A Convenient Synthesis of 1,3,4,5-Tetrahydro-2*H*-3-benzazepin-2-ones by Acid-Catalyzed Cyclization of *N*-(2-Arylethyl)-*N*-methyl-2-sulfinylacetamides

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1,3,4,5-Tetrahydro-3-methyl-2*H*-3-benzazepin-2-one derivatives were synthesized by acid-catalyzed cyclization of *N*-(2-arylethyl)-*N*-methyl-2-sulfinylacetamides. Some chemical transformations of the 2*H*-3-benzazepin-2-ones are also described.

Keywords 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one; 1,3-dihydro-2*H*-3-benzazepin-2-one; sulfoxide; Pummerer reaction; desulfurization; Raney nickel; X-ray analysis

2,3,4,5-Tetrahydro-1*H*-3-benzazepine derivatives have received considerable attention, in part due to their interesting pharmacological activities, and a variety of synthetic methods have been developed.[1)] In a series of papers we reported the synthesis of oxindoles[2,3)] and tetrahydroisoquinol-3-ones[2)] using an acid-catalyzed aromatic cyclization of α-sulfinylacetamides (a Pummerer reaction).[4)] We now describe a further extension of this method to the synthesis of 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-ones,[5)] which are excellent precursors to a variety of 2,3,4,5-tetrahydro-1*H*-3-benzazepine derivatives.

The starting α-sulfinylacetamides **4a**—**c**, **11**, and **18** were prepared by standard methods (see Experimental).

The α-(methylsulfinyl)acetamide **4a** was treated with trifluoroacetic anhydride (TFAA) in methylene chloride at 0 °C and then at room temperature for 15 h (method A) to give the tetrahydro-2*H*-3-benzazepin-2-one **5a** in 54% yield. The same benzazepinone **5a** was also obtained in 61% yield by heating **4a** under reflux in benzene in the presence of anhydrous *p*-toluenesulfonic acid (PTSA) with azeotropic removal of water (method B). Desulfurization of **5a** with Raney nickel in refluxing ethanol gave the known benzazepinone **6**.[6)] Lithium aluminum hydride reduction of **5a** in tetrahydrofuran (THF) gave the benzazepine **7** in 40% yield. Oxidation of **5a** with sodium metaperiodate followed by treatment with PTSA in refluxing methylene chloride (a Pummerer reaction) gave the dione **8** in 35% overall yield.

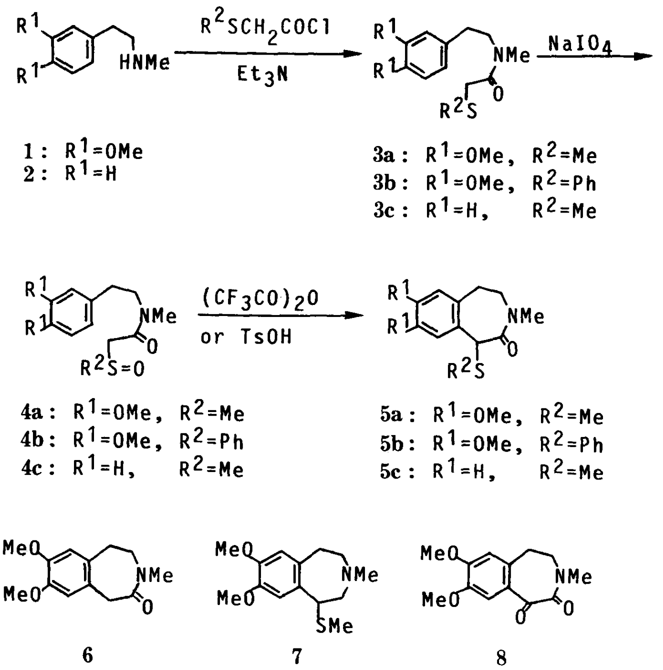

Chart 1

Similar treatment of the sulfoxide **4b** with TFAA (method A) gave **5b** in 52% yield, which, upon reduction with Raney nickel, afforded **6**. Treatment of the sulfoxide **4c** under the conditions of method A gave a complex mixture. However, when **4c** was treated with PTSA in boiling benzene (method B), the expected benzazepinone **5c** was obtained in 62% yield.

When the sulfoxide **11** was treated with TFAA in methylene chloride (method A), two isomeric benzazepinones **12** and **13** were obtained in 70 and 24% yields, respectively, after chromatographic separation on silica gel. Desulfurization of each isomer with Raney nickel gave the same benzazepinone **14**. Lithium aluminum hydride reduction of the major isomer **12** followed by desulfurization of the resulting benzazepine **15** with Raney nickel gave the known benzazepine **16**.[7)] Confirmation of the stereochemistry of **12** and **13** was given by an X-ray analysis of the minor isomer **13**, in which the phenyl and methylthio groups are *cis* to each other (Fig. 1).

We next examined the behavior of the α-(methylsulfinyl)-

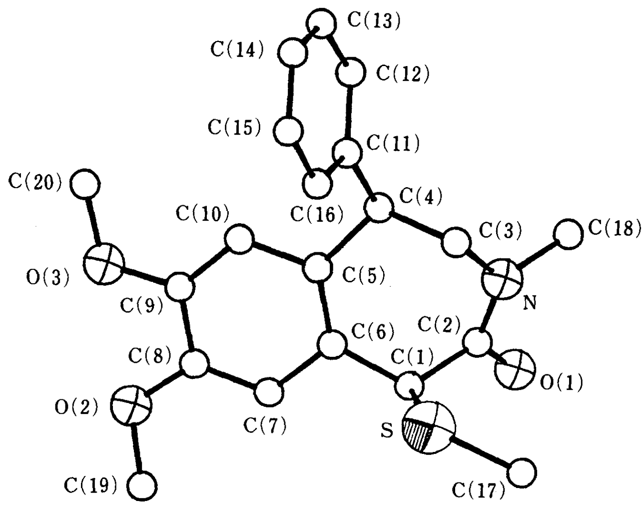

Fig. 1. Perspective ORTEP Drawing of Compound **13**

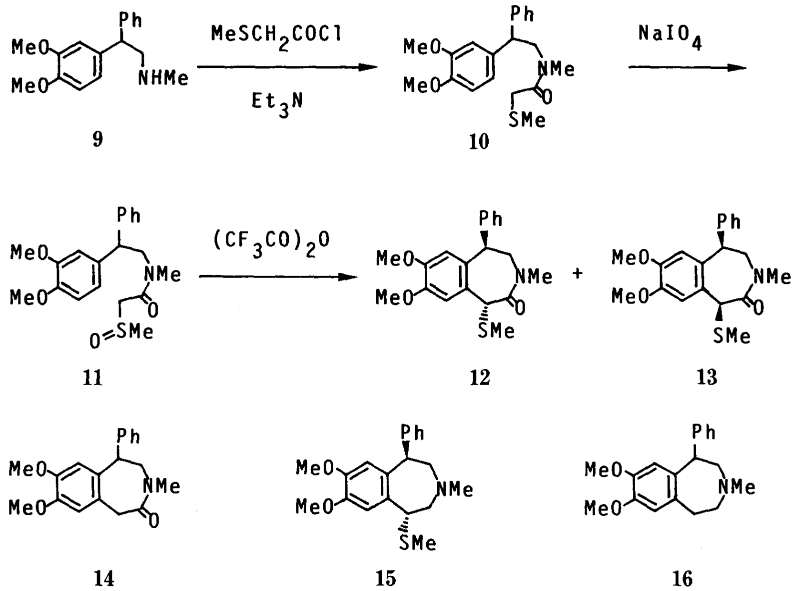

Chart 2

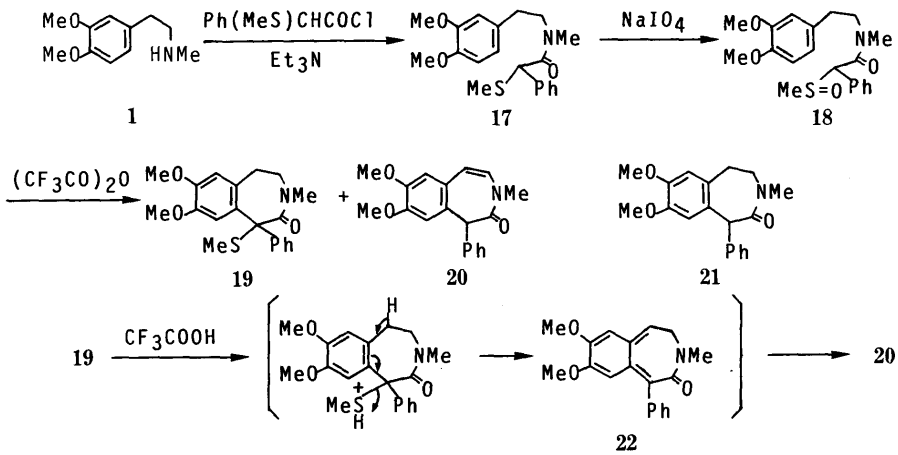

Chart 3

α-phenylacetamide **18**. When compound **18** was treated under the conditions of method A, two products were isolated after chromatographic separation on silica gel. The product distribution was dependent upon the reaction time; a shorter period of reaction (3 h) gave **19** and **20** in 65 and 28% yields, respectively, while a longer period of reaction (70 h) afforded **19** and **20** in 47 and 48% yields, respectively. One of the products was assigned as the expected benzazepinone **19** and the other as the acylenamide **20**, on the basis of spectroscopic and chemical evidence. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **19** showed the presence of an *S*-methyl signal at δ 1.85 and a multiplet due to two methylene groups between δ 2.6 and 3.5. Desulfurization of **19** with Raney nickel gave the benzazepinone **21**. On the other hand, the ^{1}H-NMR spectrum of **20** lacked the signal of a methylthio group and, instead, showed two olefinic proton signals at δ 5.70 (1H, d, $J=9$ Hz) and 6.00 (1H, d, $J=9$ Hz). A possible mechanism for the formation of **20** involves an acid-catalyzed elimination of methylmercaptan from **19** to lead to the quinodimethane **22**, which undergoes aromatization to give **20**. Indeed, treatment of **19** with trifluoroacetic acid afforded **20**.

In summary, the present study revealed that an acid-promoted aromatic cyclization of α-sulfinylacetamides provides a general synthetic route to 3-benzazepin-2-one derivatives.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 spectrophotometer. ^{1}H-NMR spectra were determined with a JEOL JNM-PMX 60 (60 MHz) spectrometer using tetramethylsilane as an internal standard. Low- and high-resolution mass spectra (MS) were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on Silica gel 60 PF_{254} (Merck) under pressure.

Materials *N*-Methyl-2-(3,4-dimethoxyphenyl)ethylamine (**1**) was prepared from homoveratrylamine according to the reported procedure.[8] *N*-Methyl-2-phenylethylamine (**2**) was purchased from Tokyo Kasai Kogyo Co., Ltd.

General Procedure for the Preparation of Sulfides 3a—c A solution of (methylthio)acetyl chloride[9] or (phenylthio)acetyl chloride[10] (26 mmol) in ethyl ether (30 ml) was added dropwise to a solution of the amine **1** or **2** (26 mmol) in triethylamine (3.9 g, 38 mmol) in ethyl ether (70 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min and diluted with water (10 ml). The organic layer was separated, washed with brine, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel using AcOEt–benzene (1 : 8) as an eluent to give **3** as a colorless oil. The following products were obtained. *N*-[2-(3,4-Dimethoxyphenyl)-ethyl]-*N*-methyl-2-(methylthio)acetamide (**3a**) (71%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635. ^{1}H-NMR ($CDCl_3$) δ: 2.16 and 2.23 (total 3H, both s, SCH_3),[11] 2.5—3.0 (2H, m), 2.96 (3H, s, NCH_3), 2.99, 3.24 (1H each, both s), 3.4—3.9 (2H, m), 3.83 and 3.86 (3H each, both s, 2×OCH_3), 6.6—6.9 (3H, m, aromatic protons). Exact MS *m/z*: Calcd for $C_{14}H_{21}NO_3S$: 283.1240. Found: 283.1262. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methyl-2-(phenylthio)acetamide (**3b**) (60%); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635. ^{1}H-NMR ($CDCl_3$) δ: 2.6—3.0 (2H, m), 2.92 and 2.96 (total 3H, both s, NCH_3),[11] 3.4—3.8 (4H, m), 3.82 (6H, s, 2×OCH_3), 6.5—6.8 (3H, m, aromatic protons), 7.1—7.5 (5H, m, aromatic protons). Exact MS *m/z*: Calcd for $C_{19}H_{23}NO_3S$, 345.1396. Found, 345.1376. *N*-Methyl-2-methylthio-*N*-(2-phenylethyl)acetamide (**3c**) (84%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s, SCH_3), 2.6—3.8 (6H, m), 2.94 (3H, s, NCH_3), 7.20 (5H, s, aromatic protons). Exact MS *m/z*: Calcd for $C_{12}H_{17}NOS$: 223.1029. Found, 223.1013.

General Procedure for the Preparation and Cyclization of 2-(Methylsulfinyl)acetamides (4a—c) A solution of sodium metaperiodate (1.63 g, 7.6 mmol) in water (44 ml) was added dropwise to a solution of a sulfide **3a—c** (7.6 mmol) in methanol (22 ml) at 0 °C and the mixture was stirred at room temperature for 15 h. The precipitated inorganic materials were filtered off, the filtrate was extracted with chloroform and the extract was dried ($MgSO_4$). The solvent was evaporated off and the respective oily sulfoxide **4a—c** was used for the next step without further purification.

Method A: TFAA (1.17 g, 5.6 mmol) was added dropwise to a solution of the sulfoxide **4** (5.6 mmol) in dry methylene chloride (40 ml) at 0 °C and the mixture was stirred at the same temperature for 1 h, and then at room temperature for 15 h. The reaction was quenched with water and the organic layer was separated. The aqueous layer was further extracted with methylene chloride and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel using AcOEt–benzene (2 : 1) as an eluent. The following products were obtained. 1,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-methylthio-2*H*-3-benzazepin-2-one (**5a**) (54%), mp 81—82 °C (from ethanol). IR ν_{max}^{KBr} cm^{-1}: 1650. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, s, SCH_3), 2.9—3.2 (2H, m, 5-H), 3.09 (3H, s, NCH_3), 3.3—3.5 and 4.6—5.2 (1H each, both m, 4-H), 3.81, 3.84 (3H each, both s, 2×OCH_3), 4.66 (1H, s, 1-H), 6.53 and 6.68 (1H each, both s, aromatic protons). *Anal.* Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59.68; H, 6.88; N, 5.05. 1,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-phenylthio-2*H*-3-benzazepin-2-one (**5b**) (53%), mp 110—111 °C (from ethanol). IR ν_{max}^{KBr} cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 3.0—3.5 (3H, m, 5-H and one of 4-H), 3.01 (3H, s, NCH_3), 3.70 and 3.82 (3H each, both s, 2×OCH_3), 4.6—5.1 (1H, m, one of 4-H), 5.03 (1H, s, 1-H), 6.46 and 6.55 (1H each, both s, aromatic protons), 7.2—7.6 (5H, m, aromatic protons). *Anal.* Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.21; H, 6.28; N, 4.01.

Method B: *p*-Toluenesulfonic acid (PTSA) monohydrate (255 mg, 1.34 mmol) was added to dry benzene (3 ml) and the mixture was heated under reflux with azeotropic removal of water for 2 h, and then cooled to room temperature under nitrogen. A solution of **4** (0.67 mmol) in benzene (1 ml) was added to the solution of PTSA in benzene *via* a syringe in one portion and the mixture was again heated under reflux with azeotropic removal of water for 2 h. After cooling to room temperature, the mixture was washed with water and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel using AcOEt–benzene (2 : 1) as an eluent. The following products were obtained. The benzazepin-2-one **5a** (58%). 1,3,4,5-Tetrahydro-3-methyl-1-methylthio-2*H*-3-benzazepin-2-one (**5c**) (62%), mp 93—94 °C (from hexane). IR ν_{max}^{KBr} cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, SCH_3), 3.0—3.36 (3H, m), 3.06 (3H, s, NCH_3), 4.5—5.1 (1H, m), 4.71 (1H, s, 1-H), 6.9—7.4 (4H, m, aromatic protons). *Anal.* Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.25; H, 6.64; N, 6.49.

1,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-2*H*-3-benzazepin-2-one (6) (a) From **5a**: Compound **5a** (118 mg, 0.40 mmol) was heated under reflux in ethanol (10 ml) containing Raney nickel (W-2) (*ca.* 2 g) for 4 h. The Raney nickel was removed by filtration and the solvent was evaporated off. The residual solid was recrystallized from hexane–AcOEt to give **6** (30 mg, 32%), mp 136—137 °C, lit.[6] mp 137—138 °C.

(b) From **5b**: Similar treatment of **5b** (63 mg, 0.18 mmol) gave **6** (30 mg, 69%).

2,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-methylthio-1*H*-3-benzazepine (7) A solution of **5a** (534 mg, 1.9 mmol) in dry THF (2 ml) was added dropwise to a suspension of lithium aluminum hydride (72 mg, 1.9 mmol) in dry THF (1.2 ml) at 0 °C, and the mixture was stirred at room temperature for 2 h. The excess hydride was decomposed by careful addition of water and the precipitated inorganic material was filtered off. The precipitate was washed with THF and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel using AcOEt as an eluent to give **7** (203 mg, 40%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, SCH_3), 2.2—3.9 (7H, m, 1-, 2-, 4-, 5-H), 3.85 (6H, s, 2×OCH_3), 6.61 (2H, br s, aromatic protons). Its picrate, mp 163—164 °C (from ethanol). *Anal.* Calcd for $C_{20}H_{24}N_4O_9S \cdot 1/4H_2O$: C, 47.95; H, 4.93; N, 11.18. Found: C, 48.14; H, 4.75; N, 10.77.

2,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1*H*-3-benzazepine-1,2-dione (8) Using the general procedure described for the preparation of **4**, **5a** (78 mg, 0.28 mmol) was oxidized with sodium metaperiodate (59 mg, 0.28 mmol) to give the sulfoxide (81.5 mg, 99%) as an oil, which was used for the next step without further purification.

The sulfoxide thus obtained (81.5 mg, 0.27 mmol) was dissolved in methylene chloride (5 ml). PTSA monohydrate (51.4 mg, 0.27 mmol) was then added to the solution and the mixture was heated under reflux for 15 h. After cooling, the mixture was washed with water, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (AcOEt–benzene, 1 : 1) to give the dione **8** (24 mg, 35%), mp 163—164 °C (from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1645, 1670. ^{1}H-NMR ($CDCl_3$) δ: 2.9—3.3 and 3.5—3.9 (total 4H, both m, H-4, H-5), 3.11 (3H, s, NCH_3), 3.87 and 3.91 (3H each, both s, 2×OCH_3), 6.65 and 7.32 (1H each, both s, aromatic protons). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.32; H, 5.97; H, 5.76.

2-(3,4-Dimethoxyphenyl)-*N*-methyl-2-phenylethylamine (9) A solution of (3,4-dimethoxyphenyl)phenylacetic acid[12] (762 mg, 2.8 mmol) and thionyl chloride (0.29 ml, 3.4 mmol) in dry THF (10 ml) was heated under reflux for 1 h. The solvent and the excess thionyl chloride were removed under reduced pressure and the resulting crude acid chloride was dissolved in dry benzene (15 ml). Methylamine hydrochloride (378 mg, 5.6 mmol) and potassium carbonate (1.19 g, 11.2 mmol) were added to the solution at 0 °C, and then water (1.5 ml) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with benzene and washed with water, dried (Na_2SO_4), and concentrated. The resulting crystals were recrystallized from AcOEt to give white needles of 2-(3,4-dimethoxyphenyl)-*N*-methyl-2-phenylacetamide (628 mg, 80%), mp 107.5—108.0 °C. IR ν_{max}^{KBr} cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 2.77 and 2.85 (total 3H, both s, NCH_3),[11] 3.79 and 3.82 (3H each, both s, 2×OCH_3), 4.84 (1H, s), 5.70 (1H, br s, NH), 6.79 (3H, s, aromatic protons), 7.26 (5H, s, aromatic protons). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.43; H, 6.78; N, 4.85.

Borane–THF complex (1 M solution in THF) (4.7 ml, 4.7 mmol) was added dropwise to a solution of the acetamide obtained above (804 mg, 2.8 mmol) in dry THF (2 ml) at 0 °C under nitrogen, and the mixture was heated under reflux for 1 h. After cooling of the mixture, 6 M hydrochloric acid (1 ml) was added. The solvent was evaporated off and the residue was diluted with water (10 ml). The mixture was made alkaline with 10% sodium hydroxide and extracted with ethyl ether (10 ml × 4). The extract was dried (NaOH) and concentrated to give the amine **9** (530 mg), which was used for the next step without purification.

***N*-[2-(3,4-Dimethoxyphenyl)-2-phenylethyl]-*N*-methyl-2-(methylthio)-acetamide (10)** Using the general procedure described for the preparation of **3**, the acetamide **10** (538 mg, 53%) was obtained from the amine **9** (759 mg, 2.8 mmol) and (methylthio)acetyl chloride (697 mg, 5.6 mmol) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 2.04 and 2.10 (total 3H, both s, SCH_3),[11] 2.79 (3H, s, NCH_3), 2.85 and 3.14 (total 2H, both s), 3.78 (6H, s, 2×OCH_3), 3.7—4.4 (3H, m), 6.76 (3H, s, aromatic protons), 7.18 (5H, s, aromatic protons). Exact MS *m/z*: Calcd for $C_{20}H_{25}NO_3S$, 359.1554. Found, 359.1584.

Synthesis and Cyclization of *N*-[2-(3,4-Dimethoxyphenyl)-2-phenylethyl]-*N*-methyl-2-(methylsulfinyl)acetamide (11) Using the general procedure described for the preparation of **4**, the sulfoxide **11** (146 mg, 70%) was obtained from the sulfide **10** (200 mg, 0.6 mmol) and sodium metaperiodate (119 mg, 0.6 mmol) as an oil. This sulfoxide was used for the next step without further purification.

According to method A, the sulfoxide **11** (2.41 g, 6.4 mmol) was treated with TFAA (0.90 ml, 6.4 mmol) in dry methylene chloride (50 ml) at room temperature for 20 h. After work-up, the crude product was chromatographed on silica gel using benzene–AcOEt (4 : 1) as an eluent. The first fraction gave *trans*-1,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1-methylthio-5-phenyl-2*H*-3-benzazepin-2-one (**12**) (1.60 g, 70%), mp 155.5—156.5 °C (from AcOEt–hexane). IR ν_{max}^{KBr} cm^{-1}: 1650. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, SCH_3 or NCH_3), 2.34 (3H, s, NCH_3 or SCH_3), 3.33 (1H, dd,

$J=4$, 14 Hz, one of 4-H), 3.67 and 3.87 (3H each, both s, $2\times OCH_3$), 4.33 (1H, dd, $J=2$, 4 Hz, 5-H), 4.80 (1H, s, 1-H), 5.33 (1H, dd, $J=2$, 14 Hz, one of 4-H), 6.33 and 6.73 (1H each, both s, aromatic protons), 6.8—7.3 (5H, m, aromatic protons). *Anal.* Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.48; N, 3.92. Found: C, 67.16; H, 6.56; N, 4.18.

The second fraction gave the *cis*-isomer **13** (595 mg, 26%), mp 164—165 °C (from AcOEt–hexane). IR ν_{max}^{KBr} cm^{-1}: 1650. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s, SCH_3), 3.10 (3H, s, NCH_3), 2.9—3.3 (1H, m, one of 4-H), 3.52 and 3.83 (3H each, both s, $2\times OCH_3$), 4.34 (1H, dd, $J=4$, 13 Hz, 5-H), 4.80 (1H, s, 1-H), 5.33 (1H, dd, $J=2$, 14 Hz, one of 4-H), 6.33 and 6.73 (1H each, both s, aromatic protons), 6.8—7.3 (5H, m, aromatic protons). *Anal.* Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.48; N, 3.92. Found: C, 67.14; H, 6.52; N, 3.91.

1,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-5-phenyl-2*H*-3-benzazepin-2-one (14) Using a procedure similar to that described for the preparation of **6**, compound **12** (400 mg, 1.1 mmol) was treated with Raney nickel to give **14** (247 mg, 72%), mp 105—105.5 °C (from hexane). IR ν_{max}^{KBr} cm^{-1}: 1650. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (3H, s, NCH_3), 3.62 and 3.86 (3H each, both s, $2\times OCH_3$), 3.95 (2H, s, 1-H), 3.7—4.1 (2H, m, one of 4-H, 5-H), 4.2—4.5 (1H, m, one of 4-H), 6.37 and 6.65 (1H each, both s, aromatic protons), 6.8—7.4 (5H, m, aromatic protons). *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.59; H, 6.81; N, 4.48.

Similar desulfurization of **13** (100 mg, 0.28 mmol) gave **14** (40 mg, 65%).

***trans*-2,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-methylthio-5-phenyl-1*H*-3-benzazepine (15)** Using a procedure similar to that described for the preparation of **7**, compound **12** (200 mg, 0.56 mmol) was reduced with lithium aluminum hydride (152 mg, 1.12 mmol) to give **15** (90 mg, 47%), mp 99—99.5 °C (from hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, SCH_3), 2.45 (3H, s, NCH_3), 2.5—3.5 (4H, m), 3.50, 3.86 (3H each, both s, $2\times OCH_3$), 3.8—4.0 (1H, m, 1-H), 4.95 (1H, dd, $J=2$, 10 Hz, 5-H), 6.14 and 6.64 (1H each, both s, aromatic protons), 7.1—7.6 (5H, m, aromatic protons). *Anal.* Calcd for $C_{20}H_{25}NO_2S$: C, 69.94; H, 7.34; N, 4.08. Found: C, 69.91; H, 7.32; N, 4.08.

2,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-1*H*-3-benzazepine (16) Using a procedure similar to that described for the preparation of **6**, compound **15** (190 mg, 0.56 mmol) was treated with Raney nickel (0.5 g) in ethanol (10 ml) to give **16** (65 mg, 39%), mp 82—83 °C (from hexane), lit.[7] mp 82—84 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s, NCH_3), 2.3—3.2 (6H, m), 3.58, 3.83 (3H each, both s, $2\times OCH_3$), 4.25 (1H, dd, $J=3$, 7 Hz, H-1), 6.22 and 6.63 (1H each, both s, aromatic protons), 7.0—7.5 (5H, m, aromatic protons).

X-Ray Analysis of 13 Crystal Data: $C_{20}H_{23}NO_3S$, triclinic, space group $P\bar{1}$; $a=7.955(2)$, $b=9.671(3)$, $c=12.724(4)$ Å, $\alpha=95.33(3)$, $\beta=101.97(2)$, $\gamma=98.93(2)$°, $D_x=1.27$ g/cm^3 and $(MoK_\alpha)=1.9$ cm^{-1}.

Data Collection: The cell dimensions and intensities were measured on a Syntex R_3 four-circle diffractometer with graphite-monochromated MoK_α radiation in the ω-scan mode within 2θ less than 40°. A total of 2475 independent refrections were collected, among which 2122 reflections [$I\geq 1.96\sigma(I)$] were regarded as observed.

Structure Determination and Refinement: The structure was solved by the direct method using the MULTAN program.[13] The atomic coordinates were refined by the block-diagonal least-squares method, using anisotropic temperature factors for all the non-hydrogen atoms and isotopic ones for hydrogen atoms. The final R value was 0.039. The atomic scattering factors were taken from "International Tables for X-Ray Crystallography."[14] Bond lengths and bond angles are listed in Table I. Atomic coordinates for non-hydrogen atoms are given in Table II.

***N*[-2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methyl-2-methylthio-2-phenylacetamide (17)** Using the general procedure described for the preparation of **3**, the amine **1** (1.07 g, 5.5 mmol) was treated with (methylthio)phenylacetyl chloride[15] (1.10 g, 5.5 mmol) to give the acetamide **17** (1.01 g, 51%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.85 and 1.97 (total 3H, both s, SCH_3),[11] 2.5—3.0 (2H, m), 2.82 and 2.96 (total 3H, both s, NCH_3),[11] 3.3—3.7 (2H, m), 3.78 and 3.82 (3H each, both s, $2\times OCH_3$), 4.0—4.7 (1H, m), 6.5—6.8 (3H, m, aromatic protons), 7.27 (5H, br s, aromatic protons). Exact MS m/z: Calcd for $C_{20}H_{25}NO_3S$: 539.1553. Found: 359.1530.

Synthesis and Cyclization of *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methyl-2-methylsulfinyl-2-phenylacetamide (18) Using a procedure similar to that described for the preparation of **4a**, the sulfide **17** (474 mg, 1.3 mmol) was oxidized with sodium metaperiodate (311 mg, 1.4 mmol) to give the oily sulfoxide **18**, which was used for the next step without further purification.

Using method A, the crude sulfoxide **18** (100 mg, 0.27 mmol) was treated with TFAA (0.04 ml, 0.27 mmol) at room temperature for 3 h. After work-up, a crude mixture was chromatographed on silica gel using benzene–AcOEt (5 : 1) as an eluent. The first fraction gave 1,3-dihydro-7,8-dimethoxy-3-methyl-1-phenyl-2*H*-3-benzazepin-2-one (**20**) (62 mg, 65%),

TABLE I. Bond Lengths (Å) and Bond Angles (°) for Compound **13** with e.s.d.'s in Parentheses

S–C(1)	1.827 (3)	S–C(17)	1.790 (3)
O(1)–C(2)	1.222 (3)	O(2)–C(8)	1.362 (3)
O(2)–C(19)	1.413 (4)	O(3)–C(9)	1.364 (3)
O(3)–C(20)	1.416 (4)	N–C(2)	1.334 (4)
N–C(3)	1.458 (4)	N–C(18)	1.452 (4)
C(1)–C(2)	1.526 (4)	C(1)–C(6)	1.510 (4)
C(3)–C(4)	1.521 (4)	C(4)–C(5)	1.534 (4)
C(4)–C(11)	1.519 (4)	C(5)–C(6)	1.381 (4)
C(5)–C(10)	1.394 (4)	C(6)–C(7)	1.408 (4)
C(7)–C(8)	1.366 (4)	C(8)–C(9)	1.400 (4)
C(9)–C(10)	1.371 (4)	C(11)–C(12)	1.374 (4)
C(11)–C(16)	1.374 (4)	C(12)–C(13)	1.384 (5)
C(13)–C(14)	1.347 (5)	C(14)–C(15)	1.360 (5)
C(15)–C(16)	1.385 (5)		
C(1)–S–C(17)	100.3 (1)	C(8)–O(2)–C(19)	117.5 (2)
C(9)–O(3)–C(20)	117.2 (2)	C(2)–N–C(3)	122.3 (2)
C(2)–N–C(18)	118.8 (2)	C(3)–N–C(18)	118.5 (2)
S–C(1)–C(2)	112.9 (2)	S–C(1)–C(6)	110.5 (2)
C(2)–C(1)–C(6)	117.3 (2)	O(1)–C(1)–N	122.9 (3)
O(1)–C(2)–C(1)	118.3 (2)	N–C(2)–C(1)	118.8 (2)
N–C(3)–C(4)	113.5 (2)	C(3)–C(4)–C(5)	114.9 (2)
C(3)–C(4)–C(11)	108.0 (2)	C(5)–C(4)–C(11)	111.3 (2)
C(4)–C(5)–C(6)	125.6 (2)	C(4)–C(5)–C(10)	115.9 (2)
C(6)–C(5)–C(10)	118.4 (2)	C(1)–C(6)–C(5)	127.3 (2)
C(1)–C(6)–C(7)	113.7 (2)	C(5)–C(6)–C(7)	119.0 (2)
C(6)–C(7)–C(8)	121.9 (2)	O(2)–C(8)–C(7)	125.5 (2)
O(2)–C(8)–C(9)	115.4 (2)	C(7)–C(8)–C(9)	119.1 (2)
O(3)–C(9)–C(8)	115.7 (2)	O(3)–C(9)–C(10)	125.4 (2)
C(8)–C(9)–C(10)	118.9 (2)	C(5)–C(10)–C(9)	122.7 (2)
O(4)–C(11)–C(12)	120.3 (2)	O(4)–C(11)–C(16)	121.4 (2)
C(12)–C(11)–C(16)	118.3 (3)	C(11)–C(12)–C(13)	120.1 (3)
C(12)–C(13)–C(14)	120.8 (3)	C(13)–C(14)–C(15)	120.2 (3)
C(14)–C(15)–C(16)	119.6 (3)	C(11)–C(16)–C(15)	121.0 (3)

e.s.d., estimated standard deviations.

TABLE II. Atomic Coordinates ($\times 10^4$) for Non-hydrogen Atoms of Compound **13** with e.s.d.'s in Parentheses

Atom	x	y	z
S	8766 (1)	1593 (0.9)	4651 (0.6)
O(1)	7469 (3)	4663 (2)	5912 (1)
O(2)	9060 (2)	4429 (2)	976 (1)
O(3)	5846 (2)	3616 (2)	−37 (1)
N	5321 (3)	2824 (3)	5173 (2)
C(1)	7957 (3)	3235 (3)	4433 (2)
C(2)	6867 (4)	3632 (3)	5231 (2)
C(3)	4547 (4)	1676 (3)	4298 (2)
C(4)	3973 (3)	2177 (3)	3203 (2)
C(5)	5470 (3)	2796 (3)	2699 (2)
C(6)	7189 (3)	3243 (3)	3244 (2)
C(7)	8412 (3)	3813 (3)	2671 (2)
C(8)	7952 (3)	3912 (3)	1589 (2)
C(9)	6206 (4)	3473 (3)	1039 (2)
C(10)	5012 (3)	2937 (3)	1601 (2)
C(11)	2757 (4)	953 (3)	2448 (2)
C(12)	991 (4)	943 (3)	2178 (2)
C(13)	−113 (4)	−175 (4)	1492 (3)
C(14)	520 (5)	−1267 (4)	1081 (3)
C(15)	2262 (5)	−1291 (3)	1348 (3)
C(16)	3381 (4)	−174 (3)	2028 (3)
C(17)	9628 (4)	1905 (4)	6085 (2)
C(18)	4283 (4)	3203 (4)	5932 (3)
C(19)	10844 (4)	4855 (3)	1490 (2)
C(20)	4126 (4)	3066 (3)	−640 (2)

149.5—150 °C (AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1650. ^{1}H-NMR ($CDCl_3$) δ: 3.14 (3H, s, NCH_3), 4.80 and 4.84 (3H each, both s, $2\times OCH_3$), 5.11 (1H, br s, 1-H), 5.70 and 6.00 (2H each, ABq, $J=9$ Hz, 4- and 5-H), 6.72 and 6.82 (1H each, both s, aromatic protons), 6.8—7.3 (5H, m, aromatic protons). *Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.91; H, 6.29; N, 4.83.

The second fraction gave 2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1-methylthio-1-phenyl-2*H*-3-benzazepin-2-one (**19**) (27 mg, 28%), mp 159—160 °C (from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (3H, s, SCH_3), 2.6—3.5 (4H, m, 4- and 5-H), 3.04 (3H, s, NCH_3), 3.84 (6H, br s, $2\times OCH_3$), 6.60 (1H, s, an aromatic proton), 7.0—7.4 (5H, m, aromatic protons), 7.70 (1H, s, an aromatic proton). *Anal.* Calcd for $C_{19}H_{23}NOS$: C, 67.20; H, 6.48; N, 3.92. Found: C, 67.22; H, 6.43; N, 4.14.

A longer period of reaction (70 h) gave **19** (45 mg, 47%) and **20** (40 mg, 48%).

Transformation of 19 into 20 A solution of **19** (200 mg, 0.56 mmol) in trifluoroacetic acid (5 ml) was stirred at room temperature overnight under nitrogen. The mixture was concentrated under reduced presssure and methylene chloride (10 ml) was added. The solution was washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel using AcOEt–hexane (1 : 1) to give **20** (100 mg, 58%) and unreacted starting material **19** (20 mg, 10%).

1,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-2*H*-3-benzazepin-2-one (21) Using a procedure similar to that described for the preparation of **6**, compound **19** (100 mg, 0.28 mmol) was reduced with Raney nickel (*ca.* 1 g) in ethanol (10 ml). Work-up gave **21** as white crystals, mp 218 °C (from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1650. ^{1}H-NMR ($CDCl_3$) δ: 2.5—3.2 (2H, m, 5-H), 2.85 and 2.96 (total 3H, both s, NCH_3), 3.3—4.0 (3H, m, 1-H, 4-H), 3.78 and 3.80 (3H each, both s, $2\times OCH_3$), 6.72 (2H, br s, aromatic protons), 7.23 (5H, br s, aromatic protons). *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.25; H, 6.71; N, 4.85.

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