A Convenient Synthesis of 3,4-Dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acids and 3,4-Dihydro-2-methyl-3-oxo-2*H*-pyrido[3,2-*b*]-1,4-oxazine-2-carboxylic Acid

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A convenient one pot synthesis of ethyl 3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylates and 3,4-dihydro-2-methyl-3-oxo-2*H*-pyrido[3,2-*b*]-1,4-oxazine-2-carboxylates and their conversion into the respective carboxylic acids are described.

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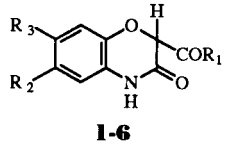
In the course of our studies directed towards the synthesis of potential immunomodulators [1] hitherto unknown 3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic acids and 3,4-dihydro-2-methyl-3-oxo-2*H*-pyrido[3,2-*b*]-1,4-oxazine-2-carboxylic acid **10a-g** were required as key intermediates. Similar 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic acid **1** was prepared by Techer *et al.* [2] *via* alkylation of sodium 2-nitrophenoxide with diethyl 2-bromomalonate in *N,N*-dimethylformamide followed by catalytic reduction of the nitro group, subsequent lactonization and ester hydrolysis. The procedure of Techer *et al.* [2] was used also for the synthesis of derivatives **2-6** in connection with the preparation of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine-2-(*N*-alkyl/aryl/hetaryl)carboxamides which possess sedative and analgetic activity [3] as well as the affinity for binding to benzodiazepine receptors [4]. Apart from these reports according to our knowledge no further methods for the synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine-2-carboxylates and corresponding carboxylic acids have been published so far.

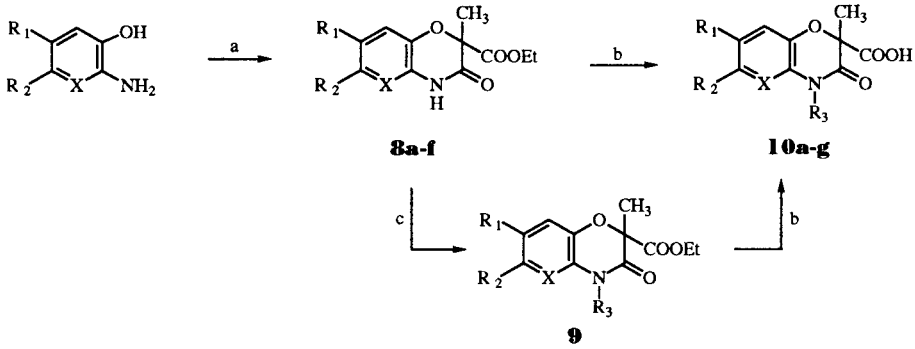
In contrast, several methods are available for the synthesis of 2-alkyl/aryl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines with interesting analgetic [5] and antimicrobial properties [6]. They include *N*-acylation of substituted 2-aminophenols with 2-haloacyl chlorides and subsequent cyclization [7], *O*-alkylation of corresponding 2-aminophenols with 2-haloesters followed by cyclization [8] and *O*-alkylation of 2-nitrophenols with 2-haloesters giving alkyl 2-alkyl-2-(2'-nitrophenoxy)carboxylates which lactonize upon reduction of the nitro group [9]. A one pot reaction for the preparation of 2-alkyl/aryl-3,4-dihydro-6/7-nitro-3-oxo-2*H*-1,4-benzoxazines by potassium fluoride assisted *O*-alkylation of 4- and 5-nitro-2-aminophenols was reported by Shridar *et al.* [10].



1-6

	R_1	R_2	R_3
1	OH	H	H
2	OEt	H	H
3	OEt	CH_3	H
4	OEt	Cl	H
5	OEt	OMe	H
6	OEt	H	Cl

Scheme 1



a: $Br(CH_3)C(COOEt)_2$, KF, DMF; b: 1*N* NaOH, 1,4-dioxane; c: NaH, CH_3I, toluene.

We report herein a facile and convenient large scale synthesis of ethyl 3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylates and ethyl 3,4-dihydro-2-methyl-3-oxopyrido[3,2-*b*]-1,4-oxazine-2-carboxylate from diethyl 2-bromo-2-methylmalonate and the corresponding 2-aminophenols or 3-amino-2-hydroxypyridine in the presence of potassium fluoride in *N,N*-dimethylformamide (Scheme 1). The compounds prepared are summarized in Table 1. They could be easily transformed into the respective carboxylic acids **10a-g** by hydrolysis with 1*N* sodium hydroxide in 1,4-dioxane.

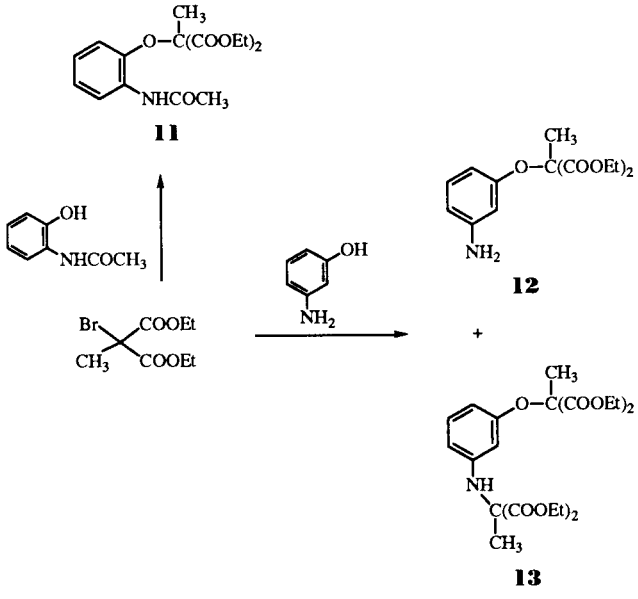
Table 1

Compounds **8a-f**, **9** and **10a-g** prepared

Compound	X	R_1	R_2	R_3
8a	CH	H	H	H
10a	CH	H	H	H
8b	CH	H	CH_3	H
10b	CH	H	CH_3	H
8c	CH	H	Cl	H
10c	CH	H	Cl	H
8d	CH	NO_2	H	H
10d	CH	NO_2	H	H
8e	CH	H	NO_2	H
10e	CH	H	NO_2	H
8f	N	H	H	H
10f	N	H	H	H
9	CH	H	H	CH_3
10g	CH	H	H	CH_3

In order to ascertain the reaction mechanism of the formation of condensed morpholinones **8a-8f** some additional experiments were performed. Thus, *N*-(2-hydroxyphenyl)acetamide afforded, when reacted with diethyl 2-bromo-2-methylmalonate under the same reaction conditions, 2-(2'-acetylaminophenoxy)-2-methylmalonic acid diethyl ester **11** in excellent yield. When 3-aminophenol was used instead of 2-aminophenol, 2-(3'-aminophenoxy)-2-methylmalonic acid diethyl ester **12** and 2-(3'-(1'',1''-bisethoxycarbonylethylamino)phenoxyl]-2-methylmalonic acid diethyl ester **13** were obtained which could be separated by column chromatography (Scheme 2). On the basis of these experiments it can be concluded that the first reaction step is *O*-alkylation of the substituted aromatic 2-aminoalcohols with diethyl 2-bromo-2-methylmalonate. The resulting intermediate cyclizes subsequently into areno/hetareno-fused 1,4-oxazinone. *N*-Alkylation competes with *O*-alkylation to a very small extent as it can be concluded from traces of *N,O*-dialkylated products (*e.g.* **14** and **15**) which were isolated in few cases.

Scheme 2



The structure of **8e**, a typical representative of the synthesized compounds, was confirmed with an homonuclear ^1H-^1H nOe experiment which showed an enhancement of the H_5 doublet at 7.78 ppm upon irradiation of the broad signal at 11.4 ppm. Compound **8a** was easily methylated with iodomethane in the presence of sodium hydride in boiling toluene. The structure of the methylated product was ascertained again to be **9** on the basis of ^1H-^1H nOe difference spectroscopy where irradiation of the singlet of the 4-methyl group at 3.30 ppm caused an enhancement of the right part of the aromatic multiplet at 7.2 ppm.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Microanalyses were performed on a Perkin-Elmer C,H,N-Analyzer 240 C. Infrared spectra were recorded on a Perkin-Elmer 325 spectrometer. The uv spectra were measured on a Carl Zeiss spectrometer DMR 4. Proton nmr spectra were recorded at 60, 250 or 300 MHz with a Varian EM 360 A, Varian VXR-300 or Bruker WM-250 spectrometer. The ^{13}C nmr spectra were measured at 75.4 or 62.9 MHz on a Varian VXR-300 and Bruker WM-250 spectrometer, respectively. Mass spectra were obtained using a Varian-MAT 311 A mass spectrometer (ionization energy 100 eV).

3,4-Dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid Ethyl Ester (**8a**). General Procedure for the Synthesis of Compounds **8a-f**.

To a stirred suspension of potassium fluoride (5.81 g, 100 mmoles) in dry *N,N*-dimethylformamide (25 ml) diethyl 2-bromo-2-methylmalonate (10.12 g, 40 mmoles) was added. Stirring was continued for 15 minutes at room temperature whereupon 2-aminophenol (4.36 g, 40 mmoles) was added. The resulting mixture was stirred for 6 hours at 60°, cooled to room temperature and poured into ice/water (100 g). The precipitate was filtered off, washed with water and recrystallized from ethanol to yield 7.61 g (81%) of **8a**, mp 143-145°; ir (potassium bromide): ν 3220, 3160, 3100 (NH), 2990, 2920 (CH), 1760 (COOEt), 1690 (CONH), 1605,

1500, 1380, 1245, 1230, 1160, 1135, 755 cm^{-1}; uv: λ max 212 nm (ε 26384), 260 nm (ε 7655); ^1H nmr (300 MHz, DMSO-d_6): δ 1.02 (t, 3H, J = 6.98 Hz, CH_2CH_3), 1.67 (s, 3H, CH_3), 4.06 (ABX_3-m, 2H, CH_2), 6.85-7.03 (m, 4H, $4H_{ar}$), 10.93 (s br, 1H, NH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 13.16 (CH_2CH_3), 19.59 (CH_3), 61.21 (CH_2), 79.71 (C-2), 115.16, 116.15, 122.39, 122.77 (C-5, 6, 7, 8), 126.31, 141.56 (C-4a, 8a), 162.62 (C=O), 167.72 (C=O); ms: (100 eV, electron impact) m/z 235 (M^+).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.35; H, 5.74; N, 5.85.

3,4-Dihydro-2,6-dimethyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid Ethyl Ester (**8b**).

This compound was obtained as white crystals (ethanol) from 2-amino-4-methylphenol (2.0 g, 16.2 mmoles) and diethyl 2-bromo-2-methylmalonate (4.05 g, 16 mmoles), yield 3.82 g (96%), mp 137-139°; ir (potassium bromide): ν 3200, 3120, 3060 (NH), 3000, 2940 (CH), 1750 (COOEt), 1695 (CONH), 1610, 1490, 1390, 1250, 1230, 1130, 1020, 820 cm^{-1}; uv: λ max 214 nm (ε 27329), 255 nm (ε 5466), 288 nm (ε 4555); ^1H nmr (300 MHz, DMSO-d_6): δ 1.01 (t, 3H, J = 6.80 Hz, CH_2CH_3), 1.61 (s, 3H, 2-CH_3), 2.14 (s, 3H, 6-CH_3), 4.01 (ABX_3-m, 2H, CH_2), 6.65 (s, 1H, H_5), 6.68 (d, 1H, J = 8.13 Hz, H_7/H_8), 6.84 (d, 1H, J = 8.31 Hz, H_7/H_8), 10.83 (s br, 1H, NH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 13.18 (CH_2CH_3), 19.57 (CH_3), 19.77 (CH_3), 61.14 (CH_2), 79.64 (C-2), 115.39, 115.89, 123.15, (C-5, 7, 8), 126.07, 139.41 (C-4a, 8a), 131.49 (C-6), 162.82 (C=O), 167.83 (C=O); ms: (100 eV, electron impact) m/z 249 (M^+).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.25; H, 6.19; N, 5.39.

3,4-Dihydro-6-chloro-2-methyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid Ethyl Ester (**8c**).

This compound was obtained as white crystals (ethanol) from 2-amino-4-chlorophenol (2.0 g, 14.0 mmoles) and diethyl 2-bromo-2-methylmalonate (3.54 g, 14 mmoles), yield 3.40 g (90%), mp 161-163°; ir (potassium bromide): ν 3200, 3120, 3060 (NH), 2960, 2865 (CH), 1750 (COOEt), 1695 (CONH), 1610, 1495, 1380, 1260, 1230, 1130, 1020, 860 cm^{-1}; uv: λ max 218 nm (ε 34276), 250 nm (ε 6144), 290 nm (ε 5174); ^1H nmr (300 MHz, DMSO-d_6): δ 1.05 (t, 3H, J = 7.08 Hz, CH_2CH_3), 1.67 (s, 3H, CH_3), 4.08 (ABX_3-m, 2H, CH_2), 6.89 (X portion of ABX system, d, 1H, J = 2.25 Hz, H_5), 7.00 (AB portion of ABX system, 2H, $J_{7,8}$ = 8.71 Hz, $J_{5,7}$ = 2.24 Hz, H_7, H_8), 11.08 (s br, 1H, NH); ^{13}C nmr(75.4 MHz, DMSO-d_6): δ 13.76 (CH_2CH_3), 20.11 (CH_3), 62.03 (CH_2), 80.40 (C-2), 115.17, 118.27, 122.86, (C-5, 7, 8), 126.47, 141.11 (C-4a, 8a), 128.28 (C-6), 162.93 (C=O), 167.93 (C=O); ms: (100 eV, electron impact) m/z 269 (M^+).

Anal. Calcd. for $C_{12}H_{12}ClNO_4$: C, 53.44; H, 4.49; N, 5.20. Found: C, 53.23; H, 4.53; N, 5.01.

3,4-Dihydro-2-methyl-7-nitro-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid Ethyl Ester (**8d**).

This compound was obtained as pink crystals (ethanol) from 2-amino-5-nitrophenol (2.0 g, 12.98 mmoles) and diethyl 2-bromo-2-methylmalonate (3.28 g, 12.98 mmoles), yield 3.49 g (96%), mp 194-195°; ir (potassium bromide): ν 3200, 3140, 3085 (NH), 2990, 2960 (CH), 1750 (COOEt), 1700 (CONH), 1610, 1540, 1510, 1340, 1240, 1125, 825, 745 cm^{-1}; uv: λ max 212 nm (ε 19632), 236 nm (ε 10009), 295 nm (ε 8854), 332 nm (ε 9624); ^1H nmr (300 MHz, DMSO-d_6): δ 1.06 (t, 3H, J = 7.08 Hz, CH_2CH_3), 1.76 (s, 3H, CH_3), 4.06 (ABX_3-m, 2H, CH_2), 7.06 (d, 1H, J = 8.73 Hz, H_5), 7.81 (d, 1H, J = 2.41 Hz, H_8), 7.94 (dd, 1H, J = 8.78 Hz, J = 2.45 Hz, H_6), 11.62 (s br, 1H, NH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 13.71 (CH_2CH_3), 20.07 (CH_3), 62.34 (CH_2), 80.60 (C-2), 112.07, 115.77, 119.30 (C-5, 6, 8), 133.30, 141.82 (C-4a, 8a), 142.55 (C-7), 162.86 (C=O), 167.46 (C=O); ms: (100 eV, electron impact) m/z 280 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 9.99. Found: C, 51.62; H, 4.33; N, 9.74.

3,4-Dihydro-2-methyl-6-nitro-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid Ethyl Ester (**8e**).

This compound was obtained as brown crystals (ethanol) from 2-amino-4-nitrophenol (2.0 g, 12.98 mmoles) and diethyl 2-bromo-2-methylmalonate (3.28 g, 12.98 mmoles), yield 3.37 g (93%), mp 192-194°; ir (potassium bromide): ν 3210, 3150, 3075 (NH), 2990 (CH), 1740 (COOEt), 1695 (CONH), 1605, 1530, 1490, 1350, 1260, 1120, 1080, 965, 880, 735 cm^{-1}; uv: λ max 215 nm (ε 13450), 236 nm (ε 17264), 328 nm (ε 4416); ^1H nmr (250 MHz, DMSO-d_6): δ 1.08 (t, 3H, J = 7.08 Hz, CH_2CH_3), 1.78 (s, 3H, CH_3), 4.16 (ABX_3-m, 2H, CH_2), 7.28 (d, 1H, J = 8.70 Hz, H_8), 7.78 (d, 1H, J = 2.40 Hz, H_5), 7.90 (dd, 1H, J = 8.78 Hz, J = 2.45 Hz, H_7), 11.40 (s br, 1H, NH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 13.73 (CH_2CH_3), 20.18 (CH_3), 62.41 (CH_2), 81.04 (C-2), 110.85, 117.22, 119.39 (C-5, 7, 8), 127.37, 142.42 (C-4a, 8a), 147.55 (C-6), 162.10 (C=O), 167.34 (C=O); ms: (100 eV, electron impact) m/z 280 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 9.99. Found: C, 51.17; H, 4.36; N, 10.36.

3,4-Dihydro-2-methyl-3-oxo-2*H*-pyrido[3,2-*b*]-1,4-oxazine-2-carboxylic Acid Ethyl Ester (**8f**).

This compound was obtained as white crystals (ethanol) from 2-amino-3-hydroxypyridine (1.10 g, 10 mmoles) and diethyl 2-bromo-2-methylmalonate (2.53 g, 10 mmoles), yield 1.98 g (84%), mp 144-145°; ir (potassium bromide): ν 3130, 3110, 3060 (NH), 2990, 2900, 2850, 2770 (CH), 1755 (COOEt), 1720 (CONH), 1615, 1510, 1470, 1350, 1240, 1125, 1110, 1020, 790, 750 cm^{-1}; uv: λ max 201 nm (ε 23535), 242 nm (ε 4903), 290 nm (ε 11440); ^1H nmr (300 MHz, DMSO-d_6): δ 1.01 (t, 3H, J = 7.10 Hz, CH_2CH_3), 1.67 (s, 3H, CH_3), 4.06 (ABX_3-m, 2H, CH_2), 6.98 (ddd, 1H, $J_{6,7}$ = 4.90 Hz, $J_{7,8}$ = 7.9 Hz, H_7), 7.40 (dd, 1H, $J_{6,8}$ = 1.0 Hz, H_8), 7.90 (dd, 1H, H_6), 11.0 (s br, 1H, NH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 13.16 (CH_2CH_3), 19.60 (CH_3), 61.56 (CH_2), 79.99 (C-2), 118.83, 123.17, 141.11 (C-6, 7, 8), 137.56, 140.58 (C-4a, 8a), 163.23 (C=O), 167.23 (C=O); ms: (100 eV, electron impact) m/z 236 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.86. Found: C, 55.83; H, 5.42; N, 11.62.

3,4-Dihydro-2,4-dimethyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid Ethyl Ester (**9**).

To a suspension of **8a** (2.00 g, 8.50 mmoles) and sodium hydride (0.21 g, 8.50 mmoles) in dry toluene (40 ml) iodomethane (1.81 g, 12.75 mmoles) was added and the resulting mixture was refluxed until tlc (silica gel, diethyl ether/hexane = 3/1) showed total conversion of the educt into **9** (*ca* 2 hours). The reaction mixture was cooled to room temperature, washed successively with water, 0.1 *N* hydrochloric acid and dried over sodium sulfate. Upon filtration and removal of toluene *in vacuo* the crude product was recrystallized from diethyl ether/hexane to give 1.59 g (75%) of **9** as white platelets, mp 76-77°; ir (potassium bromide): ν 3050, 2960, 2920, 2890 (CH), 1730 (COOEt), 1685

(CONH), 1600, 1500, 1470, 1445, 1420, 1380, 1325, 1300, 1280, 1235, 1120, 1010, 905 cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6): δ 0.99 (t, 3H, J = 7.07 Hz, CH_2CH_3), 1.70 (s, 3H, 2-CH_3), 3.30 (s, 3H, N-CH_3), 4.04 (ABX_3-m, 2H, CH_2), 7.00-7.20 (m, 4H, H_5, H_6, H_7, H_8); ^{13}C nmr (75.4 HMz, DMSO-d_6): δ 13.12 (CH_2CH_3), 19.37 (CH_3), 28.24 (N-CH_3), 61.24 (CH_2), 79.84 (C-2), 114.98, 116.38, 122.73, 123.28 (C-5, 6, 7, 8), 128.43, 142.45 (C-4a, 8a), 162.12 (C=O), 167.64 (C=O); ms: (100 eV, electron impact) m/z 249 (M^+).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.64; H, 6.22; N, 5.41.

3,4-Dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid (**10a**). General Procedure for the Synthesis of Compounds **10a-g**.

A solution of **8a** (3.00 g, 12.8 mmoles) and 1*N* sodium hydroxide (19.2 ml, 19.2 mmoles) in 1,4-dioxane (60 ml) was stirred for 18 hours at room temperature, evaporated *in vacuo* and the residue dissolved in water (80 ml). After extraction with ethyl acetate (2 x 40 ml), the aqueous phase was acidified to *p*H 1 with 18% hydrochloric acid. The precipitated product **10a** was filtered off and recrystallized from ethanol to give 2.12 g (80%) of white crystals, mp 185-187°; ir (potassium bromide): ν 3300-2900 (NH), 2800-2500 (COOH), 1765 (COOH), 1670 (CONH), 1615, 1505, 1410, 1235, 1150, 1130, 770 cm^{-1}; uv: λ max 212 nm (ε 27659), 255 nm (ε 6394); 282 nm (ε 5116); ^1H nmr (300 MHz, DMSO-d_6): δ 1.67 (s, 3H, CH_3), 6.85-7.02 (m, 4H, H_5, H_6, H_7, H_8), 10.80 (s br, 1H, NH), 13.9 (s br, 1H, COOH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 19.75 (CH_3), 79.71 (C-2), 115.06, 116.15, 122.14, 122.64 (C-5, 6, 7, 8), 126.50, 141.95 (C-4a, 8a), 163.14 (C=O), 169.31 (C=O); ms: (100 eV, electron impact) m/z 207 (M^+).

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.60; H, 4.54; N, 6.54.

3,4-Dihydro-2,6-dimethyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid (**10b**).

This compound was obtained as white crystals (ethanol) from **8b** (1.50 g, 6 mmoles), yield 1.11 g (84%), mp 184-186°; ir (potassium bromide): ν 3600-2500 (NH, COOH), 1720 (COOH), 1690 (CONH), 1615, 1495, 1380, 1290, 1235, 1145, 815 cm^{-1}; uv: λ max 216 nm (ε 26155), 260 nm (ε 5987), 290 nm (ε 5357); ^1H nmr (250 MHz, DMSO-d_6): δ 1.66 (s, 3H, 2-CH_3), 2.22 (s, 3H, 6-CH_3), 6.70 (s, 1H, H_5), 6.72 (d, 1H, J = 8.95 Hz, H_6/H_7), 6.88 (d, 1H, J = 8.95 Hz, H_7/H_8), 10.8 (s br, 1H, NH), 14.0 (s br, 1H, COOH); ^{13}C nmr (62.9 MHz, DMSO-d_6): δ 20.36 (CH_3), 20.43 (CH_3), 80.31 (C-2), 115.98, 116.55, 123.67, (C-5, 7, 8), 126.94, 140.48 (C-4a, 8a), 131.89 (C-6), 164.04 (C=O), 170.08 (C=O); ms: (100 eV, electron impact) m/z 221 (M^+).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.76; H, 5.05; N, 5.96.

3,4-Dihydro-6-chloro-2-methyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid (**10c**).

This compound was obtained as white crystals (ethanol) from **8c** (1.50 g, 5.6 mmoles), yield 1.20 g (90%), mp 191-193°; ir (potassium bromide): ν 3600-2500 (NH, COOH), 1735 (COOH), 1695 (CONH), 1610, 1495, 1375, 1285, 1230, 1140, 815 cm^{-1}; uv: λ max 219 nm (ε 35989), 255 nm (ε 4036), 296 nm (ε 3700); ^1H nmr (250 MHz, DMSO-d_6): δ 1.69 (s, 3H, CH_3), 6.92 (X portion of ABX system, d, 1H, J = 2.2 Hz, H_5), 7.02 (AB portion of ABX system, $J_{7,8}$ = 8.70 Hz, $J_{5,7}$ = 2.20 Hz, H_7, H_8), 11.0 (s br, 1H, NH), 14.0 (s br, 1H, COOH); ^{13}C nmr (62.9 MHz, DMSO-d_6): δ 20.29 (CH_3), 80.51 (C-2), 115.14, 118.30, 122.79 (C-5, 7, 8), 126.29, 128.56 (C-4a, 8a), 141.60 (C-6), 163.59 (C=O), 169.60 (C=O); ms: (100 eV, electron impact) m/z 241 (M^+).

Anal. Calcd. for $C_{10}H_8ClNO_4$: C, 49.71; H, 3.34; N, 5.80. Found: C, 49.62; H, 3.00; N, 5.52.

3,4-Dihydro-2-methyl-7-nitro-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid (**10d**).

This compound was obtained as yellow crystals (ethanol) from **8d** (1.50 g, 5.35 mmoles), yield 0.90 g (67%), mp 183-185°; ir (potassium bromide): ν 3600-2500 (NH, COOH), 1730 (COOH), 1695 (CONH), 1610, 1540, 1505, 1345, 1130, 830, 815, 745 cm^{-1}; uv: λ max 212 nm (ε 19758), 241 nm (ε 9069), 310 nm (ε 7774), 339 nm (ε 9393); ^1H nmr (300 MHz, DMSO-d_6): δ 1.71 (s, 3H, CH_3), 7.08 (d, 1H, J = 8.73 Hz, H_5), 7.77 (d, 1H, J = 2.41 Hz, H_8), 7.90 (dd, 1H, J = 8.78 Hz, J = 2.45 Hz, H_6), 11.50 (s br, 1H, NH), 14.0 (s br, 1H, COOH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 20.20 (CH_3), 80.73 (C-2), 111.99, 115.64, 119.11, (C-5, 6, 8), 133.61, 142.31, 142.51 (C-4a, 8a, 7), 163.50 (C=O), 169.02 (C=O); ms: (100 eV, electron impact) m/z 252 (M^+).

Anal. Calcd. for $C_{10}H_8N_2O_6$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.92; H, 3.32; N, 11.38.

3,4-Dihydro-2-methyl-6-nitro-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid (**10e**).

This compound was obtained as white crystals (ethanol) from **8e** (1.50 g, 5.35 mmoles), yield 1.20 g (89%), mp 181-182°; ir (potassium bromide): ν 3500-2500 (NH, COOH), 1750 (COOH), 1685 (CONH), 1630, 1610, 1540, 1490, 1350, 1330, 1280, 1240, 1140, 1085, 890, 870, 745, 710 cm^{-1}; uv: λ max 210 nm (ε 14056), 260 nm (ε 18876), 335 nm (ε 4819); ^1H nmr (300 MHz, DMSO-d_6): δ 1.72 (s, 3H, CH_3), 7.18 (d, 1H, J = 8.85 Hz, H_8), 7.72 (d, 1H, J = 2.72 Hz, H_5), 7.82 (dd, 1H, J = 8.88 Hz, J = 2.73 Hz, H_7), 11.23 (s br, 1H, NH), 14.0 (s br, 1H, COOH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 20.29 (CH_3), 81.23 (C-2), 110.74, 117.13, 119.32, (C-5, 7, 8), 127.61, 142.28 (C-4a, 8a), 148.11 (C-6), 162.76 (C=O), 168.95 (C=O); ms: (100 eV, electron impact) m/z 252 (M^+).

Anal. Calcd. for $C_{10}H_8N_2O_6$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.21; H, 3.17; N, 11.00.

3,4-Dihydro-2-methyl-3-oxo-2*H*-pyrido[3,2-*b*]-1,4-oxazine-2-carboxylic Acid (**10f**).

This compound was obtained as white crystals (ethanol) from **8f** (2.36 g, 10 mmoles), yield 1.10 g (53%), mp 185-187°; ir (potassium bromide): ν 3650-3300, 3100, 3050 (NH), 3000-2250 (COOH), 1725 (COOH), 1675 (CONH), 1530, 1450, 1380, 1290, 1130, 900, 805 cm^{-1}; uv: λ max 205 nm (δ 26469), 240 nm (ε 5720), 294 nm (ε 12116); ^1H nmr (300 MHz, DMSO-d_6): δ 1.63 (s, 3H, CH_3), 6.95 (dd, 1H, $J_{6,7}$ = 4.88 Hz, $J_{7,8}$ = 7.8 Hz, H_7), 7.37 (d, 1H, $J_{6,8}$ = 1.1 Hz, H_8), 7.87 (d, 1H, H_6), 11.4 (s br, 1H, NH), 13.8 (s br, 1H, COOH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 19.68 (CH_3), 80.05 (C-2), 118.71, 123.02, 140.79, (C-6, 7, 8), 137.98, 140.79 (C-4a, 8a), 163.79 (C=O), 168.79 (C=O); ms: (100 eV, electron impact) m/z 208 (M^+).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.92; H, 3.87; N, 13.46. Found: C, 51.79; H, 3.93; N, 13.61.

3,4-Dihydro-2,4-dimethyl-3-oxo-2*H*-1,4-benzoxazine-2-carboxylic Acid (**10g**).

This compound was obtained as white crystals (ethanol) from **9** (2.49 g, 10 mmoles), yield 1.80 g (81%), mp 184-186°; ir (potas-

sium bromide): ν 3600-3250, 3000-2350 (COOH), 1755, 1735 (COOH), 1685 (CONH), 1610, 1595, 1505, 1390, 1275, 1140, 1045, 760 cm^{-1}; uv: λ max 212 nm (ε 26711), 250 nm (ε 5306), 285 nm (ε 4391); ^1H nmr (300 MHz, DMSO-d_6): δ 1.69 (s, 3H, 2-CH_3), 3.28 (s, 3H, N-CH_3), 7.00-7.20 (m, 4H, H_5, H_6, H_7, H_8), 13.5 (s br, 1H, COOH); ^{13}C nmr (75.4 MHz, DMSO-d_6): δ 20.19 (CH_3), 28.17 (N-CH_3), 79.81 (C-2), 114.89, 116.38, 122.48, 123.16 (C-5, 6, 7, 8), 128.61, 142.83 (C-4a, 8a), 162.63 (C=O), 169.23 (C=O); ms: (100 eV, electron impact) m/z 221 (M^+).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 60.11; H, 4.96; N, 6.33.

2-(2'-Acetylaminophenoxy)-2-methylmalonic Acid Diethyl Ester (**11**).

To a stirred suspension of potassium fluoride (5.81 g, 100 mmoles) in dry *N,N*-dimethylformamide (25 ml) diethyl 2-bromo-2-methylmalonate (10.12 g, 40 mmoles) was added. After 15 minutes 2-acetamidophenol (6.06 g, 40 mmoles) was added and the mixture was stirred for additional 6 hours at 60°, poured into ice water (150 g) and extracted with diethyl ether (2 x 100 ml). The combined organic extracts were washed successively with 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide, dried over sodium sulfate, filtered and evaporated *in vacuo*. The crude product was recrystallized from *n*-hexane (70 ml) to give 9.56 g (74%) of **11**, mp 30-32°; ir (potassium bromide): ν 3350 (NH), 2990, 2940 (CH), 1745 (COOEt), 1695 (CONH), 1605, 1535, 1455, 1370, 1260, 1120, 1020, 860, 760 cm^{-1}; uv: λ max 208 nm (ε 25359), 245 nm (ε 13792), 270 nm (ε 3559); ^1H nmr (250 MHz, DMSO-d_6): δ 1.18 (t, 6H, J = 7.1 Hz, 2 CH_2CH_3), 1.62 (s, 3H, 2-CH_3), 2.12 (s, 3H, NHCOCH_3), 4.24 (q, 4H, 2 CH_2), 6.90 (dd, 1H, J = 7.8 Hz, J = 2.10 Hz, $H_{6'}$), 6.95-7.12 (m, 2H, $H_{4'}$, $H_{5'}$), 8.07 (d, 1H, J = 7.8 Hz, $H_{2'}$), 9.12 (s br, 1H, NH); ^{13}C nmr (62.9 MHz, DMSO-d_6): δ 13.59 (2 CH_2CH_3), 19.78 (CH_3), 23.94 (NHCOCH_3), 62.26 (2 CH_2), 83.06 (C-2), 119.72, 121.35, 123.49, 124.07 (C-3', 4', 5', 6'), 131.75, 143.54 (C-1', C-2'), 168.07 (C=O), 168.33 (C=O); ms: (100 eV, electron impact) m/z 323 (M^+).

Anal. Calcd. for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.09; H, 6.32; N, 4.33.

Reaction Between Diethyl 2-Bromo-2-methylmalonate and 3-Aminophenol.

To a stirred suspension of potassium fluoride (2.91 g, 50 mmoles) in dry *N,N*-dimethylformamide (20 ml) diethyl 2-bromo-2-methylmalonate (5.06 g, 20 mmoles) was added. After 15 minutes 3-aminophenol (2.18 g, 20 mmoles) was added and the mixture was stirred for additional 6 hours at 60°, poured into ice water (80 g) and extracted with diethyl ether (2 x 100 ml). The combined organic extracts containing crude **12** and **13** were extracted with 1 *N* hydrochloric acid (2 x 50 ml) to achieve the separation of **12** from **13**. The aqueous phase containing the hydrochloride of **13** was alcalized to *p*H 10 with 2 *N* sodium hydroxide and extracted with ether (2 x 100 ml). Both ethereal phases were dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield crude **12** and **13** as brown viscous oils. Crude **12** and **13** were purified by column chromatography on silica gel using as eluents chloroform and ether/*n*-hexane respectively.

2-(3'-Aminophenoxy)-2-methylmalonic Acid Diethyl Ester (**12**).

This compound was obtained in a yield of 0.71 g as a brown viscous oil; ir (film): ν 3460, 3380 (NH), 2980, 2940 (CH), 1740 (COOEt), 1605, 1490, 1465, 1375, 1275, 1235, 1135, 1110, 1015, 860, 765, 690 cm^{-1}; uv: λ max 204 nm (ε 28888), 236 nm (ε 7222), 284 nm (ε 1641); ^1H nmr (250 MHz, DMSO-d_6): δ 1.21 (t, 6H, J = 7.1 Hz, 2 CH_2CH_3), 1.61 (s, 3H, 2-CH_3), 4.22 (q, 4H, 2 CH_2), 5.12 (s br, 2H, NH_2), 6.01 (dd, 1H, J = 7.8 Hz, J = 2.10 Hz, $H_{4'}/H_{6'}$) 6.14 (m, 1H, $H_{2'}$), 6.25 (dd, 1H, J = 7.8 Hz, J = 2.10 Hz, $H_{4'}/H_{6'}$), 6.88 (dd, 1H, J = 7.8 Hz, $H_{5'}$); ^{13}C nmr (62.9 MHz, DMSO-d_6): δ 13.69, (2 CH_2CH_3), 19.89 (CH_3), 61.68 (2 CH_2), 81.84 (C-2), 105.19, 106.63, 109.21, 129.31 (C-2', 4', 5', 6'), 149.94, 154.88 (C-1', C-3'), 168.27 (C=O); ms: (100 eV, electron impact) Calcd. 281.1263, Found: 281.1263.

2-[3'-(1'', 1''-Bisethoxycarbonylethylamino)phenoxy]-2-methylmalonic Acid Diethyl Ester (**13**).

This compound was obtained in a yield of 0.30 g as a brown viscous oil; ir (film): ν 3400 (NH), 2995, 2950 (CH), 1745 (COOEt), 1610, 1495, 1450, 1380, 1280, 1225, 1115, 1020, 860, 770, 695 cm^{-1}; uv: λ max 208 nm (ε 27525), 243 nm (ε 9748), 290 nm (ε 2007); ^1H nmr (250 MHz, DMSO-d_6): δ 1.16 (t, 6H, J = 7.1 Hz, 2 CH_2CH_3), 1.18 (t, 6H, J = 7.1 Hz, 2 CH_2CH_3), 1.61 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 4.22 (q, 4H, 2 CH_2), 4.24 (q, 4H, 2 CH_2), 6.00 (s br, 1H, NH), 6.15 (dd, 1H, J = 7.8 Hz, J = 2.10 Hz, $H_{4'}/H_{6'}$), 6.22 (m, 1H, $H_{2'}$), 6.38 (dd, 1H, J = 7.8 Hz, J = 2.10 Hz, $H_{4'}/H_{6'}$), 6.95 (dd, 1H, J = 7.8 Hz, $H_{5'}$); ^{13}C nmr (62.9 MHz, DMSO-d_6): δ 13.63 (4 CH_2CH_3), 19.85 (CH_3), 21.15 (CH_3), 61.66 (2 CH_2), 61.69 (2 CH_2), 64.22 (C-1''), 82.00 (C-2), 105.69, 108.48, 109.92, 129.11 (C-2', 4', 5', 6'), 146.16, 154.58 (C-1', C-3'), 168.07 (C=O), 169.72 (C=O); ms: (100 eV, electron impact) Calcd. 453.1997, Found: 453.1998.

2-[2'-(1'',1''-Bisethoxycarbonylethylamino)phenoxy]-2-methylmalonic Acid Diethyl Ester (**14**).

This compound was isolated by column chromatography (silica gel, diethyl ether/petroleum ether = 1/3 from the mother liquid after recrystallization of crude **8a** from ethanol, yield 0.16 g (1.8% with respect to the starting 2-aminophenol), yellow viscous oil; ir (protassium bromide): ν 3400 (NH), 3000 (CH), 1735 (COOEt), 1605, 1510, 1445, 1370, 1295-1160, 1115, 1015, 855, 740 cm^{-1}; ^1H nmr (60 MHz, deuteriochloroform): δ 1.20 (t, 6H, J = 7 Hz, 2 CH_2CH_3), 1.30 (t, 6H, J = 7 Hz, 2 CH_2CH_3), 1.67 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 4.20 (q, 4H, J = 7 Hz, 2 CH_2), 4.33 (q, 4H, J = 7 Hz, 2 CH_2), 6.12 (s br, 1H, NH), 6.38-7.00 (m, 4H, 4 H-Ar); ms: (70 eV, electron impact) m/z 453 (M^+).

Anal. Calcd. for $C_{22}H_{31}NO_9$: C, 58.27; H, 6.89; N, 3.09. Found: C, 58.04; H, 6.95; N, 3.00.

2-[2'-(1'',1''-Bisethoxycarbonylethylamino)-4'-nitrophenoxy]-2-methylmalonic Acid Diethyl Ester (**15**).

This compound was isolated by column chromatography (silica gel, diethyl ether/petroleum ether = 1/3 from the mother liquid after recrystallization of crude **8e** from ethanol, yield 0.21 g (5.8% with respect to the starting 2-amino-4-nitrophenol), yellow viscous oil; ir (potassium bromide): ν 3400 (NH), 3000 (CH), 1735 (COOEt), 1605, 1520, 1445, 1350, 1275, 1220, 1110, 1015, 870, 745 cm^{-1}; ^1H nmr (60 MHz, deuteriochloroform): δ 1.20 (t, 6H, J = 7 Hz, 2 CH_2CH_3), 1.30 (t, 6H, J = 7 Hz, 2 CH_2CH_3), 1.70 (s, 6H, 2CH_3), 4.20 (q, 4H, J = 7 Hz, 2 CH_2), 4.30 (q, 4H, J = 7 Hz, 2 CH_2), 6.3 (s br, 1H, NH), 6.9-8.00 (m, 3H, 3 H-Ar); ms: (70 eV, electron impact) m/z 498 (M^+).

Anal. Calcd. for $C_{22}H_{30}N_2O_{11}$: C, 53.00; H, 6.07; N, 5.62. Found: C, 53.37: H, 6.15; N, 5.53.

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