(d, 0.35 H (*Z* isomer), J = 10.0 Hz), 5.37 (d, 0.65 H (*E* isomer), J = 16.0 Hz), 6.25–6.99 (m, 4 H), 7.12 (d, 1 H, J = 8.5 Hz), 7.34 (s, 5 H).

A mixture containing 629 mg of the above *E* and *Z* isomers of *N*-methyl-*N*-[*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]-2-phenylglycine ethyl ester and 68 mg of sodium hydroxide in 3 mL of water and 2 mL of ethanol was heated at reflux with stirring for 30 min. The mixture was cooled, acidified with 10% hydrochloric acid, diluted with 15 mL of water, and extracted with methylene chloride. The organic layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting oil was chromatographed over silica gel with a 1:1 chloroform–acetone mixture as the eluent to give 301 mg (51%) of (*E*- and (*Z*)-*N*-methyl-*N*-[*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]2-phenylglycine (**38**) as a pale oil: IR ($CHCl_3$) 3300–2450, 2203, 1712, 1613, 1595, 1381, 1199, 1112, 1062, 1033 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.60 (s, 3 H), 2.30–3.28 (m, 4 H), 3.79 (s, 3 H), 5.08 (d, 0.35 H (*Z* isomer), J = 10.0 Hz), 5.31 (d, 0.65 H, (*E* isomer), J = 16.0 Hz), 6.27–6.90 (m, 4 H), 7.14 (d, 1 H, J = 9.0 Hz), 7.36 (s, 5 H), 10.9 (s, 1 H).

Treatment of *N*-Methyl-*N*-[*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]-2-phenylglycine (38) with Acetic Anhydride. A solution containing 301 mg of (*E*)- and (*Z*)-*N*-methyl-*N*-[*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]-2-phenylglycine (**38**) in 1.5 mL of acetic anhydride was heated at 55 °C for 3 h. When the solution cooled, 10 mL of water was added and the mixture was stirred for an additional 10 min. Extraction of the aqueous mixture with benzene was followed by washing of the benzene extracts with water, a saturated aqueous sodium bicarbonate solution, and water. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure to give 134 mg of a brown oil. This oil was chromatographed over silica gel, using a 40% ether–hexane mixture as the eluent. The major component isolated from the column contained 27 mg (11%) of 1-methyl-2-phenyl-3-cyano-7-methoxy-4,5-dihydro-1*H*-benz[*g*]indole (**39**) as a crystalline solid: mp 183–184 °C; IR (KBr) 2193, 1570, 1490, 1464, 1294, 1277, 1247, 1045, 810, 766, 700 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.64–3.08 (m, 4 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 6.76–6.97 (m, 2 H), 7.38–7.66 (m, 6 H); mass spectrum, m/e 314 (M^+, base), 299, 129, 128, 109, 104, 91. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.09; H, 5.80; N, 8.90.

Acknowledgment. We gratefully acknowledge the National Cancer Institute for generous support of this research.

Registry No. **1**, 81278-07-1; **2**, 63499-45-6; **3**, 81278-08-2; **4**, 77219-99-9; **5**, 81278-09-3; **5** ethyl ester, 81278-10-6; **6**, 81278-11-7; **6** ethyl ester, 81278-12-8; **8**, 77226-66-5; **9**, 77219-98-8; **12**, 63499-47-8; **15**, 81278-13-9; **16**, 77220-00-9; **17**, 77226-67-6; **18**, 77220-01-0; **19**, 77220-02-1; **20**, 81278-14-0; **20** ethyl ester, 81278-15-1; **23**, 81278-16-2; **24**, 81278-17-3; **24** ethyl ester, 81278-18-4; **28**, 81278-19-5; **29**, 81278-20-8; **30**, 81278-21-9; **30** ethyl ester, 81278-22-0; **35**, 81278-23-1; **36**, 81278-24-2; **37**, 81278-25-3; (*E*)-**38**, 81278-26-4; (*E*)-**38** ethyl ester, 81278-27-5; (*Z*)-**38**, 81278-28-6; (*Z*)-**38** ethyl ester, 81278-29-7; **39**, 81278-30-0; ethyl 2-bromopropionate, 535-11-5; *o*-allylaniline, 32704-22-6; ethyl α-bromophenylacetate, 2882-19-1; *o*-allybenzoic acid, 61436-73-5; *N*-methyl-2-phenylglycine ethyl ester, 81278-31-1; dimethyl acetylenedicarboxylate, 762-42-5; *p*-methoxy-*o*-(3-butenyl)benzoic acid, 81278-32-2; *N,C*-diphenylglycine ethyl ester, 5634-58-2; 2-[*p*-methoxy-*o*-(3-butenyl)phenyl]-4,4-dimethyl-Δ^2-oxazoline, 81278-33-3; 2-[*p*-methoxy-*o*-(3-butenyl)phenyl]-4,4-dimethyl-Δ^2-oxazoline methiodide, 81278-34-4; *N*-methyl-*N*-[*p*-methoxy-*o*-(3-oxopropyl)benzoyl]-2-phenylglycine ethyl ester, 81278-35-5.

Supplementary Material Available: The positional and thermal parameters obtained from the least-squares refinement of structure **9** (3 pages). Ordering information is given on any current masthead page.

New Synthesis of Diazepam and the Related 1,4-Benzodiazepines by means of Palladium-Catalyzed Carbonylation

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A new synthesis of diazepam (**5**) was achieved by application of palladium-catalyzed carbonylation to the compound **3** prepared from *o*-bromoaniline derivative **1** and the amino acid **2**, and this procedure was also used for the synthesis of poisonous metabolites *dl*-cyclopeptine (**7**), *dl*-cyclopenin (**8a**), and *dl*-cyclopenol (**8b**), having a 1,4-diazepine skeleton.

Palladium-catalyzed carbonylation of aryl and vinyl halides has been developed by us as a useful method for the synthesis of heterocyclic compounds such as benzolactams,[1a] benzolactones,[1b] cyclic imides,[1c] and α-methylene lactams and lactones.[1d] The chemistry was further extended to the synthesis of the alkaloid sendaverine[1e] and a formal synthesis of a monocyclic β-lactam antibiotic, nocardicin A.[1f] The most remarkable feature of this reaction is that the synthesis of four-, five-, six-, and seven-membered lactams and lactones can be simply realized by variation of the length of carbon chain of the starting material.

In the course of synthetic studies, we have been particularly interested in exploration of a new route to 1,4-benzodiazepine derivatives having pharmacological activity in the series of the synthetic and naturally occurring products.

It was expected that our method should be extended to the synthesis of 3,4-dihydro-1*H*-benzodiazepine-2,5-dione (**4**) by insertion of carbon monoxide into aryl halide **3** (Scheme I), which could be prepared from *o*-bromoaniline derivative **1** and amino acid **2**. Now report the synthesis of the key intermediate for diazepam (**5**), and of diazepine

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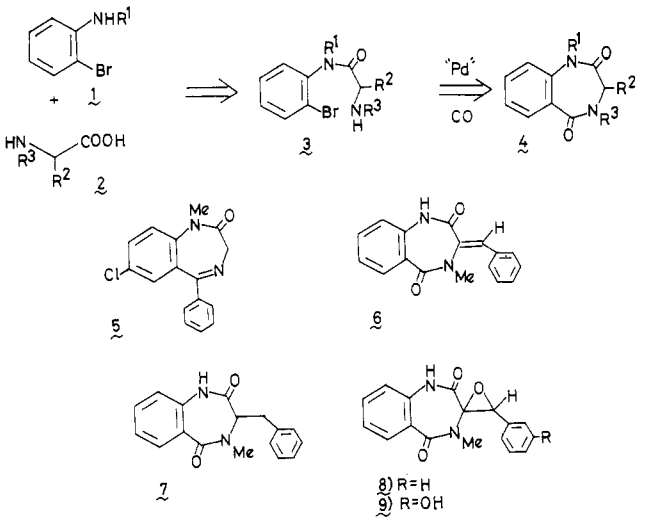
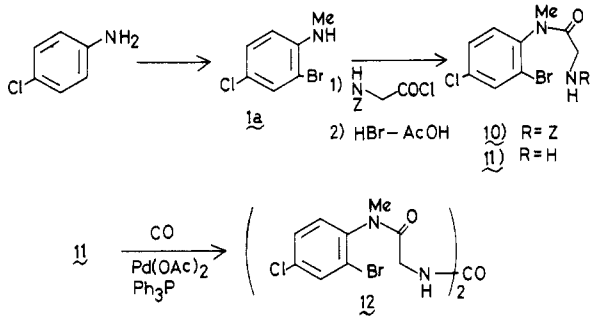
0022-3263/82/1947-2456$01.25/0

Scheme I



Scheme II



Scheme III

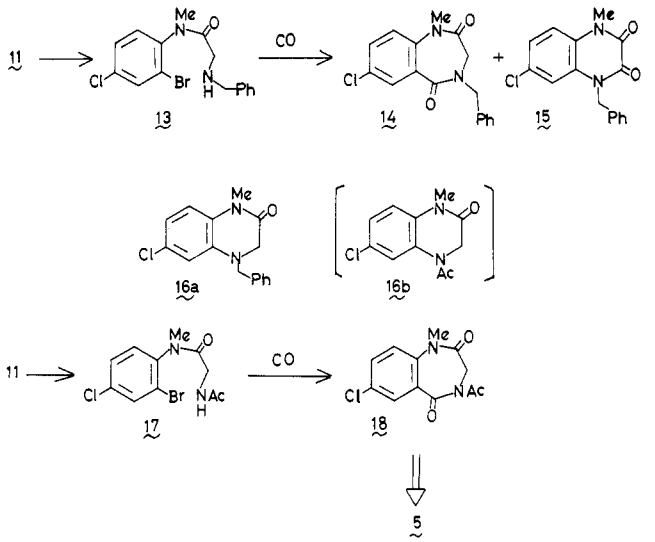


Table I. Insertion of Carbon Monoxide into Aryl Halide 13 under Various Conditions

mol % of $Pd(OAc)_2$	mol % of PPh_3	temp, °C	time, h	atm of CO	yield, % 14	yield, % 15
2	10	100	26	1	9.3	30
2	10	120	26	1	0	68
2	9	110	26	*a*	0	38
0	20	120	26	*a*	0	24
10	100	110	40	4	30.0	42

[a] The reaction was carried out under an atmosphere of argon.

metabolites 3,10-dehydrocyclopeptine (**6**), *dl*-cyclopeptine (**7**), *dl*-cyclopenin (**8**), and *dl*-cyclopenol (**9**) by this method.

For the synthesis of diazepam, commercially available *p*-chloroaniline was chosen as the starting material. N-Methylation of *p*-chloroaniline by the established method[4] followed by bromination gave **1a** in good yield. This was condensed with *N*-(benzyloxycarbonyl)glycyl chloride (**2a**) to give the compound **10** (Scheme II). Removal of the benzyloxycarbonyl group of **10** with HBr–AcOH gave the primary amine **11**. The insertion of carbon monoxide into compound **11** was carried out with 2 mol % of $Pd(OAc)_2$ and 20 mol % of PPh_3 in HMPA under a 1-atm pressure of carbon monoxide at 100 °C for 26 h. However, the desired diazepinone derivative was not obtained, and instead only a small amount of the urea derivative **12** was generated.

The secondary amine **13** which was prepared by condensation of primary amine **11** with benzaldehyde, followed by reduction with $NaBH_4$, was reacted with carbon monoxide under the same conditions to give a small amount of the desired compound **14** with an unexpected product (**15**, Scheme III). Higher reaction temperatures gave only this undesired compound (**15**), which was also obtained under the same conditions without $Pd(OAc)_2$ in an argon atmosphere (Table I). After this carbonylation reaction, the TLC of the reaction mixture showed two spots in addition to the spots of Ph_3PO and HMPA. The slower spot was assigned to **14**; the compound giving rise to the faster spot, which is assumed to be **16a**, changed during silica gel chromatography to **15**. It may be presumed that substitution of the bromine atom by the amino group on the aromatic ring in **13** in HMPA took place to furnish **16a**, which was oxidized with aerial oxygen during purification. When this reaction was carried out under a 4-atm pressure of carbon monoxide, the yield of the diazepinone derivative **14** was raised up to 30.0%.

Since the aryl halide having an amide group at the ortho position has been found by us to effectively react with carbon monoxide to give the cyclic imide,[1c] the *N*-acetyl derivative (**17**) of the compound **11** was similarly heated with a catalytic amount of $Pd(OAc)_2$ and PPh_3 under 5 atm of carbon monoxide in HMPA at 100 °C for 40 h to give the desired cyclic imide **18** in a yield of 48.0%. In this case, the compound **16b** was not obtained because the nucleophilicity of the amide group was not as strong as that of the amino group. Recently, Gates has reported that diazepam (**5**) was obtained by reaction of compound **18** with phenylmagnesium chloride followed by treatment with NH_2OH and $NaHSO_3$.[5] This sequence thus provides a new synthetic method of diazepam (**5**) by palladium-catalyzed carbonylation for generation of the crucial intermediate **18**.

Subsequently, we attempted to synthesize the key compound **23** for the synthesis of diazepine metabolites 3,10-dehydrocyclopeptine (**6**), *dl*-cyclopeptine (**7**), *dl*-cyclopenin (**8**), and *dl*-cyclopenol (**9**). Tracer experiments[6] and related studies[7] have shown that cyclopenin (**8**) and cyclopenol (**9**), metabolites of *P. Cyclopium* Westling, are formed biosynthetically via cyclopeptine (**7**) and dehydrocyclopeptine (**6**), which are reversibly interconverted in vivo.[8]

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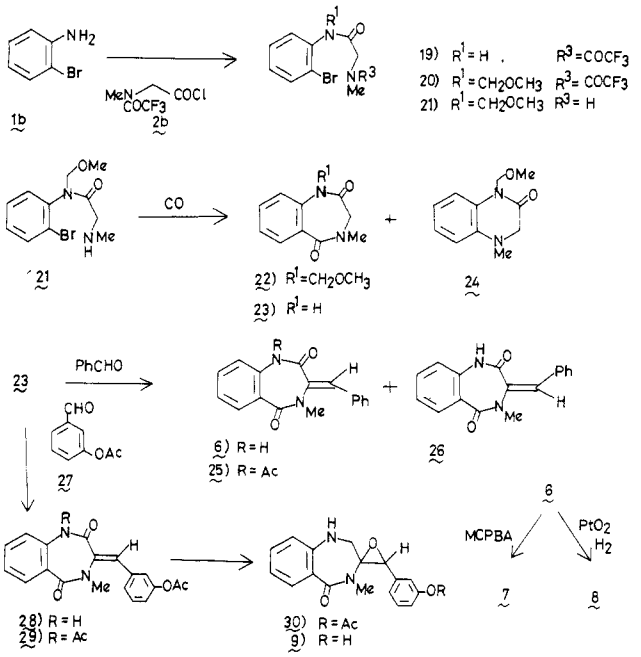
Scheme IV



Although the synthesis of these four compounds has been achieved by several groups,[6,9] all previous syntheses involved cyclization of *o*-aminohipurric acid derivatives for the construction of the 1,4-benzodiazepine skeleton. The present syntheses of these compounds were effected by preparation of the key intermediate 1,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (**23**),[10] which was obtained by the insertion of carbon monoxide into *o*-bromoaniline derivative **21** (Scheme IV).

Coupling of *N*-(trifluoroacetyl)sarcosinyl chloride (**2b**) with *o*-bromoaniline (**1b**) followed by protection of the secondary amide group of **19** with chloromethyl methyl ether[11] gave **20** as a viscous oil. Removal of trifluoroacetyl group of **20** with K_2CO_3 in methanol gave amine **21** in quantitative yield, which was subjected to palladium-catalyzed carbonylation. The insertion of carbon monoxide to this compound (**21**) in a similar manner proceeded smoothly to give the expected diazepinone derivative **22** in 41% yield with **24**. Removal of the protecting group from **22** was accomplished by stirring with 10% HCl in methanol to yield the important intermediate **23** in the known synthesis of these benzodiazepine metabolites.

The spectra of this compound (**23**) were identical with those of the product already reported by Rapoport.[9b] The syntheses of the metabolites **6**–**9** from **23** were realized by modification of the known method[9b] for the synthesis of **8**.

Condensation of benzodiazepine (**23**) with benzaldehyde gave dehydrocyclopeptine (**6**), *N*-acetyldehydrocyclopeptine (**25**), and a small amount of the *E* isomer (**26**) of **25**. Compound **25** was easily converted to **6** which was treated with MCPBA to give *dl*-cyclopenin (**8a**).[9b] Catalytic hydrogenation of **6** with PtO_2 in ethanol gave cyclopeptine (**7**).[6] The synthesis of *dl*-cyclopenol (**8**) was achieved by a route parallel to that for the synthesis of cyclopenin (**9**). Condensation of **23** with *m*-acetoxybenzaldehyde (**27**) gave benzylidene derivative **28** and *N*-acetyl derivative **29**. The latter compound (**29**) was successfully converted to **28** with sodium hypochlorite, and epoxydation **28** with MCPBA followed by hydrolysis of the *O*-acetyl group yielded *dl*-cyclopenol (**9**).[9c]

Further extension of our new synthetic procedure to the synthesis of pyrrolo-1,4-benzodiazepine antibiotics is now in progress.

Experimental Section

Melting points were measured with a hot-stage microscope (Yanaco MP-J2) and with a Yamato MP-1 melting point apparatus and are uncorrected. ^1H NMR spectra were reported in the indicated solvent on Hitachi R-40 (90 MHz), JEOL JNM-FX100 (100 MHz), and JEOL JNM-FX200 (200 MHz) spectrometers with Me_4Si as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants are reported in hertz. A JASCO IRA-2 diffraction grating infrared spectrophotometer and a Hitachi RMU-7M double-focussing mass spectrometer were used, respectively, to determine IR and mass spectra.

2-Bromo-4-chloro-*N*-methylaniline (1a). To a mixture of 4-chloro-*N*-methylaniline (7.3 g, 51.7 mmol), sodium acetate (8.2 g, 100 mmol), and glacial acetic acid (100 mL) was added slowly a solution of bromine (2.6 mL, 51.7 mmol) in glacial acetic acid (10 mL) at room temperature. After being stirred for 1 h, the reaction mixture was concentrated on rotary evaporator. The residue was rendered alkaline with 10% aqueous potassium carbonate and extracted with benzene. The extract was washed with 5% aqueous sodium thiosulfate and water and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo left a dark red viscous oil which was chromatographed on silica gel with *n*-hexane as the eluent to give 10 g (87%) of **1a** as a reddish viscous oil: IR ($CHCl_3$) 3320, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.80 and 2.89 (2 s, 3 H, NCH_3), 4.20 (br, 1 H, NH), 6.40 (d, 1 H, J = 8 Hz), 7.08 (dd, 1 H, J = 3, 8 Hz), 7.35 (d, 1 H, J = 3 Hz).

2-Bromo-*N*-[*N*-(benzyloxycarbonyl)glycyl]-4-chloro-*N*-methylaniline (10). To a suspension of *N*-(benzyloxycarbonyl)glycine (7.1 g, 34 mmol) in anhydrous ether (100 mL) was added phosphorus pentachloride (7 g, 34 mmol) portionwise at room temperature. After being stirred for 1 h, the mixture was concentrated in vacuo, and a solution of the residue in benzene (30 mL) was added to a solution of **1a** (5 g, 22.6 mmol) in dichloromethane (50 mL) at 0 °C. After being stirred at room temperature for 1 h, the mixture was diluted with ethyl acetate, and the organic phase was washed with saturated aqueous sodium hydrogen carbonate and water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel. Elution with *n*-hexane–ethyl acetate (2:1) gave 7.6 g (81%) of **10** as a colorless viscous oil: IR ($CHCl_3$) 3330, 1725, 1670 cm^{-1}; NMR ($CDCl_3$) δ 3.20 (s, 3 H, NCH_3), 3.50–3.75 (m, 2 H), 5.07 (s, 2 H), 5.67 (br, 1 H, NH), 7.25–7.80 (m, 8 H); mass spectrum, m/e 410, 412, 414 (M^+).

2-Bromo-4-chloro-*N*-glycyl-*N*-methylaniline (11). To a solution of **10** (13.9 g, 34 mmol) in dichloromethane (10 mL) was added anhydrous HBr in a 25% acetic acid solution (100 mL), and the mixture was stirred at room temperature for 1 h. After the reaction mixture was concentrated on a rotary evaporator, the residue was dissolved in the minimum amount of water and washed with ether to remove benzyl bromide. The aqueous phase was basified with 10% aqueous potassium carbonate and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave 7.2 g (77%) of **11** as a pale yellow viscous oil: IR ($CHCl_3$) 3370, 3300, 1670 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (s, 3 H, NCH_3), 3.00–3.55 (m, 3 H); mass spectrum, m/e 277, 279, 281 (M^+), 197, 199 (M^+ – Br).

***N*-(*N*-Benzylglycyl)-2-bromo-4-chloro-*N*-methylaniline (13).** A mixture of **11** (420 mg, 1.5 mmol), anhydrous magnesium sulfate (5 g), and benzaldehyde (161 mg, 1.5 mmol) in anhydrous benzene (30 mL) was stirred at room temperature for 4 h. The insoluble material was separated on a filter, and the solvent of the filtrate was removed in vacuo. The residual oil was dissolved in ethanol (20 mL), and sodium borohydride (113 mg, 3 mmol) was added portionwise at 0 °C. After being stirred at room temperature for 1 h, the mixture was diluted with ethyl acetate,

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washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with dichloromethane–ethyl acetate–methanol (4:4:1) as the eluent to give 515 mg (93%) of **13** as colorless viscous oil: IR ($CHCl_3$) 3310, 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.57 (s, 1 H, NH), 3.03 (s, 3 H, NCH_3), 7.25 (m, 7 H), 7.66 (d, 1 H, J = 2 Hz); mass spectrum, m/e 366, 368, 370 (M^+).

***N*-(*N*-Acetylglycyl)-2-bromo-4-chloro-*N*-methylaniline (17).** A mixture of **11** (1 g, 3.6 mmol) and potassium carbonate (810 mg, 5.8 mmol) in dichloromethane (50 mL) was cooled to 0 °C, and acetyl chloride (320 mg, 4 mmol) was added. The mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. After dilution with ethyl acetate, the organic phase was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent left a viscous oil which was crystallized by the titration with ether to give 980 mg (85%) of **17** as colorless crystals. Recrystallization of **17** from *n*-hexane–acetone gave pure **17** as colorless leaflets: mp 111–112 °C; IR (Nujol) 3250, 1680, 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.97 (s, 3 H, $NCOCH_3$), 3.20 (s, 3 H, NCH_3), 3.50–3.80 (m, 2 H), 6.40–6.70 (m, 1 H), 7.20–7.50 (m, 2 H), 7.73 (d, 1 H, J = 2 Hz); mass spectrum, m/e 318, 320, 322 (M^+).

Anal. Calcd for $C_{11}H_{12}N_2O_2BrCl$: C, 41.34; H, 3.78; N, 8.77; Br, 25.00; Cl, 11.09. Found: C, 41.27; H, 3.81; N, 8.74; Br, 24.76; Cl, 10.88.

***N*,*N*'-Bis[[*N*-(2-Bromo-4-chlorophenyl)-*N*-methylcarbamoyl]methyl]urea (12).** A mixture of **11** (800 mg, 2.6 mmol), triphenyl phosphine (734 mg, 2.8 mmol), tri-*n*-butylamine (925 mg, 5 mmol), and palladium acetate (68 mg, 0.28 mmol) in HMPA (5 mL) was heated under 5 atm of carbon monoxide at 100 °C for 20 h. After dilution with ethyl acetate, the organic phase was washed with 10% aqueous hydrochloric acid and water and dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (1:2) as the eluent to give 100 mg of **12** as colorless crystals which were recrystallized from *n*-hexane–acetone: mp 224–226.5 °C; IR (Nujol) 3400, 1660, 1615 cm^{-1}; NMR ($CDCl_3$) δ 3.20 (s, 6 H), 3.60 (m, 4 H), 6.02 (br, 2 H), 7.20–7.80 (m, 6 H); mass spectrum, m/e 578, 580, 582 (M^+).

Anal. Calcd for $C_{19}H_{18}N_4O_3BrCl$: C, 39.27; H, 3.12; N, 9.64; Found: C, 39.10; H, 3.16; N, 9.45.

4-Benzyl-7-chloro-3,4-dihydro-1-methyl-1,4-benzodiazepine-2,5-dione (14) and 4-Benzyl-6-chloro-1-methylquinoxaline-2,3-dione (15). A mixture of **13** (87 mg, 0.23 mmol), triphenyl phosphine (60 mg, 0.23 mmol), tri-*n*-butylamine (74 mg, 0.4 mmol), and palladium acetate (5.1 mg, 0.023 mmol) in HMPA (2 mL) was heated under 4 atm of carbon monoxide at 110 °C for 40 h. After dilution with ethyl acetate, the organic phase was washed with 10% aqueous hydrochloric acid and water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by preparative TLC (33% acetone in dichloromethane) to give 23 mg (30%) of **14** and 30 mg (42%) of **15**. Recrystallization of **14** from *n*-hexane–acetone gave pure **14** as colorless prisms: mp 135–137 °C; IR ($CHCl_3$) 1675, 1640 cm^{-1}; NMR ($CDCl_3$) δ 3.35 (s, 3 H, NCH_3), 3.75–3.80 (m, 2 H), 4.29 (d, 1 H, J = 14 Hz), 5.39 (d, 1 H, J = 14 Hz), 7.12 (d, 1 H, J = 8 Hz), 7.28 (m, 5 H), 7.48 (dd, 1 H, J = 3, 8 Hz), 7.93 (d, 1 H, J = 3 Hz); mass spectrum, m/e 314, 316 (M^+).

Anal. Calcd for $C_{17}H_{15}N_2O_2Cl$: C, 64.87; H, 4.80; N, 8.90; Cl, 11.26; Found: C, 64.86; H, 4.80; N, 8.79; Cl, 11.46.

Recrystallization of **15** from acetone gave pure **15** as colorless leaflets: mp 241–242 °C; IR (Nujol) 1700, 1670, 1590 cm^{-1}; NMR ($CDCl_3$) δ 3.68 (s, 3 H, NCH_3), 5.42 (s, 2 H), 7.00–7.60 (m, 8 H); mass spectrum, m/e 300, 302 (M^+), 209, 211 ($M^+ - CH_2Ph$).

Anal. Calcd for $C_{16}H_{13}N_2O_2Cl$: C, 63.90; H, 4.36; N, 9.31; Cl, 11.79. Found: C, 63.68; H, 4.49; N, 9.07; Cl, 11.71.

***N*-Acetyl-7-chloro-3,4-dihydro-1-methyl-1*H*-1,4-benzodiazepine-2,5-dione (18).** A mixture of **17** (740 mg, 2.3 mmol), triphenyl phosphine (602 mg, 2.3 mmol), tri-*n*-butylamine (851 mg, 4.6 mmol), and palladium acetate (52 mg, 0.23 mmol) in HMPA (3 mL) was heated under 5 atm of carbon monoxide at 100 °C for 40 h. The reaction mixture was diluted with ethyl acetate, and the organic phase was washed with 10% aqueous hydrochloric acid and water and dried over anhydrous sodium sulfate. After removal of the solvent, the residual oil was chromatographed on silica gel. Elution with *n*-hexane–acetone (1:1) gave 298 mg (48%) of **18** which was recrystallized from acetone to give pure **18** as colorless leaflets: mp 206–208 °C (lit.[5] mp 207.5–209 °C); IR (Nujol) 1700, 1675 cm^{-1}; NMR ($CDCl_3$) δ 2.67 (s, 3 H, $NCOCH_3$), 3.40 (s, 3 H, NCH_3), 3.50–4.00 (m, 1 H), 4.80–5.60 (m, 1 H), 7.23 (d, 1 H, J = 9 Hz), 7.62 (dd, 1 H, J = 2.5, 9 Hz), 7.93 (d, 1 H, J = 2.5 Hz); mass spectrum, m/e 266, 268 (M^+), 223, 225 ($M^+ - COCH_3$).

Anal. Calcd for $C_{12}H_{11}N_2O_3Cl$: C, 54.05; H, 4.16; N, 10.50; Cl, 13.29. Found: C, 54.31; H, 3.98; N, 10.66; Cl, 13.32.

2-Bromo-*N*-[*N*-methyl-*N*-(trifluoroacetyl)glycyl]aniline (19). To a suspension of sarcosine (13.8 g, 155 mmol) in dichloromethane (100 mL) was added trifluoroacetic anhydride (35.7 g, 170 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo, and the remaining trifluoroacetic acid was removed by coevaporation with benzene to leave the viscous oil. Phosphorus pentachloride (32.2 g, 155 mmol) was added slowly to a solution of the residue in anhydrous ether (100 mL). After stirring for 3 h, the mixture was concentrated in vacuo and a solution of the residue in benzene (30 mL) was added slowly to a solution of **1b** (20.5 g, 119 mmol) in anhydrous ethyl acetate (100 mL) at 0 °C. After being stirred at room temperature for 1 h, the mixture was diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and water, and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residual oil was crystallized by the titration with ether to give 33 g (82%) of **19** as pale yellow crystals which were recrystallized from *n*-hexane–acetone to give pure **19** as colorless needles: mp 119–120 °C; IR (Nujol) 3250, 1700, 1660, 1580 cm^{-1}; NMR ($CDCl_3$) δ 3.30 and 3.33 (2 s, 3 H, NCH_3), 4.26 (s, 2 H), 7.07 (dd, 1 H, J = 2, 8 Hz), 7.27 (dd, 1 H, J = 2, 8 Hz), 7.58 (dd, 1 H, J = 2, 8 Hz), 8.06 (br, 1 H, NH), 8.28 (dd, 1 H, J = 2, 8 Hz); mass spectrum, m/e 338, 340 (M^+), 259 ($M^+ - Br$).

Anal. Calcd for $C_{11}H_{10}N_2O_2BrF_3$: C, 38.96; H, 2.97; N, 8.26. Found: C, 38.75; H, 2.89; N, 8.24.

2-Bromo-*N*-(methoxymethyl)-*N*-[*N*-methyl-*N*-(trifluoroacetyl)glycyl]aniline (20). To a slurry of *n*-hexane-washed sodium hydride (50% dispersion of mineral oil, 1.08 g, 22.5 mmol) in tetrahydrofuran (30 mL) was added slowly a solution of **19** (5.07 g, 15 mmol) in tetrahydrofuran (30 mL) at 0 °C under a nitrogen atmosphere, and stirred for 1.5 h. Chloromethyl methyl ether (1.8 g, 22.5 mmol) was added dropwise, and the mixture was stirred for 30 min at the same temperature and then allowed to come to room temperature. After 3 h, saturated aqueous ammonium chloride was added to the reaction mixture at 0 °C, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed. The residual oil was chromatographed on silica gel with *n*-hexane–ethyl acetate (2:1) as the eluent to give 5.1 g (88%) of **20** as a colorless viscous oil: IR ($CHCl_3$) 1700, 1585 cm^{-1}; NMR ($CDCl_3$) δ 3.20 and 3.22 (2 s, 3 H, NCH_3), 3.45 (s, 3 H, OCH_3), 3.52 (d, 1 H, J = 17 Hz), 4.10 (d, 1 H, J = 17 Hz), 4.50 (d, 1 H, J = 10 Hz), 5.55 (d, 1 H, J = 10 Hz), 7.20–7.95 (m, 4 H); mass spectrum, m/e 382, 384 (M^+), 350, 352 ($M^+ - CH_3OH$), 303 ($M^+ - Br$).

2-Bromo-*N*-(methoxymethyl)-*N*-(*N*-methylglycyl)aniline (21). To a solution of **20** (5 g, 13 mmol) in methanol (40 mL) was added a solution of potassium carbonate (5.4 g, 39 mmol) in water (10 mL), and the mixture was stirred at room temperature for 3 h. The mixture was diluted with ethyl acetate, and the organic phase was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with ethyl acetate as the eluent to give 3.5 g (93%) of **21** as a reddish viscous oil: IR ($CHCl_3$) 3350, 1680, 1585 cm^{-1}; NMR ($CDCl_3$) δ 2.00 (s, 1 H, NH), 2.35 (s, 3 H, NCH_3), 3.01 (s, 2 H), 3.45 (s, 3 H, OCH_3), 4.47 (d, 1 H, J = 10 Hz), 5.62 (d, 1 H, J = 10 Hz), 7.20–7.90 (m, 4 H); mass spectrum, m/e 255, 257 ($M^+ - OCH_3$), 242, 244 ($M^+ - CH_2NCH_3$), 207 ($M^+ - Br$).

1-(Methoxymethyl)-3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepine-2,5-dione (22) and 1-(Methoxymethyl)-4-methylquinoxalin-2-one (24). A mixture of **21** (760 mg, 2.65 mmol), triphenyl phosphine (694 mg, 2.65 mmol), tri-*n*-butylamine (740 mg, 4 mmol), and palladium acetate (60 mg, 0.27 mmol) in HMPA (3 mL) was heated under 5 atm of carbon monoxide at 120 °C for 48 h. After dilution with ethyl acetate, the organic phase was washed with 10% aqueous hydrochloric acid and water and dried

over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel with benzene–ether (1:1) as the eluent. The first fraction gave 143 mg (30.5%) of **24** as a pale yellow viscous oil: IR ($CHCl_3$) 1690, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (s, 3 H, NCH_3), 3.37 (s, 3 H, OCH_3), 3.70 (s, 2 H), 5.28 (s, 2 H), 6.60–7.40 (m, 4 H); mass spectrum, m/e 206 (M^+). The second fraction gave 220 mg (41%) of **22** as a colorless viscous oil: IR ($CHCl_3$) 1690, 1640, 1605 cm^{-1}; NMR ($CDCl_3$) δ 3.26 (s, 3 H, NCH_3) 3.45 (s, 3 H, OCH_3), 3.68 (d, 1 H, J = 15 Hz), 4.12 (d, 1 H, J = 15 Hz), 4.73 (d, 1 H, J = 9.5 Hz), 5.43 (d, 1 H, J = 9.5 Hz); mass spectrum, m/e 234 (M^+), 219 ($M^+ - CH_3$), 202 ($M^+ - CH_3OH$), 189 ($M^+ - CH_2OCH_3$).

3,4-Dihydro-4-methyl-1*H*-1,4-benzodiazepine-2,5-dione (23). A solution of **22** (160 mg) in 10% aqueous hydrochloric acid (0.5 mL) and methanol (6 mL) was heated at 50 °C for 3 h. The reaction mixture was diluted with ethyl acetate, and the organic phase was washed with saturated aqueous sodium hydrogen carbonate and water and dried over anhydrous sodium sulfate. After removal of the solvent, the crystalline residue was slurried in acetone, collected, and washed with acetone to give 110 mg (84.6%) of **23** as colorless crystals which were recrystallized from methanol: mp 246–247.5 °C (lit.[9b] mp 246–247 °C); IR (Nujol) 3200, 1690, 1630 cm^{-1}; NMR (Me_2SO-d_6) δ 3.13 (s, 3 H, NCH_3), 3.81 (s, 2 H), 6.95–8.00 (m, 4 H), 10.45 (br, 1 H, NH); mass spectrum, m/e 190 (M^+).

3,10-Dehydrocyclopeptine (6), 1-Acetyl-3,10-dehydrocyclopeptine (25) and *trans*-3,3-Benzylidene-3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepine-2,5-dione (26). A mixture of **24** (6.75 mg, 35.5 mmol), benzaldehyde (5.5 g, 51.8 mmol), sodium acetate (3.2 g, 39 mmol), and acetic anhydride (10 mL) was heated at 150 °C for 3 h. Water was added, and the mixture was stirred at room temperature for 1 h and extracted with ethyl acetate. The extract was washed with water successively and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (1:1) as the eluent. The first fraction gave 2.6 g (23%) of **25** as colorless crystals: mp 180–181 °C (lit.[9b] mp 177–179 °C); IR ($CHCl_3$) 1710, 1690, 1650, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.54 (s, 3 H, $NCOCH_3$), 3.16 (s, 3 H, NCH_3), 6.99 (s, 1 H, C=CH), 7.10–7.90 (m, 9 H); mass spectrum, m/e 320 (M^+), 277 ($M^+ - COCH_3$). The second fraction gave 1.2 g (12%) of **6** as colorless crystals: mp 203–204 °C (lit.[9b] mp 201–205 °C); IR ($CHCl_3$) 3370, 1670, 1630 cm^{-1}; NMR ($CDCl_3$) δ 3.17 (s, 3 H, NCH_3), 6.90 (s, 1 H, C=CH), 6.95–8.10 (m, 9 H), 8.95 (br, 1 H, NH); mass spectrum, m/e 278 (M^+). The third fraction gave 180 mg (1.8%) of **26** as colorless crystals: mp 187–189 °C (lit.[9b] mp 185 °C); IR (Nujol) 3050, 1670, 1620, 1600 cm^{-1}; NMR ($CDCl_3$) δ 3.49 (s, 3 H, NCH_3), 6.68 (s, 1 H, C=CH), 6.70–8.00 (m, 9 H), 9.41 (br, 1 H, NH); mass spectrum, m/e 278 (M^+).

Conversion of 25 to 6. A solution of **25** (500 mg, 1.56 mmol) and 10% aqueous sodium hypochlorite (3 mL) in dioxane (3 mL) was stirred at room temperature for 10 min. After dilution with ethyl acetate, the mixture was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was dissolved in dioxane (3 mL), and a solution of potassium iodide (830 mg, 5 mmol) in 5% aqueous acetic acid (3 mL) was added. The resulting reddish solution was decolorized with 5% aqueous sodium thiosulfate and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was crystallized with ether to give 250 mg (60%) of **6**.

***dl*-Cyclopeptine (7).** A solution of **6** (278 mg, 1 mmol) in ethanol (15 mL) was hydrogenated in the presence of platinum oxide (30 mg) at room temperature and an atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residual oil was crystallized from ethyl acetate–petroleum ether to give 235 mg (84%) of **7** which was recrystallized from *n*-hexane–acetone to give pure **7** as colorless prisms: mp 100.5–103 °C (lit.[6] mp 95–98 °C, for *l*-cyclopeptine); IR (KBr) 3600, 3050, 1690, 1605 cm^{-1}; NMR ($CDCl_3$) δ 2.55–3.70 (m, 5 H), 4.10–4.50 (m, 1 H), 6.80–7.60 (m, 8 H), 7.75–8.20 (m, 1 H), 8.90–9.50 (m, 1 H); mass spectrum, m/e 280 (M^+), 189 ($M^+ - CH_2Ph$).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.94; H, 5.92; N, 9.94.

***dl*-Cyclopenin (8).** A mixture of **6** (200 mg, 0.72 mmol) and MCPBA (1.24 g, 6.1 mmol) in dichloromethane (30 mL) was stirred at room temperature for 30 days. After dilution with ethyl acetate, the organic phase was washed with 10% aqueous sodium thiosulfate, saturated aqueous sodium hydrogen carbonate and water, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (1:1) as the eluent to give 50 mg (23.6%) of **8** as colorless crystals which were recrystallized from *n*-hexane–acetone to give pure **8** as colorless prisms: mp 191–193 °C (lit.[9b] mp 193–195 °C); IR (KBr) 1695, 1670, 1480, 1250, 1380, 980 cm^{-1}; NMR ($CDCl_3$) δ 3.23 (s, 3 H, NCH_3), 2.60 and 4.57 (small peaks), 3.99 (s, 1 H), 6.50–7.70 (m, 9 H), 9.20 (br, 1 H, NH); mass spectrum, m/e 294 (M^+).

***trans*-3-(3-Acetoxybenzylidene)-3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepine-2,5-dione (28) and 1-Acetyl-*trans*-3-(3-acetoxybenzylidene)-3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepine-2,5-dione (29).** A mixture of **23** (7.6 g, 40 mmol), **27** (9.8 g, 60 mmol), sodium acetate (4.2 g, 50 mmol), and acetic anhydride (15 mL) was heated at 150 °C for 3 h. After dilution with water, the mixture was stirred at room temperature for 1 h and extracted with ethyl acetate, and the extract was washed with water several times and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on siilica gel with *n*-hexane–ethyl acetate (1:1) as the eluent. The first fraction gave 3.7 g (24.4%) of **29** as colorless crystals which were recrystallized from *n*-hexane–ethyl acetate to give pure **29** as colorless prisms: mp 180–182 °C (lit.[9c] mp 178–181 °C); IR (Nujol) 1760, 1715, 1650, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 3 H, $OCOCH_3$), 2.53 (s, 3 H, $NCOCH_3$) 3.17 (s, 3 H, NCH_3), 6.92 (s, 1 H, C=CH), 7.00–8.00 (m, 8 H); mass spectrum, m/e 377 ($m^+ - COCH_3$). The second fraction gave 1.35 g (10%) of **28** as colorless gum: IR ($CHCl_3$) 3380, 3200, 1760, 1635, 1605, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.29 (s, $OCOCH_3$), 3.17 (s, 3 H, NCH_3), 6.85 (s, 1 H, C=CH), 6.90–8.00 (m, 8 H), 8.87 (br, 1 H, NH); mass spectrum, m/e 378 (M^+), 335 ($M^+ - COCH_3$).

Conversion of 29 to 28. A mixture of **29** (100 mg, 0.264 mmol) and 10% aqueous sodium hypochlorite (1 mL) in dioxane (2 mL) was stirred at room temperature for 5 min. After dilution with ethyl acetate, the organic phase was washed with water and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. To a solution of the residue in dioxane (2 mL) was added a solution of potassium iodide (129 mg, 0.78 mmol) in 5% aqueous acetic acid (2 mL). After being stirred at room temperature for 5 min, the mixture was decolorized with 5% aqueous sodium thiosulfate and diluted with ethyl acetate. The organic phase was washed with water and dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (1:1.5) as the eluent to give 50 mg (56%) of **28**.

***dl*-Cyclopenol *O*-Acetate (30).** A mixture of **28** (420 mg, 1.25 mmol) and MCPBA (2.53 g, 12.5 mmol) in dichloromethane (30 mL) was stirred at room temperature for 27 days. After dilution with ethyl acetate, the organic phase was washed with 10% aqueous sodium thiosulfate, saturated aqueous sodium hydrogen carbonate, and water and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (1:1) as the eluent to give 110 mg (24%) of **30** as colorless crystals. Recrystallization of **30** fron *n*-hexane–acetone gave pure **30** as colorless prisms: mp 193–195 °C (lit.[9c] mp 191–192.5 °C); IR (Nujol) 3200, 1770, 1700, 1650, 1610 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 3 H, $OCOCH_3$), 3.19 (s, 3 H, NCH_3), 3.97 (s, 1 H), 6.30–6.55 (m, 2 H), 6.85– 7.60 (m, 6 H), 9.25 (br, 1 H, NH); mass spectrum, m/e 352 (M^+), 310 ($M^+ - COCH_3$).

***dl*-Cyclopenol (9).** To a solution of **30** (100 mg, 0.28 mmol) in methanol (15 mL) was added a solution of potassium hydroxide (20 mg, 0.3 mmol) in water (10 mL), and the mixture was stirred at room temperature for 1 h. After dilution with ethyl acetate, the mixture was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (1:2) as the eluent to give 74 mg (84%) of **9** as colorless crystals which were recrystallized from *n*-hexane–acetone to give pure **9** as colorless prisms: mp 209–210.5 °C (lit.[9c] mp 210–212 °C); IR (KBr) 3200, 1695, 1630 cm^{-1}; NMR (Me_2SO-d_6) δ 3.05 (s, 3 H, NCH_3), 4.13 (s, 1 H), 5.80–6.15 (m, 2 H), 6.50–7.60 (m, 6 H), 9.27 (br, 1 H), 10.77 (br, 1 H); mass spectrum, m/e 310 (M^+).

Registry No. 1a, 54625-55-7; 1b, 615-36-1; 2a, 15050-24-5; 2b, 81245-91-2; 6, 31965-37-4; 7, 65027-11-4; 8, 19357-57-4; 9, 81245-92-3; 10, 79844-42-1; 11, 79854-96-9; 12, 79844-43-2; 13, 79844-44-3; 14, 79844-45-4; 15, 79844-46-5; 17, 79844-47-6; 18, 72952-48-8; 19, 81255-43-8; 20, 81245-93-4; 21, 81245-94-5; 22, 81245-95-6; 23, 3415-35-8; 24, 81245-96-7; 25, 81245-97-8; 26, 31965-37-4; 27, 34231-78-2; 28, 81245-98-9; 29, 81245-99-0; 30, 81246-00-6; 4-ClC_6H_4NHMe, 932-96-7; Cbz-Gly-OH, 1138-80-3; sarcosine, 107-97-1.

Isoxazolines by Cycloadditions of Mesitonitrile Oxide with Benzo[*b*]thiophene *S*-Oxide and *S*,*S*-Dioxide. Structural Studies, Theoretical Explanations, and Kinetics

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1,3-Dipolar cycloadditions of mesitonitrile oxide have been investigated with benzo[*b*]thiophene *S*-oxide and *S*,*S*-dioxide derivatives having a methyl, phenyl, piperidino, chloro, or bromo substituent on the active thiophene double bond. These dipolarophiles are more reactive than the original sulfur compound. The *S*-oxide and *S*,*S*-dioxide derivatives show nearly the same ability to form adducts. Among the two possible regioisomers, only one, the 2,3-dihydrobenzo[*b*]thieno[2,3-*d*]isoxazolines are formed. The regioselectivity is discussed in terms of frontier molecular orbital interactions on the basis of the photoelectronic spectra (IPs) and CNDO/S calculations. There is no stereoselectivity with the *S*-oxide compounds, and both syn and anti adducts are obtained. The chloro and bromo derivatives do not lead to any adduct.

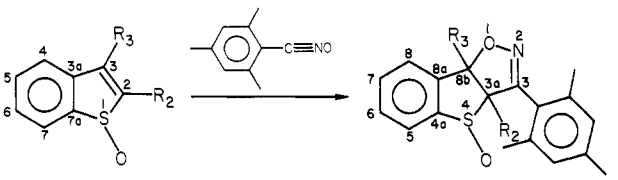
1,3-Dipolar cycloaddition reactions have been investigated for a long time, and their synthetic applications lead to various heterocycles.[1-8] Numerous studies based on quantum calculations have been carried out,[4-6] and the mechanism has been discussed at length.[7,8] Only a few reports are available on cycloaddition reactions involving a thiophene or benzo[*b*]thiophene ring.[9,10] Some adducts have been reported in the benzo[*b*]thiophene *S*,*S*-dioxide series without any stereochemical determinations.[11-13] The benzo[*b*]thiophene *S*-oxide series, whose synthesis has been extensively developed in our laboratory, remain to be investigated.[14,15]

Oxidation of the sulfur atom in benzo[*b*]thiophene compounds to a sulfoxide or a sulfone strongly decreases their aromatic character[16-18] and leads to a double bond mostly localized between C_2 and C_3. These oxidized compounds are more reactive with 1,3-dipoles such as mesitonitrile oxides than with benzo[*b*]thiophene itself.

Results and Discussion

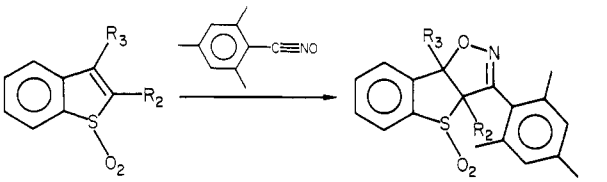
Cycloaddition of benzo[*b*]thiophenes and mesitonitrile oxide can lead to two different types of isomers, depending on the bonding of the oxygen atom of the dipole with C_2 or C_3 of the dipolarophile double bond. We call the two possible regioisomers, respectively, I (O–C_3) and II (O–C_2). Stereoisomers are formed only in the *S*-oxide series, according to the positions of the S–O bond and the substituent in C_{3a} being syn (on the same side of the benzo[*b*]thiophene plane) or anti (one on each side). In the case of a cycloaddition with the sulfone series, only two adducts

Scheme I. Experimental Results with Benzo[*b*]thiophene *S*-Oxide and *S*,*S*-Dioxide Series



1a, R_2 = H; R_3 = CH_3
c, R_2 = H; R_3 = C_6H_5

2a-syn, 2a-anti
2c-syn, 2c-anti



3, R_2 = H; R_3 = H
a, R_2 = H; R_3 = CH_3
b, R_2 = CH_3; R_3 = H
c, R_2 = H; R_3 = C_6H_5
d, R_2 = H; R_3 = 

4, R_2 = H; R_3 = H
a, R_2 = H; R_3 = CH_3
b, R_2 = CH_3; R_3 = H
c, R_2 = H; R_3 = C_6H_5
d, R_2 = H; R_3 = 

can be formed, regioisomers I and II, while addition to a sulfoxide can lead to four adducts: two epimers, syn and

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