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# Syntheses of Medium-Sized Heterocycles Using an Intramolecular Michael Reaction

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1,2,3,5-Tetrahydro-2-oxo-4,1-benzoxazepine-3-acetates (**5**, **13**, **16**), 2,3,5,6-tetrahydro-2-oxo-1*H*-4,1-benzoxazocine-3-acetates (**21**), and 1,2,3,5,6,7-hexahydro-2-oxo-4,1-benzoxazonine-3-acetate (**25**) were obtained from 3-[[2-(ω-hydroxyalkyl)phenyl]carbamoyl]acrylates (**4**, **12**, **15**, **20**, **24**) by the intramolecular Michael addition previously developed for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazine-2-acetates. In the case of 5-phenyl-3-oxo-4,1-benzoxazepine-3-acetates (**13**), the 3,5-*cis* and 3,5-*trans* isomers were obtained in a ratio of 1 : 1. Under basic conditions, each isomer was equilibrated to a mixture of *cis*- and *trans*-**13** in a ratio of 1 : 3. A deuterium exchange experiment revealed that the isomerization proceeded through the retro-Michael reaction. The stereochemistry of *trans*-**13e** was confirmed by X-ray analysis.

Among the compounds (**13**) synthesized, *N*-isopropyl (*cis*-**13c**), *N*-benzyl (*cis*- and *trans*-**13e**) and *N*-phenethyl (*cis*-**13f**) derivatives showed considerable anxiolytic activity in the conflict test in rats.

**Keywords**——2-oxo-4,1-benzoxazepine-3-acetate; 2-oxo-1*H*-4,1-benzoxazocine-3-acetate; 2-oxo-4,1-benzoxazonine-3-acetate; GABA analog; intramolecular Michael addition; X-ray analysis; anxiolytic activity

In the previous paper,[1] we reported a new synthesis of a series of 3,4-dihydro-2*H*-1,4-benzoxazine-2-acetates (**1**), which are cyclic γ-aminobutyric acid (GABA)[2] and/or γ-amino-β-hydroxybutyric acid (GABOB)[2a,b] analogs, by a one-pot reaction involving an intramolecular Michael addition reaction of 4-(2-hydroxyanilino)-2-butenoates prepared from 2-aminophenols and 4-bromo-2-butenoate. This paper describes the synthesis of medium-sized heterocycles such as benzoxazepine, benzoxazocine, and benzoxazonine, which also include a GABA and/or a GABOB moiety, by applying the intramolecular Michael reaction. The biological activity of the medium-sized heterocycles was also examined.

Reaction of 2-aminobenzyl alcohols (**2**) with fumaric acid chloride monoethyl ester (**3**) smoothly gave fumaramides (**4**) in good yields and these products were treated with potassium carbonate in ethanol at room temperature to afford 1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepine-3-acetates (**5**) in high yields. Under the same reaction conditions, however, an intermediate (**7**), obtained from **2** (X = H, $R^1 = CH_2Ph$) and methyl 4-bromo-2-butanoate (**6**), rearranged to methyl 1-benzyl-1,4-dihydro-2*H*-3,1-benzoxazine-2-propionate (**8**) in 39% yield.[3] Moreover, all attempted cyclizations of an analogous intermediate (**10**), prepared from 2-(benzylamino)methylphenol (**9**) and **3**, to a 2,3,4,5-tetrahydro-3-oxo-1,4-benzoxazepine-2-acetic acid derivative were unsuccessful. Secondary 2-aminobenzyl alcohols (**11**) also reacted with **3** to give fumaramides (**12**) in good yields. Treatment of **12** with potassium carbonate in ethanol yielded *cis–trans* mixtures of 2-oxo-5-phenyl-4,1-benzoxazepine-3-acetates (**13**) in a ratio of 1 : 1 in high yields. The products were separated by column chromatography on silica

gel. In the case of **12** (X=Cl, $R^1=CH_2Ph$), only the *trans*-isomer (**13g**) was obtained in 83% yield. Equilibration of **13e** under basic conditions, in which a *cis–trans* mixture was obtained in a ratio of 1 : 3, indicated that the *trans* isomer is more stable. Furthermore, a deuterium exchange experiment revealed that the isomerization proceeded *via* a retro-Michael reaction. The structure of *trans*-**13e** was confirmed by X-ray crystallographic analysis[4] (Fig. 1). In addition, tertiary 2-aminobenzyl alcohols (**14**) were converted to the corresponding 2-oxo-4,1-benzoxazepine-3-acetates (**16**) in 12—92% yields by treatment of the intermediates (**15**) with potassium carbonate. The physicochemical data and elemental analyses of **5**, **13**, and **16** are summarized in Table I.

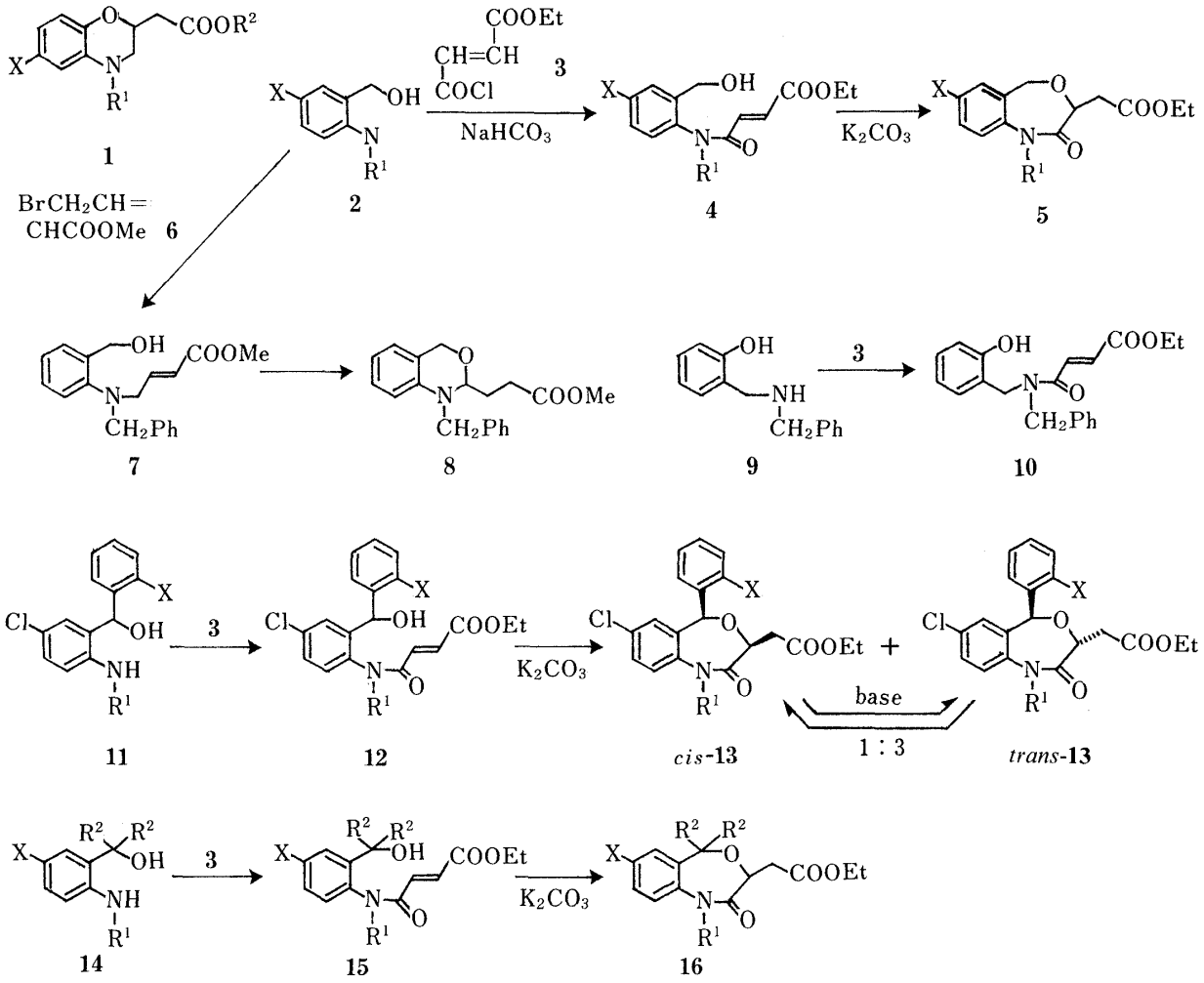



Chart 1

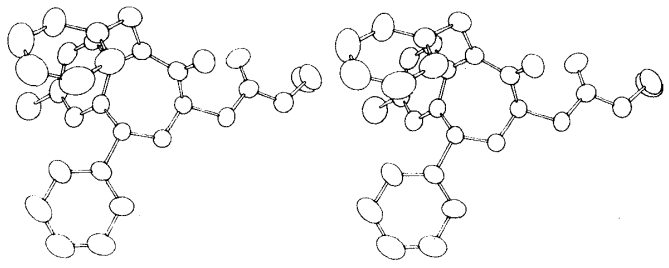
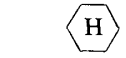


Fig. 1. Stereoscopic Drawings of the Structure of *trans*-**13e**

TABLE I. Physicochemical Properties and Analytical Data of Ethyl 1,2,3,5-Tetrahydro-2-oxo-4,1-benzoxazepine-3-acetates (**5**, **13**, and **16**)

| Compd. | X | $R^1$ | $R^2$ | Yield (%) | mp (°C) | Recryst.[a] solvent | Formula | Analysis (%) Calcd (Found) C | H | N | $^1$H-NMR ($CDCl_3$) $C_3$-H (1H) $\delta$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | H | H | — | 17 | 96—97 | I | $C_{13}H_{15}NO_4$ | 62.64 | 6.07 | 5.62 | 4.72 (dd) |
| | | | | | | | | (62.65 | 5.97 | 5.83) | |
| **5b** | H | Me | — | 91 | 90—91 | I | $C_{14}H_{17}NO_4$ | 63.86 | 6.51 | 5.32 | 4.32 (dd) |
| | | | | | | | | (64.02 | 6.46 | 5.22) | |
| **5c** | H | iso-Pr | — | 93 | 99—101 | I | $C_{16}H_{21}NO_4$ | 65.95 | 7.27 | 4.81 | 4.17 (dd) |
| | | | | | | | | (65.98 | 7.30 | 4.91) | |
| **5d** | H |  | — | 87 | 79—80 | H–I | $C_{19}H_{25}NO_4$ | 68.86 | 7.60 | 4.23 | 4.14 (dd) |
| | | | | | | | | (68.59 | 7.46 | 4.24) | |
| **5e** | H | $CH_2Ph$ | — | 95 | 95—97 | I | $C_{20}H_{21}NO_4$ | 70.78 | 6.24 | 4.13 | 4.41 (dd) |
| | | | | | | | | (71.00 | 6.18 | 4.22) | |
| **5f** | H | $(CH_2)_2Ph$ | — | 90 | Oil | — | $C_{21}H_{23}NO_4$ | 71.37 | 6.56 | 3.96 | 4.17 (dd) |
| | | | | | | | | (71.62 | 6.72 | 3.83) | |
| **5g** | Cl | $CH_2Ph$ | — | 93 | 107—109 | I | $C_{20}H_{20}ClNO_4$ | 64.25 | 5.39 | 3.75 | 4.37 (dd) |
| | | | | | | | | (64.56 | 5.40 | 3.90) | |
| *cis*-**13a** | H | Me | — | 47 | 182—184 | E | $C_{20}H_{20}ClNO_4$ | 64.25 | 5.39 | 3.75 | 4.52 (t) |
| | | | | | | | | (64.11 | 5.43 | 3.72) | |
| *trans*-**13a** | H | Me | — | 15 | 98—99 | E–H | $C_{20}H_{20}ClNO_4$ | 64.25 | 5.39 | 3.75 | 4.42 (dd) |
| | | | | | | | | (64.11 | 5.18 | 3.75) | |
| *cis*-**13b** | H | Et | — | 26 | 105—107 | E–H | $C_{21}H_{22}ClNO_4$ | 65.03 | 5.72 | 3.61 | 4.50 (t) |
| | | | | | | | | (65.12 | 5.79 | 3.52) | |
| *trans*-**13b** | H | Et | — | 12 | Oil | — | $C_{21}H_{22}ClNO_4$ | 65.03 | 5.72 | 3.61 | 4.40 (dd) |
| | | | | | | | | (65.36 | 5.89 | 3.50) | |
| *cis*-**13c** | H | iso-Pr | — | 49 | 128—130 | E–H | $C_{22}H_{24}ClNO_4$ | 65.75 | 6.02 | 3.49 | 4.44 (t) |
| | | | | | | | | (65.69 | 6.11 | 3.56) | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *trans*-**13c** | H | iso-Pr | — | 47 | Oil | — | $C_{22}H_{24}ClNO_4$ | 65.75 | 6.02 | 3.49 | 4.31 (dd) |
| | | | | | | | | (65.51 | 6.29 | 3.59) | |
| *cis*-**13d** | H |  | — | 30 | 114—116 | H | $C_{25}H_{28}ClNO_4$ | 67.94 | 6.39 | 3.17 | 4.43 (t) |
| | | | | | | | | (67.98 | 6.38 | 3.18) | |
| *trans*-**13d**[b] | H |  | — | — | Oil | — | $C_{25}H_{28}ClNO_4$ | 67.94 | 6.39 | 3.17 | 4.29 (dd) |
| | | | | | | | | (68.18 | 6.60 | 3.01) | |
| *cis*-**13e** | H | $CH_2Ph$ | — | 47 | 117—118 | E | $C_{26}H_{24}ClNO_4$ | 69.40 | 5.38 | 3.11 | 4.68 (dd) |
| | | | | | | | | (69.42 | 5.33 | 3.04) | |
| *trans*-**13e** | H | $CH_2Ph$ | — | 47 | 116—117 | E | $C_{26}H_{24}ClNO_4$ | 69.40 | 5.38 | 3.11 | 4.49 (dd) |
| | | | | | | | | (69.31 | 5.19 | 3.07) | |
| *cis*-**13f** | H | $(CH_2)_2Ph$ | — | 48 | 133—135 | E–H | $C_{27}H_{26}ClNO_4$ | 69.89 | 5.65 | 3.02 | 4.52 (dd) |
| | | | | | | | | (70.01 | 5.65 | 2.94) | |
| *trans*-**13f** | H | $(CH_2)_2Ph$ | — | 42 | Oil | — | $C_{27}H_{26}ClNO_4$ | 69.89 | 5.65 | 3.02 | 4.38 (dd) |
| | | | | | | | | (69.72 | 5.51 | 2.81) | |
| *trans*-**13g** | Cl | $CH_2Ph$ | — | 83 | 126—127 | E–H | $C_{26}H_{23}Cl_2NO_4$ | 64.47 | 4.79 | 2.89 | 4.49 (dd) |
| | | | | | | | | (64.67 | 4.65 | 2.91) | |
| **16a** | H | iso-Pr | Me | 71 | Oil | — | $C_{18}H_{25}NO_4$ | 67.69 | 7.89 | 4.39 | 4.42 (t) |
| | | | | | | | | (68.03 | 7.93 | 4.12) | |
| **16b** | H | $CH_2Ph$ | Me | 50 | 105—106 | E–H | $C_{22}H_{25}NO_4$ | 71.91 | 6.86 | 3.81 | 4.57 (t) |
| | | | | | | | | (72.03 | 6.83 | 3.81) | |
| **16c** | H | iso-Pr | Ph | 92 | 169—170 | E–H | $C_{28}H_{29}NO_4$ | 75.82 | 6.59 | 3.16 | 4.79 (t) |
| | | | | | | | | (75.94 | 6.62 | 3.33) | |
| **16d** | H | $CH_2Ph$ | Ph | 12 | 189—191 | E–H | $C_{32}H_{29}NO_4$ | 78.18 | 5.95 | 2.85 | 4.90 (t) |
| | | | | | | | | (77.89 | 5.81 | 2.73) | |
| **16e** | Cl | iso-Pr | Ph | 68 | 153—154 | E–H | $C_{28}H_{28}ClNO_4$ | 70.36 | 5.90 | 2.93 | 4.76 (t) |
| | | | | | | | | (70.15 | 6.06 | 2.88) | |
| **16f** | Cl | $CH_2Ph$ | Ph | 17 | 158—159 | E–H | $C_{32}H_{28}ClNO_4$ | 73.06 | 5.37 | 2.66 | 4.89 (t) |
| | | | | | | | | (73.23 | 5.27 | 2.59) | |

*a*) Recrystallization solvents used were as follows: E, ethyl acetate; H, hexane; I, isopropyl ether. *b*) Pure *trans* isomer could not be obtained. All attempts at separation were unsuccessful.

Similarly, 2-aminophenethyl alcohols (**19**) reacted with **3** to give fumaramides (**20**), which were converted to 2,3,5,6-tetrahydro-2-oxo-1*H*-4,1-benzoxazocine-3-acetates (**21**) in good yields by treatment with potassium carbonate in ethanol. However, phenyl-substituted analogs (**20**: $R^2$ = Ph), prepared by successive reaction of *o*-fluoronitrobenzene (**17**) with the anion of ethyl phenylacetate,[5] reduction of the resulting phenylacetate (**18**) with lithium borohydride in tetrahydrofuran, reduction with hydrazine in the presence of Raney nickel[6] in ethanol, and finally treatment of **19** with **3**, were hardly cyclized to the corresponding 2-oxo-1*H*-4,1-benzoxazocines (**21**) under the same reaction conditions. Therefore, the Michael addition of **20** ($R^2$ = Ph) with potassium carbonate in the presence of a phase transfer catalyst in dichloromethane was attempted. When the fumaramides (**20**: $R^2$ = Ph) were treated with potassium carbonate in the presence of 18-crown-6 in dichloromethane, 2-oxo-6-phenyl-1*H*-4,1-benzoxazocine-3-acetates (**21**: $R^2$ = Ph) were obtained in 30—55% yields (Table II). Theoretically, the products (**21**) having a phenyl substituent at the 6-position could consist of at least two stereoisomers (*cis* and *trans*), but we could isolate only one isomer, the stereochemistry of which has not been determined yet.

We also applied the Michael addition reaction to the synthesis of a 9-membered heterocycle, 4,1-benzoxazonine.[7] 3-(2-Aminophenyl)propanol (**23**), prepared from *o*-nitrocinnamaldehyde (**22**) by reduction and *N*-benzylation, reacted with **3** to yield **24** as an intermediate, which was treated with potassium carbonate in ethanol or with potassium carbonate in the presence of 18-crown-6 in dichloromethane at room temperature to give the desired 1,2,3,5,6,7-hexahydro-2-oxo-4,1-benzoxazonine-3-acetate (**25**) in low (6—9%) yield together with a dimer (**26**) as a by-product. The structures of **25** and **26** were confirmed by the physicochemical data (see Experimental). Although the yield of **25** was low, the procedure provides a new method for the synthesis of 9-membered heterocycles.

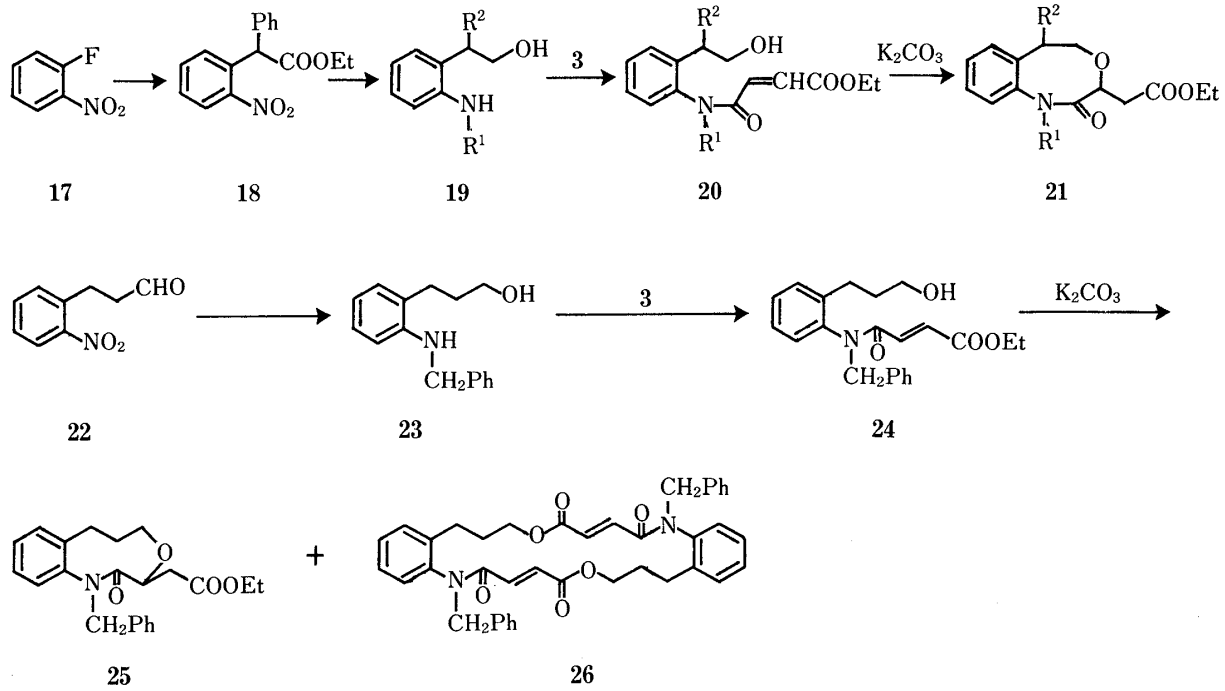



Chart 2

The compounds (**5**, **13**, **16**, and **21**) synthesized here were assessed for biological activity,[8] especially on the central nervous system (CNS). Among the 2-oxo-5-phenyl-4,1-benzoxazepine-3-acetates, *cis*-**13c**, -**13e**, -**13f**, and *trans*-**13e** showed considerable anxiolytic activity in the conflict test[9] (20 mg/kg, *i.p.*) in rats. However, the other medium-sized

TABLE II. Physicochemical Properties and Analytical Data of Ethyl 1-Alkyl-2,3,5,6-tetrahydro-2-oxo-1*H*-4,1-benzoxazocine-3-acetates (**21**)

| Compd. **21** | $R^1$ | $R^2$ | Yield[a] (%) | mp (°C) | Formula | Analysis (%) Calcd (Found) C | H | N | $^1$H-NMR ($CDCl_3$) $C_3$-H (1H) $\delta$ |
|---|---|---|---|---|---|---|---|---|---|
| **a** | Me | H | 50[b] | Oil | $C_{15}H_{19}NO_4$ | 64.96 (65.24 | 6.91 7.13 | 5.05 4.91) | 3.8—4.2 |
| **b** | iso-Pr | H | 65[b] | 71—72 | $C_{17}H_{23}NO_4$ | 66.86 (66.71 | 7.59 7.66 | 4.59 4.36) | 3.89 (t) |
| **c** | $CH_2Ph$ | H | 70[b] | 81—82 | $C_{21}H_{23}NO_4$ | 71.37 (71.26 | 6.56 6.61 | 3.96 3.81) | 3.97 (t) |
| **d** | Me | Ph | 30[c] | 138—139 | $C_{21}H_{23}NO_4$ | 71.37 (71.17 | 6.56 6.68 | 3.96 3.91) | 3.9—4.3 |
| **e** | iso-Pr | Ph | 40[c] | 110—111 | $C_{23}H_{27}NO_4$ | 72.42 (72.51 | 7.13 7.03 | 3.67 3.66) | 3.99 (t) |
| **f** | $CH_2Ph$ | Ph | 55[c] (17)[c] | 131—132 | $C_{27}H_{27}NO_4$ | 75.50 (75.71 | 6.34 6.45 | 3.26 3.14) | 4.06 (t) |

*a*) Recrystallization from isopropyl ether. *b*) Method a (see Experimental). *c*) Method b (see Experimental).

heterocycles (**5**, **16**, and **21**) showed no significant biological activity on the CNS.

## 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 $\delta$ 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).

**Ethyl 3-[*N*-[2-(Hydroxymethyl)phenyl]-*N*-methylcarbamoyl]acrylate (4b)**——Fumaric acid chloride monoethyl ester (**3**, 13 g) was added dropwise to a cooled suspension of 2-(methylamino)benzyl alcohol[10] (**2b**, 11 g) and $NaHCO_3$ (8 g) in $CH_2Cl_2$ (150 ml). The mixture was stirred for 1 h at room temperature, then the organic layer was washed with water, dried and evaporated. The crystalline residue was recrystallized from iso-$Pr_2O$ to give **4b** (11 g, 52%) as colorless prisms. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3350, 1720, 1660, 1620. $^1$H-NMR ($CDCl_3$) $\delta$: 1.21 (3H, t, $J$=7 Hz, $OCH_2\underline{CH_3}$), 3.28 (3H, s, N–$CH_3$), 4.10 (2H, q, $J$=7 Hz, $OC\underline{H_2}CH_3$), 4.54 (2H, s, –$C\underline{H_2}$–OH), 6.53 (1H, d, $J$=15 Hz, olefin. H), 6.83 (1H, d, $J$=15 Hz, olefin. H), 7.0—7.7 (4H, m, Ar-H) (Table III).

The other compounds (**4**) were similarly prepared from the corresponding **2** and are included in Table III; the starting materials **2c**—**f** and **2g** were prepared by reductive alkylation[11] of 2-aminobenzyl alcohol[12] (**2a**) and 2-amino-5-chlorobenzyl alcohol.[13]

**Ethyl 1,2,3,5-Tetrahydro-1-methyl-2-oxo-4,1-benzoxazepine-3-acetate (5b)**——A suspension of **4b** (9.6 g) and $K_2CO_3$ (1.0 g) in EtOH (100 ml) was stirred for 1 h at room temperature. The solvent was removed and the residue was extracted with EtOAc. The extracts were washed with water, dried and evaporated. The residue was recrystallized from iso-$Pr_2O$ to give **5b** (8.7 g, 91%) as colorless prisms. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1730, 1660. $^1$H-NMR ($CDCl_3$) $\delta$: 1.21 (3H, t, $J$=7 Hz, $OCH_2\underline{CH_3}$), 2.62 (1H, dd, $J$=17, 6 Hz, –$C\underline{H_2}$–COOEt), 3.02 (1H, dd, $J$=17, 8 Hz, –$C\underline{H_2}$–COOEt), 3.44 (3H, s, N–$CH_3$), 4.08 (2H, q, $J$=7 Hz, $OC\underline{H_2}CH_3$), 4.32 (1H, dd, $J$=6, 8 Hz, 3-H), 4.53 (1H, d, $J$=11 Hz, 5-H), 4.67 (1H, d, $J$=11 Hz, 5-H), 7.1—7.5 (4H, m, Ar-H).

The other compounds (**5**) listed in Table I were similarly prepared from the corresponding **4**.

**Ethyl 3-[*N*-Benzyl-*N*-[4-chloro-2-(α-hydroxybenzyl)phenyl]carbamoyl]acrylate (12e)**——Fumaric acid chloride monoethyl ester (**3**, 2.2 g) was added to a cooled solution of 2-(benzylamino)-5-chloro-α-phenylbenzyl alcohol (**11e**, 3.9 g), which was prepared by reductive alkylation of 2-amino-5-chloro-α-phenylbenzyl alcohol,[14] in $CH_2Cl_2$ (80 ml) in the presence of $NaHCO_3$ (1.2 g). The reaction mixture was stirred for 1 h, then worked up as described for **4b**. The residue was chromatographed on silica gel with toluene–EtOAc (5 : 1) to give **12e** (4.6 g, 85%) as a colorless oil. *Anal.* Calcd for $C_{26}H_{24}ClNO_4$: C,69.40; H, 5.38; N, 3.11. Found: C, 69.61; H, 5.43; N, 2.99. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400, 1720,

TABLE III. Physicochemical Properties and Analytical Data of Ethyl 3-[*N*-[2-Hydroxymethyl)phenyl]carbamoyl]acrylates (**4**)

| Compd. **4** | X | $R^1$ | Yield (%) | mp (°C) | Recryst.[a] solvent | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N |
| **a** | H | H | 76 | 136—137 | A | $C_{13}H_{15}NO_4$ | 62.64 | 6.07 | 5.62 |
| | | | | | | | (62.49 | 6.02 | 5.81) |
| **b** | H | Me | 52 | 76—77 | I | $C_{14}H_{17}NO_4$ | 63.86 | 6.51 | 5.32 |
| | | | | | | | (63.86 | 6.35 | 5.22) |
| **c** | H | iso-Pr | 77 | 87—88 | I | $C_{16}H_{21}NO_4$ | 65.95 | 7.27 | 4.81 |
| | | | | | | | (65.86 | 7.15 | 5.02) |
| **d** | H |  | 75 | 103—104 | I | $C_{19}H_{25}NO_4$ | 68.86 | 7.60 | 4.23 |
| | | | | | | | (68.79 | 7.72 | 4.25) |
| **e** | H | $CH_2Ph$ | 87 | Oil | — | $C_{20}H_{21}NO_4$ | 70.78 | 6.24 | 4.13 |
| | | | | | | | (71.11 | 6.50 | 3.92) |
| **f** | H | $(CH_2)_2Ph$ | 77 | 81—82 | I | $C_{21}H_{23}NO_4$ | 71.37 | 6.56 | 3.96 |
| | | | | | | | (71.41 | 6.51 | 4.05) |
| **g** | Cl | $CH_2Ph$ | 88 | Oil | — | $C_{20}H_{20}ClNO_4$ | 64.25 | 5.39 | 3.75 |
| | | | | | | | (64.53 | 5.58 | 3.84) |

*a*) Recrystallization solvents used were as follows: A, ethanol; I, isopropyl ether.

1660, 1620. $^1$H-NMR ($CDCl_3$) $\delta$: 1.20 (3H, t, $J$=7 Hz, $CH_3$), 4.11 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 4.41 (1H, d, $J$=14 Hz, N–$CH_2$–Ph), 5.47 (1H, d, $J$=14 Hz, N–$CH_2$–Ph), 5.63 (1H, s, CH), 5.90 (1H, d, $J$=16 Hz, olefin. H). 6.47 (1H, d, $J$=16 Hz, olefin. H), 7.1—8.0 (13H, m, Ar-H). MS *m/z*: 451, 449 ($M^+$).

The other compounds (**12a—d, f, g**) were similarly prepared from 2-(alkylamino)-5-chloro-α-phenylbenzyl alcohol (**11a—d, f**) and 2-(benzylamino)-5-chloro-α-(2-chlorophenyl)benzyl alcohol (**11g**); the starting materials **11a**,[14] **11b—d**, **11f**, and **11g** were prepared by reductive alkylation of 2-amino-5-chloro-α-phenylbenzyl alcohol[14] and 2-amino-5-chloro-α-(2-chlorophenyl)benzyl alcohol,[15] respectively. **12a**, an oil (88%), *Anal.* Calcd for $C_{20}H_{20}ClNO_4$: C, 64.25: H, 5.39; N, 3.75. Found: C, 64.29; H, 5.31; N, 3.63. **12b**, an oil (84%), *Anal.* Calcd for $C_{21}H_{22}ClNO_4$: C, 65.03; H, 5.72; N, 3.61. Found: C, 65.35; H, 5.83; N, 3.50. **12c**, an oil (88%), *Anal.* Calcd for $C_{22}H_{24}ClNO_4$: C, 65.75; H, 6.02; N, 3.49. Found: C, 65.91; H, 6.11; N, 3.22. **12d**, an oil (90%), *Anal.* Calcd for $C_{25}H_{28}ClNO_4$: C, 67.94; H, 6.39; N, 3.17. Found: C, 67.99; H, 6.51; N, 2.90. **12f**, an oil (81%), *Anal.* Calcd for $C_{27}H_{26}ClNO_4$: C, 69.89; H, 5.65; N, 3.02. Found: C, 69.98; H, 5.82; N, 2.87. **12g**, an oil (87%), *Anal.* Calcd for $C_{26}H_{23}Cl_2NO_4$: C, 64.47; H, 4.79; N, 2.89. Found: C, 64.38; H, 4.68; N, 2.68.

**Ethyl (3,5-*cis*)- and (3,5-*trans*)-1-Benzyl-7-chloro-1,2,3,5-tetrahydro-2-oxo-5-phenyl-4,1-benzoxazepine-3-acetate (*cis*- and *trans*-13e)**——A suspension of **12e** (4.5 g) and $K_2CO_3$ (0.7 g) in EtOH (60 ml) was stirred at room temperature. After being stirred for 1 h, the reaction mixture was worked up as described for **5b** to give the oily residue (4.5 g), which was chromatographed on silica gel with toluene–EtOAc (50 : 1). The first effluent gave *cis*-**13e** (2.1 g, 47%) as colorless cubes. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1730, 1680. $^1$H-NMR ($CDCl_3$) $\delta$: 1.24 (3H, t, $J$=7 Hz, $CH_3$), 2.86 (1H, dd, $J$=17, 6 Hz, –$C\underline{H}_2$–COOEt, 3.21 (1H, dd, $J$=17, 8 Hz, –$C\underline{H}_2$–COOEt), 3.71 (1H, d, $J$=16 Hz, N–$C\underline{H}_2$–Ph), 4.14 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 4.68 (1H, dd, $J$=6, 8 Hz, 3-H), 4.73 (1H, dd, $J$=16 Hz, N–$CH_2$–Ph), 5.91 (1H, s, 5-H), 6.9—7.5 (13H, m, Ar-H). The second effluent gave *trans*-**13e** (2.1 g, 47%) as colorless cubes. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1730, 1680. $^1$H-NMR ($CDCl_3$) $\delta$: 1.24 (3H, t, $J$=7 Hz, $CH_3$), 2.76 (1H, dd, $J$=17, 6 Hz, –$C\underline{H}_2$–COOEt), 3.13 (1H, dd, $J$=17, 8 Hz, –$C\underline{H}_2$–COOEt), 4.14 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 4.49 (1H, dd, $J$=6, 8 Hz, 3-H), 4.84 (1H, d, $J$=15 Hz, N–$CH_2$–Ph), 5.43 (1H, s, 5-H), 5.46 (1H, d, $J$=15 Hz, N–$CH_2$–Ph), 6.52 (1H, br s, 6-H), 7.0—7.4 (12H, m, Ar-H).

The other compounds (**13**) listed in Table I were similarly prepared from the corresponding **12**.

**Treatment of *cis*-13e with NaOD in $CD_3OD$**——A solution of *cis*-**13e** (100 mg) in $CD_3OD$ (2.0 ml) was treated with a few drops of 40% NaOD/$D_2O$ at room temperature. The reaction mixture was stirred for 2 h, then EtOAc was added. The EtOAc layer was separated, washed with water, dried and evaporated to give a deuterio-**13e** as an oil. The $^1$H-NMR spectrum showed a loss of the signals due to the methylene protons of the ester group and two singlets at 4.60 and 4.42 ppm (total 1H) due to the C-3 methine proton. MS *m/z*: 442, 440 ($M^+$ for $C_{25}H_{17}D_5ClNO_4$).

**Ethyl 1-Benzyl-1,2,3,5-tetrahydro-5,5-dimethyl-2-oxo-4,1-benzoxazepine-3-acetate (16b)**——Fumaric acid chloride monoethyl ester (**3**, 0.74 g) was added to a cooled solution of 2-(benzylamino)-α,α-dimethylbenzyl alcohol (**14b**, 1.0 g), which was prepared by reductive alkylation of 2-amino-α,α-dimethylbenzyl alcohol,[16] in $CH_2Cl_2$ (30 ml) in the presence of $NaHCO_3$ (0.45 g). After being stirred for 1 h, the reaction mixture was worked up as described for **4b** to

TABLE IV. Physicochemical Properties and Analytical Data of Ethyl 3-[*N*-Alkyl-*N*-[2-(2-hydroxy-1-phenylethyl)phenyl]carbamoyl]acrylates (**20**)

| Compd. **20** | $R^1$ | $R^2$ | Yield (%) | mp (°C) | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| **a** | Me | H | 71 | Oil | $C_{15}H_{19}NO_4$ | 64.96 (65.31 | 6.91 7.04 | 5.05 4.81) |
| **b** | iso-Pr | H | 71[a] | 91—93 | $C_{17}H_{23}NO_4$ | 66.86 (69.91 | 7.59 7.38 | 4.59 4.43) |
| **c** | $CH_2Ph$ | H | 84 | Oil | $C_{21}H_{23}NO_4$ | 71.37 (71.58 | 6.56 6.88 | 3.96 3.99) |
| **d** | Me | Ph | 74[b] | 112—114 | $C_{21}H_{23}NO_4$ | 71.37 (71.07 | 6.56 6.58 | 3.96 4.25) |
| **e** | iso-Pr | Ph | 70 | Oil | $C_{23}H_{27}NO_4$ | 72.42 (72.39 | 7.13 7.40 | 3.67 3.43) |
| **f** | $CH_2Ph$ | Ph | 88 | Oil | $C_{27}H_{27}NO_4$ | 75.50 (75.61 | 6.34 6.57 | 3.26 3.19) |

*a*) Recrystallization from ethyl acetate–hexane. *b*) Recrystallization from isopropyl ether.

give ethyl 3-[*N*-benzyl-*N*-[2-(dimethylcarbinyl)phenyl]carbamoyl]acrylate (**15b**, 1.3 g, 87%) as a crude oil. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400, 1720, 1660, 1620. Without purification, a suspension of **15b** (1.3 g) and $K_2CO_3$ (0.24 g) in EtOH (20 ml) was stirred for 3 h at room temperature. The reaction mixture was worked up as described for **5b**. The residue was chromatographed on silica gel with toluene–EtOAc (40 : 1) to give **16b** (0.65 g, 50%) as colorless needles. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1725, 1670. $^1$H-NMR ($CDCl_3$) $\delta$: 1.20 (3H, t, $J$=7 Hz, $OCH_2\underline{CH_3}$), 1.30 (3H, s, 5-$CH_3$), 1.62 (3H, s, 5-$CH_3$), 2.63 (1H, dd, $J$=17, 7 Hz, –$C\underline{H_2}$–COOEt), 3.01 (1H, dd, $J$=17, 7 Hz, –$C\underline{H_2}$–COOEt), 4.09 (2H, q, $J$=7 Hz, $OC\underline{H_2}CH_3$), 4.53 (1H, t, $J$=7 Hz, 3-H), 4.73 (1H, d, $J$=15 Hz, N–$CH_2$–Ph), 5.40 (1H, d, $J$=15 Hz, N–$CH_2$–Ph), 7.1—7.5 (9H, m, Ar-H).

The other compounds (**16a**, **c**—**f**) were similarly prepared from **14a**, **c**—**f** without purification of the intermediates (**15a**, **c**—**f**).

**Ethyl α-(2-Nitrophenyl)phenylacetate (18)**——A mixture of NaH (oil-free, 9.9 g), ethyl phenylacetate (67 g), and *o*-fluoronitrobenzene (57 g) in dry dimethylformamide (DMF) (200 ml) was stirred for 30 min under cooling. The reaction mixture was carefully poured into dil. HCl and the resulting aqueous solution was extracted with toluene. The extracts were washed with water, dried and evaporated to give an oil, which was chromatographed on silica gel with toluene–hexane (2 : 1) to give **18** (50 g, 44%) as a colorless oil. *Anal.* Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.45; H, 5.21; N, 5.03. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1730, 1520, 1350. $^1$H-NMR ($CDCl_3$) $\delta$: 5.62 (1H, s, CH). MS *m/z*: 285 ($M^+$).

**2-(2-Aminophenyl)-2-phenylethanol (19: $R^1$=H, $R^2$=Ph)**——A mixture of **18** (40 g) and $LiBH_4$ (6.1 g) in dry tetrahydrofuran (THF) (150 ml) was stirred for 24 h at 5 °C. The mixture was poured into 20% AcOH (80 ml) and the aqueous solution was extracted with EtOAc. The extracts were washed with water, dried and evaporated to give the nitro alcohol (33 g) as a crude oil, which was reduced by the method of Balcom *et al.*[6] using 100% hydrazine hydrate (16 ml) and Raney Ni. After the usual work-up, a reddish-brown oil (28 g) was obtained. This crude product was converted to the oxalate and recrystallized from MeOH–ether to give colorless scales (24 g, 65%), mp 134—136 °C. *Anal.* Calcd for $C_{14}H_{16}NO \cdot 3/4(COOH)_2$: C, 66.30; H, 5.92; N, 4.99. Found: C, 66.14; H, 6.01; N, 4.76. $^1$H-NMR ($CD_3OD$) $\delta$: 4.0—4.2 (2H, two d, $J$=6, 8 Hz, $CH_2$), 4.34 (1H, dd, $J$=6, 8 Hz, CH).

**Ethyl 3-[*N*-Benzyl-*N*-[2-(2-hydroxy-1-phenylethyl)phenyl]carbamoyl]acrylate (20f)**——Fumaric acid chloride monoethyl ester (**3**, 2.7 g) was added dropwise to a suspension of $NaHCO_3$ (2.0 g) and 2-[2-(benzylamino)phenyl]-2-phenylethanol (**19f**, 5.8 g), which was prepared by reductive alkylation of 2-(2-aminophenyl)-2-phenylethanol (**19**: $R^1$=H, $R^2$=Ph), in $CH_2Cl_2$ (50 ml) under cooling. After being stirred for 20 min, the reaction mixture was worked up as described for **4b**. The resulting residue was chromatographed on silica gel with toluene–EtOAc (5 : 1) to give **20f** (6.4 g, 88%) as a colorless oil. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400, 1720, 1660, 1620. $^1$H-NMR ($CDCl_3$) $\delta$: 1.14 (3H, t, $J$=7 Hz, $CH_3$), 3.7—4.3 (5H, m, $OC\underline{H_2}CH_3$, Ar(Ph)C$\underline{H}$–C$\underline{H_2}$–OH), 4.50 (1H, d, $J$=14 Hz, N–$CH_2$–Ph), 5.33 (1H, d, $J$=14 Hz, N–$CH_2$–Ph), 5.73 (1H, d, $J$=15 Hz, olefin. H), 6.23 (1H, d, $J$=15 Hz, olefin. H), 6.9—7.6 (14H, m, Ar-H) (Table IV).

The other compounds (**20**) were similarly prepared from the corresponding **19** and are included in Table IV; the starting materials **19a**—**c** and **19d**, **e** were prepared by reductive alkylation of **19** ($R^1$=$R^2$=H) and **19** ($R^1$=H, $R^2$=Ph).

**Ethyl 1-Benzyl-2,3,5,6-tetrahydro-2-oxo-6-phenyl-1*H*-4,1-benzoxazocine-3-acetate (21f)**——Method a: A suspension of **20f** (500 mg) and $K_2CO_3$ (70 mg) in EtOH (10 ml) was stirred for 4 d at room temperature. The mixture was worked up as described for **5b** to give an oily residue (300 mg). The residue was chromatographed on silica gel with toluene–EtOAc (40 : 1) to give **21f** (83 mg, 17%) as colorless needles after recrystallization from iso-$Pr_2O$. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1730, 1660. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22 (3H, t, $J$=7 Hz, $CH_3$), 2.76 (1H, dd, $J$=17, 7 Hz, –C<u>H</u>$_2$–COOEt), 3.02 (1H, dd, $J$=17, 7 Hz, –C<u>H</u>$_2$–COOEt), 3.7—3.9 (2H, m, 5-H), 4.06 (1H, t, $J$=7 Hz, 3-H), 4.09 (2H, q, $J$=7 Hz, OC<u>H</u>$_2$$CH_3$), 4.3—4.5 (1H, m, 6-H), 4.42 (1H, d, $J$=14 Hz, N–C<u>H</u>$_2$–Ph), 5.90 (1H, d, $J$=14 Hz, N–C<u>H</u>$_2$–Ph), 6.3 (2H, m, Ar-H), 6.7—7.5 (12H, m, Ar-H).

Method b: A mixture of **20f** (5.0 g), 18-crown-6 (1.5 g), and $K_2CO_3$ (0.8 g) in $CH_2Cl_2$ (50 ml) was stirred for 3 d at room temperature. After removal of the solvent, the residue was chromatographed on silica gel with toluene–EtOAc (40 : 1) to give **21f** (2.77 g, 55%). The physicochemical data were identical with those of **21f** obtained by Method a.

**3-[2-(Benzylamino)phenyl]propanol (23)**——A solution of *o*-nitrocinnamaldehyde (**22**, 25 g) in MeOH (250 ml) was treated with $NaBH_4$ (1.4 g) to give *o*-nitrocinnamyl alcohol (24 g, 96%) as colorless crystals. A solution of this material (7.2 g) in EtOH (80 ml) was subjected to catalytic hydrogenation over 5% Pd–C (2 g) at ordinary temperature and pressure until the absorption of hydrogen ceased. After removal of the catalyst, the filtrate was evaporated to give 3-(2-aminophenyl)propanol (5.7 g, 94%) as colorless crystals. Recrystallization from iso-$Pr_2O$ gave colorless needles, mp 63—64 °C. *Anal.* Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.62; H, 8.83; N, 9.34. A solution of this aminoalcohol (3.9 g) and benzaldehyde (2.8 g) in AcOH (60 ml) was treated with $NaBH_4$ (1.0 g) to give **23** as a colorless oil (5.4 g, 86%), after chromatography on silica gel with toluene–EtOAc (10 : 1). *Anal.* Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.62; H, 8.15; N, 5.77. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400. $^1$H-NMR ($CDCl_3$) $\delta$: 1.8 (2H, m, –$CH_2$C<u>H</u>$_2$$CH_2$–), 2.57 (2H, t, $J$=8 Hz, Ar–C<u>H</u>$_2$$CH_2$–), 3.56 (2H, t, $J$=6 Hz, –C<u>H</u>$_2$–OH), 4.28 (2H, s, N–C<u>H</u>$_2$–Ph), 6.4—7.3 (9H, m, Ar-H).

**Ethyl 3-[*N*-Benzyl-*N*-[2-(3-hydroxypropyl)phenyl]carbamoyl]acrylate (24)**——A solution of **23** (2.65 g) in $CH_2Cl_2$ (30 ml) was treated with **3** (1.9 g) to give **24** (3.31 g, 82%) as a colorless oil, after chromatography on silica gel with toluene–EtOAc (2 : 1). *Anal.* Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.99; H, 6.71; N, 3.50. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3400, 1720, 1660, 1630. $^1$H-NMR ($CDCl_3$) $\delta$: 1.18 (3H, t, $J$=7 Hz, $CH_3$), 1.7 (2H, m, –$CH_2$C<u>H</u>$_2$$CH_2$OH), 2.4 (2H, m, Ar–C<u>H</u>$_2$$CH_2$–), 3.51 (2H, t, $J$=7 Hz, –C<u>H</u>$_2$OH), 4.40 (1H, d, $J$=14 Hz, N–C<u>H</u>$_2$–Ph), 5.30 (1H, d, $J$=14 Hz, N–C<u>H</u>$_2$–Ph), 6.53 (1H, d, $J$=15 Hz, olefin. H), 6.87 (1H, d, $J$=15 Hz, olefin. H).

**Ethyl 1-Benzyl-1,2,3,5,6,7-hexahydro-2-oxo-4,1-benzoxazonine-3-acetate (25) and the 22-Membered Ring Compound (26)**——Method a: A suspension of **24** (1.47 g) and $K_2CO_3$ (0.28 g) in EtOH (30 ml) was stirred for 5 d at room temperature. The mixture was worked up at described for **5b** to give an oily residue (1.0 g), which was chromatographed on silica gel with toluene–EtOAc (10 : 1) to give **25** (89 mg, 6%) as a colorless oil. *Anal.* Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.95; H, 6.94; N, 3.56. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1730, 1655. $^1$H-NMR ($CDCl_3$) $\delta$: 1.20 (3H, t, $J$=7 Hz, $CH_3$), 1.7 (2H, m, 6-H), 2.8 (2H, m, –C<u>H</u>$_2$COOEt), 4.05 (2H, q, $J$=7 Hz, OC<u>H</u>$_2$$CH_3$), 4.53 (1H, d, $J$=14 Hz, N–C<u>H</u>$_2$–Ph), 5.01 (1H, d, $J$=14 Hz, N–C<u>H</u>$_2$–Ph), 6.4—7.3 (9H, m, Ar-H). MS *m/z*: 367 ($M^+$).

Method b: A suspension of **24** (1.47 g), $K_2CO_3$ (0.28 g), and 18-crown-6 (0.53 g) in $CH_2Cl_2$ (20 ml) was heated under reflux for 3 d with stirring. The reaction mixture was chromatographed on silica gel with toluene–EtOAc (10 : 1) to give **25** (140 mg, 9%) as a colorless oil. The elution was continued with the same eluent to give **26** (220 mg, 17%) as colorless crystals, which were recrystallized from acetone to give colorless prisms, mp 145—148 °C and 221—222 °C (double mp). *Anal.* Calcd for $C_{40}H_{38}N_2O_6 \cdot 1/2(CH_3)_2CO$: C, 74.20; H, 6.15; N, 4.17. Found: C, 74.08; H, 5.99; N, 4.24. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1720, 1660, 1630. $^1$H-NMR ($CDCl_3$) $\delta$: 3.8 (4H, m, –COOC<u>H</u>$_2$–), 4.87 (4H, s, N–C<u>H</u>$_2$–Ph), 6.43 (2H, d, $J$=15 Hz, olefin. H), 6.82 (2H, d, $J$=15 Hz, olefin. H). MS *m/z*: 642 ($M^+$).

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3) Compound **8** was obtained as an oil. *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.51; H, 6.76; N, 4.23. The spectral data were as follows: IR $\nu_{max}^{neat}$ $cm^{-1}$: 1735. $^1$H-NMR ($CCl_4$): 1.90 (2H, q, $J$=7 Hz, –C<u>H</u>$_2$$CH_2$COOMe), 2.28 (2H, t, $J$=7 Hz, –$CH_2$C<u>H</u>$_2$COOMe), 3.52 (3H, s, $CH_3$), 4.38 (2H, s, $CH_2$), 4.62 (1H, t, $J$=7 Hz, CH), 4.72 (2H, s, $CH_2$), 6.5—7.3 (9H, m, Ar-H). MS *m/z*: 311 ($M^+$), 224 ($M^+ - CH_2CH_2COOMe$).

4) Colorless columnar crystals of *trans*-**13e** obtained from ethyl acetate are triclinic, space group $P\bar{1}$, $a=10.897$ (4), $b=13.313$ (4), $c=8.927$ (2) Å, $\alpha=105.52$ (2), $\beta=95.69$ (2), $\gamma=109.80$ (2)°, $U=1148.1$ Å$^3$, $Z=2$, $D_c=1.30$ gcm$^{-3}$. The structure was solved by the direct method (MULTAN 78, G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect.*, **A27**, 368 (1971)).
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