Synthesis of 2(3*H*)-Benzoxazolinone Derivatives as Potential Beta-3-adrenergic Receptor Ligands

J. F. Delhomel, S. Yous, P. Depreux* and D. Lesieur

Laboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques et Biologiques,
3, rue du Professeur Laguesse, BP 83, 59006 Lille cedex, France

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Beta-3-subtype-adrenoceptors mediate lipolysis and in the search for potential beta-3-adrenergic receptor agonists for the treatment of obesity, we designed new arylethanolamines, structures B_1 and B_2, derived from 2(3*H*)-benzoxazolinone. To obtain these target compounds as starting materials, various *N*-benzyl-[2(3*H*)-benzoxazolinon-6-yl]ethylamines were used.

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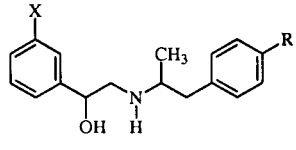
Beta-subtype adrenergic receptors have been divided into beta-1 and beta-2 subtypes [1]. This distinction has led to the discovery of drugs capable of blocking the beta-1-subtype (beta blockers) or stimulating the beta-2-subtype (bronchodilatators). More recently, it was reported that the adrenoceptors that mediate lipolysis are neither beta-1 nor beta-2 but "atypical" [2], and are now called beta-3 [3, 4]. The discovery of the beta-3 adrenergic receptor offered the opportunity of developing beta-3 agonists for the treatment of various metabolic diseases [5, 6]. Among a series of phenethanolamines reported by Beecham as beta-3 agonists, A_1, A_3 and their active metabolites A_2, A_4 showed the best selectivity [7,8] (structure **A**, Figure 1).

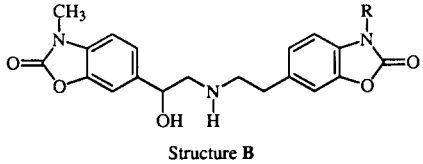


Structure **A**

A_1, X = H, R = $COOCH_3$
A_2, X = H, R = COOH
A_3, X = Cl, R = OCH_2COOCH_3
A_4, X = Cl, R = OCH_2COOH

Figure 1

The structure of these compounds mimics that of epinephrine and norepinephrine, and the beta-3 selectivity is confered by substitution on the nitrogen atom with an arylalkyl group bearing an acidic function (carboxylic or oxyacetic).

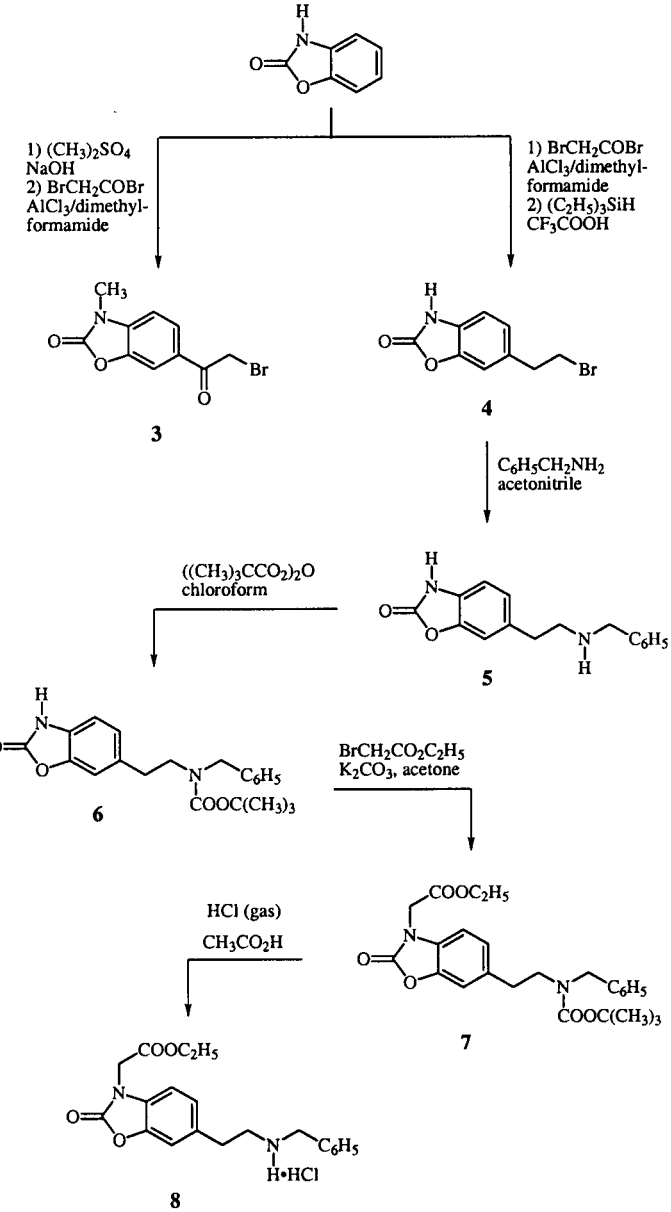


Structure **B**

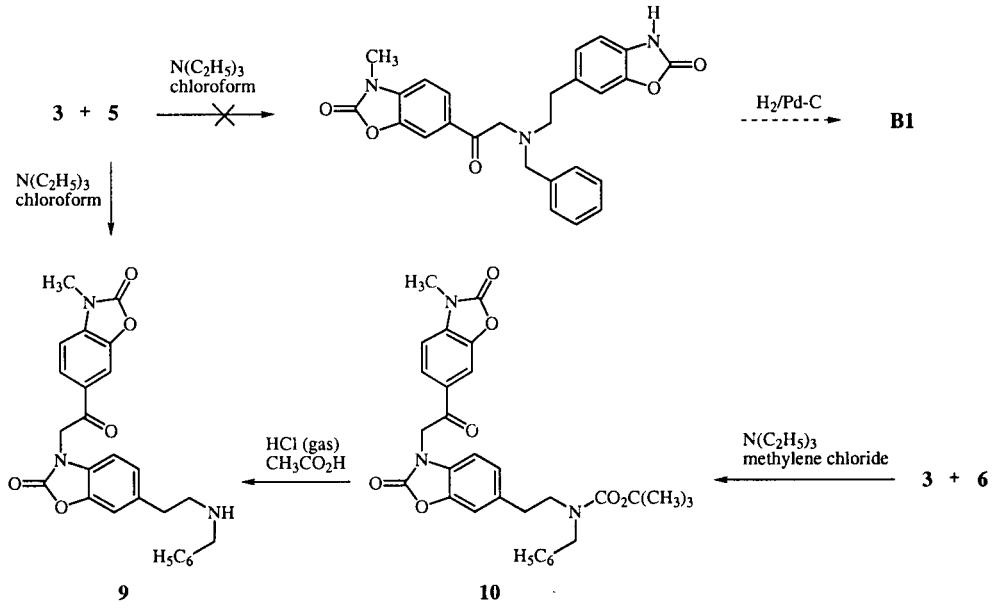
B_1, R = H, HCl
B_2, R = CH_2COOH, HCl

Figure 2

Scheme 1



Scheme 2



Previous work in our laboratory [9-12] showed that the 2(3*H*)-benzoxazolinone heterocycle can be considered as a cyclic bioisoster of pyrocatechol and that (2(3*H*)-benzoxazolin-6-yl)-ethanolamines display very good affinities for adrenergic receptors. Starting from all these structure-activity relationships we designed compounds of general structure **B** (Figure 2) which includes two benzoxazolinone heterocycles: the first one filling the place of the phenyl ring of the phenethanolamine moiety, the second one bearing the acidic functionality of the arylalkyl group.

In order to synthesize the target compounds $\mathbf{B_1}$ and $\mathbf{B_2}$, it required the preparation of the starting materials as the key intermediates **3**, **4** and **8** shown in Scheme 1.

Compounds **3** and **4** were obtained by previously described procedures [13-15]. Substitution of the bromine atom of **4** with benzylamine in acetonitrile led to **5**, the amino group of which being then protected with di-*tert*-butyl carbonate in chloroform to afford **6**. *N*-alkylation of the heterocyclic nitrogen atom with ethyl bromoacetate and potassium carbonate in dry acetone gave **7** and finally elimination of the *tert*-butoxycarbonyl protecting group occurred in acidic medium leading to **8**.

The synthesis of compound $\mathbf{B_1}$ was first attempted by condensation of **5** with **3** in dry chloroform with triethylamine (Scheme 2). Unfortunately, this reaction led to compound **9** by exclusive alkylation of the heterocyclic nitrogen atom of 2(3*H*)-benzoxazolinone.

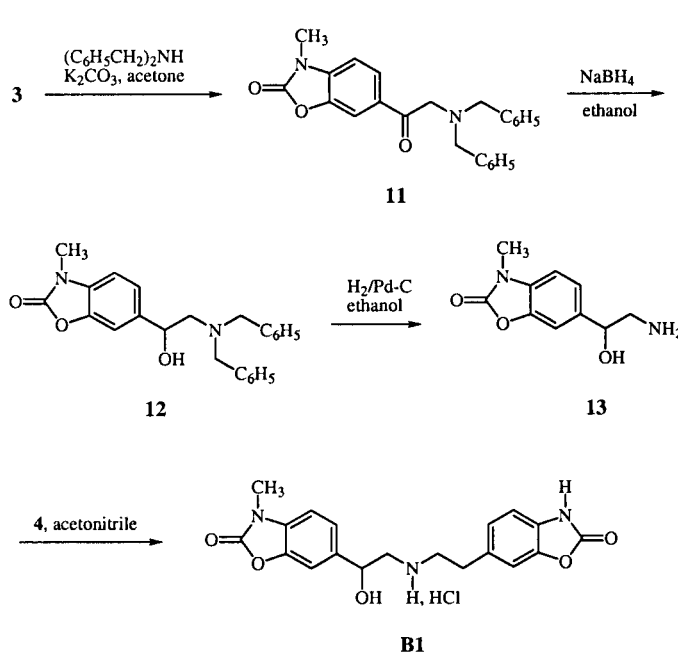
Elucidation of the structure of **9** resulted from the ^{1}H nmr spectral analysis as well as from an unequivocal synthesis: condensation of **3** with **6** gave compound **10** which was deprotected in acidic medium leading to **9**.

To obtain to $\mathbf{B_1}$, we therefore adopted the synthetic route described in Scheme 3.

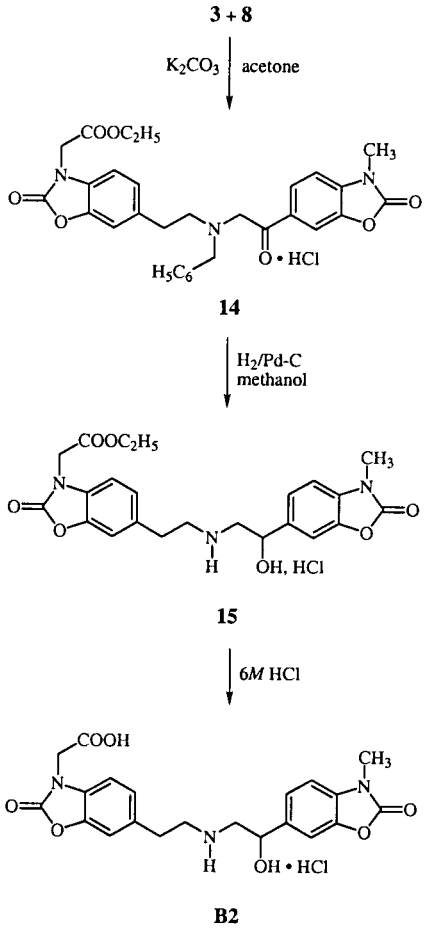
Starting from **3**, the key-intermediate **13** was obtained as follows: substitution of the bromine atom of **3** with dibenzylamine in dry acetone, in the presence of potassium carbonate led to **11**. Reduction of the ketonic group with sodium borohydride in alcoholic medium afforded **12**. Debenzylation with hydrogen in the presence of palladium led to compound **13**. Finally, the target compound $\mathbf{B_1}$ was obtained by *N*-alkylation of **13** with **4**.

To obtain to $\mathbf{B_2}$, we adopted the synthetic route described in Scheme 4.

Scheme 3



Scheme 4



Substitution of the bromine atom of **3** with **8** led to compound **14** which was then treated with hydrogen (palladium on charcoal) in methanol to afford the aminoalcohol **15** that was finally transformed into its acidic analog by hydrolysis in acidic medium.

EXPERIMENTAL

Melting points were determined using a Büchi 530 melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 297 spectrometer and the ^{1}H nmr spectra were recorded using a Brücker AC 300 spectrometer. Chemical shifts are reported in ppm with tetramethylsilane as internal standard. All compounds were found homogenous by tlc (Merck silica gel 60F254, ethyl acetate/acetone, 60/40, v/v). Elemental analyses were performed by the "Service Central de Microanalyses", CNRS, Vernaison, France.

Compounds **3** and **4** were synthetized according to the previously described procedures [13-15].

N-Benzyl-2-[2(3*H*)-benzoxazolinon-6-yl]ethylamine (**5**).

Benzylamine (2.5 ml, 23 mmoles) was added with stirring to a solution of **4** (4.5 g, 19 mmoles) in dry acetonitrile (70 ml). The reaction was allowed to proceed for 7 days after which time the hydrobromide salt of the title compound had precipitated. The solid was filtered, dissolved in 2*M* sodium hydroxide (17 ml), giving the sodium salt of the benzoxazolinone ring which was separated by bubbling carbon dioxide into the solution. The solid was collected and air-dried to yield 3.97 g (78%) of pure **5**, mp 145-146°; ir (potassium bromide): ν 3000-2890 (NH), 1750 (CO) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.73 (m, 4H), 3.71 (s, 2H), 6.33 (broad s, 2H, deuterium oxide exchangeable), 6.97-7.31 (m, 8H).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C,71.69; H, 5.91; N, 10.43.

N-Benzyl-*N*-*tert*-butoxycarbonyl-2-[2(3*H*)-benzoxazolinon-6-yl]ethylamine (**6**).

To a solution of compound **5** (5 g, 18.6 mmoles) in chloroform (50 ml) was added portionwise di-*tert*-butyl carbonate (4.2 g, 19.3 mmoles) dissolved in chloroform (10 ml). The resulting solution was stirred for 1 hour at room temperature, washed with 0.5 *M* hydrochloric acid, dried over magnesium sulfate and evaporated *in vacuo* to afford a residue that was recrystallized from diethyl ether to give 5.82 g (85%) of pure **6**, mp 101-102°; ir (potassium bromide): ν 1750 (benzoxazolinone CO), 1660 (carbamate CO) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.34 (s, 9H), 2.74 (m, 2H), 3.32 (m, 2H), 4.37 (s, 2H), 6.92-7.37 (m, 8H), 11.55 (broads, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.56; N, 7.60. Found: C, 68.30; H, 6.69; N, 7.70.

N-Benzyl-*N*-*tert*-butoxycarbonyl-2-[3-ethoxycarbonylmethyl-2(3*H*)benzoxazolinon-6-yl]ethylamine (**7**).

To a solution of **6** (5.7 g, 16 mmoles) in anhydrous acetone (50 ml) was added anhydrous potassium carbonate (3.5 g, 25 mmoles) and ethyl bromoacetate (2.5 ml, 22 mmoles). The reaction mixture was stirred at 40° for 2 hours, filtered, evaporated *in vacuo* and the residue triturated in petroleum ether to give 6.61 g (91%) of pure **7**, mp 61-63°; ir (potassium bromide): ν 1750 (benzoxazolinone and ethyl ester CO) cm^{-1}, 1670 (carbamate CO); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.23 (t, J = 7.1 Hz, 3H), 1.34 (s, 9H), 2.77 (m, 2H), 3.35 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 4.38 (s, 2H), 4.75 (s, 2H), 6.98-7.37 (m, 8H).

Anal. Calcd. for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 65.79; H, 6.92; N, 5.95.

N-Benzyl-2-[3-ethoxycarbonylmethyl-2(3*H*)-benzoxazolinon-6-yl]ethylamine Hydrochloride (**8**).

A solution of compound **7** (5 g, 11 mmoles) in acetic acid (50 ml) saturated with gaseous hydrochloric acid was stirred for 2 hours at room temperature and evaporated *in vacuo*. The residue was recrystallized from ethanol to give 2.75 g (64%) of pure **8**, mp 251-252°; ir (potassium bromide): ν 1750 (benzoxazolinone and ethyl ester CO) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.22 (t, J = 7.1 Hz, 3H), 3.10 (m, 4H), 4.15 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 4.77 (s, 2H), 7.11-7.61 (m, 8H), 9.60 (broad s, 2H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{20}H_{22}N_2O_4$•HCl: C, 61.46; H, 5.93; N, 7.17. Found: C, 61.48; H, 6.05; N, 7.25.

N-Benzyl-*N*-*tert*-butoxycarbonyl-2-[3-[2-(3-methyl-2(3*H*)-benzoxazolinon-6-yl)-2-oxoethyl]-2(3*H*)-benzoxazolinon-6-yl]ethylamine (**10**).

To a solution of **6** (0.4 g, 1.1 mmoles) in methylene chloride (10 ml) were added successively triethylamine (0.22 ml, 2.2 mmoles)

and compound **3** (0.3 g, 1.1 mmoles). The reaction mixture was stirred at reflux for 3 hours. The organic layer was washed with 0.5 *M* hydrochloric acid, dried over magnesium sulfate, and evaporated. Recrystallization of the residue from methanol gave 0.3 g (50%) of pure **10**, mp 192-194°; ir (potassium bromide): ν 1760 (benzoxazolinone CO), 1670 (ketone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.35 (s, 9H), 2.78 (m, 2H), 3.38 (m, 2H), 3.40 (s, 3H), 4.39 (s, 2H), 5.56 (s, 2H), 6.95-8.07 (m, 11H).

Anal. Calcd. for $C_{31}H_{31}N_3O_7$: C, 66.77; H, 5.60; N, 7.53. Found: C, 66.82; H, 5.67; N, 7.42.

N-Benzyl-2-[3-[2-(3-methyl-2(3*H*)-benzoxazolinon-6-yl)-2-oxoethyl]-2(3*H*)-benzoxazolinon-6-yl]ethylamine (**9**).

Method A.

Compound **3** (1.1 g, 4 mmoles) and triethylamine (0.7 ml, 4.7 mmoles) were added successively to a solution of **5** (1 g, 3.7 mmoles) in chloroform (50 ml). The reaction mixture was stirred at reflux for 20 hours. The precipitate was filtered, and recrystallized from methanol saturated with ammonia to give 0.9 g (54%) of pure **9**.

Method B.

A solution of **10** (0.45 g, 0.8 mmole) in acetic acid saturated with gaseous hydrochloric acid (5 ml), was stirred for 5 minutes. The solvent was evaporated *in vacuo* and the residue was recrystallized from methanol saturated with ammonia to give 0.2 g (54%) of pure **9**, mp 171°; ir (potassium bromide): ν 1770 (benzoxazolinone CO), 1680 (ketone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.75 (m, 4H), 3.41 (s, 3H), 3.71 (s, 2H), 5.55 (s, 2H), 7.01-8.06 (m, 11H).

Anal. Calcd. for $C_{26}H_{23}N_3O_5$: C, 68.25; H, 5.06; N, 9.18. Found: C, 68. 38; H, 5.17; N, 9 32.

N,N-Dibenzyl-2-[3-methyl-2(3*H*)-benzoxazolinon-6-yl]-2-oxoethylamine (**11**).

To a solution of **3** (10 g, 37 mmoles) in dry acetone (200 ml) was added anhydrous potassium carbonate (6.2 g, 45 mmoles), and *N,N*-dibenzylamine (8 g, 41 mmoles). The reaction mixture was refluxed for 3 hours, filtered and evaporated *in vacuo*. The residue was partionated between chloroform and water. The organic layer was washed with water, dried over magnesium sulfate, evaporated and the residue obtained recrystallized from methanol to give 11 g (77%) of pure **11**, mp 157-158°; ir (potassium bromide): ν 1780 (2(3*H*)-benzoxazolinone CO), 1675 (ketone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.37 (s, 3H), 3.71 (s, 4H), 3.88 (s, 2H), 7.22-7.83 (m, 13H).

Anal. Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C,74.32; H, 5.88; N, 7.23.

N,N-Dibenzyl-2-[3-methyl-2(3*H*)-benzoxazolinon-6-yl]-2-hydroxyethylamine (**12**).

Sodium borohydride (1.7 g, 45 mmoles) was added over a period of 10 minutes to a suspension of **11** (14.5 g, 37 mmoles) in absolute ethanol (200 ml). The reaction mixture was then stirred 30 minutes at room temperature and 30 minutes at reflux. The solvent was evaporated *in vacuo*, and 0.5 *M* hydrochloric acid (100 ml) was added to the residue. The resulting precipitate was filtered, treated with an aqueous solution of sodium hydrogen carbonate and extracted with chloroform. The organic layer was dried over magnesium sulfate, filtered and evaporated to give 13.22 g (92%) of pure **12**, mp 152-153°; ir (potassium bromide): ν 3400 (OH), 1780 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.53 (dd, J = 13 Hz, J = 6.6 Hz, 1H), 2.63 (dd, J = 13 Hz, J = 3.54 Hz, 1H), 3.31 (s, 3H), 3.54, 3.67 (two d, J = 13.80 Hz, 4H), 4.80 (m, 1H), 5.20 (d, 1H, deuterium oxide exchangeable), 7.07-7.29 (m, 13H).

Anal. Calcd. for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.29; H, 6.27; N, 7.08.

2-[3-Methyl-2(3*H*)-benzoxazolinon-6-yl]-2-hydroxyethylamine (**13**).

A solution of **12** (1 g, 2.6 mmoles) in ethanol (150 ml) containing 10% palladium on charcoal (200 mg) was hydrogenated at 1 atmosphere for 3 hours at room temperature. After filtering the catalyst, the solution was evaporated *in vacuo*, the residue was taken up in petroleum ether, filtered and dried to give 0.5 g (95%) of **13**, mp 135-137°; ir (potassium bromide): ν 3350 (OH), 3100 (NH_2), 1770 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.60 (m, 2H), 3.20 (broad s, 2H, deuterium oxide exchangeable), 3.30 (s, 3H), 4.50 (m, 1H), 7.20-7.30 (m, 3H).

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.67; H, 5.80; N, 13.45. Found: C, 57. 45; H, 5.95; N, 13.32.

N-[2-[2(3*H*)-Benzoxazolinon-6-yl]ethyl]-2-[3-methyl-2(3*H*)-benzoxazolinon-6-yl]-2-hydroxyethylamine Hydrochloride ($\mathbf{B_1}$).

Compound **4** (2.4 g, 10 mmoles) was added to a stirred solution of **13** (2 g, 9.6 mmoles) in acetonitrile (30 ml). The reaction mixture was stirred at 70° for 10 hours, after which time the hydrobromide salt of the title compound had precipitated. The precipitate was filtered, and partitioned between chloroform and 1*M* sodium hydroxide. Carbon dioxide was bubbled and the organic phase was dried, evaporated *in vacuo* to give a residue that was taken up in methanol saturated with gaseous hydrochloric acid. The resulting precipitate was filtered and recrystallized from water to give 1.44 g (30%) of pure $\mathbf{B_1}$, mp 260°; ir (potassium bromide): ν 3340 (NH), 3250 (OH), 1770 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.19-3.05 (m, 6H), 3.35 (s, 3H), 5.07 (m, 1H), 6.31 (broads, 1H, deuterium oxide exchangeable), 7.05-7.37 (m, 6H), 9.01 and 9.37 (broad s, 2H, deuterium oxide exchangeable), 11.72 (broad s, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{19}H_{19}N_3O_5$•HCl: C, 56.23; H, 4.97; N, 10.35. Found: C, 56.31; H, 4.77; N, 10.13.

N-Benzyl-*N*-[2-[3-ethoxycarbonylmethyl-2(3*H*)-benzoxazolinon-6-yl]ethyl]-2-[3-methyl-2(3*H*)-benzoxazolinon-6-yl]-2-oxoethylamine Hydrochloride (**14**).

A mixture of compound **8** (2 g, 5 mmoles), and anhydrous potassium carbonate (2.3 g, 16 mmoles) in dry acetone was heated under reflux. After 10 minutes compound **3** (1.5 g, 5.5 mmoles) was added and the resulting reaction mixture was refluxed for 1 hour, filtered, evaporated *in vacuo* to give a residue which was taken up in acetone saturated with gaseous hydrogen chloride. The resulting solution was evaporated *in vacuo* and recrystallized from acetonitrile to give 1.65 g (57%) of pure **14**, mp 184-185°, ir (potassium bromide): ν 1750 (benzoxazolinone and ethyl ester CO), 1670 (ketone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.22 (t, J = 7.05 Hz, 3H), 3.28 (m, 4H), 3.41 (s, 3H), 4.17 (q, J = 7.05 Hz, 2H), 4.55 (s, 2H), 4.76 (s, 2H), 5.19 (s, 2H), 7.13-7.94 (m, 11H), 10.63 (broad s, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{30}H_{29}N_3O_7$•HCl: C, 62.11; H, 5.21; N, 7.24. Found: C, 62.32; H, 5.34; N, 7.18.

N-[2-[3-Ethoxycarbonylmethyl-2(3*H*)-benzoxazolinon-6-yl]ethyl]-2-[3-methyl-2(3*H*)-benzoxazolinon-6-yl]-2-hydroxyethylamine Hydrochloride (**15**).

A solution of **14** (3 g, 5.2 mmoles) in methanol (20 ml) containing 10% palladium on charcoal (600 mg) was hydrogenated at 1 atmosphere for 14 hours. After filtration of the catalyst, the solution was evaporated *in vacuo*. The residue was taken up in an aqueous solution of 0.05 *M* potassium carbonate (100 ml) and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated to dryness. The residue was purified by column chromatography (silica gel- chloroform). The fractions containing the desired material were evaporated *in vacuo*, and the residue treated with diethyl ether saturated with gaseous hydrogen chloride. The precipitate was collected and dried to give 0.92 g (36%) of pure **15**, mp 262-264°; ir (potassium bromide): ν 1760 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.23 (t, J = 7.0 Hz, 3H), 3.08-3.24 (m, 6H), 3.36 (s, 3H), 4.20 (q, J = 7.0 Hz, 2H), 4.75 (s, 2H), 5.12 (d, 1H), 6.33 (broad s, 1H, deuterium oxide exchangeable), 7.13-7.38 (m, 6H), 9.01 and 9.37 (broad s, 2H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{23}H_{25}N_3O_7$•HCl: C, 56.16; H, 5.33; N, 8.54. Found: C, 56.09; H, 5.40; N, 8.72.

N-[2-[3-Carboxymethyl-2(3*H*)-benzoxazolinon-6-yl]ethyl]-2-[3-methyl-2(3*H*)-benzoxazolinon-6-yl]-2-hydroxyethylamine Hydrochloride (**B_2**).

Compound **15** (0.2 g, 0.4 mmole) was dissolved in 6 *M* hydrochloric acid (40 ml). The solution was heated under reflux for 5 minutes, cooled to 4° to obtain a precipitate that was filtered and recrystallized from water to give 0.93 g (50%) of pure **B_2**, mp >260°, ir (potassium bromide): ν 3320 (OH), 2400 (NH_2^+), 1750 (benzoxazolinone CO), 1710 (carboxylic acid CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.05-3.19 (m, 6H), 3.35 (s, 3H), 4.65 (s, 2H), 5.07 (d, J = 8.8 Hz, 1H), 6.32 (broad s, 1H, deuterium oxide exchangeable), 7.30-7.38 (m, 6H), 8.97 and 9.31 (broad s, 2H, deuterium oxide exchangeable), 13.31 (broad s, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{21}H_{21}N_3O_7$•HCl: C, 54.37; H, 4.78; N, 9.05. Found: C, 54.46; H, 4.86; N, 9.23.

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