Conformational Study of Anticholinesterase Carbamates in the Furylbenzene Series by ^{1}H and ^{13}C NMR Spectroscopy

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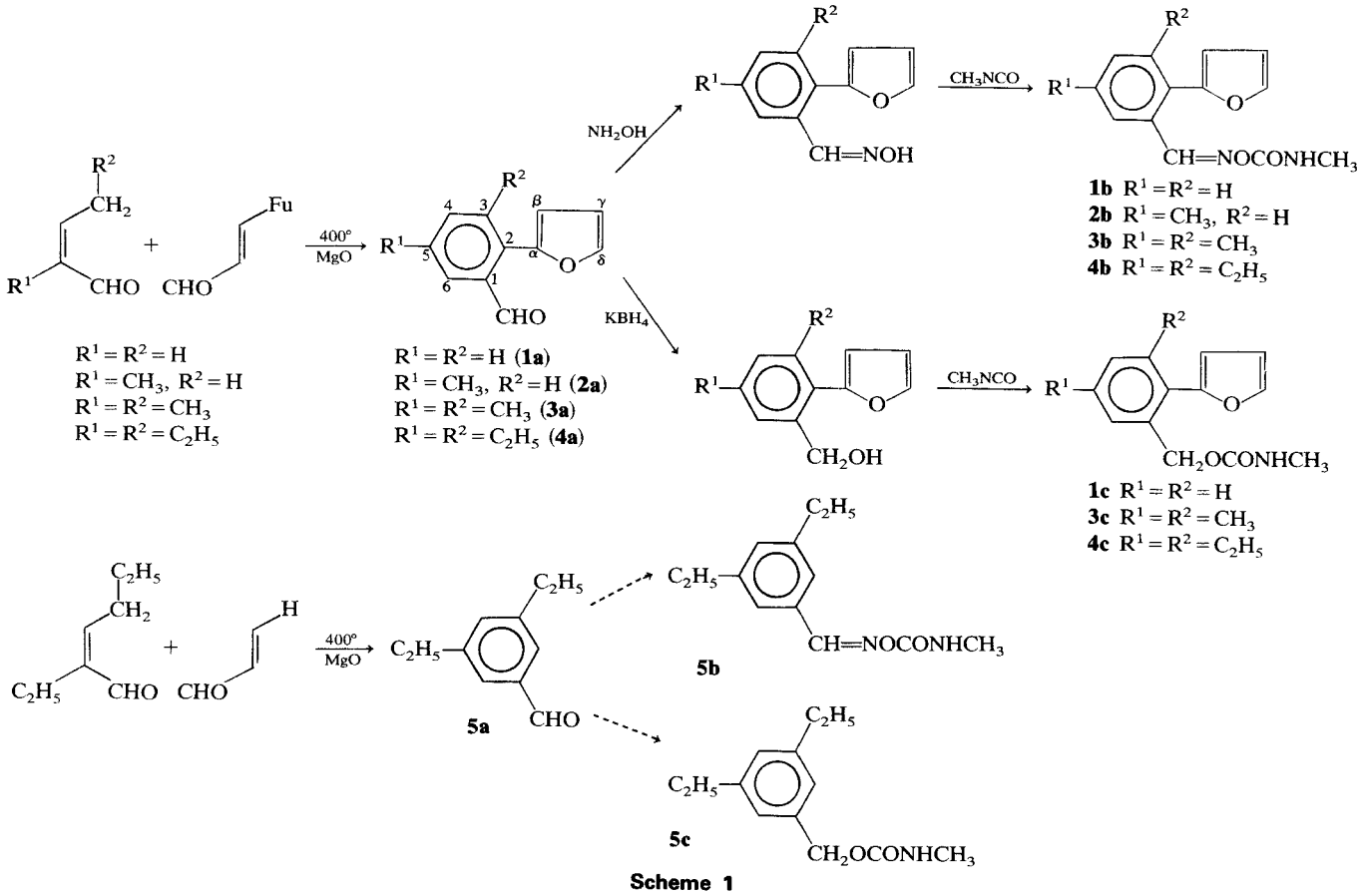
The structural analysis of carbamates derived from 2-(α-furyl)benzaldoximes and 2-(α-furyl)benzyl alcohols was carried out by ^{1}H and ^{13}C NMR spectroscopy. The conjugative and steric effects of alkyl substituents introduced on the benzene rings were found to modify the relative orientation of the aromatic and furan rings. The existence of a close relationship between the stereochemistry of the studied compounds and their anticholinesterase activity has been proposed.

INTRODUCTION

In a previous paper[1] we demonstrated the anticholinesterase activity of the *N*-methylcarbamates of 3,5-dialkyl-2-(α-furyl)benzaldoximes (**1b**, **2b**, **3b**, **4b**) and the *N*-methylcarbamates of 3,5-dialkyl-2-(α-furyl)benzyl alcohols (**1c**, **3c**, **4c**). The non-alkyl substituted carbamates exhibit the strongest activities.[1] Before studying the modes of interaction of these compounds with the active sites of the protein, it is essential to examine their stereochemistry. To carry out this study, it was necessary to examine the precursors, 3,5-dialkyl-2-(α-furyl)benzaldehydes (**1a**, **2a**, **3a**, **4a**), which have been synthesized by heterogeneous catalysis in the vapour phase.[2]

A preliminary study was carried out by ^{1}H NMR and the structural analysis of all the compounds was achieved by ^{13}C NMR. The syntheses of all the compounds, which will be detailed in the Experimental Section, are shown in Scheme 1.



Scheme 1

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RESULTS

^{1}H NMR

The three protons of the furan ring form an ABX system, the X part (H-δ) overlapping with the absorptions of the aromatic protons. The complete analysis of this system was achieved only for the 3,5-dimethyl- and 3,5-diethyl-2-(α-furyl)benzaldehydes, and was supported by the calculation of the spectra (Bruker ITRCAL-Program). Owing to the appreciable difference between the H-β, H-δ and H-γ, H-δ coupling constants, the multiplets corresponding to H-β and H-γ are clearly differentiated, so that the assignment of their signals was possible in the whole series. In the Experimental section, the chemical shifts of **3a** and **4a** are those calculated, while for the other compounds the shifts are measured at the centre of the multiplets.

Two noticeable modifications of the spectra arise when introducing alkyl groups. On the one hand, the position of the signals corresponding to H-β and H-γ are reversed when going from **1a** to **3a** and **4a**: H-β undergoes a gradual shielding effect, whereas the shifts of H-γ exhibit no regular trend (in **1b** and **2b** H-β and H-γ have the same chemical shift, but they are distinct in **3b** and **4b**). On the other hand, the aldehydic or oximic proton in series **a** and **b** is considerably shifted to high field ($\delta_{1,2} - \delta_{3,4} \sim 0.5$–$1.0$ ppm). The interpretation of these effects assumes the rotation of one of the rings out of the plane of the other; H-β is then in the shielding cone of the aromatic ring while the proton of the functional group experiences the effect of the anisotropy of the furan ring.

^{13}C NMR

The chemical shifts and their assignments are listed in Table 1 for the 2-(α-furyl)benzaldehydes, and in Tables 2 and 3 for the *N*-methylcarbamates of 2-(α-furyl)benzaldoximes and *N*-methylcarbamates of 2-(α-furyl)benzyl alcohols, respectively.

The assignments were made by comparison with model molecules such as α-furylbenzene,[3] 3,5-diethylbenzaldehyde (**5a**)[2] and the *N*-methylcarbamate of 3,5-diethylbenzaldoxime (**5b**), and also according to the classical effects of substitution on an aromatic ring (see Ref. 4, p. 81). The multiplicities of the signals in the off-resonance proton decoupled (SFORD) and fully proton coupled spectra were also used. The cases of the carbon atoms for which assignments were more critical are discussed below.

In the furan ring the differentiation between C-β and C-γ is based on the study of the long-range couplings of these carbons by comparison with monosubstituted furan rings (see Refs. 3, 5 and 6 and the revision in Refs. 7 and 8). The coupling constants

Table 1. ^{13}C chemical shifts in the a series, 2-(α-furyl)benzaldehydes

	R^1	R^2	CO	C-1	C-2	C-3	C-4	C-5	C-6	C-α	C-β	C-γ	C-δ	R^1 and R^{2b}
1a	H	H	191.9	132.9	133.1	128.2[a]	133.3	127.9[a]	127.9	150.9	111.1	111.8	143.8	—
2a	CH_3	H	192.0	132.7	130.6	128.2	134.2	137.9	127.9	151.1	110.5	111.7	143.4	21
3a	CH_3	CH_3	192.2	135.5	131.0	138.7	136.2	138.7	125.1	148.5	112.4	110.8	142.8	20.3 21
4a	C_2H_5	C_2H_5	192.0	136.0	130.7	145.4	133.7	145.2	123.9	148.2	112.2	110.7	142.7	CH_2 15.2, 15.7 CH_3 26.4, 28.6

[a] The assignment may be reversed.
[b] The assignment is not specified.

Table 2. ^{13}C chemical shifts in the b series, *N*-methylcarbamates of 2-(α-furyl)benzaldoxime

	R^1	R^2	CH=N	C-1	C-2	C-3	C-4	C-5	C-6	C-α	C-β	C-γ	C-δ	CO	N—Me	R^1 and R^{2c}
1b	H	H	152.9	126.5	131.3	127.9[a]	131.0	127.8[a]	127.4[a]	151.3	110.3	111.7	143.4	155.7	27.6	—
2b	CH_3	H	152.9	126.3	128.7	127.6[b]	132.0	137.8	127.9[b]	151.5	109.7	111.6	143.0	155.8	27.6	21.0
3b	CH_3	CH_3	152.7	129.6	128.9	138.8	133.9	138.8	124.6	149.3	111.5	110.7	142.5	155.9	27.5	20.2 21.0
4b	C_2H_5	C_2H_5	152.9	130.1	128.7	145.4	131.3	145.4	123.6	149.1	111.3	110.7	142.5	155.8	27.6	15.6, 15.4 26.8, 28.7

[a] Assignment not specified: δ 127.4, 127.8, 127.9.
[b] Assignment not specified: δ 127.6 and 127.9.
[c] Assignment not specified.

Table 3. ^{13}C chemical shifts in the c series, *N*-methylcarbamates of 2-(α-furyl)benzyl alcohols

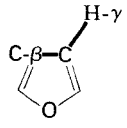
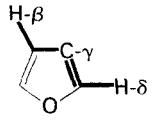
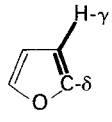
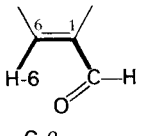
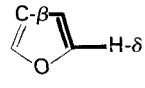
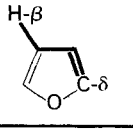
	R^1	R^2	CH_2	C-1	C-2	C-3	C-4	C-5	C-6	C-α	C-β	C-γ	C-δ	CO	N—Me	R^1 and R^{2c}
1c	H	H	65.2	132.4	130.0	127.6[a]	129.6	127.4[a]	128.1[a]	152.1	108.7	111.4	142.2	156.9	27.5	—
3c	CH_3	CH_3	65.0	136.2	127.6	138.4	130.6	138.4	126.9	150.6	109.7	110.4	141.8	156.8	27.4	20.3 21.1
4c	C_2H_5	C_2H_5	65.8	136.6	127.4	145.0[b]	127.9	145.1[b]	125.8	150.4	109.7	110.4	141.8	156.9	27.4	CH_3 15.8, 15.2 CH_2 27.0, 28.7

[a] Assignment not specified: δ = 127.4, 127.6 and 128.1.
[b] Assignment not specified: δ = 145.0 and 145.1.
[c] Assignment not specified.

were measured for the 2-(α-furyl)benzaldehydes (Table 4). In this same series of compounds the strong ^2J(C-γ, H-δ) coupling was not entirely suppressed in the SFORD spectra, so that a characteristic fine structure remains. This observation was used to differentiate C-β and C-γ in the two other series of compounds.

In the aromatic ring, distinction between C-1 and C-2 is very easy in series **a**: the strong ^2J(C-1, C*H*O) coupling can be directly observed in the spectra without decoupling or as a residual coupling in the off resonance spectra. In series **b**, the assignments proposed for C-1 and C-2 are based, on the one hand, on the shielding effect due to the transformation of the aldehydic group to the carbamate of an oxime function (**5a**: C-1 137.1 ppm; **5b**: C-1 129.9 ppm) and, on the other hand, on the effect of the alkyl substituent on position 5. In series **c**, carbon atom C-1, which bears a CH_2 group whose protons are involved in its relaxation mechanisms, has a systematically higher intensity than the other quaternary carbon atom C-2, which is flanked by two or three quaternary carbon atoms. Among the tertiary carbon atoms C-4 is easily identified in all the compounds; deshielded by the aldehydic group in series **a**, it is somewhat less deshielded in series **b** by the carbamate of the oxime group (**5a**: C-4 134.0 ppm; **5b** C-4 132.2 ppm). In series **c**, the assignment was carried out in the knowledge that the effects of the alkyl substituents on C-4 are comparable to those observed in series **a** and **b**.

Table 4. ^{13}CH coupling constants in the 2-(α-furyl) benzaldehydes (the accuracy of the measurement is ±1.6 Hz)

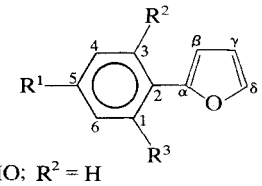
		1a	2a	3a
^1J(CH)	CHO	180.6	181.1	179.3
	C-β	174.8	174.7	174.8
	C-γ	176.2	176.0	175.5
	C-δ	203.5	201.8	202.3
^2J(CH)		^2J(C-β, C-γ) = 5.3	3.9	4.9
		^2J(C-γ, H-β) = 3.7 ^2J(C-γ, H-δ) = 13.1	3.8 13.4	3.9 13.4
		^2J(C-δ, H-γ) = 11.3	10.8	10.3
^3J(CH)		^3J(CHO, H-6) = 3.7	4.1	4.0
		^3J(C-β, H-δ) = 5.3	4.9	4.9
		^3J(C-δ, H-β) = 6.9	8.0	7.3

The assignment of the signals of the tertiary carbon atoms C-3, C-5 and C-6 was not possible in the non-substituted compounds **1a**, **1b**, and **1c**, except for the signal corresponding to C-6 in **1a** where the use of a relaxation reagent, Gd(fod)$_3$, led to its identification. A labile complex is formed between the chelate Gd(fod)$_3$ and the aldehyde **1a** which produces variations in the relaxation rates $1/T_1$, which are functions of the geometry of the complex $[1/T_1 = f(1/r^6)]$, where r is the distance between the Gd^{3+} ion and the observed carbon atom.[9] A much more rapid relaxation is observed for the signal at 127.9 ppm than for the signal at 128.4 ppm; the absorption of 127.9 ppm is, thus, assigned to C-6, which is near the CHO group.

DISCUSSION

The inhibiting ability of the studied compounds on the active site of the enzyme may depend on the electronic density (due to the extent of conjugation between the different groups in the molecule) and on the shape of the molecule. The major structural problem is, therefore, the relative orientation of the aromatic and furan rings.

The conjugative and steric effects of the substituents are very important in the **a**, **b** and **c** series. 5-Methyl- and 5-formyl-2-(α-furyl)benzene have been chosen as models to evaluate the conjugation effect; the aryl substituents are then at optimal conjugative positions with regard to the furan ring. To investigate the steric effects we used 1, 3, 5-trimethyl-2-(α-furyl)benzene as a model. The following numbering was adopted for purposes of comparison



R^1 = Me, CHO; R^2 = H
$R^1 = R^2 = CH_3$
$R^3 = CH_3$, CHO, CH=NOCONHCH$_3$, CH$_2$OCONHCH$_3$

The analysis of the different effects was undertaken by calculating, for the carbon atoms of the aromatic and furan rings, the difference, Δδ, between the chemical shifts measured in the model molecules or the molecules in the series **a**, **b**, **c** and the chemical shifts measured in (α-furyl)benzene taken as a reference molecule (Table 5). In the furan ring, the carbons sensitive to conjugation effects are C-β and, to a smaller degree, C-δ. These are deshielded on the introduction of an electron-attracting CHO group, and slightly shielded on the introduction of a weakly donating CH_3 group. The C-β carbon in the furan ring and C-1 and C-3 in the aromatic ring appear to be particularly sensitive probes for the study of steric effects. The examination of molecular models indicates that the rings may be coplanar in (α-furyl)benzene, H-β then having a weak interaction with H-1 or H-3. In 1, 3, 5-trimethyl-2-(α-furyl)benzene the dihedral angle between the planes of the rings must be near 90°. The rotation of the furan ring with respect to the

Table 5. ^{13}C substituent effects on the (α-furyl)benzene skeleton[a] (positive sign = downfield shift)

	R^1	R^2	R^3	C-1	C-2	C-3	C-4	C-5	C-6	C-α	C-β	C-γ	C-δ
[a]	CH_3	H	H	+0.3	−2.3	+0.3	+1.0	+10.0	+1.0	+0.6	−0.5	+0.2	−0.2
6	CH_3	CH_3	CH_3	+14.3	−2.8	+14.3	−0.6	+10.8	−0.6	−2.2	+3.9	−1.5	−0.8
[a]	CHO	H	H	−0.2	+3.8	−0.2	+1.3	+8.4	+1.3	−1.7	+3.0	+0.4	+1.4
1a	H	H	CHO	+9.1	+2.0	+4.4	+4.6	+0.6	−0.8	−3.1	+6.1	+0.2	+1.8
2a	CH_3	H	CHO	+8.9	−0.3	+4.4	+5.4	+10.6	−0.8	−2.9	+5.5	+0.1	+1.4
3a	CH_3	CH_3	CHO	+11.8	−0.05	+14.9	+7.4	+11.4	−3.6	−5.5	+7.4	−0.8	+0.8
1b	H	H	CH=NOCONHCH$_3$	+2.7	+0.4	+4.1	+2.3			−2.7	+5.3	+0.1	+1.4
2b	CH_3	H	CH=NOCONHCH$_3$	+2.5	−2.2	+3.8	+3.3			−2.5	+4.7	0.0	+1.0
3b	CH_3	CH_3	CH=NOCONHCH$_3$	+5.8	−2.0	+15.0	+5.2	+11.5		−4.7	+6.5	−0.9	+0.5
1c	H	H	CH_2OCONHCH$_3$	+8.6	−1.0	+3.8	+0.9	+0.1		−1.9	+3.7	−0.2	+0.2
3c	CH_3	CH_3	CH_2OCONHCH$_3$	+12.4	−3.3	+14.6	+1.9	+11.1		−3.4	+4.7	−1.2	−0.2

[a] See Ref. 3 and text.

aromatic ring leads to a distinct deshielding effect for C-β, C-1 and C-3 (for C-1 and C-3 this downfield shift is superimposed on the normal effect due to the substitution of a proton by a CH_3 group). Moreover, a sensitive upfield shift is found for C-α, C-γ and C-δ; this must be due to a general increase in electronic density in the furan ring due to loss of conjugation with the aromatic ring.

Table 5 indicates that the rotation of one of the rings out of the plane of the other occurs in two steps in series **a**, **b** and **c**. On the introduction of a functional substituent in position 1 (**1a**, **1b**, **1c**), a downfield shift of C-1, C-3 and C-β is first observed. This result demonstrates that there is a significant torsional angle between the planes of the rings. Nevertheless, a certain degree of conjugation between the two rings is maintained at this step. In fact, the introduction of a methyl group in position 5, the effect of which is solely electronic (**2a**, **2b**), diminishes the downfield shift of C-β and C-δ without significantly modifying the positions of C-α and C-γ.

The introduction of a second methyl group at C-3 (**3a**, **3b**, **3c**) increases the downfield shift of C-1 and C-β, which means that the angle between the planes of the rings is again increased. The simultaneous high field shifts of C-α, C-γ and C-δ demonstrate that the two rings are now not conjugated and the torsional angle of the two rings must then be very near 90°.

The variations in the chemical shift of C-4 permit the analysis of the consequences of ring rotation on the conjugation of the aldehydic or the oxime carbamate groups with the aromatic ring. In **1a** a deshielding effect is observed for C-4 which, for an aldehydic group in *para* position, is abnormally weak (4.6 ppm instead of 5.5 ppm[10]); it is still weak in **2a** if the *ortho* effect of the methyl group in position 5 is taken into account. The aldehydic group is, thus, only partially conjugated with the aromatic ring. The additional downfield shift of C-4 (+2 ppm) on the introduction of a methyl group in position 3 certainly results, in part, from the better conjugation of the formyl group with the aromatic ring. Thus, when the angle between the planes of the two rings is near 90°, the formyl group is coplanar with the aromatic ring. The same effects are observed for the oxime carbamate (Table 5).

In the four compounds of series **b**, the oxime carbon atom resonates nearly at the same frequency; this indicates that the substituents on the double bond have the same configuration. In the oxime which is the precursor of **3b**, the oxime carbon atom resonates at 149.6 ppm, a frequency close to that published for the *syn*-oxime of benzaldehyde, and which is relatively remote from the frequency of the *anti*-oxime of benzaldehyde (146.6 ppm) (see Refs. 4. p. 131, and 11). It then appears likely that the oximes and the derived carbamates have all been obtained in the *syn* configuration, the most favourable form from a steric point of view.

CONCLUSIONS

The ^{13}C NMR spectra of 2-(α-furyl)benzaldehydes and their corresponding carbamates have allowed a more precise evaluation of the qualitative information obtained from the ^{1}H NMR spectra. Thus, the compounds in the **3** and **4** series showed a dihedral angle between the planes of the rings of approximately 90° and, in the case of the aldehydes (series **a**), the CHO group is coplanar with the phenyl group.

These results show a close relationship between the stereochemistry of biologically active compounds and their activity. It is now clear that carbamates **1b** and **1c**, which present the highest anticholinesterase activities,[1] are also those in which the dihedral angle between the ring planes is small. For this skeleton, therefore, the value of this angle is an important parameter for the anticholinesterase activity. We have already demonstrated that the anticholinesterase activity of **1b** and **1c** is nearly the same. These results are in good accord with the weak conjugation effect observed between the functional group and the aromatic ring.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Varian XL100 spectrometer of the Groupe de Mesures Physiques de Paris Centre under the following conditions: observation frequency, 25.2 MHz; concentration, 0.5 M in $CDCl_3$, temperature, 298 K; pulse width, 8 μs (corresponding to a flip angle of circa 30°).

The spectra were normally recorded with proton broad band decoupling, with a spectral width of

6250 Hz and 8K data points; the accuracy of the chemical shifts is ±0.06 ppm. Some of the spectra were recorded with proton single frequency off-resonance decoupling (SFORD) or without decoupling of the protons. In these cases the spectra were recorded with a spectral width of 4000 Hz and 8 K data points; the accuracy of the coupling constants is ±1.6 Hz.

The ^{1}H NMR spectra were recorded on a CW Bruker WP80 spectrometer for the aldehydes (series **a**) (~0.5 M solutions in $CDCl_3$; observation frequency, 80 MHz) and on a Varian EM360 spectrometer for series **b** and **c** (~0.5 M solutions in $CDCl_3$; observation frequency, 60 MHz). TMS was the internal standard.

The molecular weight and the purity of the compounds were confirmed by mass spectrometry on an AEI-MS 30 spectrometer; IR spectra were recorded on a Perkin–Elmer 357G spectrometer.

3, 5-Dialkyl-2-(α-furyl)benzaldehydes

The preparations have been previously described.[2]

1a. NMR ($CDCl_3$, 80 MHz) δ_H: 6.6 (H-β), 6.4 (H-γ), 7.6 (H-δ) [*m*, $J(\beta\gamma)$ 3 Hz] 7.3–8 (*m*, 4H benzenic), 10.3 (*s*, CHO); *ms* (70 eV) *m/e* (rel. int.) 172 (93), 171 (43), 144 (49), 143 (13), 115 (100).

2a. NMR ($CDCl_3$, 60 MHz) δ_H: 6.5 (H-β), 6.48 (H-γ), 7.51 (H-δ), 7.46 (H-3), 7.4 (H-4), 7.7 (H-6), 10.3 (*s*, CHO), 2,3 (5-Me); *ms* (70 eV) (rel. int.) 186 (46), 158 (100), 157 (26), 129 (82), 115 (66).

3a. NMR ($CDCl_3$, 80 MHz) δ_H: 6.4 (H-β), 6.5 (H-γ), 7.6 (H-δ) [$J(\beta\gamma)$ 3.4 Hz, $J(\beta\delta)$ 1.8 Hz, $J(\gamma\delta)$ 1Hz], 7.3 (*m*, H-4), 7.6 (*m*, H-6), 9.8 (*s*, CHO), 2.5 (*s*, 3-Me), 2.3 (*s*, 5-Me); *ms* (70 eV) (rel. int.) 200 (70), 199 (2), 172 (100), 171 (27), 143 (44), 115 (22).

4a. NMR ($CDCl_3$, 80 MHz) δ_H: 6.3 (H-β), 6.4 (H-γ), 7.5 (H-δ) [$J(\beta\gamma)$ 3.3 Hz, $J(\beta\delta)$ 1.6 Hz, $J(\gamma\delta)$ 1.2 Hz], 7.3 (*m*, H-4), 7.6 (*m*, H-6), 9.7 (*s*, CHO), 1.2 (*t*, 3Me), 1.3 (*t*, 5-Me), 2.6 (*q*, 3-CH_2), 2.7 (*q*, 5-CH_2); *ms* (70 eV) (rel. int.) 228 (56), 227 (1), 200 (60), 199 (21), 185 (100), 171 (33), 115 (19).

5a. was obtained by condensation of 2-ethyl-2-hexenal with acrolein. NMR ($CDCl_3$) δ_C: 137.1 (C-1), 126.7 (C-2), 145.3 (C-3), 134.0 (C-4), 192.5 (CO), 15.4 (CH_3), 28.7 (CH_2).

N-Methylcarbamates of 3, 5-Dialkyl-2-(α-furyl)-benzaldoximes and 3, 5-dialkyl-2-(α-furyl)benzyl alcohols

The aldehydes were converted into the oximes by reaction with hydroxylamine chlorhydrate (NaOH 10%) or reduced to the alcohols by the action of KBH_4 in refluxing methanol. The oximes and the alcohols, dissolved in anhydrous diethyl ether, were reacted with a slight excess of methyl isocyanate, with trimethylamine as a catalyst, giving the *N*-methylcarbamates (**1b**, **2b**, **3b**, **4b**, **1c**, **3c**, **4c**).

1b. m.p. 99.5–100 °C, Cream coloured crystals; IR (KBr): 3360 (NH), 1725 (C=O); NMR δ_H: 6.6 (H-β+H-γ), 7.7 (H-δ), 7.4–8.1 (*m*, H-3, 4, 5, 6), 9.2 (*s*, CH=N), 6.4 (broad *s*, NH), 3.0 (*d*, N—Me, J = 5 Hz); *ms* (70 eV) (rel. int.) 244 (4), 187 (22), 170 (71), 169 (100), 158 (7), 140 (90), 115 (27).

2b. Uncrystallized brown oil; IR (film) 3360 (NH), 1730 (C=O); NMR δ_H: 6.4 (H-β+H-γ), 7.5 (H-δ), 7.5 (*m*, H-3), 7.2 (*m*, H-4), 7.7 (*m*, H-6), 8.8 (*s*, CH=N), 6.2 (broad *s*, NH), 2.9 (*d*, N—Me, J = 5 Hz), 2.3 (*s*, 5-Me); *ms* (70 eV) (rel. int.) 258 (4), 201 (11), 184 (50), 183 (100), 156 (16), 154 (39), 128 (18), 115 (16).

3b. m.p. 107 °C, Cream coloured crystals; IR (KBr): 3370 (NH), 1710 (C=O); NMR δ_H: 6.4 (H-β), 6.5 (H-γ), 7.6 (H-δ), 7.3 (*m*, H-3), 7.6 (*m*, H-6), 8.3 (*s*, CH=N), 6.2 (broad *s*, NH), 3.0 (*d*, N—Me, J = 5 Hz), 2.4 (*s*, 3-Me), 2.3 (*s*, 5-Me); *ms* (70 eV) (rel. int.) 272 (10), 215 (57), 198 (100), 197 (92), 170 (39), 169 (15), 168 (67), 115 (20).

4b. Uncrystallized brown oil; IR (film) 3350 (NH), 1725 (C=O); NMR δ_H: 6.4 (H-β), 6.6 (H-γ), 7.6 (H-δ), 7.3 (*m*, H-3), 7.6 (*m*, H-6), 8.2 (*s*, CH=N), 6.2 (broad *s*, NH), 3.0 (*d*, N—Me, J = 5 Hz), 1.30 (*t*, 3-CH_3), 1.33 (*t*, 5-CH_3), 2.6 (*q*, 3-CH_2), 2.7 (*q*, 5-CH_2); *ms* (70 eV) (rel. int.) 300 (1), 143 (15), 226 (100), 225 (99), 196 (42), 168 (78).

5b. Uncrystallized brown oil; NMR ($CDCl_3$) δ_C: 129.9 (C-1), 128.6 (C-2), 145.3 (C-3), 132.2 (C-4), 145.0 (CN), 153.6 (CO).

1c. m.p. 58 °C, cream coloured crystals; IR (film) 3330 (NH), 1695 (C=O); NMR δ_H: 6.8 (H-β), 6.6 (H-γ), 7.5 (H-δ), 7.3–7.9 (*m*, H-3, 4, 5, 6), 4.9 (*s*, CH_2), 4.8 (broad *s*, NH), 1.4 (*d*, N—Me, J = 5 Hz); *ms* (70 eV) (rel. int.) 231 (84), 174 (77), 145 (100), 127 (46), 115 (36).

3c. m.p. 93.5–94 °C, Cream coloured crystals; IR (KBr) 3330 (NH), 1690 (C=O); NMR δ_H: 6.4 (H-β), 6.6 (H-γ), 7.6 (H-δ), 7.5 (*m*, H-4), 7.6 (*m*, H-6), 5 (*s*, CH_2), 4.7 (broad *s*, NH), 2.8 (*d*, N—Me, J = 5 Hz), 2.4 (*s*, 3-Me), 2.2 (*s*, 5-Me); *ms* (70 eV) (rel. int.) 259 (100), 202 (55), 173 (80), 157 (47), 115 (30).

4c. Uncrystallized brown oil, IR (film) 3340+3450 (NH), 1710+1725 (C=O); NMR δ_H: 6.3 (H-β), 6.4 (H-γ), 7.4 (H-δ), 7 (*m*, H-4), 7.1 (*m*, H-6), 4.9 (*s*, CH_2), 4.9 (broad *s*, NH), 2.6 (*d*, N—Me, J = 5 Hz), 1.0 (*t*, 3-Me), 1.2 (*t*, 5-Me), 2.5 (*q*, 3-CH_2), 2.8 (*q*, 5-CH_2).

5c. Uncrystallized brown oil; NMR ($CDCl_3$) δ_C: 136.5 (C-1), 124.9 (C-2), 144.3 (C-3), 127.1 (C-4).

1,3,5-Trimethyl 2-(α-furyl)benzene (see text)

This is obtained by reduction of **3a**; NMR ($CDCl_3$, 60 MHz) δ_H: 6.3 (H-β), 6.5 (H-γ), 7.5 (H-δ), 7.3 (*m*, H-4+H-6), 2.2 (*s*, 1-Me+3-Me), 2.3 (*s*, 5-Me); NMR ($CDCl_3$) δ_C: 138.1 (C-1, C-3, C-5), 128.1 (C-2, C-4, C-6), 152.2 (C-α), 108.9 (C-β), 110.1 (C-γ), 141.2 (C-δ).

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