Attempted Synthesis of Ethyl 3,4-Dihydro-2*H*-1,4-benzoxazine-3-carboxylate and 3-Acetate Derivatives

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Ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-3-carboxylate derivatives **2** were obtained and isolated in low yields from the condensation of 2-aminophenol and ethyl 2,3-dibromopropanoate. They can be obtained by hydrogenation of ethyl 2*H*-1,4-benzoxazine-3-carboxylate in satisfactory yield. Using 2-iminophenol did not direct the condensation with ethyl 2,3-dibromopropanoate towards **2** but was fruitfull for the preparation of ethyl 2-(4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl)acetate from ethyl bromocrotonate.

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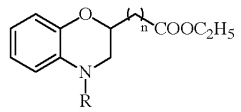
The 3,4-dihydro-2*H*-1,4-benzoxazine framework is often encountered in pharmacologically active compounds [1]. In our group we have developped *inter alia* the synthesis of new calcium antagonists [2] and new imidazolinic derivatives [3] having this skeleton. Ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate was the starting material to enter in this series.

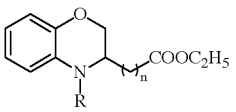
Usually the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate was performed by treating 2-aminophenol with ethyl 2,3-dibromopropanoate to afford the benzoxazinic compound **1a** [4] and not the isomeric derivative **2a** (Scheme 1).

The influence of the substitution on the nitrogen atom of the starting aminophenol (R = CH_3, R = Ts) has been investigated [1c,5,6]. In all cases the structures **1b,c** were obtained; Bartsch [5] has demonstrated that the correct structure for the 2,3-dihydro-1,4-benzoxazine obtained from the 2-*N*-tosylaminophenol is **1c** and not **2c** [6].

For our own part we have reacted 7-hydroxyindoline **5** [7], which may be considered as 2-aminosubstituted phenol, with ethyl 2,3-dibromopropanoate to obtain (Scheme 2) compound **6** in 83% yield which structure has been unambigously determined by 2D NMR assignement.

Scheme 1





1a	R = H	n = 0	**2a**	R = H	n = 0
1b	R = CH_3	n = 0	**2b**	R = CH_3	n = 0
1c	R = Ts	n = 0	**2c**	R = Ts	n = 0
1d	R = Boc	n = 0	**2d**	R = Boc	n = 0
3e	R = Bn	n = 1	**4c**	R = Tos	n = 1
			4e	R = Bn	n = 1

So the direct condensation of ethyl 2,3-dibromopropanoate with 2-substituted aminophenols always led to benzoxazines **1**. Since structures of type **2** correspond to strained aminoacid, it would be of interest to develop new methods to reach these structures.

One approach to prepare **2** was to start from 1,4-benzoxazine derivatives, introducing at the correct position an ester group; an other was to generate the ester function by modification of a 3-functional group already present on the 2,3-dihydro-1,4-benzoxazine moiety. The first approach was illustrated with the benzoxazinic derivative **7**. Coudert *et al.* [8] have reacted ethyl chloroformate with the lithio derivative of benzoxazine **7** to afford the ethyl 1,4-benzoxazine-3-carboxylate **8** which was a very good precursor for compounds **2** (Scheme 3). Thus the catalytic hydrogenation of **8** in ethanol over palladium on carbon (Pd/C) gave the desired ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-3-carboxylate **2d** in 49% yield; this reduction was reluctant in our conditions: 50 atm, 25% weight of palladium, 3 days at room temperature. The nmr data of **2d** were consistent with the structure and different from compound **1d** [9].

The second approach to compounds **2** was the oxidation of products having an hydroxymethyl group at the 3-position such as in compound **9** [10]. The use of Dess-Martin periodinate reagent, Magtrieve™ reagent, potassium permanganate and Swern oxidation led only to degradation products (Scheme 4).

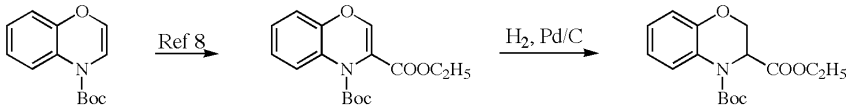
Although oxidation of **9** was fruitless, more success has been achieved by Bartsch in the hydrolysis of the nitrile group of compound **10** [5] which afforded (Figure 1) the required ester **2c** (68% yield).

Nevertheless, within our hand, the deprotection of the nitrogen atom of **2c** afforded degradation products; so we decided to carefully investigate the condensation of various

Scheme 2

5 **6**

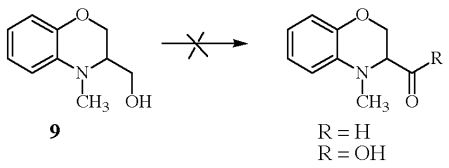
Scheme 3



substituted 2-aminophenols **11** with ethyl 2,3-dibromopropanoate using potassium carbonate as base in acetone at reflux (Scheme 5). From **11a** we can isolate after tedious chromatographic separation, in low yield (4%), the "inverse" benzoxazine **2a** from the normal benzoxazine **1a** which is produced in high yield. With substituted aminophenols **11e-g** the yields of benzoxazines **2** slightly increased, but were still low (see Table 1). Compounds **2** were relatively unstable and thus they were treated with iodomethane in the presence of potassium carbonate to afford in moderate yield the *N*-methyl derivatives **12**.

The assignements for structures **2** were based on ^{1}H nmr and ^{13}C nmr data which are reported in the Table 2 and Table 3. As an illustrative example the chemical shifts for carbon C-2 and for C-3 in compound **2e** were 65.6 ppm and 53.1 ppm respectively; while for compound **1e** the chemical shifts for the same carbons were respectively 72.4 ppm and 42.3 ppm. The ^{1}H NMR spectra indicated *inter alia* a chemical shift for the angular proton of **2e** equal to 4.10 ppm compared to 4.67 ppm for **1e**.

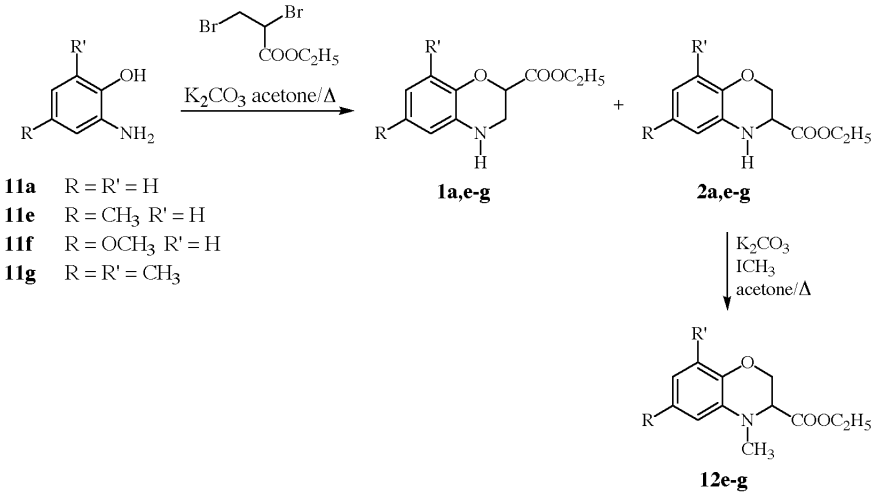
Scheme 4



More experiments were carried out in order to increase the yield of compounds **2**: use of a mixture of 2-propanol/-acetone 1:99 or 50:50 v/v, addition of water, replacement of potassium carbonate with potassium hydrogenocarbonate; all these modifications were not conclusive.

It was thus possible to obtain benzoxazine **2** in low yield by direct condensation of 2-aminophenol. Compounds **2** might result either from a Michael addition on ethyl 2-bromoacrylate, generated *in situ*, or from a direct displacement of a bromine atom by the oxygen atom rather than the nitrogen atom of the 2-aminophenol.

Scheme 5



Scheme 6

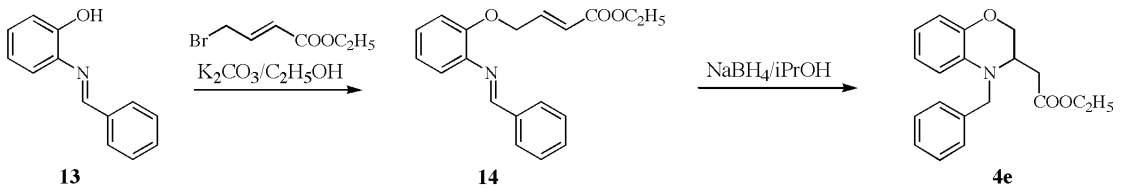
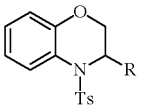


Table 1

Yield (%)	**a**	**e**	**f**	**g**
1	81	74	51	68
2	4	13	9	13
12	-	44	38	45

We have envisaged to direct the reaction towards the formation of benzoxazines **2** by masking or decreasing the nucleophilicity of the nitrogen atom of the 2-aminophenol. This approach has been described using trifluoroacetyl or *p*-toluenesulfonyl group as withdrawing groups on the nitrogen atom for the preparation of ethyl 2-(4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl)acetate **4c** [11]. Since the use of the *p*-toluenesulfonyl group was unfruitfull for obtaining **2c** [5] we planned to use an imine as the precursor of the amino group. We first tested this approach in the synthesis of ethyl 2-(4-benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl)acetate **4e** (Scheme 6).

The aminophenol **11a** reacted with benzaldehyde to afford the imine **13** [12] which was treated with ethyl bromocrotonate to afford imine **14**. The *in situ* reduction of **14** with sodium borohydride in isopropanol gave the corresponding amine which spontaneously undergoes an intramolecular Michael addition to afford the benzoxazine **4e** in a global yield of 65%. During the reduction, a small amount of compound **15** was formed and isolated in 8% yield (Figure 2). Application of this imine methodology



10 R = CN
2c R = $COOC_2H_5$

Figure 1

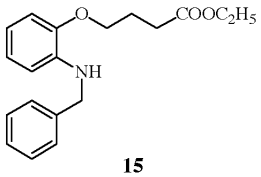


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Figure 2

for the synthesis of compounds **2** resulted in a mixture of products. The usual isomeric benzoxazine **3e** [13] was produced in satisfactory yield by an initial reduction of imine **13** to the 2-benzylaminophenol, followed by condensation with ethyl bromocrotonate.

In conclusion we have described the formation of 3,4-dihydro-2*H*-1,4-benzoxazine-3-carboxylate during the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate. Using a precursor that posseses the ethoxycarbonyl group in position-3 of the benzoxazine framework, the obtention of **2** was easy.

Table 2

^{1}H NMR δ (deuteriochloroform) *J* (Hz)

Compound	H_2	H_3	OCH_2CH_3	Other	ArH
2a	4.24 (dd, 1H, *J* = 6.0, 10.5) 4.44 (dd, 1H, *J* = 3.1, 10.5)	4.13 (dd, 1H, *J* = 3.1, 6.0)	4.25 (q, 2H, *J* = 7.1, CH_2) 1.30 (t, 3H, *J* = 7.1, CH_3)	4.31 (br s, 1H, NH)	6.64-6.72 (m, 2H); 6.78-6.83 (m, 2H).
2c[5b]	3.53 (dd, 1H, *J* = 3.2, 11.2) 4.58 (dd, 1H, *J* = 1.8, 11.2)	5.14 (dd, 1H, *J* = 1.8, 3.2)	4.15 (q, 2H, *J* = 7.1, CH_2) 1.17 (t, 3H, *J* = 7.1, CH_3)	2.39 (s, 3H, CH_3)	6.78 (dd, *J* = 1.7, 7.9, 1H); 6.93-7.00 (m, 2H); 7.26 (d, 2H, *J* = 8.3); 7.60 (d, 2H, *J* = 8.3); 7.81 (dd, 1H, *J* = 1.6, 8.3).
2d	4.13-4.24 (m, 1H) 4.70 (dd, 1H, *J* = 1.9, 11.9)	5.15 (br s, 1H)	4.24 (q, 2H, *J* = 7.1, CH_2) 1.22 (t, 3H, *J* = 7.1, CH_3)	1.56 (s, 9H, CH_3)	6.88-6.98 (m, 3H); 8.14 (br s, 1H, H_5).
2e	4.22 (dd, 1H, *J* = 5.5, 10.5); 4.37 (dd, 1H, *J* = 3.1, 10.5)	4.10 (dd, 1H, *J* = 3.1, 5.5)	4.21(q, 2H, *J* = 7.2, CH_2) 1.28 (t, 3H, *J* = 7.2, CH_3)	2.19 (s, 3H, CH_3) 4.32 (br s, 1H, NH)	6.43-6.50 (m, 2H); 6.68 (d, 1H, *J* = 7.9).
2f	4.01-4.28 (m, 2H)	4.05 (dd,1H, *J* = 3.2, 5.1)	4.23 (q, 2H, *J* = 7.0, CH_2) 1.22 (t, 3H, *J* = 7.0, CH_3)	3.68 (s, 3H, OCH_3) 4.50 (br s, 1H, NH)	6.12-6.26 (m, 2H); 6.62 (d, 1H, *J* = 8.5).
2g	4.17 (dd, 1H, *J* = 6.0, 11.0) 4.40 (dd, 1H, *J* = 3.1, 11.0)	4.08 (dd, 1H, *J* = 3.1, 6.0)	4.21 (q, 2H, *J* = 7.0, CH_2) 1.27 (t, 3H, *J* = 7.0, CH_3)	2.12 (s, 3H, CH_3); 2.18 (s, 3H, CH_3); 4.35 (br s, 1H, NH)	6.37 (s, 2H).
12e	3.97 (t,1H, *J* = 2.3) 4.15-4.21 (m, 1H)	4.57 (dd, 1H, *J* = 2.3, 10.8)	4.23 (q, 2H, *J* = 7.0, CH_2) 1.25 (t, 3H, *J* = 7.0, CH_3)	2.27 (s, 3H, CH_3) 2.98 (s, 3H, NCH_3)	6.42-6.50 (m, 2H); 6.65 (d, 1H, *J* = 7.8).
12f	3.95 (t, 1H, *J* = 2.5) 4.13-4.20 (m,1H)	4.55 (dd, 1H, *J* = 2.5, 10.7)	4.22 (q, 2H, *J* = 7.0, CH_2) 1.28 (t, 3H, *J* = 7.0, CH_3)	2.96 (s, 3H, NCH_3) 3.75 (s, 3H, OCH_3)	6.15 (dd, 1H, *J* = 2.8, 8.6); 6.27 (d, 1H, *J* = 2.8); 6.67 (d, 1H, *J* = 8.6).
12g	3.96 (t, 1H, *J* = 2.1) 4.15-4.25 (m, 1H)	4.62 (dd, 1H, *J* = 2.1, 10.7)	4.20 (q, 2H, *J*=7.0, CH_2) 1.25 (t, 3H, *J* = 7.0, CH_3)	2.11 (s, 3H, CH_3); 2.23 (s, 3H, CH_3); 2.97(s, 3H, NCH_3)	6.33-6.36 (m, 2H).

Table 3

^{13}C NMR, Mass Spectra and IR Spectral Data of Compounds **2, 12**

Compound	Molecular Formula	^{13}C NMR δ (deuteriochloroform)							Mass Spectra $(M+1)^+$	IR (film) (cm^{-1})
		C_2	C_3	CO	ArCH	ArC	Other	OCH_2CH_3		
2a	$C_{11}H_{13}NO_3$	67.5	53.2	170.5	116.2, 117.0, 119.4, 122.2	132.2, 143.6		62.0, 14.4	208	3379, 1741
2c[5b]	$C_{18}H_{19}NO_5S$	64.2	55.8	167.8	117.6, 121.8, 123.9, 125.9, 127.4(2), 130.2(2)	123.4, 135.8, 144.8, 145.9	21.8 (CH_3)	62.3, 14.1	362	1756, 1360, 1158
2d	$C_{16}H_{21}NO_5$	66.1	56.0	169.3 152.6	117.4(2), 121.9, 124.1	126.4, 145.7	28.6(3×CH_3) 82.7 (C)	62.1, 14.5	308	1749, 1660
2e	$C_{12}H_{15}NO_3$	65.6	53.1	170.5	116.4, 116.7, 119.7	131.4, 131.7, 141.3	21.2 (CH_3)	61.8, 14.2	222	3300, 1748
2f	$C_{12}H_{15}NO_4$	65.9	53.5	170.4	101.8, 104.6, 117.4	133.0, 138.0, 151.1	55.8 (OCH_3)	62.0, 14.5	238	3300, 1744
2g	$C_{13}H_{17}NO_3$	65.7	53.3	170.7	114.3, 121.7	125.9, 130.7, 131.3, 139.6	15.6(CH_3) 20.8 (CH_3)	61.2, 14.3	236	3300, 1747
12e	$C_{13}H_{17}NO_3$	65.6	61.0	171.8	114.8, 115.2, 125.7	130.9, 139.5, 142.2	21.0 (CH_3) 39.7 (NCH_3)	61.1, 14.1	236	1754
12f	$C_{13}H_{17}NO_4$	65.5	60.8	169.4	98.8, 101.0, 115.8	135.6, 137.6, 155.1	37.7 (NCH_3) 55.5 (CH_3)	61.3, 14.2	252	1756
12g	$C_{14}H_{19}NO_3$	65.9	60.6	170.7	110.4, 120.2	125.0, 130.7: 134.5, 139.7	16.0 (CH_3) 21.3 (CH_3) 38.3 (NCH_3)	61.2, 14.5	250	1757

EXPERIMENTAL

Both ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker instrument Avance DPX250 (250 MHz); for samples in deuteriochloroform solution with tetramethylsilane as internal standard, chemical shifts (δ values) were reported in parts per million and coupling constants (*J* values) in Hz. The IR spectra were recorded as a thin film on sodium chloride plates for the oils and in a potassium bromide pellet for solids on a Perkin-Elmer spectrometer FT Par agon1000 PC. Mass spectra were recorded on a Perkin-Elmer mass spectrometer SCIEX API 300 (ionspray or heat nebuliser). Melting points were measured using a Kofler hot stage apparatus and are uncorrected. Flash column chromatography was performed on silica gel (Merck 60, 230-400 mesh). Thin layer chromatography was performed on pre-coated silica gel plates (Merck 60, F254, 0.25mm). The solvents were HPLC grade.

General Procedure for the Synthesis of Compounds **2**.

To a stirred suspension of 2-aminophenol **11** (18 mmoles) and potassium carbonate (50 mmoles) in acetone (100 ml) was added ethyl 2,3-dibromopropanoate (19.8 mmoles). The mixture was refluxed for 18 hours. After filtration the filtrate was concentrated *in vacuo* to give a residue which was separated twice on silica gel using ethyl acetate/petroleum ether 7:3 as eluent to give first compound **1** and then compound **2**.

4-(*tert*-Butyl)-3-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine-3,4-dicarboxylate (**2d**).

To a solution of compound **8** [8] (230 mg, 0.64 mmole) in ethanol (25 ml), palladium on charcoal/10% (70 mg) was added. Hydrogen was admitted in the pressure steel vessel (50 atm) and the mixture stirred at room temperature for 3 days. After filtration and evaporation *in vacuo* the residue was separated on silica gel using ethyl acetate/petroleum ether 3:7 to give an oil; 113 mg (49%).

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.25; H, 7.01; N, 4.73.

Ethyl 2-(4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl)acetate (**4e**).

A mixture of ethyl 4-bromocrotonate (0.52 ml, 2.83 mmoles), potassium carbonate (719 mg, 5.21 mmoles) and imine **13** [12] (505 mg, 2.56 mmoles) in ethanol (6 ml) was stirred at room temperature for 3 days. After filtration and evaporation the residue was dissolved in ethanol (18 ml); silica gel (2.10 g) was added and the mixture was cooled at 0 °C. Sodium borohydride (261 mg, 6.83 mmoles) was portionwise added in 15 minutes and the mixture was stirred for 30 hours at room temperature. The mixture was filtrated over filter aid and evaporated *in vacuo*; water was added and the mixture was extracted with ethyl acetate; the organic layers were dried over magnesium sulfate and evaporated. The residue was separated on silica gel (petroleum ether/ethyl acetate 75:25) to afford **4e** as white solid (518 mg, 65%); mp 57 °C (ethyl acetate). IR (potassium bromide): ν (cm^{-1}) 1723 (CO). ^{1}H nmr (deuteriochloroform): δ 1.22 (t, 3H, *J* = 7.1Hz, CH_3); 2.58 (dd, 1H, *J* = 5.1Hz, 16.1Hz, CH_2CO); 2.71(dd, 1H, *J* = 8.4Hz, 16.1Hz, CH_2CO); 3.83-3.89 (m, 1H, CH), 4.03-4.16 (m, 1H, CH_2O); 4.09 (q, 2H, *J* = 7.1Hz, OCH_2); 4.27 (dd, 1H, *J* = 4.3Hz, 10.9Hz, CH_2O); 4.43 (d, 1H, *J* = 16.5Hz, NCH_2); 4.54 (d, 1H, *J* = 16.5Hz, NCH_2); 6.57-6.67 (m, 2H, Harom); 6.75-6.87 (m, 2H, Harom); 7.22-7.37 (m, 5H, Harom). ^{13}C nmr (deuteriochloroform): δ 14.3 (CH_3); 35.1 (CH_2); 53.6 (CH); 54.4 (CH_2); 60.9 (CH_2); 66.7 (CH_2); 113.5 (CH); 116.6 (CH); 117.9 (CH); 122.2 (CH); 127.0 (2CH); 127.4 (CH); 128.9 (2CH); 133.9 (C); 138.3 (C); 143.5 (C); 171.8 (CO); ms: (ionspray) m/z 312 $(M+1)^+$.

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.92; H, 6.94; N, 4.67.

Ethyl 2,3,5,6-Tetrahydro[1,4]oxazino[2,3,4-*hi*]indole-2-carboxylate (**6**).

Using the general procedure as for **2**, starting from 7-hydroxyindoline **5** [7], compound **6** was obtained in 83% yield. IR (film): ν (cm^{-1}) 1753 (CO); ^{1}H nmr (pyridin-d_5, 400 MHz): δ 1.15 (t, 3H, *J* = 7.0Hz, CH_3); 2.70-2.78 (m, 2H, H_6); 2.89 (q, 1H, *J* = 8.9Hz, H_5); 3.03 (dd, 1H, *J* = 2.8Hz, 12.0Hz, H_{3a}); 3.22-3.28 (m, H, H_5); 3.49 (dd, 1H, *J* = 4.3Hz, 12.0Hz, H_{3b}); 4.09-4.17 (m, 2H, *J* = 7.0Hz, OCH_2); 5.23 (dd, 1H, *J* = 2.8Hz, 4.3Hz, H_2); 6.67-6.75 (m, 2H, Harom); 6.90-6.95 (m, 1H, Harom). ^{13}C nmr (deuteriochloroform): δ 15.0 (CH_3); 30.2 (CH_2); 49.5 (CH_2); 56.9 (CH_2); 62.5 (CH_2); 75.2 (CH); 113.7 (CH); 118.0 (CH); 121.6 (CH); 131.1 (C); 138.6 (C); 142.7 (C); 170.2 (CO); ms: (ionspray) m/z 234 $(M+1)^+$.

Anal. Calc. For $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found C, 67.33; H, 6.29; N, 5.81.

General Procedure for Methylation of Compounds **2**: Compounds **12**.

A stirred suspension of compound **2** (10 mmoles), potassium carbonate (30 mmoles), iodomethane (30 mmoles) in acetone (75 ml) was refluxed for 18 hours. After filtration, the filtrate was concentrated *in vacuo* to give a residue which was twice separated on silica gel using ethyl acetate/petroleum ether 7:3 as eluent to give compound **12**.

Ethyl 4-[2-(Benzylamino)phenoxy]butanoate (**15**).

This compound was obtained from the reduction of **14** in 8% yield as an oil. IR (film): ν (cm^{-1}) 3425 (NH), 1733 (CO). ^{1}H nmr (deuteriochloroform): δ 1.23 (t, 3H, *J* = 7.2Hz, CH_3); 2.09-2.19 (m, 2H, CH_2); 2.49 (t, 2H, *J* = 6.5Hz, CH_2); 4.05 (t, 2H, *J* = 6.5Hz, OCH_2); 4.10 (q, 2H, *J* = 7.2Hz, OCH_2); 4.37 (s, 2H, CH_2); 4.68 (br s, 1H, NH); 6.55-6.67 (m, 2H, Harom); 6.75-6.84 (m, 2H, Harom); 7.23-7.40 (m, 5H, Harom). ^{13}C nmr (deuteriochloroform): δ 14.4 (CH_3); 24.9 (CH_2); 31.3 (CH_2); 48.1 (CH_2); 60.7 (CH_2); 67.4 (CH_2); 110.4 (CH); 110.6 (CH); 116.7 (CH); 121.6 (CH); 127.2 (2CH); 127.5 (CH); 128.8 (2CH); 138.4 (C); 139.9 (C); 146.0 (C); 173.4 (CO); ms: (ionspray) m/z 314 $(M+1)^+$.

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.96; H, 7.29; N, 4.60.

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