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# A New Synthetic Approach to the 3-Benzazepine Skeleton through Pinacol–Pinacolone Rearrangement

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Treatment of 2′-(β-*N*-benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene oxide (**13**), prepared from laudanosine (**9**) via 2′-(β-*N*-benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene (**11**), with methanolic potassium hydroxide gave the diol **1**, and the epoxide **13** and diol **1** were treated with acetic acid in the presence of *p*-toluenesulfonic acid to afford 2,3-dihydro-7,8-dimethoxy-5-(3,4-dimethoxyphenyl)-3-methyl-1*H*-3-benzazepine (**17**). 2,3-Dihydro-3-methyl-7,8-methylenedioxy-5-(3,4-methylenedioxyphenyl)-1*H*-3-benzazepine (**18**) was also obtained from 2-methyl-6,7-methylenedioxy-1-(3,4-methylenedioxybenzyl)isoquinoline through stilbene **12**, epoxide **14**, and diol **2**.

The 3-benzazepine skeleton is observed in the rhoeadine, isopavine, and cephalotaxine alkaloids[1,2] and is found to be an important intermediate for the total syntheses of these alkaloids. Several synthetic methods for the 3-benzazepine skeleton have been applied to the total synthesis of alkaloids.[3] We have now investigated application of the pinacol rearrangement and related epoxide reactions[4,5] for the synthesis of these benzazepine alkaloids. Three types of products appeared possible from pinacol rearrangement of unsymmetrical stilbene diol as shown in Scheme I.[6]

Laudanosine (**9**) was treated with benzyloxycarbonyl chloride in the presence of aqueous sodium hydroxide to give the stilbene **11**, which indicated a *trans*-stilbene chromophore at 330 nm[7] in the uv spectrum (MeOH) and a urethane system at 1680 $cm^{-1}$ in the ir spectrum ($CHCl_3$). Oxidation of the stilbene **11** with *m*-chloroperbenzoic acid proceeded smoothly to afford the epoxide **13**, which on treatment with methanolic potassium hydroxide solution yielded the dihydroxyurethane **1**. The NMR spectrum ($CDCl_3$) revealed the presence of two protons attached to hydroxyl and phenyl groups (δ 4.75 as broad singlet) and the ir spectrum showed hydroxyl and urethane groups at 3400 and 1680 $cm^{-1}$, respectively. The compound **1** was treated with acetone in the presence of perchloric acid to give the acetonide **15**, whose ir spectrum showed urethane at 1680 $cm^{-1}$, and the NMR spectrum revealed the presence of two methyl groups due to an acetonide (δ 1.70 as singlet), which suggested that two phenyl groups were located trans to each other because of the same chemical shift of two methyl groups on an acetonide. The compound **2** was obtained by the same way as described for the compound **1** from benzylisoquinoline **10** through the stilbene **12** and the epoxide **14**. The diol **2** was also converted into the acetonide **16**.

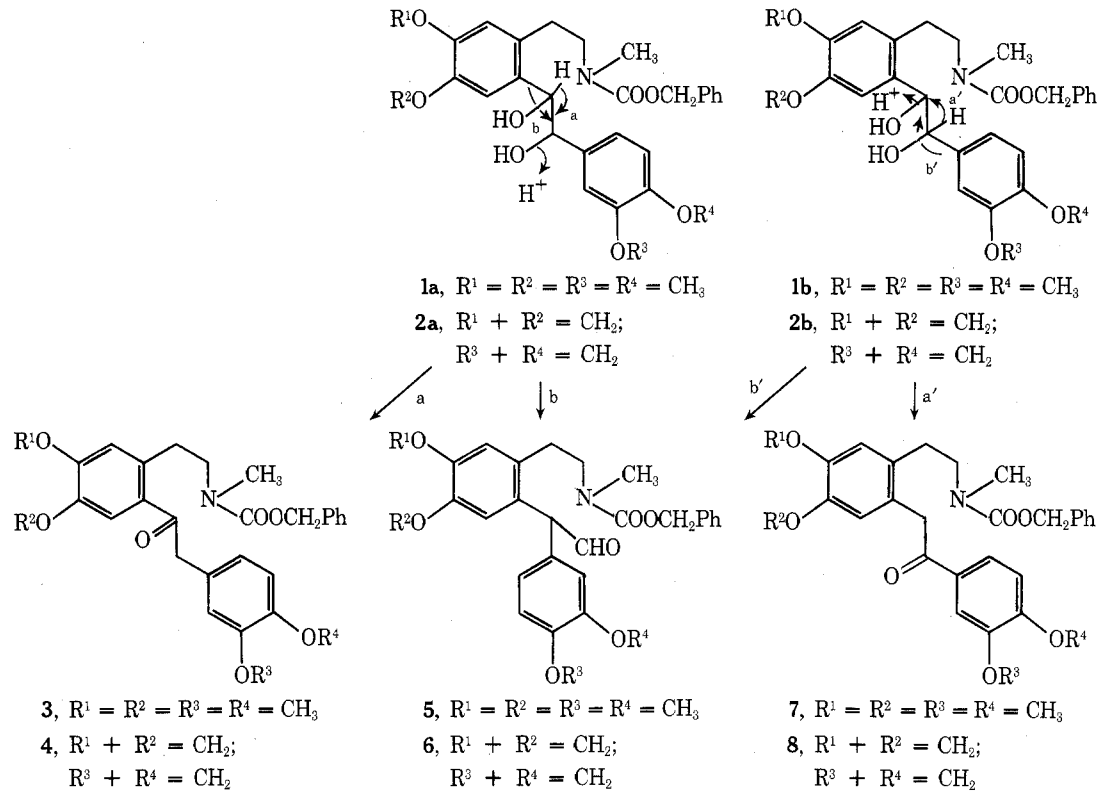
Compounds **1** and **13** were, independently, treated with acetic acid in the presence of *p*-toluenesulfonic acid to afford the same compound **17** in 46 and 25.3% yield, respectively, whose NMR spectrum showed the presence of an *N*-methyl group (δ 2.90). The uv spectrum showed $\lambda_{max}$ 306 nm which shifted to 298 nm on addition of concentrated hydrochloric acid. This shift indicated the presence of a conjugated enamine system. All spectral data of the product **17** were identical with those of an authentic sample.[8] The diol **2** was also treated under the same condition as described above to give the compound **18** in 11.6% yield.

## Experimental Section

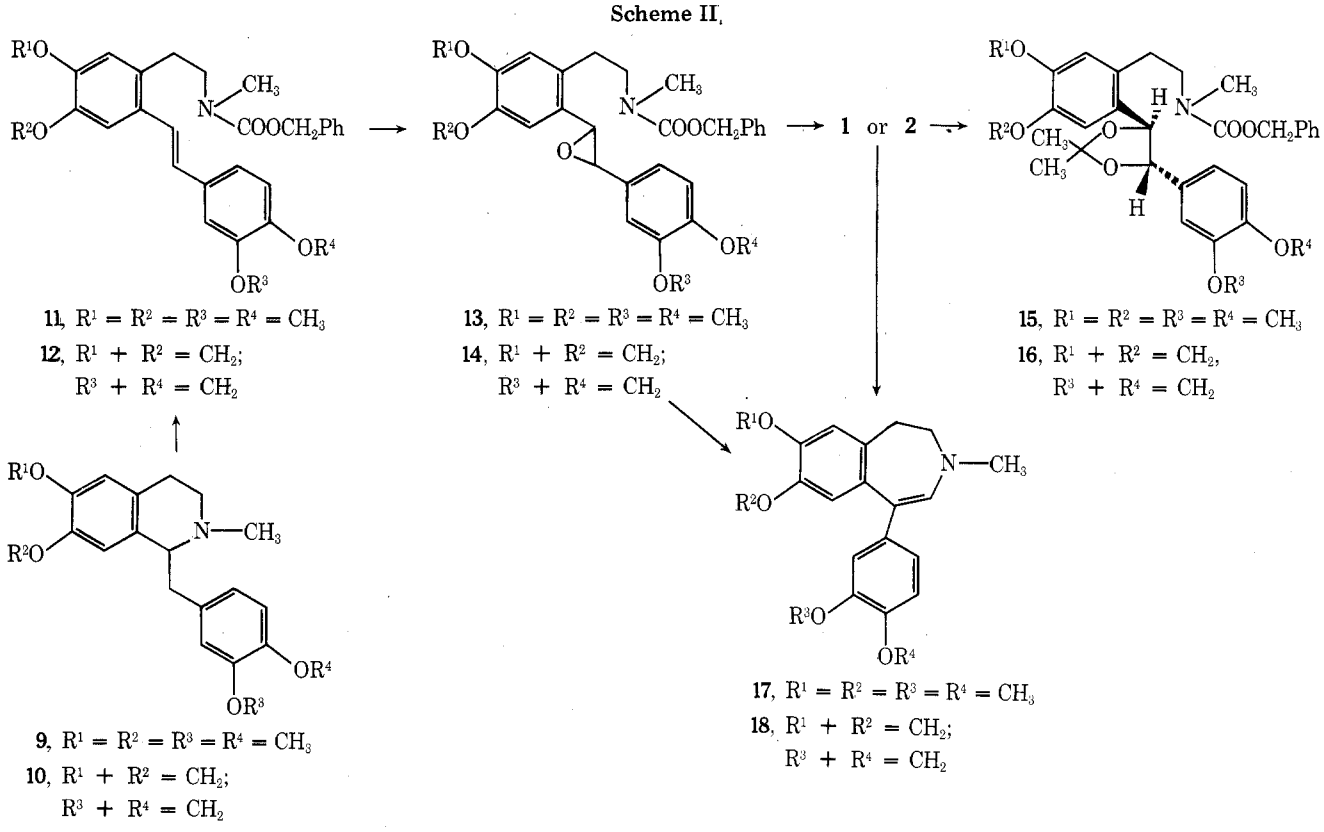
Melting points are uncorrected. NMR spectra were measured with a JNM-PMX-60 spectrometer (tetramethylsilane as an internal reference), ir spectra with a Hitachi 215 spectrophotometer, uv spectra with a Hitachi 124 spectrophotometer, and mass spectra with a Hitachi RMU-7 spectrometer.

**2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene (11).** To a stirred solution of laudanosine (**9**, 25 g) in methylene chloride (200 ml) were added in portions a solution of benzyloxycarbonyl chloride (13.2 g) in methylene chloride (200 ml) and a solution of sodium hydroxide (3.4 g) in water (100 ml) separately within 1 h at room temperature. After the stirring had been continued for 1 h at room temperature, the organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water, dried over $Na_2SO_4$, and evaporated to leave an orange, viscous oil, which was triturated with ethanol to give the stilbene **11** (25.9 g, 75.3%) as colorless prisms: mp 126–127 °C; uv (MeOH) 295 and 330 nm; ir ($CHCl_3$) 1680 $cm^{-1}$

**Scheme I**




**Scheme II**




(C=O); NMR ($CDCl_3$) $\delta$ 2.88 (3 H, s, $NCH_3$) and 5.08 ppm (2 H, s, $CO_2CH_2Ph$); mass spectrum *m/e* 491 ($M^+$).

Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.85; H, 6.77; N, 2.85. Found: C, 70.95; H, 6.81; N, 2.83.

**2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-dimethylenedioxystilbene (12).** 1,2,3,4-Tetrahydro-2-methyl-6,7-methylenedioxy-1-(3,4-methylenedioxybenzyl)isoquinoline (**10**, 10.2 g) was treated with benzyloxycarbonyl chloride (5.6 g) and a solution of sodium hydroxide (1.57 g) in water (40 ml) by the same way as described for compound **11** to give the stilbene **12** (10.9 g, 75.7%) as colorless prisms: mp 114–115 °C; uv (MeOH) 293 and 340 nm; ir ($CHCl_3$) 1680 $cm^{-1}$ (C=O); NMR ($CCl_4$) $\delta$ 2.82 (3 H, s, $NCH_3$), 5.01 (2 H, s, $CO_2CH_2Ph$), and 5.83 and 5.86 ppm (4 H, each s, 2 $OCH_2O$).

Anal. Calcd for $C_{27}H_{25}NO_6$: C, 70.57; H, 5.49; N, 3.05. Found: C, 70.36; H, 5.50; N, 2.98.

**2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene Oxide (13).** To a stirred solution of stilbene

11 (2 g) in methylene chloride (50 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (1 g) in methylene chloride (50 ml) at 0 °C. After the stirring had been continued for 4 h at room temperature, a saturated sodium sulfite aqueous solution (50 ml) was added to the above reaction mixture. The methylene chloride layer was separated and washed with potassium carbonate aqueous solution and water, dried over $K_2CO_3$, and evaporated to give a brownish, viscous oil, which was chromatographed on silica gel (50 g). Elution with chloroform afforded the epoxide **13** (1.86 g, 89.9%) as a pale brown oil: uv (MeOH) 280 nm; ir ($CHCl_3$) 1680 $cm^{-1}$ (C=O); NMR ($CDCl_3$) $\delta$ 2.77 (3 H, s, $NCH_3$), 4.99 (2 H, s, $CO_2CH_2Ph$), and 6.30–8.0 ppm (10 H, m, aromatic protons); mass spectrum *m/e* 507 ($M^+$).

**2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-dimethylenedioxystilbene Oxide (14).** Stilbene **12** (5 g) was treated with *m*-chloroperbenzoic acid (4.4 g) as described above to give the epoxide **14** (3.5 g, 67.7%) as a pale brown oil: uv (MeOH) 287 nm; ir ($CHCl_3$) 1680 $cm^{-1}$ (C=O); NMR ($CCl_4$) $\delta$ 2.81 (3 H, s, $NCH_3$), 5.05 (2 H, s, $CO_2CH_2Ph$), 5.80, 5.83 (4 H, each s, 2 $OCH_2O$), and 6.33–7.96 ppm (10 H, m, aromatic protons).

**Reaction of 2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene Oxide (13) with Potassium Hydroxide in Methanol.** A solution of stilbene oxide **13** (1.58 g) in 1 N methanolic potassium hydroxide (10 ml) was refluxed for 1.5 h. After the solvent had been distilled off under reduced pressure, the residue was dissolved in chloroform. The chloroform layer was washed with water, dried over $K_2CO_3$, and evaporated to leave a brown oil, which was chromatographed on silica gel (30 g). Elution with chloroform afforded the diol **1** (1.172 g, 71.4%) as a pale brown oil: ir ($CHCl_3$) 3400 (OH) and 1680 $cm^{-1}$ (C=O); NMR ($CDCl_3$) $\delta$ 2.74 (3 H, s, $NCH_3$), 3.60, 3.70, 3.74, 3.82 (12 H, each s, 4 $OCH_3$), 4.0–4.6 br (2 H, s, 2 OH, disappeared by $D_2O$ exchange), 4.75 [2 H, broad s, CH(OH)CH(OH)], 4.96 (2 H, $CO_2CH_2Ph$), and 6.25–7.5 ppm (10 H, m, aromatic protons); mass spectrum *m/e* 507 ($M^+ - 18$).

Anal. Calcd for $C_{29}H_{35}NO_8$: C, 66.27; H, 6.71; N, 2.67. Found: C, 66.15; H, 6.93; N, 2.62.

The diol **1** (399 mg) was converted to the acetonide **15** with acetone–perchloric acid in a usual way. The resulting crude acetonide was chromatographed on silica gel (30 g). Elution with benzene–ethyl acetate (3:1) afforded the acetonide **15** (170 mg, 39.6%) as an oil: ir ($CHCl_3$) 1680 $cm^{-1}$ (C=O); NMR ($CDCl_3$) $\delta$ 1.70 [6 H, s, $O_2C(CH_3)_2$], 2.68 (3 H, s, $NCH_3$), 4.5–5.0 (2 H, m, OCHCHO), 5.10 (2 H, s, $CO_2CH_2Ph$), and 6.3–7.5 ppm (10 H, m, aromatic protons); mass spectrum *m/e* 565 ($M^+$).

Anal. Calcd for $C_{32}H_{39}NO_8$: C, 67.94; H, 6.95; N, 2.48. Found: C, 67.75; H, 6.85; N, 2.27.

**Reaction of 2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-dimethylenedioxystilbene Oxide (14) with Potassium Hydroxide in Methanol.** Stilbene oxide **14** (3.5 g) was similarly treated with 1 N methanolic potassium hydroxide (60 ml) to afford the diol **2** (2.2 g, 60.6%) as a pale brown oil: ir ($CHCl_3$) 3400 (OH) and 1680 $cm^{-1}$ (C=O); NMR ($CCl_4$) $\delta$ 2.70 (3 H, s, $NCH_3$), 4.0–4.4 br (2 H, s, 2 OH), 4.55 br [2 H, s, CH(OH)CH(OH)], 4.96 (2 H, s, $CO_2CH_2Ph$), 5.85, 5.88 (4 H, each s, 2 $OCH_2O$), and 6.36–7.4 ppm (10 H, m, aromatic protons).

Anal. Calcd for $C_{27}H_{27}NO_8$: C, 65.71; H, 5.52; N, 2.84. Found: C, 65.35; H, 5.50; N, 3.16.

The diol **2** (500 mg) was converted into the acetonide **16** with acetone–perchloric acid in a usual way to afford the acetonide **16** (340 mg, 62.9%) as an oil: ir ($CHCl_3$) 1680 $cm^{-1}$ (C=O); NMR ($CCl_4$) $\delta$ 1.55 [6 H, s, $O_2C(CH_3)_2$], 2.66 (3 H, s, $NCH_3$), 4.3–4.9 (2 H, m, OCHCHO), 5.06 (2 H, s, $CO_2CH_2Ph$), 5.65, 5.63 (4 H, each s, 2 $OCH_2O$), and 6.41–7.6 ppm (10 H, m, aromatic protons).

Anal. Calcd for $C_{30}H_{31}NO_8 \cdot 1.5CHCl_3$: C, 62.40; H, 5.40; N, 2.31. Found: C, 61.95; H, 5.20; N, 2.33.

**Reaction of Diol 1 with *p*-Toluenesulfonic Acid in Acetic Acid.** A solution of diol **1** (772 mg) and *p*-toluenesulfonic acid (1 g) in acetic acid (20 ml) was refluxed for 2 h. After the solvent had been distilled off under reduced pressure, the residue was dissolved in chloroform.

The organic layer was washed with 10% sodium hydroxide and water, dried over $K_2CO_3$, and evaporated to afford a brown oil, which was triturated with methanol to give the azepine **17** (240 mg, 46%) as colorless needles: mp 116–117 °C; uv (MeOH) 306 nm; NMR ($CDCl_3$) $\delta$ 2.90 (3 H, s, $NCH_3$), 3.60, 3.81, 3.86, 3.90 (12 H, each s, 4 $OCH_3$), and 6.20–6.81 ppm (6 H, m, aromatic and olefinic protons); mass spectrum *m/e* 355 ($M^+$). This was identical with an authentic specimen[8] (mixture melting point and comparison of spectroscopic data).

**Reaction of 2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene Oxide (13) with *p*-Toluenesulfonic Acid in Acetic Acid.** A solution of stilbene oxide **13** (1.86 g) was treated with *p*-toluenesulfonic acid (1 g) in acetic acid (30 ml) under the same conditions as described for the diol **1** to give the azepine **17** (330 mg, 25.4%) as needles, mp 116–117 °C, identical with the authentic sample as described above.

**Reaction of Diol 2 with *p*-Toluenesulfonic Acid in Acetic Acid.** A solution of diol **2** (1 g) was similarly treated with *p*-toluenesulfonic acid (1 g) in acetic acid (40 ml) to afford the azepine **18** (76.2 mg, 11.6%) as a glass: uv (MeOH) 315 nm; NMR ($CCl_4$) $\delta$ 2.83 (3 H, s, $NCH_3$), 5.73, 5.83 (4 H, each s, 2 $OCH_2O$), and 6.0–7.2 ppm (6 H, m, aromatic and olefinic protons); mass spectrum *m/e* 323 ($M^+$).

Anal. Calcd for $C_{19}H_{17}NO_4 \cdot 0.5H_2O$: C, 68.66; H, 5.46. Found: C, 68.49; H, 5.21.

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**Registry No.**—**1,** 59643-46-8; **2,** 59643-47-9; **9,** 20412-65-1; **10,** 7688-68-8; **11,** 59643-48-0; **12,** 59643-49-1; **13,** 59643-50-4; **14,** 59643-51-5; **15,** 59643-52-6; **16,** 59643-53-7; **17,** 32407-74-2; **18,** 59643-54-8; benzyloxycarbonyl chloride, 501-53-1.

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