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Syntheses of 3,4-Dihydro-2*H*-1,4-benzoxazine-2-acetates and Related Compounds

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The intramolecular Michael addition of 4-(2-hydroxyanilino)-2-butenoates (**3**), -2-butenonitrile, and their 3-phenyl analogs (**8**) gave 3,4-dihydro-2*H*-1,4-benzoxazine-2-acetates (**4**), -2-acetonitrile (**6**), and their 3-phenyl analogs (**9**), respectively, in good yields. In addition, 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine-2-acetates (**13**) and 3,4-dihydro-2-(*p*-nitrobenzyl)-2*H*-1,4-benzoxazine (**16**) were synthesized from 2-hydroxyanilines (**1**) by the addition reaction of fumaric acid chloride monoester (**11**) and *p*-nitrocinnamyl bromide (**14**), respectively. In order to examine the biological activities of the 2*H*-1,4-benzoxazine analogs, 2-(2-dialkylaminoethyl)-(**18**) and 2-(2,2-diphenylethyl)-2*H*-1,4-benzoxazines (**19**, **20**) were prepared.

Among the compounds synthesized, **4b** and **19a** showed considerable anxiolytic activity in the conflict test in rats, while the oxalates of **18a**—**c** showed potent anticonvulsant activity.

Keywords——2*H*-1,4-benzoxazine-2-acetate; 2*H*-1,4-benzoxazine-2-acetonitrile; 2-(2-dialkylaminoethyl)-2*H*-1,4-benzoxazine; GABA analog; intramolecular Michael addition; anxiolytic activity; anticonvulsant activity

γ-Aminobutyric acid (GABA) is considered to be an inhibitory neurotransmitter and plays an important role[1] in the central nervous system (CNS). Many attempts at the synthesis of GABA analogs as agonists or antagonists for the CNS active agents have been reported.[1c,2] Since 3,4-dihydro-2*H*-1,4-benzoxazine-2-acetic acid derivatives could be considered to be GABA and/or γ-amino-β-hydroxybutyric acid (GABOB)[1a,b] analogs, we were interested in the biological activities of these derivatives. This report describes a new synthesis of 3,4-dihydro-2*H*-1,4-benzoxazine-2-acetic acid derivatives by an intramolecular Michael addition reaction and their biological activities.

The synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines having an acetic acid moiety at position 2 or 3 has not been much investigated.[3-5] We studied an intramolecular Michael addition of methyl 4-(2-hydroxyanilino)-2-butenoates (**3**), obtained from 2-hydroxyanilines (**1**) and methyl 4-bromo-2-butenoate (**2**). Treatment of **3a** ($X=R^1=H$) with a catalytic amount of potassium carbonate or triethylamine in methanol at room temperature gave methyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-acetate (**4a**: $X=R^1=H$) in high yield. The structure of **4a** was confirmed by the physicochemical data. When equimolar amounts of **1** ($R^1=CH_2Ph$) and **2** were treated with a slight excess of sodium hydrogen carbonate in methanol at room temperature, **4** ($R^1=CH_2Ph$) was directly obtained in excellent yield. The *N*-benzyl group of **4** ($R^1=CH_2Ph$) was removed by hydrogenolysis (5% palladium carbon) and the resulting amine was converted into *N*-substituted derivatives (**4**) in the usual ways. The amide derivatives (**4**: $R^2=NR^3R^4$) were also prepared by successive hydrolysis and amidation of **4** ($X=H$, $R^1=CH_2Ph$). Many compounds **4** were thus prepared, and are listed in Table I.

4-Bromo-2-butenonitrile (**5**) also reacted with **1** (X=H, $R^1=CH_2Ph$) in the presence of 1.1 eq of sodium hydrogen carbonate and a catalytic amount of triethylamine in methanol to afford 3,4-dihydro-2*H*-1,4-benzoxazine-2-acetonitrile (**6**) in 94% yield. In addition, 3-aryl-4-bromo-2-butenoate (**7**: Y=COOMe) and 4-bromo-3-phenyl-2-butenonitrile (**7**: Y=CN) were reacted with **1** (X=H, $R^1=CH_2Ph$) in the presence of sodium hydrogen carbonate to give the *o*-hydroxyalkenylanilines (**8**), which were then treated with a catalytic amount of potassium carbonare to afford 2-aryl-3,4-dihydro-2*H*-1,4-benzoxazine-2-acetates (**9**: Y=COOMe) and 3,4-dihydro-2-phenyl-2*H*-1,4-benzoxazine-2-acetonitrile (**9**: Y=CN), respectively, in good yields despite the presence of a sterically hindered substituent at the *β*-position in **8**. For the purpose of testing the biological activity, **9** (Z=H, Y=COOMe) was converted into **10** by successive hydrogenolysis and then N-alkylation or N-acylation (Table II).

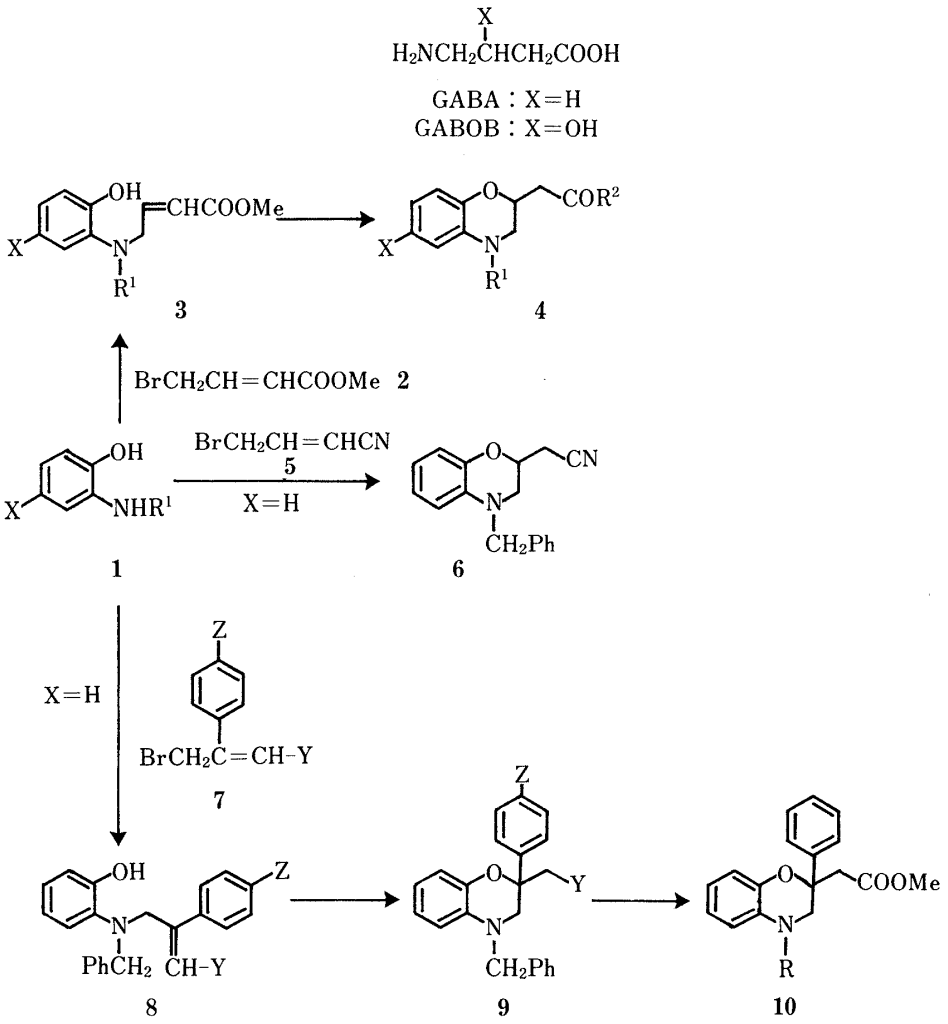


Chart 1

Similarly, fumaric acid chloride monoethylester (**11**) reacted with **1** to give the fumaramides (**12**) which, upon treatment with potassium carbonate in ethanol, yielded 3-oxo-2*H*-1,4-benzoxazine-2-acetates (**13**)[4] in 26—90% yields.

From a mechanistic consideration of the intramolecular Michael addition, cinnamyl halide could be cyclized with **1** to give a 3,4-dihydro-2*H*-1,4-benzoxazine. When *p*-nitrocinnamyl bromide (**14**: $Z=NO_2$) was reacted with **1** (X=H, $R^1=CH_2Ph$) in the presence of sodium hydrogen carbonate in methanol, followed by treatment of the resulting intermediate (**15**: $Z=NO_2$) with potassium carbonate, 3,4-dihydro-2-(*p*-nitrobenzyl)-2*H*-1,4-

TABLE I. Physicochemical Properties and Analytical Data of 3,4-Dihydro-2*H*-1,4-benzoxazines (**4**)

Compd. **4**	X	R^1	R^2	Yield (%)	mp (°C)	Recryst.[a] solvent	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR ($CDCl_3$) C_2-H (1H) δ
a	H	H	OMe	95	120—128[e]	M–A	$C_{11}H_{13}NO_3 \cdot HCl$	54.21 (54.11	5.79 5.77	5.75 5.66)	4.53[b]
b	H	CH_2Ph	OMe	93	101—102	M	$C_{18}H_{19}NO_3$	72.70 (72.81	6.44 6.44	4.71 4.58)	4.62
c	Me	CH_2Ph	OMe	95	80—81	M	$C_{19}H_{21}NO_3$	73.29 (73.16	6.80 6.76	4.50 4.35)	4.63
d	Cl	CH_2Ph	OMe	90	100—101	M	$C_{18}H_{18}ClNO_3$	65.16 (65.09	5.47 5.39	4.22 4.18)	4.63
e	NO_2	CH_2Ph	OMe	91	77—78	M–I	$C_{18}H_{18}N_2O_5$	63.15 (63.14	5.30 5.29	8.18 8.01)	4.67
f	H	Me	OMe	64	45—46	A–H	$C_{12}H_{15}NO_3$	65.14 (65.01	6.83 6.78	6.33 6.21)	4.64
g	H	$CH_2CH=CH_2$	OMe	83	Oil	—	$C_{14}H_{17}NO_3$	67.99 (67.84	6.93 6.91	5.66 5.56)	4.57
h	H	$(CH_2)_2Ph$	OMe	16	63—64	A–H	$C_{19}H_{21}NO_3$	73.29 (73.03	6.80 6.74	4.50 4.37)	4.57
i	H	COMe	OMe	83	108—109	M	$C_{13}H_{15}NO_4$	62.64 (62.61	6.07 6.05	5.62 5.45)	4.66
j	H	COPh	OMe	90	102—103	M	$C_{18}H_{17}NO_4$	69.44 (69.69	5.50 5.34	4.50 4.63)	4.78
k	H	$COCH_2Ph$	OMe	83	115—116	M	$C_{19}H_{19}NO_4$	70.14 (70.02	5.89 5.86	4.31 4.18)	4.53
l	H	CONHMe	OMe	58	106—107	M	$C_{13}H_{16}N_2O_4$	59.08 (58.96	6.10 6.03	10.60 10.58)	4.66
m	H	CONHPh	OMe	84	118—119	A–H	$C_{18}H_{18}N_2O_4$	66.24 (66.48	5.56 5.56	8.58 8.74)	4.67
n	H	H	OH	71	159—167[e] (dec.)	A–M	$C_{10}H_{11}NO_3 \cdot HCl$	52.29 (52.05	5.26 5.24	6.09 6.08)	4.70[c]
o	H	CH_2Ph	OH	63	148—150	A	$C_{17}H_{17}NO_3$	72.06 (71.84	6.05 6.04	4.94 4.94)	4.62[d]
p	H	CH_2Ph		68	57—59	A	$C_{21}H_{24}N_2O_3$	71.57 (71.77	6.86 6.59	7.95 7.88)	4.67
q	H	CH_2Ph		87	119—121	A	$C_{22}H_{26}N_2O_2$	75.40 (75.37	7.48 7.45	7.99 7.87)	4.67

a) Recrystallization solvents used were as follows: A, ether; H, hexane; I, isopropyl ether; M, methanol. *b*) ^{1}H-NMR spectrum was taken as the free base. *c*) ^{1}H-NMR spectrum was taken in CD_3OD solution. *d*) ^{1}H-NMR spectrum was taken in $CDCl_3$–DMSO-d_6 solution. *e*) As the hydrochloride.

TABLE II. Physicochemical Properties and Analytical Data of 2-Aryl-3,4-dihydro-2*H*-1,4-benzoxazines (**9** and **10**)

Compd.	Z	Y	R	Yield (%)	mp (°C)	Recryst.[a] solvent	Formula	Analysis (%) Calcd (Found)			^{1}H-NMR ($CDCl_3$) C_3-H (2H)
								C	H	N	δ
9a	H	COOMe	—	55[b]	76—77	M–I	$C_{24}H_{23}NO_3$	77.19	6.21	3.75	3.72 (s)
								(77.01	6.18	3.78)	
9b	Cl	COOMe	—	95	123—124	I	$C_{24}H_{22}ClNO_3$	70.67	5.44	3.43	3.71 (s)
								(70.68	5.38	3.38)	
9c	H	CN	—	65[b]	136—137	M	$C_{23}H_{20}N_2O$	81.15	5.92	8.23	3.51 (s)
								(81.02	5.79	8.15)	
10a	—	—	H	94	94—95	A	$C_{17}H_{17}NO_3$	72.06	6.05	4.96	3.68 (s)
								(71.82	5.97	4.80)	
10b	—	—	Me	75	61—62	H	$C_{18}H_{19}NO_3$	72.70	6.44	4.71	3.48 (dd)
								(72.91	6.47	4.68)	3.63 (dd)
10c	—	—	$CH_2CH=CH_2$	81	Oil	—	$C_{20}H_{21}NO_3$	74.28	6.55	4.33	3.63 (s)
								(74.32	6.41	4.19)	
10d	—	—	COMe	79	112—113	A	$C_{19}H_{19}NO_4$	70.14	5.89	4.31	3.87 (br d)
								(70.25	5.85	4.71)	4.83 (br d)
10e	—	—	COPh	71	120—121	M	$C_{24}H_{21}NO_4$	74.40	5.46	3.62	3.76 (d)
								(74.43	5.33	3.49)	5.25 (d)

a) Recrystallization solvent used were as follows: A, ether; H, hexane; I, isopropyl ether; M, methanol. *b*) Overall yield from **1**.

benzoxazine (**16**) was obtained in 81% yield. However, in the case of cinnamyl bromide (**14**: Z=H) all attempts at intramolecular Michael cyclization of the intermediate (**15**: Z=H) were unsuccessful owing to the weak electron-withdrawing nature of the phenyl group.

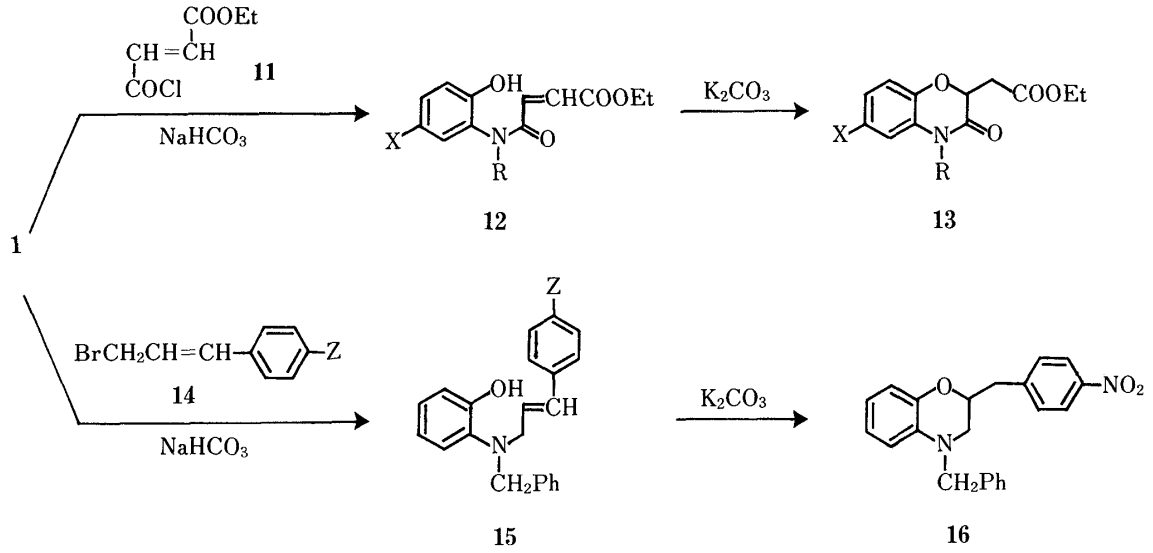


Chart 2

For comparison with the biological activity of the 3,4-dihydro-2*H*-1,4-benzoxazine analogs, we also prepared several 2-(2-dialkylaminoethyl)-(**18**) and 2-(2,2-diphenylethyl)-3,4-dihydro-2*H*-1,4-benzoxazines (**19** and **20**) (Chart 3). Reduction of **4b** and **4h** with lithium aluminum hydride afforded 3,4-dihydro-2-(2-hydroxyethyl)-2*H*-1,4-benzoxazines (**17**: $n=1$ and 2, $X=H_2$) in good yields. Sodium borohydride reduction[6] of the *N*-hydroxysuccinimide ester of **13b** gave 2-(2-hydroxyethyl)-3-oxo-2*H*-1,4-benzoxazine (**17**: $n=1$, X=O) in 59% yield. The alcohols (**17**) were converted to **18** by successive mesylation and treatment with amines. On the other hand, **4b** and **4h** were treated with a large excess of phenylmagnesium bromide in ether to give the alcohols (**19**), which were converted into **20** by treatment with *p*-toluenesulfonic acid. Table III lists **18**, **19**, and **20** thus prepared.

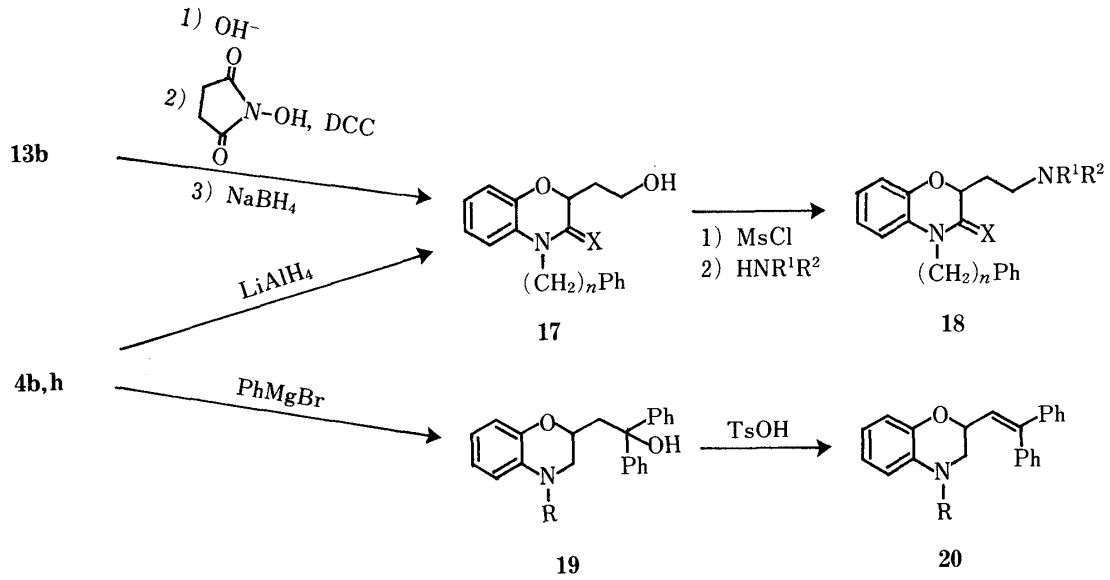
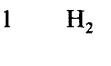
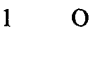
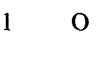


Chart 3

TABLE III. Physicochemical Properties and Analytical Data of 2-(2-Substituted ethyl)-3,4-dihydro-2*H*-1,4-benzoxazines (**18**, **19**, and **20**)

Compd.	*n*	X	NR^1R^2	R	Yield (%)	mp (°C)	Recryst.[a] solvent	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR[b] ($CDCl_3$) C_2-H (1H) δ
18a	1	H_2	NEt_2	—	80	161—163[e]	M	$C_{21}H_{28}N_2O \cdot (COOH)_2$	66.64 (66.82	7.30 7.33	6.76 6.51)	4.23 (m)
18b	1	H_2		—	79	178—180[e]	M	$C_{25}H_{28}N_2O \cdot (COOH)_2$	70.11 (69.81	6.54 6.44	6.06 6.14)	4.22 (m)
18c	2	H_2	NEt_2	—	82	150—154[e]	M	$C_{22}H_{30}N_2O \cdot (COOH)_2$	67.27 (66.98	7.53 7.54	6.54 6.43)	4.08 (m)
18d	1	O	NEt_2	—	73	162—163[e]	M	$C_{21}H_{26}N_2O_2 \cdot (COOH)_2$	64.47 (64.36	6.59 6.73	6.54 6.47)	4.83 (dd)
18e	1	O		—	69	74—75	I	$C_{25}H_{26}N_2O_2$	77.69 (77.39	6.78 6.61	7.25 7.20)	4.82 (dd)
18f	1	O		—	76	220—223[f] (dec.)	M	$C_{22}H_{27}N_3O_2 \cdot 2HCl$	60.27 (60.17	6.66 6.56	9.58 9.64)	4.83 (dd)
19a	—	—	—	CH_2Ph	84	104—106	I	$C_{29}H_{27}NO_2$	82.63 (82.73	6.46 6.48	3.32 3.35)	4.22 (m)
19b	—	—	—	$(CH_2)_2Ph$	81	110—111	I	$C_{30}H_{29}NO_2$	82.72 (82.74	6.71 6.81	3.22 3.40)	4.08 (m)
19c[c]	—	—	—	H	92	128—129	I	$C_{22}H_{21}NO_2$	79.73 (79.94	6.39 6.47	4.23 4.10)	4.14 (m)
20a[d]	—	—	—	CH_2Ph	94	88—89	I	$C_{29}H_{25}NO$	86.32 (86.26	6.25 6.34	3.47 3.30)	4.63 (dt)
20b	—	—	—	H	94	116—117	M	$C_{22}H_{19}NO$	84.31 (84.30	6.11 6.03	4.47 4.64)	4.67 (dt)

a) Recrystallization solvents used were as follows: I, isopropyl ether; M, methanol. *b*) ^{1}H-NMR spectra were taken as the free base in the cases of **18**. *c*) Obtained from **19a** by hydrogenolysis. *d*) Obtained from **19c** by dehydration. *e*) As the oxalate. *f*) As the hydrochloride.

Among the compounds synthesized in this work, **4b** and **19a** showed considerable anxiolytic activity (minimal effective dose: 20 mg/kg, *i.p.*)[7] in the conflict test[8] in rats. The oxalates of 2-(2-dialkylaminoethyl)-3,4-dihydro-2*H*-1,4-benzoxazines (**18a—c**) showed potent anticonvulsant activity[7] in the anti-pentylenetetrazole and anti-bicuculline testing systems in mice.

Experimental

Melting points were measured on a micro hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were taken with a Hitachi 215 or a Hitachi 260-10 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a Varian T-60, EM-390 or XL-100A spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given as δ values (ppm): s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet. Mass spectra (MS) were taken with a Hitachi RMU-6D or a JEOL JMS-01SC spectrometer. All organic extracts were dried over anhydrous sodium sulfate. Column chromatography was performed with Kieselgel 60 (Merck, 230—400 mesh).

2-(Benzylamino)phenols (1b—e)——2-(Benzylamino)phenols (**1b—e**) were prepared by $NaBH_4$ reduction of the corresponding 2-(benzylideneamino)phenols, obtained from the appropriate 2-aminophenols and benzaldehyde. **1b** (X=H, $R^1=CH_2Ph$), mp 90—91 °C (from ether–hexane), *Anal.* Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.14; H, 6.48; N, 7.03. **1c** (X=Me, $R^1=CH_2Ph$), mp 110—111 °C (from ether–hexane), *Anal.* Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.52; H, 7.07; N, 6.60. **1d** (X=Cl, $R^1=CH_2Ph$), mp 121—123 °C (from ether–hexane), *Anal.* Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.54; H, 5.11; N, 6.04. **1e** ($X=NO_2$, $R^1=CH_2Ph$), mp 155—168 °C (dec.) (from ether), *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.93; H, 4.77; N, 11.49.

Methyl 4-(2-Hydroxyanilino)-2-butenoate (3a)——Methyl 4-bromo-2-butenoate (**2**, 0.90 g) was added dropwise to a stirred mixture of 2-aminophenol (**1a**, 0.55 g) and $NaHCO_3$ (0.50 g) in MeOH (10 ml) at room temperature. The mixture was stirred for 3 h, then the solvent was removed and the residue was extracted with EtOAc. The extracts were washed with water, dried, and evaporated. The residue was chromatographed on a silica gel column. Elution with toluene–EtOAc (6 : 1) gave **3a** (0.54 g, 52%) as a pale yellow oil. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.68; H, 6.39; N, 6.57. IR ν_{max}^{KBr} cm^{-1}: 3500—3200, 1720, 1660. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s, CH_3), 3.92 (2H, dd, J=5, 1.5 Hz, N-C<u>H</u>$_2$–CH=), 6.04 (1H, dt, J=16, 1.5 Hz, =C<u>H</u>–COOMe), 6.4—6.9 (4H, m, Ar-H), 7.07 (1H, dt, J=16, 5 Hz, –C<u>H</u>=CH–COOMe). MS m/z: 207 (M^+), 192, 175, 148, 108.

The other intermediates (**3**) were not isolated from the reaction mixture but were directly transformed into **4**.

Methyl 3,4-Dihydro-2*H*-1,4-benzoxazine-2-acetate (4a)——A solution of **3a** (0.54 g) in MeOH (2 ml) was treated with a catalytic amount of K_2CO_3 (10 mg) for 20 min at room temperature. The product was extracted with CH_2Cl_2 and the extracts were washed with water, dried, and evaporated to give **4a** (0.54 g, quantiative yield) as a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 3500, 1730. ^{1}N-HMR ($CDCl_3$) δ: 2.54 and 2.77 (each 1H, each dd, J=16, 6 Hz, –C<u>H</u>$_2$–COOMe), 3.12 (1H, dd, J=12, 7 Hz, 3-H), 3.42 (1H, dd, J=12, 3 Hz, 3-H), 3.69 (3H, s, CH_3), 4.53 (1H, m, 2-H), 6.4—6.9 (4H, m, Ar-H). MS m/z: 207 (M^+), 176, 148, 134, 120.

Methyl 4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-acetate (4b)——A solution of **2** (80 g) in MeOH (50 ml) was added dropwise to a stirred suspension of **1b** (89 g) and $NaHCO_3$ (41 g) in MeOH (500 ml) at room temperature. The resulting crystals were recrystallized from MeOH to give **4b** (124 g, 93%) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1730.

Debenzylation of 4b——A suspension of **4b** (3.7 g) in MeOH (60 ml) was hydrogenated over 5% Pd–C (0.7 g) at room temperature. After removal of the catalyst, the filtrate was evaporated to give **4a** (2.6 g) as an oil, which was converted to the hydrochloride (2.9 g, 94%).

Methyl 3,4-Dihydro-4-methyl-2*H*-1,4-benzoxazine-2-acetate (4f)——A mixture of **4a** (5.0 g), methyl iodide (14. 2g), and K_2CO_3 (7.6 g) in acetone (100 ml) was stirred for 4 h at 40 °C. Afer removal of the solvent, the residue was extracted with EtOAc. The extracts were washed with water, dried and evaporated to give crude crystals. Recrystallization from ether–hexane gave **4f** (3.4 g, 64%) as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 1730.

Methyl 4-Benzoyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-acetate (4j)——Benzoyl chloride (2.8 g) was added dropwise to a cooled solution of **4a** (2.8 g) and K_2CO_3 (3.0 g) in CH_2Cl_2 (100 ml). The mixture was stirred for 1 h at room temperature, then the product was extracted with CH_2Cl_2. The extracts were washed with water, dried and evaporated. The crystalline residue was recrystallized from MeOH to give **4j** (3.8 g, 90%) as colorless pillars. IR ν_{max}^{KBr} cm^{-1}: 1730, 1645.

Methyl 3,4-Dihydro-4-methylcarbamoyl-2*H*-1,4-benzoxazine-2-acetate (4l)——Methyl isocyanate (1.5 g) was added dropwise to a cooled solution of **4a** (2.0 g) and triethylamine (3.0 g) in CH_2Cl_2 (100 ml). The mixture was stirred for 4 h, then the organic phase was washed with water, dried and evaporated. The crystalline residue was recrystallized from MeOH to give **4l** (1.5 g, 58%) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3400, 1730, 1650.

3,4-Dihydro-2*H*-1,4-benzoxazine-2-acetic Acid (4n)——A suspension of **4a** (2.5 g) in 1 N HCl (50 ml) was heated

to 80 °C for 3 h. The solution was evaporated to dryness and the crystalline residue was recrystallized from MeOH–ether to give **4n**·HCl (2.0 g, 71%) as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 3000—2300, 1700.

4-Benzyl-3,4-dihydro-2-morpholinocarbonylmethyl-2*H*-1,4-benzoxazine (4p)——PCl_5 (1.0 g) was added to a cooled solution of **4o** (1.0 g) in CH_2Cl_2 (60 ml). The mixture was stirred for 4 h, then the solution was evaporated to give the crude acid chloride of **4o**. Morpholine (2.0 g) was added to a cooled solution of the acid chloride in CH_2Cl_2 (50 ml), the mixture was stirred for 1 h at room temperature, and the organic phase was washed with water, dried and evaporated. The residue was purified by column chromatography on silica gel with CH_2Cl_2–EtOAc (4 : 1), followed by recrystallization from ether to give **4p** (0.82 g, 68%) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1655.

4-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazine-2-acetonitrile (6)——4-Bromo-2-butenonitrile (**5**, 27 g) was added to a stirred suspension of **1b** (36 g) and $NaHCO_3$ (17 g) in MeOH (120 ml). The mixture was stirred for 24 h, then triethylamine (0.1 ml) was added to the reaction mixture and stirring was continued for 1 h. The resulting crystals were recrystallized from MeOH to give **6** (44 g, 94%) as colorless prisms, mp 86—87 °C. *Anal.* Calcd for $C_{17}H_{16}NO_2$: C, 77.25; H, 6.10; N, 10.60. Found: C, 76.97; H, 6.13; N, 10.48. IR ν_{max}^{KBr} cm^{-1}: 2260. ^{1}H-NMR ($CDCl_3$) δ: 2.70 (2H, d, J=6 Hz, –C$\underline{H}_2$CN), 3.0—3.6 (2H, m, 3-H), 4.46 (2H, s, N–C$\underline{H}_2$–Ph), 4.3—4.7 (1H, m, 2-H), 6.8 (4H, m, Ar-H), 7.33 (5H, br s, Ar-H).

1-Substituted 2-Aryl-3-bromopropenes (7a—c)——Bromination of methyl 3-phenyl-2-butenoate, methyl 3-(4-chlorophenyl)-2-butenoate, and 3-phenyl-2-butenonitrile with *N*-bromosuccinimide (NBS) gave **7a** (Y=COOMe, Z=H) [bp 121—122 °C (0.05 mmHg)],[9] **7b** (Y=COOMe, Z=Cl) [mp 77—78 °C (from iso-Pr_2O). *Anal.* Calcd for $C_{11}H_{10}BrClO_2$: C, 45.62; H, 3.48. Found: C, 45.63; H, 3.35], and **7c** (Y=CN, Z=H) [bp 142—143 °C (0.3 mmHg). *Anal.* Calcd for $C_{10}H_8BrN$: C, 54.08; H 3.63; N, 6.31. Found: C, 53.71; H, 3.44; N, 6.20], respectively, in 75—85% yields.

Methyl 4-Benzyl-2-(4-chlorophenyl)-3,4-dihydro-2*H*-1,4-benzoxazine-2-acetate (9b)——A suspension of **1b** (6.0 g), **7b** (9.6 g), and $NaHCO_3$ (3.0 g) in MeOH (60 ml) was stirred for 24 h. The resulting crystals were recrystallized from CH_2Cl_2–MeOH to give **8b** (10.5 g, 88%) as colorless prisms, mp 128—130 °C. *Anal.* Calcd for $C_{24}H_{22}ClNO_3$: C, 70.67; H, 5.44; N, 3.43. Found: C, 70.57; H, 5.23; N, 3.43. IR ν_{max}^{KBr} cm^{-1}: 3300, 1715, 1630. ^{1}H-NMR ($CDCl_3$) δ: 3.75 (3H, s, CH_3), 3.92 (2H, s, CH_2), 4.65 (2H, s, N–C$\underline{H}_2$–Ph), 6.02 (1H, s, olefin. H), 6.6—7.6 (13H, m, Ar-H). A mixture of **8b** (9.4 g), MeOH (50 ml), and CH_2Cl_2 (70 ml) was treated with K_2CO_3 (0.32 g) for 10 min. The product was extracted with EtOAc. The extracts were washed with water, dried and evaporated to give **9b** (8.9 g, 95%) as colorless prisms after recrystallization from iso-Pr_2O. IR ν_{max}^{KBr} cm^{-1}: 1740.

The other compounds (**9a**, **c**) were obtained without isolation of the corresponding intermediates (**8**).

Methyl 3,4-Dihydro-3-phenyl-2*H*-1,4-benzoxazine-2-acetate (10a)——Compound **9a** (6.6 g) was hydrogenated over 5% Pd–C (0.7 g) in the usual manner to give **10a** (4.7 g, 94%) as colorless prisms after recrystallization from ether. IR ν_{max}^{KBr} cm^{-1}: 3400, 1740.

Ethyl 3-[(2-Hydroxyphenyl)carbamoyl]acrylate (12a)——A solution of **11** (3.5 g) in dioxane (10 ml) was added dropwise to a stirred suspension of **1a** (2.2 g) and $NaHCO_3$ (2.0 g) in dioxane (60 ml). The reaction mixture was stirred for 3 h at room temperature, then poured into water and extracted with EtOAc. The extracts were washed with water, dried and evaporated. The crystalline residue was recrystallized from EtOH to give **12a** (3.8 g, 81%) as colorless prisms, mp 152—153 °C. *Anal.* Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.26; H, 5.48; N, 5.82. IR ν_{max}^{KBr} cm^{-1}: 1720, 1660. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.29 (3H, t, J=7 Hz, CH_3), 4.20 (2H, q, J=7 Hz, OC$\underline{H}_2$CH$_3$), 6.75 (1H, d, J=16 Hz, olefin. H), 6.7—7.1 (3H, m, Ar-H), 7.27 (1H, d, J=16 Hz, olefin. H), 7.6 (1H, m, Ar-H).

The other compounds (**12**) were similarly prepared from the corresponding 2-aminophenols. **12b**, a colorless oil (89%), *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.27; H, 5.94; N, 4.13. **12c**,colorless prisms (from EtOH, 77%), mp 153—155 °C. *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.54; H, 6.09; N, 5.79. **12d**, yellow needles (from EtOH, 83%), mp 150—153 °C. *Anal.* Calcd for $C_{12}H_{12}ClNO_4$: C, 53.44; H, 4.49; N, 5.19. Found: C, 53.40; H, 4.46; N, 5.26.

Ethyl 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazine-2-acetate (13a)——A suspension of **12a** (2.5 g) and K_2CO_3 (0.7 g) in EtOH (70 ml) was stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The extracts were washed with water, dried and evaporated. The crystalline residue was recrystallized from EtOH to give **13a** (2.0 g, 80%) as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1730, 1680.

The other compounds (**13b—d**) listed in Table IV were similarly prepared.

4-Benzyl-3,4-dihydro-2-(*p*-nitrobenzyl)-2*H*-1,4-benzoxazine (16)——A suspension of **1b** (200 mg), *p*-nitrocinnamyl bromide (**14a**, 270 mg), and $NaHCO_3$ (100 mg) in MeOH (4 ml) was stirred for 7 h at room temperature. The solution was evaporated and the residue was extracted with CH_2Cl_2. The extracts were washed with water, dreid and evaporated to give **15a** as a crude oil. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (2H, d, J=5 Hz, CH_2), 4.07 (2H, s, N–C$\underline{H}_2$–Ph), 6.2—6.6 (2H, m, olefin. H). A solution of **15a** in MeOH (6 ml) was treated with K_2CO_3 (10 mg) for 30 min. The solvent was removed and the residue was extracted with CH_2Cl_2. The extracts were washed with water, dried and evaporated. The residue was crystallized from ether–EtOH to give **16** (290 mg, 81%) as pale yellow prisms, mp 78—79 °C. *Anal.* Calcd for $C_{22}H_{20}N_2O_3$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.26; H, 5.51; N, 7.79. IR ν_{max}^{KBr} cm^{-1}: 1515, 1345. ^{1}H-NMR ($CDCl_3$) δ: 2.9—3.4 (4H, m, CH_2 and 3-H), 4.46 (2H, s, N–C$\underline{H}_2$–Ph), 4.2—4.7 (1H,

TABLE IV. Physicochemical Properties and Analytical Data of Ethyl 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazine-2-acetates (**13**)

Compd. **13**	X	R	Yield[a] (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR ($CDCl_3$) C_2-H (1H, dd) δ
a	H	H	80	106—107	$C_{12}H_{13}NO_4$	61.27 (61.10	5.57 5.39	5.96 5.82)	4.96
b	H	CH_2Ph	90	Oil	$C_{19}H_{19}NO_4$	70.14 (70.27	5.89 5.70	4.31 4.11)	4.95
c	Me	H	42	117—118	$C_{13}H_{15}NO_4$	62.64 (62.86	6.07 6.03	5.62 5.65)	4.92
d	Cl	H	26	151—152	$C_{12}H_{12}ClNO_4$	53.44 (53.48	4.49 4.36	5.19 5.18)	4.90[b]

a) After recrystallization from ethanol. *b*) ^{1}H-NMR spectrum was taken in $CDCl_3$–DMSO-d_6 solution.

m, 2-H).

4-Benzyl-3,4-dihydro-2-(2-hydroxyethyl)-2*H*-1,4-benzoxazine (17a)——$LiAlH_4$ (0.58 g) was added portionwise to a stirred solution of **4b** (3.0 g) in dry ether (50 ml). The mixture was refluxed for 1 h and then treated successively with water (0.6 ml), 15% NaOH aq. (0.6 ml), and water (1.8 ml) under ice-cooling. The resulting precipitates were removed by filtration and the filtrates were evaporated. The residue was crystallized from iso-Pr_2O to give **17a** (2.4 g, 92%) as colorless needles, mp 57—59 °C. *Anal.* Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.15; H, 7.20; N, 5.18. IR ν_{max}^{KBr} cm^{-1}: 3600—3200. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.2 (3H, m, $-CH_2-CH_2-OH$), 3.0—3.4 (2H, m, 3-H), 3.86 (2H, t, $J=7$ Hz, $-CH_2-OH$), 4.2—4.5 (1H, m, 2-H), 4.42 (2H, s, $N-CH_2-Ph$), 6.5—6.9 (4H, m, Ar-H), 7.29 (5H, br s, ArH).

Similarly, **17b** was obtained as a colorless oil (86%) from **4h**. *Anal.* Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.33; H, 7.71; N, 4.81.

4-Benzyl-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-2*H*-1,4-benzoxazine (17c)——A solution of **13b** (25 g) in EtOH (300 ml) and 10% NaOH aq. (60 ml) was stirred for 2 h at room temperature. After removal of the solvent, the residue was poured into water (500 ml). The solution was washed with EtOAc, acidified with dil. HCl and extracted with EtOAc. The extracts were dried and evaporated to give the carboxylic acid derivative of **13b** as a colorless crystalline powder (21 g, 91%), mp 125—126 °C. *Anal.* Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.51; H, 5.06; N, 4.71. *N*-Hydroxysuccinimide (1.1 g) and dicyclohexylcarbodiimide (2.3 g) were added to a stirred suspension of this acid (3.0 g) in EtOAc (150 ml). The whole was stirred for 4 h, then the resulting precipitates were removed by filtration and the filtrates were evaporated. $NaBH_4$ (1.1 g) was added portionwise to the residue in tetrahydrofuran (50 ml). After being stirred for 3 h, the mixture was poured into cold water and extracted with EtOAc. The extracts were washed with water, dried and evaporated. The residue was purified by column chromatography on silica gel with toluene–EtOAc (10 : 1) to give **17c** as colorless crystals. Recrystallization from ether–hexane gave colorless needles (1.7 g, 59%), mp 78—79 °C. *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.13; H, 6.05; N, 4.96. IR ν_{max}^{KBr} cm^{-1}: 3600—3200, 1680. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.6 (3H, m, $-CH_2-CH_2-OH$), 3.87 (2H, t, $J=7$ Hz. $-CH_2-OH$), 4.83 (1H, dd, $J=6$, 7 Hz, 2-H), 5.12 (2H, s, $N-CH_2-Ph$), 6.8—7.1 (4H, m, Ar-H), 7.03 (5H, br s, Ar-H).

4-Benzyl-2-[2-(*N*-benzyl-*N*-methylamino)ethyl]-3,4-dihydro-2*H*-1,4-benzoxazine (18b)——A solution of methanesulfonyl chloride (0.90 g) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of **17a** (1.7 g) and triethylamine (2.0 g) in CH_2Cl_2 (40 ml) at room temperature. The mixture was stirred for 10 min, washed with water, dried and evaporated to give the crude mesylate of **17a** as an oil (2.2 g, quant. yield). IR ν_{max}^{neat} cm^{-1}: 1365, 1350, 1180. A mixture of the mesylate (1.0 g) and *N*-benzyl-*N*-methylamine (0.77 g) in toluene (15 ml) was heated to 80 °C for 3 h. After cooling, the organic phase was washed with water, dried and evaporated to give **18b** (0.90 g, 82%) as an oil after chromatography on silica gel with toluene–EtOAc (4 : 1). This oily product was converted to the crystalline oxalate, colorless needles (1.1 g, 79%).

4-Benzyl-3,4-dihydro-2-(2-hydroxy-2,2-diphenylethyl)-2*H*-1,4-benzoxazine (19a)——Phenylmagnesium bromide, prepared from magnesium (3.6 g) and bromobenzene (24 g) in dry ether (100 ml), was added dropwise to a cooled solution of **4b** (15.0 g) in dry benzene (70 ml). The mixture was stirred for 3 h at 40—45 °C, then sat. NH_4Cl aq. (100 ml) was carefully added under cooling. The organic layer was washed with water, dried and evaporated to give **19a** (17.6 g, 84%) as a colorless crystalline powder. IR ν_{max}^{KBr} cm^{-1}: 3500.

4-Benzyl-3,4-dihydro-2-(β-phenylstyryl)-2*H*-1,4-benzoxazine (20a)——A solution of **19a** (3.6 g) and *p*-TsOH · H_2O (0.35 g) in benzene (50 ml) was heated for 3 h with azeotropic removal of the resulting water. The reaction

mixture was washed successively with sat. $NaHCO_3$ aq. and water, then dried and evaporated to give **20a** (3.2 g, 94%) as pale yellow prisms.

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