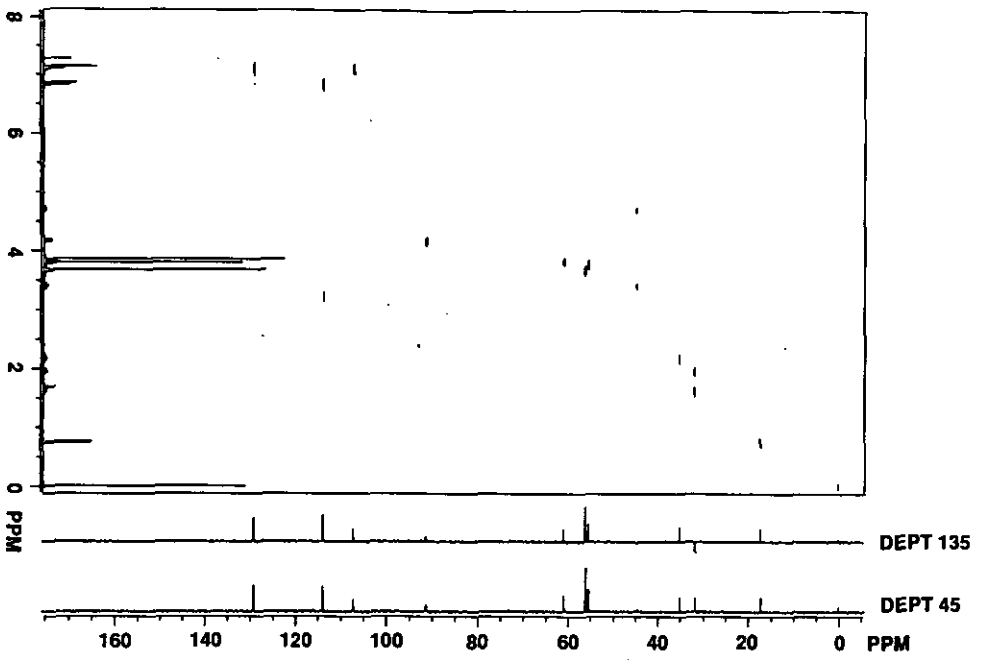


Figure 3. Heteronuclear proton-carbon correlation spectrum of 5-methyl-6-(4-methoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazine.

In conclusion, the central nervous system depressant activity of 3,4,5-trimethoxybenzamides may be strongly influenced by the nature of the amine function incorporated into the benzamide unit. In this instance a series of novel 3,4,5-trimethoxbenzamides in which the amine moiety was either 3,6-dihydro-1,2-oxazine or tetrahydro-1,2-oxazine has been prepared and fully characterized. The availability of these compounds will permit an evaluation of the impact of the presence of unsaturation, the extent and position of alkyl substitution or the position of the oxygen atom with respect to the amino nitrogen, on the pharmacological properties of this class of potential neurosedatives.

EXPERIMENTAL

Ir Spectra. Ir spectra were obtained using a Nicolet 20 DXB Fourier transform spectrophotometer. Liquids were sampled as 10% solutions in chloroform and solid samples as KBr discs.

Nmr Spectra. The ^{1}H and ^{13}C nmr spectra were recorded using 10-20% solutions in $CDCl_3$ and a GE QE-300 (300 MHz) NMR spectrometer. Chemical shifts are reported downfield in ppm (δ) with respect to tetramethylsilane as internal reference. Note that Bz is the 3,4,5-trimethoxybenzoyl group and Ph is the C_6H_5 or C_6H_4OR group.

4-Phenyl-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (I). To a mixture of 4-phenyl-3,6-dihydro-1,2-oxazinium chloride (1.98 g; 10.0 mmol), 3,4,5-trimethoxybenzoyl chloride (2.3 g; 10.0 mmol) and benzene (10 ml), under nitrogen, was added dropwise trimethylamine (2.1 g; 20.8 mmol). During the addition the reaction flask was cooled in ice. The mixture was stirred for 1 h at room temperature, then it was refluxed for 2 h. After cooling, 10% aqueous hydrochloric acid solution was added until the mixture was neutral. The benzene layer was washed with saturated aqueous sodium bicarbonate solution then with water after which it was dried with anhydrous sodium sulfate. The crude product was chromatographed on alumina using a mixture of hexane-chloroform (5:95) as eluent. The white solid product (3.33 g, 93.7%) was finally recrystallized from isopropanol: mp 117-119°C; ir 3011, 2963, 2943, 2930, 2888, 2842, 2831, 1659, 1638, 1586, 1507, 1495, 1467, 1444, 1430, 1415, 888, 854, 840, 817, 769, 748, 709, 694, 674 cm^{-1}; ^{1}H nmr δ 3.90 (s, 3H, OCH_3), 3.90 (s, 6H, 2 X OCH_3), 4.53 (m, 2H, CH_2N), 4.76 (m, 2H, CH_2O), 6.22 (m, 1H, 5C=CH), 7.03 (s, 2H, Bz), 7.32 (m, 5H, Ph); ^{13}C nmr δ 43.7 (C3), 141.4 (C4), 118.2 (C5) 70.9 (C6), 134.2, 124.9, 128.8, 128.3 (4Ph), 128.4 (Bz1), 106.2 (Bz2,6), 152.8 (Bz3,5), 140.1 (Bz4), 169.6 (C=O), 60.9 (OCH_3), 56.3 (2 X OCH_3). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.61; H, 5.81; N, 3.91.

4-Phenyl-*N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazine (Ia). A mixture of 4-phenyl-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (0.41 g; 1.15 mmol), 5% palladium on charcoal (0.061 g) and ethyl acetate (50 ml) was subjected to hydrogenation at one atmosphere in a standard manifold gas buret assembly. Upon completion of the hydrogenation, the mixture was filtered through Celite to remove the catalyst and the solvent was evaporated at reduced pressure. The crude material was recrystallized from ether/pentane (1:1). The product was a white crystalline solid (0.19 g, 77.8%) : mp 132-134°C; ir 3060, 3004, 2981, 2970, 2936, 2914, 2860, 2838, 1635, 1584, 1506, 1468, 1451, 1436, 1413, 883, 865, 849, 827, 771, 761, 754, 704, 690, 671 cm^{-1}; ^{1}H nmr δ 2.01, 2.22 (m, 1H each O-CH_2-CH_2), 3.10 (m, 1H, N-CH_2-CH), 3.35, 4.67 (m, 1H each, N-CH_2), 3.91 (s, 3H, OCH_3), 3.91 (s, 6H, 2 X OCH_3), 3.93, 4.20 (m, 1H each, O-CH_2),

7.02 (s, 2H, Bz), 7.35 (m, 5H, Ph); ^{13}C nmr δ 50.3 (C3), 39.6 (C4), 31.5 (C5), 72.6 (C6), 128.6 (Bz1), 106.3 (Bz2,6), 152.6 (Bz3,5), 141.3 (Bz4), 169.1 (C=O), 60.9 (OCH_3), 56.2 (2 X OCH_3), 140.3, 127.0, 128.8, 127.3(4Ph). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.95; H, 6.48; N, 4.16.

The following *N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro- and tetrahydro-1,2-oxazines were prepared in an analogous manner.

3-Methyl-6-phenyl-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (II). White crystals from isopropanol (3.04 g, 82.4%) ; mp 122-124°C; ir 3032, 3008, 2996, 2973, 2945, 2941, 2934, 2913, 2867, 2835, 1785, 1711, 1664, 1650, 1585, 1506, 1494, 1465, 1416, 870, 853, 838, 813, 794, 774, 757, 743, 703, 689, 666 cm^{-1}; ^{1}H nmr δ 1.54 (d, J=6.7 Hz, 3H, CH_3), 3.81 (s, 6H, 2 X OCH_3), 3.89 (s, 3H, OCH_3), 5.08 (br s, 1H, CHN), 5.39 br s, 1H, CHO), 5.90 (m, 1H, *N*-CH-C<u>H</u>), 6.06 (m, 1H, O-CH-C<u>H</u>), 7.13 (s, 2H, Bz), 7.20 - 7.40 (m, 5H) (Ph); ^{13}C nmr δ 48.4 (C3), 126.2 (C4), 129.2 (C5), 81.2 (C6), 136.6 (C1, Ph), 128.7 (C2,6 Ph), 128.1 (C3,5 Ph), 129.3 (C4, Ph), 128.0 (Bz1), 106.7 (Bz2,6), 152.6 (Bz3,5), 141.1 (Bz4), 167.8 (C=O), 60.9 (OCH_3), 56.2 (2 X OCH_3), 18.4 (CH_3). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.43; H, 6.09; N, 3.59.

3-Methyl-6-phenyl-*N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazine (IIa). White solid from 1:2 ether-pentane (0.54 g, 76.7%); mp 84-86°C; ir 3011, 2987, 2971, 2956, 2940, 2931, 2881, 2873, 2866, 2834, 1621, 1605, 1577, 1506, 1450, 1419, 1404, 891, 857, 846, 830, 790, 771, 763, 751, 736, 718, 704, 680 cm^{-1}; ^{1}H nmr δ 1.49 (d, J = 6.9 Hz, 3H, CH_3), 1.90, 2.71 (m, 1H each, NCH-C<u>H</u>$_2$), 1.79, 2.48 (m, 1H each, O-CH-C<u>H</u>$_2$), 3.85 (s, 3H, OCH_3), 3.69 (s, 6H, 2 X OCH_3), 4.69 (m, 1H, CHO), 5.02 (m, 1H, CHN), 7.10 (s, 2H, Bz), 7.21 (br s, 2H, H (2,6), 6Ph), 7.30 (m, 2H, H (3,5), 6Ph); ^{13}C nmr ($CDCl_3$) δ 46.0 (C3), 26.3 (C4), 27.8 (C5), 85.1 (C6), 138.7 (C1, 6Ph), 128.6 (C2, 6, 6Ph), 126.4 (C3,5, 6Ph), 128.6 (C4, 6Ph), 128.5 (Bz1), 106.9 (Bz2,6), 152.4 (Bz3,5), 140.2 (Bz4), 167.7 (C=O), 60.8 (OCH_3), 56.0 (2 X OCH_3), 15.7 (3CH_3). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.88; H, 6.80; N, 4.04.

5-Ethyl-6-phenyl-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (III). White crystalline solid from is.opropanol (4.86 g, 71.3%); mp 80-82°C; ir 2998, 2964, 2941, 2905, 2888, 2839, 1683, 1638, 1588, 1504, 1496, 1465, 1455, 1438, 1416, 861, 846, 818, 772, 757, 751, 740, 703, 656 cm^{-1}; ^{1}H nmr δ 0.99 (t, J=7.4 Hz, 3H, C<u>H</u>$_3$CH$_2$), 1.82 (m, 2H, CH_3C<u>H</u>$_2$), 3.73 (s, 6H, 2 X OCH_3), 3.83 (s, 3H, OCH_3), 4.54 (AB, Δ_{AB}= 0.38; J = 16.9 Hz, 2H, CH_2N), 5.21 (s, 1H, CHO),

5.83 (m, 1H, C=CH), 6.64 (s, 2H, Bz), 7.20 - 7.40 (m, 5H, Ph); ^{13}C nmr δ 42.9 (C3), 116.3 (C4), 129.4 (C5), 83.8 (C6), 137.9 (C1, Ph), 129.4 (C2,6; Ph), 128.4 (C3,5; Ph), 129.0 (C4, Ph), 128.6 (Bz1), 106.3 (Bz2,6), 152.0 (Bz3,5), 139.8 (Bz4), 168.9 (C=O), 60.8 (OCH_3), 56.0 (2 X OCH_3), 11.4 ($\underline{C}H_3CH_2$), 25.4 ($CH_3\underline{C}H_2$). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.91; H, 6.57; N, 3.54.

5-Amyl-3-methyl-6-phenyl-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (IV). White solid from isopropanol (5.21 g, 68.3%); mp 98-100°C; ir 2995, 2978, 2962, 2932, 2872, 2852, 1637, 1581, 1505, 1465, 1459, 1413, 869, 855, 809, 773, 750, 732, 707, 690, 670 cm^{-1}; ^{1}H nmr δ 1.54 (d, 3H, CH_3), [0.82 (t, J=7.0 Hz, 3H), 1.16 (m, 4H), 1.27 (m, 2H), 1.66 (m, 2H)] (C_5H_{11}), 3.77 (s, 6H, 2 X OCH_3), 3.88 (s, 3H, OCH_3), 5.05 (br s, 1H, CHN), 5.29 (br s, 1H, CHO), 5.78 (m, 1H, C=CH), 7.13 (s, 2H, Bz), 7.20 - 7.40 (m, 5H, Ph); ^{13}C nmr δ 49.2 (C3), 123.3 (C4), 128.5 (C5), 84.4 (C6), 136.6 (C1, Ph), 128.6 (C2,6; Ph), 128.7 (C3,5; Ph), 129.2 (C4; Ph), 128.5 (Bz1), 106.6 (Bz2,6), 152.4 (Bz3,5), 140.3 (Bz4), 167.2 (C=O), 60.8 (OCH_3), 56.0 (2 X OCH_3), 18.6 (CH_3), (13.9, 22.3, 26.7, 31.3, 32.2) (C_5H_{11}). Anal. Calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19. Found: C, 71.20; H, 7.48; N, 3.34.

5-Amyl-3-methyl-6-phenyl-*N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazine (IVa). White solid from 1:1 ether-pentane (0.43 g, 79.8%); mp 98-100°C; ir 2998, 2984, 2962, 2932, 2872, 2852, 2826, 1637, 1581, 1502, 1466, 1459, 1448, 1413, 869, 854, 836, 809, 773, 750, 732, 707, 689, 671 cm^{-1}; ^{1}H nmr δ [0.80 (t, J=7.0 Hz,3H), 0.90 - 1.34; (m, 8H)] (C_5H_{11}), 1.53 (d, J=6.9 Hz, 2H, CH_3), 1.75, 1.92 (m, 1H each, NCHC$\underline{H}_2$), 2.28 (m, 1H, O-CH-C$\underline{H}$), 3.62 (s, 6H, 2 X OCH_3), 3.82 (s, 3H, OCH_3), 4.26 (m, 1H, CHO), 5.10 (br s, 1H, a, CHN), 7.13 (m, 2H, H (3,5), Ph), 7.13 (s, 2H, Bz), 7.25 (m, 2H, H (2,6), Ph), 7.33 (m, 1H, H (4), Ph); ^{13}C nmr δ 47.1 (C3), 35.1 (C4), 31.7 (C5), 91.1 (C6), 137.6 (C1; Ph), 128.5 (C2,6; Ph), 128.5 (C3,5; Ph), 127.7 (C4; Ph), 128.9 (Bz1), 106.5 (Bz2,6), 152.1 (Bz3,5), 140.0 (Bz4), 167.0 (C=O), 60.8 (OCH_3), 55.9 (2 X OCH_3), 16.4 (CH_3), (13.9, 22.5, 31.0, 25.6, 33.9) (C_5H_{11}). Anal. Calcd for $C_{26}H_{35}NO_5$: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.97; H, 7.69; N, 3.26.

5-Methyl-6-(4-methoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (V). White solid from isopropanol (3.81 g, 64.8%); mp.85-87°C; ir 3011, 2999, 2980, 2963, 2937, 2923, 2904, 2884, 2838, 1677, 1637, 1612, 1584, 1511, 1463, 1452, 1444, 1429, 1414, 865, 859, 836, 819, 785, 771, 748, 732, 714, 679 cm^{-1}; ^{1}H nmr δ 1.56 (s, 3H, CH_3), 3.75 (s, 6H, 2 X OCH_3), 3.76 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.84 (s, 3H, OCH_3), 4.50 (AB, Δ_{AB}= 0.49, J = 17.7 Hz, 2H, CH_2N), 5.10 (br s, 1H, CHO), 5.81 (m, 1H, C=CH), 6.62 (s, 2H, Bz), 6.85 (AB, Δ_{AB}= 0.30, J = 8.2 Hz, 4H, $C_6\underline{H}_4OCH_3$,);

^{13}C nmr δ 42.5 (C3), 118.1 (C4), 127.2 (C5), 83.9 (C6), 132.4 (C1, Ph), 130.8 (C2,6; Ph), 113.6 (C3,5; Ph), 160.0 (C4; Ph),
128.7 (Bz1), 106.2 (Bz2,6), 152.0 (Bz3,5), 139.5 (Bz4), 168.9 (C=0), 60.8 (OCH_3), 55.9 (2 X OCH_3), 19.4 ($5CH_3$), 55.1 ($C_6H_4O\underline{C}H_3$). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.96; H, 6.18; N, 3.64.

5-Methyl-6-(4-methoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazine (Va). White crystalline solid from 10:1 diethyl ether-pentane (8.46 g, 94.3%); mp 116-118°C; ir 3000, 2994, 2975, 2957, 2929, 2906, 2870, 2835, 1626, 1614, 1583, 1514, 1473, 1459, 1439, 1420, 854, 847, 828, 814, 775, 749, 740, 728, 686, 674 cm^{-1}; ^{1}H nmr δ 0.75 (d, J=6.6 Hz, 3H, CH_3), 1.65, 1.96 (m, 1H each, $NCH_2C\underline{H}_2$), 2.18 (m, 1H, H (5)), 3.41, 4.72 (m, 1H each, NCH_2), 3.79 (s, 6H, 2 X OCH_3), 3.67 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.85 (s, 3H, OCH_3), 4.18 (m, 1H, CHO), 6.98 (AB, Δ_{AB}= 0.27, J = 8.7 Hz, $C_6\underline{H}_4OCH_3$), 7.13 (s, 2H, Bz); ^{13}C nmr δ 44.5 (C3), 31.6 (C4), 34.9 (C5), 91.2 (C6), 130.1 (C1, $\underline{C}_6H_4OCH_3$), 129.1 (C2,6; $\underline{C}_6H_4OCH_3$), 113.8 (C3,5; $\underline{C}_6H_4OCH_3$), 159.9 (C4; $\underline{C}_6H_4OCH_3$), 127.9 (Bz1), 106.7 (Bz2,6), 152.3 (Bz3,5), 140.0 (Bz4), 167.9 (C=O), 60.9 (OCH_3), 55.9 (2 X OCH_3), 17.1 (CH_3), 55.3 ($C_6H_4O\underline{C}H_3$). Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.72; H, 6.77; N, 3.52.

5-Ethyl-6-(4-methoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (VI). Pale yellow viscous liquid (4.83 g, 72.9%); ir 3015, 2969, 2940, 2914, 2882, 2840, 1680, 1612, 1585, 1512, 1465, 1440, 1417, 871, 857, 829, 751, 723 cm^{-1}; ^{1}H nmr δ 1.00 (t, J = 7.4 Hz, 3H, $5C\underline{H}_3CH_2$), 1.84 (m, 2H, $5CH_3C\underline{H}_2$), 3.75 (6H, 2 X OCH_3), 3.76 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.84 (s, 3H, OCH_3), 4.53 (AB, Δ_{AB}= 0.55, J = 17.6 Hz, 2H, CH_2N), 5.16 (m, 1H, CHO), 5.81 (m, 1H, C=CH), 6.59 (s, 2H, Bz), 6.82 (AB, Δ_{AB}= 0.30, J = 8.7 Hz, 4H, $C_6\underline{H}_4OCH_3$); ^{13}C nmr δ 42,6 (C3), 116.0 (C4), 127.5 (C5), 83.2 (C6), 138.0 (C1,Ph), 130.9 (C2,6; $\underline{C}_6H_4OCH_3$), 113.6 (C3,5; $\underline{C}_6H_4OCH_3$), 160.0 (C4; 6Ph), 128.8 (Bz1), 106.2 (Bz2,6), 151.9 (Bz3,5), 139.5 (Bz4), 168.9 (C=O), 60.8 (OCH_3), 55.9 (2 X OCH_3), 11.4 (5 $\underline{C}H_3CH_2$), 25.5 ($5CH_3\underline{C}H_2$), 55.1 ($C_6H_4O\underline{C}H_3$).

3,5-Dimethyl-6-(4-methoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (VII). White crystalline solid from isopropanol (5.31 g, 55.9%); mp 97-99°C; ir 2992, 2976, 2963, 2956, 2937, 2875, 2835, 1676, 1632, 1610, 1582, 1513, 1508, 1479, 1463, 1455, 1436, 1416, 873, 863, 844, 815, 805, 788, 773, 750, 732, 728, 679 cm^{-1}; ^{1}H nmr δ 1.42 (s, 3H, $5C\underline{H}_3$), 1.52 (d, J = 6.6 Hz, 3H, $3C\underline{H}_3$), 3.80 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.80 (s, 6H, 2 X OCH_3), 3.88 (s, 3H, OCH_3), 5.06 (br s, 1H, CHN), 5.18 (br s, 1H, CHO), 5.79 (m, 1H, C=CH), 7.03 (AB, Δ_{AB}= 0.29, J = 8.6 Hz, 4H, $C_6\underline{H}_4OCH_3$), 7.13 (s, 2H, Bz); ^{13}C nmr δ 48.9 (C3), 124.7 (C4), 127.9 (C5), 84.4 (C6), 132.6 (C1; $\underline{C}_6H_4OCH_3$), 130.3 (C2,6; $\underline{C}_6H_4OCH_3$),

114.1 (C3,5; $\underline{C}_6H_4OCH_3$), 160.3 (C4; $\underline{C}_6H_4$ OCH_3), 128.5 (Bz1), 106.6 (Bz2,6), 152.5 (Bz3,5), 140.0 (Bz4), 167.6 (C=O), 60.9 (OCH_3), 56.2 (2 X OCH_3), 18.8 (3$\underline{C}$H3), 18.6 (5$\underline{C}H_3$), 55.3 ($C_6H_4O\underline{C}H_3$). Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.62; H, 6.46; N, 3.47.

3,5-Dimethyl-6-(4-methoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazine (VIIa). White solid from 1:1 diethyl ether-pentane (0.39 g, 88.6%); mp 123-125°C; ir 2998, 2982, 2964, 2940, 2902, 2877, 1627, 1615, 1579, 1514, 1507, 1465, 1451, 1417, 1405, 865, 848, 835, 816, 805, 765, 749, 737, 696 cm^{-1}; ^1H nmr δ 0.72 (d, J = 6.6 Hz, 3H, 5$\underline{C}H_3$), 1.52 (d, J = 7.0 Hz, 3H, 3$\underline{C}H_3$), 1.75, 2.18 (m, 1H each, NCHC$\underline{H}_2$)), 2.24 (m, 1H, OCHC$\underline{H}$), 3.64 (s, 6H, 2 X OCH_3), 3.79 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.83 (s, 3H, OCH_3), 4.82 (br s, 1H, CHN), 5.10 (br s, 1H, CHO), 6.99 (AB, Δ_{AB}= 0.29, J = 8.7 Hz, 4H, $C_6\underline{H}_4OCH_3$), 7.08 (s, 2H, H (2,6), Bz); ^{13}C nmr δ 48.2 (C3), 34.3 (C4), 31.7 (C5), 86.4 (C6), 130.0 (C1, $\underline{C}_6H_4OCH_3$), 127.0 (C2,6; $\underline{C}_6H_4OCH_3$), 113.6 (C3,5; $\underline{C}_6H_4OCH_3$), 159.1 (C4, $\underline{C}_6H_4OCH_3$), 129.8 (Bz1), 106.6 (Bz2,6), 152.3 (Bz3,5), 140.0 (Bz4), 167.5 (C=O), 60.8 (OCH_3), 56.2 (2 X OCH_3), 19.2 ($3CH_3$), 15.9 ($5CH_3$), 55.3 ($C_6H_4O\underline{C}H_3$). Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: 66.56; H, 7.11; N, 3.66.

5-Ethyl-3-methyl-6-(4-methoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (VIII). White solid from isopropanol (4.84 g, 55.4%); mp 94-96°C; ir 2966, 2937, 2913, 2838, 1637, 1614, 1581, 1516, 1505, 1463, 1452, 1434, 1413, 872, 856, 827, 809, 771, 749, 734, 722 cm^{-1}; ^1H nmr δ 0.91 (t, J = 7.4 Hz, 3H, $5C\underline{H}_3CH_2$), 1.53 (d, J = 6.6 Hz, 3H, $3CH_3$), 1.69 (m, 2H, $5CH_3C\underline{H}_2$), 3.79 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.79 (s, 6H, 2 X OCH_3), 3.88 (s, 3H, OCH_3), 5.07 (br s, 1H, CHN), 5.25 (s, 1H, CHO), 5.76 (m, 1H, C=CH), 7.01 (AB, Δ_{AB}= 0.28, J = 8.6 Hz, 4H, $C_6\underline{H}_4OCH_3$), 7.09 (s, 2H, H (2,6), Bz): ^{13}C nmr δ 48.9 (C3), 122.4 (C4), 128.2 (C5), 84.0 (C6), 128.2 (C1, $\underline{C}_6H_4OCH_3$), 130.0 (C2, 6, $\underline{C}_6H_4OCH_3$), 113.9 (C3,5, $\underline{C}_6H_4OCH_3$), 160.2 (C4, $\underline{C}_6H_4OCH_3$), 128.0 (Bz1), 106.6 (Bz2,6), 152.4 (Bz3,5), 140.1 (Bz4), 167.2 (C=O), 60.7 (OCH_3), 56.0 (2 X OCH_3), 18.6 ($3CH_3$), 11.3 ($5CH_3CH2$), 24.9 ($5CH_3\underline{C}H_2$), 55.2 ($C_6H_4O\underline{C}H3$). Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.56; H, 6.72; N, 3.45.

5-Ethyl-3-methyl-6-(4-methoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazine (VIIIa). White solid from diethyl ether (0.13 g, 95.2%); mp 106-108°C; ir 2994, 2970, 2941, 2894, 2881, 2839, 1635, 1615, 1577, 1515, 1505, 1455, 1416, 1405, 878, 864, 848, 835, 814, 800, 785, 768, 745, 737, 717, 701, 672 cm^{-1}; ^1H nmr δ 0.78 (t, J = 7.4 Hz, 3H, $C\underline{H}_3CH_2$), 1.20 (m, 2H, $CH_3C\underline{H}_2$), 1.50 (d, J = 6.8 Hz, 3H, $3CH_3$), 1.83, 2.14 (m, 1H each, *N*CHC$\underline{H}_2$), 1.95 (m, 1H, O-CH-C$\underline{H}$), 3.65 (s, 6H, 2 X OCH_3), 3.80 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.84 (s, 3H, OCH_3), 4.82 (br s, 1H, CHN), 5.10 (br s 1H, CHO), 7.00 (AB, Δ_{AB}= 0.32, J = 8.7 Hz, 4H, $C_6\underline{H}_4OCH_3$), 7.10 (s, 2H, Bz); ^{13}C nmr δ 49.0 (C3), 29.9 (C4), 39.0 (C5), 86.6 (C6),

129.5 (C1, $\underline{C}_6H_4OCH_3$), 127.5 (C2,6; $\underline{C}_6H_4OCH_3$), 113.6 (C3,5; $\underline{C}_6H_4OCH_3$), 159.2 (C4; $\underline{C}_6H_4OCH_3$), 129.5 (Bz1), 106.6 (Bz2,6), 152.3 (Bz3,5), 140.1 (Bz4), 167.0 (C=O), 60.8 (OCH_3), 55.8 (2 X OCH_3), 18.9 (3$\underline{C}H_3$), 12.4 (5$\underline{C}H_3CH_2$), 22.2 (5$CH_3\underline{C}H_2$), 55.2 ($C_6H_4O\underline{C}H_3$). Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.11; H, 7.28; N, 3.26. Found: C, 67.13; H, 7.20; N, 3.31.

5-Ethyl-6-(4-ethoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (IX). Pale yellow viscous liquid (4.09 g. 45/3%); ir 3021, 2969, 2940, 1750, 1711, 1612, 1585, 1511, 1479, 1463, 1457, 1438, 1418, 828, 780, 761, 757 cm^{-1}; ^1H nmr δ 0.99 (t, J = 7.4 Hz, 3H, 5$\underline{C}H_3CH_2$), 1.40 (t, J= 7.0 Hz, 3H, $C_6H_4OCH_2\underline{C}H_3$), 1.85 (m, 2H, 5$CH_3\underline{C}H_2$), 3.74 (s, 6H, 2 X OCH_3), 3.83 (OCH_3), 3.95 (q, J = 7.0 Hz, 2H, $C_6H_4O\underline{C}H_2CH_3$), 4.53 (AB, Δ_{AB}= 0.30, J = 8.7 Hz, 2H, CH_2N), 5.15 (s, 1H, CHO), 5.80 (s, 1H, C=CH), 6.60 (s, 2H, Bz), 6.83 (AB, Δ_{AB}= 0.30, J = 8.7 Hz, 4H, $C_6\underline{H}_4OCH_2CH_3$); ^{13}C nmr δ 42.5 (C3), 116.0 (C4), 127.3 (C5), 83.2 (C6), 128.0 (C1; $\underline{C}_6H_4OCH_2CH_3$), 130.8 (C2,6; $\underline{C}_6H_4OCH_2CH_3$), 114.0 (C3,5; $\underline{C}_6H_4OCH_2CH_3$), 159.5 (C4, $\underline{C}_6H_4OCH_2CH_3$), 128.7 (Bz1), 106.2 (Bz2,6), 151.9 (Bz3,5), 139.5 (Bz4), 168.9 (C=O), 60.8 (Bz4 O$\underline{C}H_3$), 55.9 (Bz3,5 O$\underline{C}H_3$), 11.4 (5$\underline{C}H_3CH_2$), 25.5 (5$CH_3\underline{C}H_2$), 14.8 ($C_6H_4OCH_2\underline{C}H_3$), 63.3 ($C_6H_4O\underline{C}H_2CH_3$).

3,5-Dimethyl-6-(4-ethoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)-3,6-dihydro-1,2-oxazine (X). White crystalline solid from isopropanol (3.89 g, 66.8%); mp 90-92°C; ir 3126, 3032, 2993, 2976, 2963, 2955, 2935, 2920, 2875, 2835, 1677, 1632, 1610, 1582, 1513, 1508, 1479, 1463, 1455, 1436, 1416, 881, 873, 862, 843, 826, 815, 805, 788, 773, 750, 732, 728, 679 cm^{-1}; ^1H nmr δ 1.41 (t, J = 7.0 Hz, 3H, $C_6H_4OCH_2\underline{C}H_3$), 1.42 (s, 3H, 5$CH_3$), 1.52 (d, J = 6.6 Hz, 3H, 3CH_3), 3.80 (s, 6H, 2 X OCH_3), 3.88 (s, 3H, OCH_3), 4.00 (q, J = 7.0 Hz, 2H, $C_6H_4OC\underline{H}_2CH_3$), 5.03 (br s, 1H, CHN), 5.18 (br s, 1H, CHO), 5.78 (m, 1H, C=CH), 7.01 (AB, Δ_{AB}= 0.29, J = 8.6 Hz, 4H, $C_6\underline{H}_4OCH_2CH_3$), 7.14 (s, 2H, Bz); ^{13}C δ 48.8 (C3), 124.7 (C4), 127.8 (C5), 84.5 (C6), 128.4 (C1,$\underline{C}_6H_4OCH_2CH_3$), 130.0 (C2,6; $\underline{C}_6H_4OCH_2CH_3$), 114.6 (C3,5; $\underline{C}_6H_4OCH_2CH_3$), 159.7 (C4, $\underline{C}_6H_4OCH_2CH_3$), 128.6 (Bz1), 106.7 (Bz2,6), 152.5 (Bz3,5), 140.0 (Bz4), 167.5 (C=O), 60.9 (OCH_3), 56.2 (2 X OCH_3), 18.8 (3CH_3), 18.6 (5CH_3), 14.8 ($C_6H_4OCH_2\underline{C}H_3$), 63.5 ($C_6H_4O\underline{C}H_2CH_3$). Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.13; H, 6.70; N, 3.25.

3,5-Dimethyl-6-(4-ethoxyphenyl)-*N*-(3,4,5-trimethoxybenzoyl)tetrahydro-1,2-oxazine (Xa). White solid from 1:1 ether-pentane (0.44 g, 92.4%); mp 132-134°C; ir 2997, 2980, 2972, 2940, 2894, 2835, 1624, 1610, 1579, 1513, 1478, 1453, 1415, 867, 851, 835, 821, 805, 762, 750, 737, 693, 677 cm^{-1}; ^1H nmr δ 0.88 (d, 3H, J = 7.3 Hz, 5$\underline{C}H_3$), 1.41 (t, J = 7.0 Hz, 3H, $C_6H_4OCH_2\underline{C}H_3$), 1.51 (d, J = 6.9 Hz, 3H, 3CH_3), 1.71, 2.24 (m, 1H each, *N*$CHC\underline{H}_2$), 2.24 (m, 1H, O-CH-C$\underline{H}$), 3.64 (s,

6H, 2 X OCH_3), 3.83 (s, 3H, OCH_3), 4.01 (q, J = 7.0 Hz, 2H, $C_6H_4OC\underline{H}_2CH_3$), 4.87 (m, 1H, CHN), 5.05 (m, 1H, CHO), 6.83 (d, J = 8.7 Hz, 2H, H (3,5), 6 Ph), 7.09 (s, 2H, Bz), 7.12 (d, J = 8.7 Hz, 2H, H (2,6), 6Ph); ^{13}C nmr δ 47.8 (C3), 34.3 (C4), 31.7 (C 5), 86.5 (C6), 129.7 (C1; $\underline{C}_6H_4OEt$), 126.9 (C 2,6; $\underline{C}_6H_4OEt$); 114.1 (C 3,5; $\underline{C}_6H_4OEt$), 158.4 (C 4; $\underline{C}_6H_4OEt$), 128.9 (Bz 1), 106.5 (Bz 2,6), 152.3 (Bz 3.5), 140.0 (Bz 4), 167.1 (C=O), 60.8 (OCH_3), 55.9 (2 X OCH_3), 19.2 (3 $\underline{C}H_3$), 15.9 (5 $\underline{C}H_3$), 14.8 ($C_6H_4OC\underline{H}_2CH_3$), 63.4 ($C_6H_4OCH_2\underline{C}H_3$). Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.28; N, 3.26. Found: C, 67.26; H, 7.12; N, 3.34.

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