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Synthesis of Saframycins. II. Preparations and Reactions of N-Methyl-2,5-piperazinediones

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An efficient synthesis of 4-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione **5** and 1-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione **10** from (*Z*)-1-acetyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione **2** is described.

The 1-methyl-2,5-piperazinedione **10** is shown to be a useful intermediate for preparation of the 1,5-imino-3-benzazocine derivative **16**, which is the skeleton of the "right half" of saframycins.

Keywords—*N*-methyl-2,5-piperazinedione; preparation; 1,5-imino-3-benzazocine; saframycin; protective group

In recent years several isoquinolinequinones¹⁾ have been isolated from *Actinomycetes* and marine sponge. Saframycins^{1,2)} are antitumor antibiotics produced by *Streptomyces laven-dulae*. They constitute a class of the dimeric isoquinolinequinone antibiotic group, which includes safracins³⁾ and renieramycins.⁴⁾ In this group, saframycin A (**20**) has been shown to possess the highest antitumor activity. Two total syntheses of saframycin B (**19**) have been reported by Fukuyama and Sachleben,^{5a)} and by us,^{5b)} but a total synthesis of **20** has not been accomplished. Arai *et al.*⁶⁾ suggested that the dimeric quinone skeletons which are common to all saframycins may be formed by cyclization of two molecules of tyrosine to form a 2,5-piperazinedione biosynthetic precursor. 2,5-Piperazinediones are among the most ubiquitous peptides found in nature.⁷⁾ For the synthesis of 2,5-piperazinediones containing an alkyl substituent on the amide nitrogen, direct introduction of the substituent as the desired position (at N-1 or N-4 in **1**) should be one of the most important steps, but in general, alkylation of the 2,5-piperazinediones by lower alkyl halides gives a mixture from which mono-*N*-alkyl derivatives can not be readily separated.⁸⁾ We report herein the regioselective syntheses of 3-arylmethyl-4-methyl-2,5-piperazinedione (**5**) and 3-arylmethyl-1-methyl-2,5-piperazinedione (**10**) from (*Z*)-1-acetyl-3-arylidene-2,5-piperazinedione (**2**)⁹⁾ using an acetyl group and a 4-methoxybenzyl group for the protection of the amide nitrogen, and the synthesis of the hexahydro-1,5-imino-3-benzazocine derivative (**16**)¹⁰⁾ from the 2,5-piperazinedione (**10**), to provide a basis for approaching the synthesis of saframycin A (**20**).

As shown in Chart 1, the 4-methyl-2,5-piperazinedione (**5**) can be readily prepared from **2** in three steps. Namely, the *Z* isomer **2** was alkylated with methyl iodide in the presence of sodium hydride¹¹⁾ in dimethylformamide (DMF) at 25 °C to afford **3** in 84.4% yield. Treatment of **3** with hydrazine hydrate afforded the 4-methyl derivative (**4**) in 74.2% yield. Catalytic reduction of **4** in ethanol in the presence of 20% palladium on carbon gave **5** in 62.1% yield.

Next, we planned to synthesize the 1-methyl-2,5-piperazinedione (**10**) from **2**, utilizing a protecting group for an amide nitrogen (Chart 2). The protection of the N-H group of amides is important in synthetic amide chemistry, and several methods for the protection of amide nitrogen have been developed.¹²⁾ The benzyl group is the most stable protecting group, and it

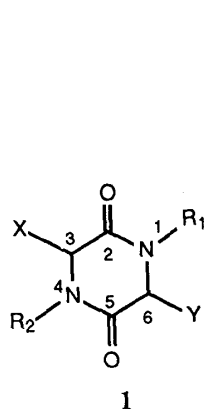


Fig. 1

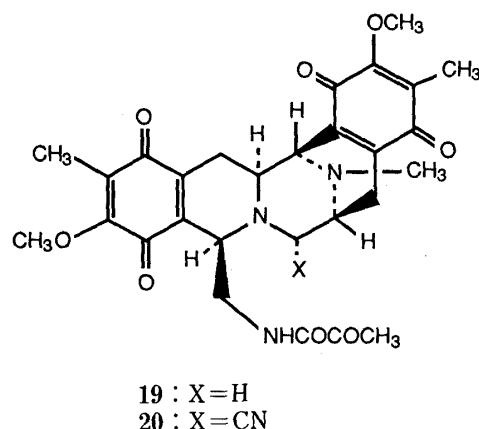
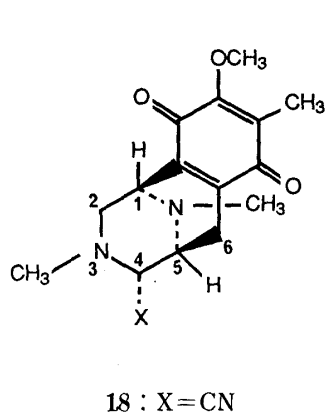


Fig. 2

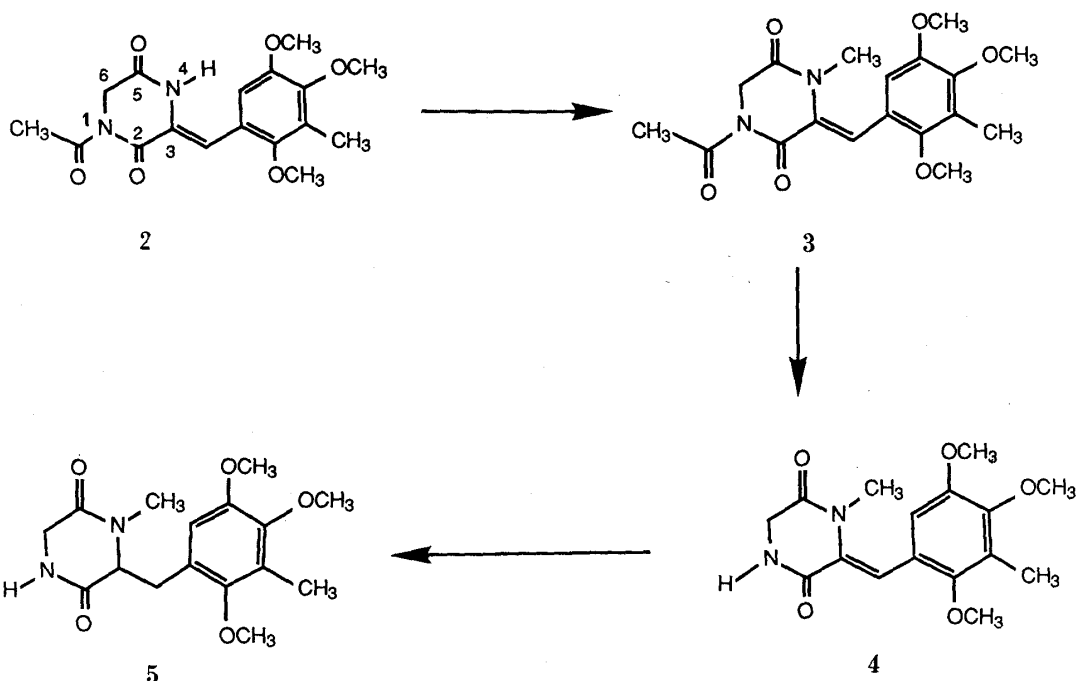


Chart 1

can be removed under reductive conditions.¹³⁾ Benzylation of **2** with benzyl bromide in the presence of sodium hydride in DMF at 25 °C furnished **6a** in 84% yield, and successive treatment with hydrazine hydrate afforded **7a** in 80.7% yield. Methylation of **7a** with methyl iodide in the presence of sodium hydride in DMF at 25 °C furnished **8a** in 70% yield. Catalytic hydrogenation of **8a** led to **11** in 72% yield. Deprotection of **11** was not possible according to the procedure of Nakatsuka *et al.*¹⁴⁾ On the other hand, it is well known that the 4-methoxybenzyl group is a better protecting group than the benzyl group in terms of ease of removal.¹⁵⁾ Thus, 4-methoxybenzylation of **2** with 4-methoxybenzyl chloride in the presence of sodium hydride in DMF at 25 °C furnished **6b** in quantitative yield, and successive treatment with hydrazine hydrate afforded **7b** in 50.2% yield. Methylation of **7b** with methyl iodide in the presence of sodium hydride in DMF at 25 °C furnished **8b** in 75.1% yield. The oxidative removal of the 4-methoxybenzyl group can not be used in this case, because **8b** is susceptible to oxidative demethylation. Thus, facile deprotection of the 4-methoxybenzyl group of **8b** occurred on treatment with concentrated H₂SO₄ and trifluoroacetic acid at 25 °C,

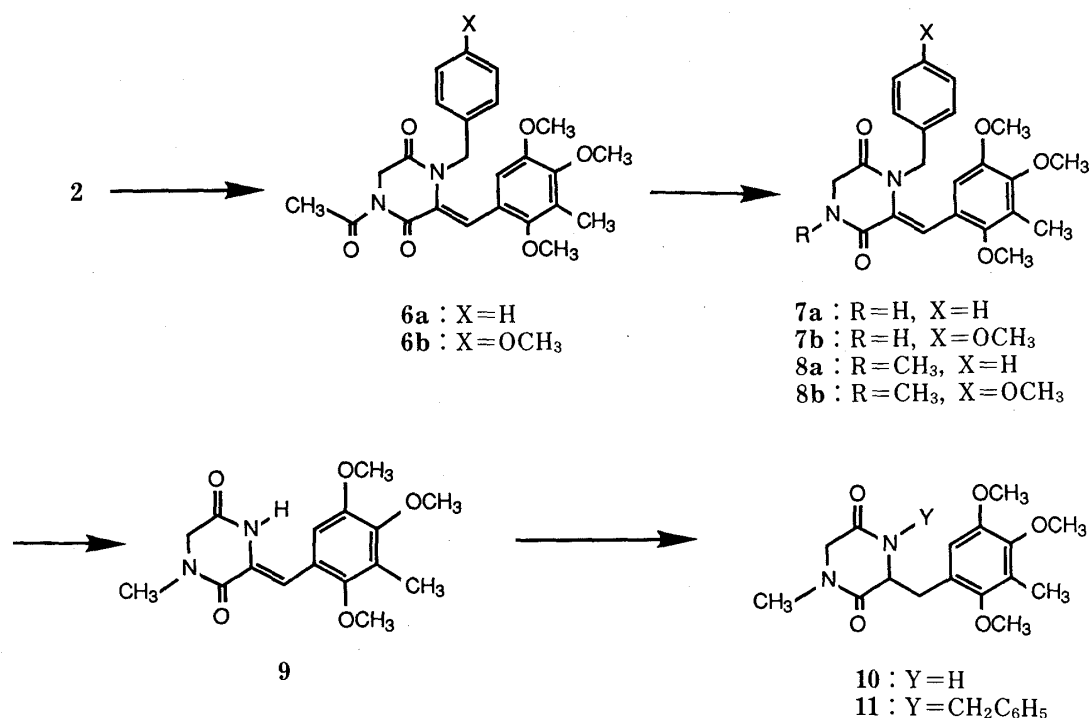


Chart 2

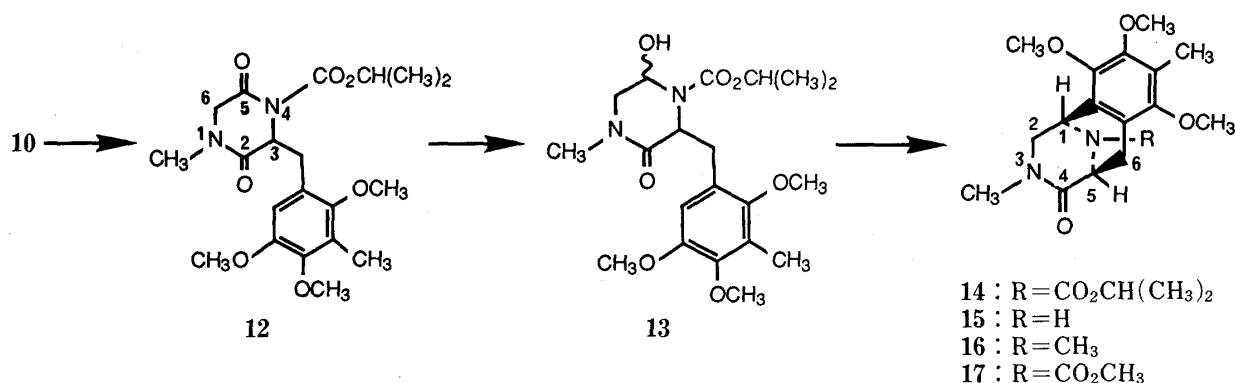


Chart 3

to give **9** in 69% yield. Catalytic hydrogenation of **9** furnished the 1-methyl-2,5-piperazinedione (**10**) in 68.3% yield.

The structures of the 4-methyl derivative (**5**) and 1-methyl derivative (**10**) were determined on the basis of elemental analyses and spectral data. In particular, in the proton nuclear magnetic resonance (¹H-NMR) spectrum of **5**, irradiation of the doublet absorption at δ 6.565 (N–H) led to the collapse of the signal at δ 3.579 (6-H) from a doublet of doublets to a doublet. The same simplification was obtained by D₂O exchange. In the ¹H-NMR spectrum of **10**, irradiation of the broad absorption at δ 6.757 (N–H) led to the collapse of the signal at δ 4.261 (3-H) from a multiplet to a doublet of doublets. The same simplification was obtained by D₂O exchange.

Thus, we succeeded in a simple and efficient synthesis of the 4-methyl-2,5-piperazinedione (**5**) and the 1-methyl-2,5-piperazinedione (**10**). Next, we turned our attention to the construction of the 1,5-imino-3-benzazocine derivative (**16**) from **10** (Chart 3).

The 1-methyl derivative (**10**) was converted into the imide (**12**) in 81.4% yield according to our procedure.¹⁶⁾ The chemoselective reduction of **12** at the C-5 position to the corresponding alcohol (**13**), a crucial step for the synthesis of the “right half” of saframycins,

was achieved as follows. Compound **12** was reduced with an excess of lithium tri-*tert*-butoxyaluminumhydride in tetrahydrofuran (THF) to afford a diastereomeric mixture of the alcohol (**13**), which, on treatment with formic acid at 60 °C, afforded the desired 1,5-imino-3-benzazocine derivatives (**14**) in 84.3% yield. The structure of the cyclization product (**14**) was fully supported by the molecular weight determined by mass spectrometry and the spectral data.¹⁷⁾

Hydrolysis and decarboxylation of **14** with concentrated H₂SO₄ and trifluoroacetic acid gave rise to the secondary amine (**15**) in 89.9% yield; in its ¹H-NMR spectrum, a high-field shift of signals assignable to two methine protons (at C-1 and C-5) was observed. Finally, methylation of **15** with formalin and formic acid gave a 99.0% yield of **16**, which was identical with an authentic sample on comparison of spectroscopic (¹H-NMR, ¹³C-NMR, infrared (IR), ultraviolet (UV), mass spectrum (MS)), and thin layer chromatography (TLC) data. Transformation of **16** to the *p*-quinone **18**, the "right half" of saframycin A (**20**), has been reported by Kurihara and co-workers.¹⁸⁾

Thus, we succeeded in a simple and efficient synthesis of the 4-methyl-2,5-piperazinedione (**5**) and the 1-methyl-2,5-piperazinedione (**10**). Compound **10** was shown to be a useful intermediate for preparation of the 1,5-imino-3-benzazocine derivative **16**. We are presently exploring further versatile synthetic approaches to this class of compounds.

Experimental

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Mass spectra (electron impact) were obtained on a JEOL JMS-D 300 spectrometer. IR spectra were recorded on Hitachi 260-10 and 270-30 spectrophotometers. UV spectra were determined in methanol with a Hitachi 340 spectrometer. ¹H-NMR were obtained at 400 MHz with a JEOL GX 400. ¹³C-NMR were measured at 100 MHz with a JEOL GX 400. NMR spectra were taken in CDCl₃ and chemical shifts are reported in δ values in parts per million relative to tetramethylsilane as an internal standard. Column chromatography was performed with E. Merck silica gel 60 (70–230 mesh). Elemental analyses were obtained by using a Perkin-Elmer model 240B elemental analyzer, and were performed by Miss A. Koike of the Instrument Center of this college.

(Z)-1-Acetyl-4-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (3)—Sodium hydride (60% oil dispersion, washed with dry hexane three times, 259.2 mg, 10.8 mmol) was added to a stirred solution of **2** (3.078 g, 9 mmol) in dry DMF (15 ml) under ice-cooling, and stirring was continued for 30 min at 0 °C. Methyl iodide (0.68 ml, 10.9 mmol) in dry DMF (5 ml) was added. The reaction mixture was stirred for 12 h at 25 °C, poured into ice-water, and extracted with benzene. The extract was washed with brine, dried over Na₂SO₄, and evaporated to give **3** (2.43 g, 84.4%), which was used without further purification. Recrystallization from benzene gave an analytical sample as pale yellow prisms, mp 164–165 °C. *Anal.* Calcd for C₁₈H₂₂N₂O₆: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.48; H, 6.12; N, 7.69. MS *m/z* (%): 362 (M⁺, 41), 331 (18), 290 (18), 289 (100), 274 (7), 220 (9), 43 (9). IR (KBr): 1705, 1680, 1625 cm⁻¹. UV $\lambda_{\max}$ nm (log ϵ): 242 (4.11), 324 (4.11). ¹H-NMR δ : 2.217 (3H, s, ArCH₃), 2.641 (3H, s, COCH₃), 2.925 (3H, s, NCH₃), 3.670 (3H, s, OCH₃), 3.813 (3H, s, OCH₃), 3.850 (3H, s, OCH₃), 4.530 (2H, s, 6-H₂), 6.592 (1H, s, ArH), 7.400 (1H, s, C=CH).

(Z)-4-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (4)—Hydrazine hydrate (0.5 ml) was added to a stirred solution of **3** (2.43 g, 6.71 mmol) in DMF (20 ml), and the resulting solution was stirred for 1 h at 25 °C. The reaction mixture was poured into water and extracted with benzene. The extract was washed with brine, dried over Na₂SO₄, and evaporated to give a solid, recrystallization of which from AcOEt gave **4** (1.592 g, 74.2%) as pale yellow prisms, mp 171–172 °C. *Anal.* Calcd for C₁₆H₂₀N₂O₅ · 1/5H₂O: C, 59.32; H, 6.37; N, 8.65. Found: C, 59.52; H, 6.36; N, 8.70. MS *m/z* (%): 320 (M⁺, 23), 290 (18), 289 (200). IR (KBr): 3180, 1690, 1675, 1630 cm⁻¹. UV $\lambda_{\max}$ nm (log ϵ): 222 (4.23), 246 sh (4.17), 298 (4.18), 314 sh (4.15). ¹H-NMR δ : 2.212 (3H, s, ArCH₃), 2.917 (3H, s, NCH₃), 3.653 (3H, s, OCH₃), 3.813 (3H, s, OCH₃), 3.837 (3H, s, OCH₃), 4.149 (2H, d, *J* = 2.2 Hz, 6-H₂), 6.587 (1H, s, ArH), 7.235 (1H, s, C=CH), 7.444 (1H, brs, NH).

4-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione (5)—The arylidene derivative **4** (1.27 g, 3.97 mmol) was dissolved in ethanol (40 ml) and hydrogenated over 20% palladium on carbon (635 mg) at 1 atm for 4 h. After removal of the catalyst by filtration, the filtrate was partitioned between CHCl₃ and water. The organic phase was dried over Na₂SO₄, and evaporated to give a residue, recrystallization of which from acetone gave **5** (793.4 mg, 62.1%) as colorless needles, mp 160–161 °C. *Anal.* Calcd for C₁₆H₂₂N₂O₅ · 1/5H₂O: C, 58.96; H, 6.93; N, 8.59. Found: C, 59.02; H, 6.99; N, 8.48. MS *m/z* (%): 322 (M⁺, 9), 196 (13), 195 (100), 165 (15), 150 (7). IR (KBr): 3640, 3470, 1650 cm⁻¹. UV $\lambda_{\max}$ nm (log ϵ): 278 sh (3.52), 284 (3.56). ¹H-NMR δ : 2.185 (3H, s, ArCH₃), 2.885 (1H, d,

$J = 17.1$ Hz, 6-H), 2.954 (3H, s, NCH_3), 3.121 (1H, dd, $J = 13.9$, 4.6 Hz, ArCH), 3.217 (1H, dd, $J = 13.9$, 4.8 Hz, ArCH), 3.579 (1H, dd, $J = 17.1$, 3.9 Hz, 6-H), 3.654 (3H, s, OCH_3), 3.781 (6H, s, $2 \times \text{OCH}_3$), 4.128 (1H, dd, $J = 4.8$, 4.6 Hz, 3-H), 6.525 (1H, s, ArH), 6.565 (1H, d, $J = 3.9$ Hz, NH).

(Z)-1-Acetyl-4-benzyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (6a)—Sodium hydride (60% oil dispersion, washed with dry hexane three times, 264 mg, 11 mmol) was added to a stirred solution of **2** (3.2 g, 9.2 mmol) in dry DMF (40 ml) under ice-cooling, and stirring was continued for 30 min at 0°C . Benzyl bromide (1.28 ml, 10.8 mmol) in dry DMF (20 ml) was added. The reaction mixture was stirred for 1 h at 25°C , poured into ice-water, and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4 , and evaporated to give **6a** (3.358 g, 84%), which was used without further purification. Recrystallization from benzene gave an analytical sample as pale yellow prisms, mp $154.5\text{--}156^\circ\text{C}$. *Anal.* Calcd for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.98; H, 5.96; N, 6.27. MS m/z (%): 438 (M^+ , 83), 408 (16), 407 (52), 392 (18), 366 (24), 365 (100), 332 (14), 306 (11), 305 (26), 91 (46). IR (KBr): 1720, 1700 cm^{-1} . UV λ_{max} nm (log ϵ): 242 sh (4.07), 340 (4.08). $^1\text{H-NMR}$ δ : 2.233 (3H, s, ArCH₃), 2.596 (3H, s, COCH_3), 3.538 (3H, s, OCH_3), 3.837 (3H, s, OCH_3), 3.882 (3H, s, OCH_3), 4.553 (2H, s, 6-H₂), 4.730 (2H, s, NCH_2), 6.695 (1H, s, ArH), 6.886–6.901 (2H, m, $2 \times$ ArH), 7.187–7.203 (4H, m, $3 \times$ ArH and $\text{C}=\text{CH}$).

(Z)-4-Benzyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (7a)—Hydrazine hydrate (0.8 ml) was added to a stirred solution of **6a** (3.358 g, 7.73 mmol) in DMF (60 ml), and the resulting solution was stirred for 1 h at 25°C . The reaction mixture was poured into water, and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4 , and evaporated to give a solid, recrystallization of which from acetone–ether gave **7a** (2.469 g, 80.7%) as pale yellow prisms, mp $161\text{--}161.5^\circ\text{C}$. *Anal.* Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.93; H, 6.24; N, 6.68. MS m/z (%): 396 (M^+ , 36), 366 (24), 365 (100), 290 (15), 274 (19), 91 (29). IR (KBr): 3170, 1680, 1620 cm^{-1} . UV λ_{max} nm (log ϵ): 240 sh (4.09), 300 (4.08), 330 sh (4.40). $^1\text{H-NMR}$ δ : 2.224 (3H, s, ArCH₃), 3.504 (3H, s, OCH_3), 3.809 (3H, s, OCH_3), 3.861 (3H, s, OCH_3), 4.139 (2H, d, $J = 2.4$ Hz, 6-H₂), 4.739 (2H, s, NCH_2), 6.616 (1H, s, ArH), 6.900–6.923 (2H, m, $2 \times$ ArH), 7.155–7.209 (4H, m, $3 \times$ ArH and NH), 7.216 (1H, s, $\text{C}=\text{CH}$).

(Z)-4-Benzyl-1-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (8a)—Sodium hydride (60% oil dispersion, washed with dry hexane three times, 144 mg, 6 mmol) was added to a stirred solution of **7a** (1.584 g, 4 mmol) in dry DMF (16 ml) under ice-cooling, and stirring was continued for 30 min at 0°C . Methyl iodide (0.37 ml, 6 mmol) in dry DMF (8 ml) was added. The reaction mixture was stirred for 1 h at 25°C , poured into ice-water, and extracted with CH_2Cl_2 . The extract was washed with brine, dried over Na_2SO_4 , and evaporated to give the residue. Chromatography on a silica gel (60 g) column with hexane–AcOEt (1 : 1) as the eluent gave **8a** (1.15 g, 70%) as a pale yellow amorphous powder. MS m/z (%): 410 (M^+ , 8), 380 (25), 379 (100), 288 (12), 91 (37). High-resolution MS Calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_5$: 410.1841. Found: 410.1839. IR (CHCl_3): 1680, 1625 cm^{-1} . UV λ_{max} nm (log ϵ): 242 sh (4.09), 296 (4.09), 325 (4.03). $^1\text{H-NMR}$ δ : 2.216 (3H, s, ArCH₃), 3.078 (3H, s, NCH_3), 3.499 (3H, s, OCH_3), 3.802 (3H, s, OCH_3), 3.852 (3H, s, OCH_3), 4.114 (2H, s, 6-H₂), 4.714 (2H, s, NCH_2), 6.590 (1H, s, ArH), 6.885–6.909 (2H, m, $2 \times$ ArH), 7.155–7.261 (4H, m, $3 \times$ ArH and $\text{C}=\text{CH}$).

4-Benzyl-1-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione (11)—The arylidene derivative **8a** (1.89 g, 4.61 mmol) was dissolved in ethanol (15 ml) and hydrogenated over 10% palladium on carbon (0.4 g) at 1 atm for 72 h. After removal of the catalyst by filtration, the filtrate was evaporated to give the residue, recrystallization of which from AcOEt gave **11** (1.36 g, 72%) as colorless prisms, mp $135\text{--}136.5^\circ\text{C}$. *Anal.* Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.82; H, 6.99; N, 6.68. MS m/z (%): 412 (M^+ , 7), 196 (13), 195 (100), 91 (16). IR (KBr): 1655 cm^{-1} . UV λ_{max} nm (log ϵ): 284 (3.60). $^1\text{H-NMR}$ δ : 2.212 (3H, s, ArCH₃), 2.706 (1H, d, $J = 17.1$ Hz, 6-H), 2.782 (3H, s, NCH_3), 3.055 (1H, dd, $J = 13.7$, 4.2 Hz, ArCH), 3.252 (1H, dd, $J = 13.7$, 4.6 Hz, ArCH), 3.476 (1H, d, $J = 17.1$ Hz, 6-H), 3.676 (3H, s, OCH_3), 3.780 (3H, s, OCH_3), 3.794 (1H, d, $J = 15.1$ Hz, NCH), 3.801 (3H, s, OCH_3), 4.133 (1H, dd, $J = 4.6$, 4.2 Hz, 3-H), 5.478 (1H, d, $J = 15.1$ Hz, NCH), 6.441 (1H, s, ArH), 7.220–7.346 (5H, m, $5 \times$ ArH).

Debenzylation of **11** with 20% palladium on carbon in ethanol at 80°C (3 atm H_2) for 24 h failed, and only the starting material was recovered.

(Z)-1-Acetyl-4-(4-methoxyphenylmethyl)-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (6b)—Sodium hydride (60% oil dispersion, washed with dry hexane three times, 0.3 g, 12.5 mmol) was added to a stirred solution of **2** (3.48 g, 10 mmol) in dry DMF (80 ml) under ice-cooling, and stirring was continued for 30 min at 0°C . 4-Methoxybenzyl chloride (1.956 g, 12.5 ml) in dry DMF (20 ml) was added. The reaction mixture was stirred for 12 h at 25°C , poured into ice-water, and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4 , and evaporated to give **6b** (4.68 g, 100%), which was used without further purification. Recrystallization from AcOEt–ether gave an analytical sample as pale yellow prisms, mp $130.5\text{--}131^\circ\text{C}$. *Anal.* Calcd for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_7$: C, 64.09; H, 6.02; N, 5.91. Found: C, 64.03; H, 6.01; N, 5.91. MS m/z (%): 468 (M^+ , 10), 122 (9), 121 (100). IR (KBr): 1725, 1705 cm^{-1} . UV λ_{max} nm (log ϵ): 222 (4.42), 276 (3.86), 284 (3.89), 342 (4.09). $^1\text{H-NMR}$ δ : 2.238 (3H, s, ArCH₃), 2.560 (3H, s, COCH_3), 3.549 (3H, s, OCH_3), 3.739 (3H, s, OCH_3), 3.839 (3H, s, OCH_3), 3.880 (3H, s, OCH_3), 4.528 (2H, s, 6-H₂), 4.655 (2H, s, NCH_2), 6.716 (1H, s, ArH), 6.720 (2H, d, $J = 8.4$ Hz, $2 \times$ ArH), 6.852 (2H, d, $J = 8.4$ Hz, $2 \times$ ArH), 7.375 (1H, s, $\text{C}=\text{CH}$).

(Z)-4-(4-Methoxyphenylmethyl)-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (7b)—

Hydrazine hydrate (1.0 ml) was added to a stirred solution of **6b** (4.68 g, 10 mmol) in DMF (100 ml), and the resulting solution was stirred for 1 h at 25 °C. The reaction mixture was poured into water, and extracted with benzene. The extract was washed with brine, dried over Na₂SO₄, and evaporated to give a solid, recrystallization of which from AcOEt-ether gave **7b** (2.140 g, 50.2%) as pale yellow prisms, mp 153–155 °C. *Anal.* Calcd for C₂₃H₂₆N₂O₆: C, 64.77; H, 6.15; N, 6.57. Found: C, 64.80; H, 6.24; N, 6.45. MS *m/z* (%): 426 (M⁺, 13), 395 (13), 274 (9), 122 (9), 121 (100). IR (KBr): 3250, 1710, 1640 cm⁻¹. UV λ_{max} nm (log ε): 223 (4.48), 276 (4.07), 284 (4.14), 301 (4.11), 324 sh (4.14). ¹H-NMR δ: 2.229 (3H, s, ArCH₃), 3.553 (3H, s, OCH₃), 3.720 (3H, s, OCH₃), 3.819 (3H, s, OCH₃), 3.862 (3H, s, OCH₃), 4.106 (2H, d, *J* = 2.0 Hz, 6-H₂), 4.668 (2H, s, NCH₂), 6.653 (1H, s, ArH), 6.711 (2H, d, *J* = 9.0 Hz, 2 × ArH), 6.859 (2H, d, *J* = 9.0 Hz, 2 × ArH), 7.202 (1H, s, C=CH), 7.827 (1H, brs, NH).

(Z)-4-(4-Methoxyphenylmethyl)-1-methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (8b)—Sodium hydride (60% oil dispersion, washed with dry hexane three times, 108 mg, 4.5 mmol) was added to a stirred solution of **7b** (1.278 g, 3.0 mmol) in dry DMF (12 ml) under ice-cooling, and stirring was continued for 30 min at 0 °C. Methyl iodide (0.28 ml, 4.5 mmol) in dry DMF (6 ml) was added. The reaction mixture was stirred for 1 h at 25 °C, poured into ice-water, and extracted with CHCl₃. The extract was washed with brine, dried over Na₂SO₄, and evaporated to give the residue. Chromatography on a silica gel (50 g) column with hexane–AcOEt (1 : 2) as the eluent gave **8b** (991.4 mg, 75.1%) as a pale yellow amorphous powder. MS *m/z* (%): 440 (M⁺, 16), 423 (18), 409 (38), 304 (11), 288 (12), 121 (100). High-resolution MS Calcd for C₂₄H₂₈N₂O₆: 440.1947. Found: 440.1935. IR (CHCl₃): 1680, 1625 cm⁻¹. UV λ_{max} nm (log ε): 224 (4.48), 276 (4.12), 284 (4.17), 300 (4.18), 322 sh (4.14). ¹H-NMR δ: 2.221 (3H, s, ArCH₃), 3.056 (3H, s, NCH₃), 3.549 (3H, s, OCH₃), 3.728 (3H, s, OCH₃), 3.813 (3H, s, OCH₃), 3.852 (3H, s, OCH₃), 4.086 (2H, s, 6-H₂), 4.634 (2H, s, NCH₂), 6.625 (1H, s, ArH), 6.706 (2H, d, *J* = 8.8 Hz, 2 × ArH), 6.856 (2H, d, *J* = 8.8 Hz, 2 × ArH), 7.241 (1H, s, C=CH).

(Z)-1-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethylene)-2,5-piperazinedione (9)—Concentrated H₂SO₄ (2.0 ml) was added to a stirred solution of **8b** (1.134 g, 2.58 mmol) in trifluoroacetic acid (30 ml), and stirring was continued for 12 h at 25 °C. The reaction mixture was poured into water (200 ml) and extracted with CH₂Cl₂. The extract was washed with brine, dried over Na₂SO₄, and evaporated to give a solid. Recrystallization from AcOEt gave **9** (569 mg, 69%) as pale yellow prisms, mp 158–159.5 °C. *Anal.* Calcd for C₁₆H₂₀N₂O₅: C, 59.99; H, 6.29; N, 8.75. Found: C, 59.84; H, 6.36; N, 8.61. MS *m/z* (%): 320 (M⁺, 31), 290 (18), 289 (100), 273 (6), 220 (10), 131 (13). IR (KBr): 3330, 1705, 1645 cm⁻¹. UV λ_{max} nm (log ε): 225 (4.23), 240 sh (4.15), 302 (4.27), 322 sh (4.17). ¹H-NMR δ: 2.233 (3H, s, ArCH₃), 3.104 (3H, s, NCH₃), 3.622 (3H, s, OCH₃), 3.827 (6H, s, 2 × OCH₃), 4.149 (2H, s, 6-H₂), 6.640 (1H, s, ArH), 6.914 (1H, s, C=CH), 9.349 (1H, s, NH).

1-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-2,5-piperazinedione (10)—The arylidene derivative **9** (498.1 mg, 1.57 mmol) was dissolved in ethanol (16 ml) and hydrogenated over 20% palladium on carbon (250 mg) at 1 atm for 4 h. After removal of the catalyst by filtration, the filtrate was evaporated and the residue was partitioned between CHCl₃ and water. The organic phase was dried over Na₂SO₄, and evaporated to give the residue, recrystallization of which from AcOEt–ether gave **10** (342.1 mg, 68.3%) as colorless prisms, mp 164–165 °C. *Anal.* Calcd for C₁₆H₂₂N₂O₅: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.49; H, 6.97; N, 8.55. MS *m/z* (%): 322 (M⁺, 10), 196 (13), 195 (100), 165 (17), 150 (10). IR (KBr): 3300, 1695, 1655 cm⁻¹. UV λ_{max} nm (log ε): 228 (3.91), 276 sh (3.35), 284 (3.42). ¹H-NMR δ: 2.195 (3H, s, ArCH₃), 2.933 (3H, s, NCH₃), 2.993 (1H, dd, *J* = 13.7, 7.1 Hz, ArCH), 3.288 (1H, dd, *J* = 13.7, 4.2 Hz, ArCH), 3.424 (1H, d, *J* = 17.6 Hz, 6-H), 3.667 (3H, s, OCH₃), 3.779 (1H, d, *J* = 17.6 Hz, 6-H), 3.784 (3H, s, OCH₃), 3.793 (3H, s, OCH₃), 4.261 (1H, m, 3-H), 6.557 (1H, s, ArH), 6.757 (1H, brs, NH).

1-Methyl-3-(2,4,5-trimethoxy-3-methylphenylmethyl)-4-isopropoxycarbonyl-2,5-piperazinedione (12)—A solution of **10** (1.61 g, 5 mmol), triethylamine (2.09 ml, 15 mmol), and 4-dimethylaminopyridine (1.83 g, 15 mmol) in dry methylene chloride (100 ml) was cooled with ice-water, and isopropyl chloroformate (3.41 ml, 30 mmol) was added dropwise over 10 min. The solution was stirred for 1 h at 25 °C. The organic layer was washed with 1 N HCl, dried over Na₂SO₄, and concentrated *in vacuo* to give the residue, recrystallization of which from ether gave **12** (1.66 g, 81.4%) as colorless prisms, mp 67.5–68.5 °C. *Anal.* Calcd for C₂₀H₂₈N₂O₇: C, 58.81; H, 6.91; N, 6.86. Found: C, 58.75; H, 7.01; N, 6.78. MS *m/z* (%): 408 (M⁺, 11), 322 (4), 196 (13), 195 (100), 165 (12). IR (KBr): 1740, 1730, 1680 cm⁻¹. UV λ_{max} nm (log ε): 212 (4.41), 234 sh (3.84), 278 (3.72), 284 (3.74). ¹H-NMR δ: 1.340 (3H, d, *J* = 6.1 Hz, CHCH₃), 1.361 (3H, d, *J* = 6.1 Hz, CHCH₃), 2.165 (3H, s, ArCH₃), 2.647 (1H, d, *J* = 17.8 Hz, 6-H), 2.800 (3H, s, NCH₃), 3.115 (1H, dd, *J* = 13.8, 3.9 Hz, ArCH), 3.434 (1H, dd, *J* = 13.8, 5.1 Hz, ArCH), 3.485 (1H, d, *J* = 17.8 Hz, 6-H), 3.611 (3H, s, OCH₃), 3.769 (3H, s, OCH₃), 3.782 (3H, s, OCH₃), 5.007 (1H, dd, *J* = 5.1, 3.9 Hz, 3-H), 5.100 (1H, sept, OCH), 6.430 (1H, s, ArH).

7,9,10-Trimethoxy-3,8-dimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine-11-carboxylic Acid Isopropyl Ester (14)—A stirred solution of **12** (300 mg, 0.735 mmol) in dry THF (20 ml) was cooled with ice-water, and lithium tri-*tert*-butoxyaluminumhydride (750 mg, 2.95 mmol) was added over 15 min. After continued stirring at the same temperature for 1 h, the reaction mixture was filtered through a celite pad, which was then washed with CHCl₃ (200 ml), and the combined filtrate was concentrated *in vacuo*. The crude diastereomeric mixture of the alcohols **13** obtained was used for the next step without isolation. A solution of **13** in formic acid (10 ml) was heated at 60 °C for 1 h. The reaction mixture was diluted with water (50 ml) and extracted with CHCl₃ (50 ml × 3). The combined organic

extracts were washed with 10% NH_4OH (50 ml), and then with water (50 ml), dried over Na_2SO_4 , and concentrated *in vacuo* to give the residue (340 mg). Chromatography on a silica gel (15 g) column with hexane–AcOEt (2:1) as the eluent gave **14** (243 mg, 84.3%) as a colorless amorphous powder. MS m/z (%): 392 (M^+ , 100), 320 (35), 306 (38), 278 (68), 234 (79), 204 (22). High-resolution MS Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_6$: 392.1947. Found: 392.1946. IR (CHCl_3): 1705, 1690, 1655, 1645 cm^{-1} . UV λ_{max} nm (log ϵ): 206 (4.63), 224 sh (4.05), 272 sh (3.24), 278 (3.26). $^1\text{H-NMR}$ (at 50°C) δ : 1.254 (6H, d, $J=6.3\text{ Hz}$, $\text{CH}(\text{CH}_3)_2$), 2.173 (3H, s, ArCH_3), 2.846 (3H, s, NCH_3), 2.969 (1H, m, 6-H α), 3.139 (1H, dd, $J=17.1, 1.2\text{ Hz}$, 6-H β), 3.195 (1H, d, $J=11.7\text{ Hz}$, 2-H β), 3.661 (3H, s, OCH_3), 3.798 (3H, s, OCH_3), 3.869 (1H, dd, $J=11.7, 4.4\text{ Hz}$, 2-H α), 3.908 (3H, s, OCH_3), 4.944 (2H, m, 5-H and OCH), 5.540 (1H, m, 1-H). $^{13}\text{C-NMR}$ (at 50°C) δ : 9.4 (q), 22.2 (q), 22.2 (q), 27.2 (t), 34.3 (t), 44.8 (q), 52.7 (d), 55.3 (d), 59.9 (q), 60.1 (q), 60.4 (q), 69.5 (d), 122.5 (s), 125.2 (s), 125.8 (s), 126.2 (s), 145.6 (s), 150.2 (s), 153.6 (s), 168.3 (s).

7,9,10-Trimethoxy-3,8-dimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (15)—Concentrated H_2SO_4 (0.2 ml) was added to a stirred solution of **14** (84.8 mg, 0.216 mmol) in trifluoroacetic acid (4 ml), and the resulting solution was stirred for 12 h at 25°C . The reaction mixture was poured into water and extracted with CH_2Cl_2 . The extract was washed with brine, dried over Na_2SO_4 , and evaporated to give a solid, recrystallization of which from AcOEt–ether gave **15** (59.5 mg, 89.9%) as colorless prisms, mp $153.5\text{--}155.5^\circ\text{C}$. Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.81; H, 7.35; N, 9.10. MS m/z (%): 306 (M^+ , 26), 235 (20), 234 (100), 204 (14). IR (KBr): 3390, 1655 cm^{-1} . UV λ_{max} nm (log ϵ): 207 (4.23), 225 sh (3.98), 272 (2.85), 278 (2.90). $^1\text{H-NMR}$ δ : 2.183 (3H, s, ArCH_3), 2.291 (1H, s, NH), 2.856 (3H, s, NCH_3), 2.908 (1H, dd, $J=17.6, 6.6\text{ Hz}$, 6-H α), 2.081 (1H, dd, $J=17.6, 1.2\text{ Hz}$, 6-H β), 3.213 (1H, d, $J=11.7\text{ Hz}$, 2-H β), 3.671 (3H, s, OCH_3), 3.795 (3H, s, OCH_3), 3.839 (1H, dd, $J=11.7, 4.7\text{ Hz}$, 2-H α), 3.883 (3H, s, OCH_3), 3.967 (1H, d, $J=6.4\text{ Hz}$, 5-H), 4.458 (1H, d, $J=4.7\text{ Hz}$, 1-H).

7,9,10-Trimethoxy-3,8,11-trimethyl-4-oxo-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (16)—Formaldehyde (37% solution water, 0.96 ml) was added to a stirred solution of **15** (45.9 mg, 0.15 mmol) in formic acid (2.16 ml) at 50°C . The mixture was stirred for 1 h at 70°C , then removal of the solvent *in vacuo* afforded the residue, which was partitioned between CHCl_3 and 5% NaHCO_3 solution. The organic phase was washed with brine, dried over Na_2SO_4 , and evaporated to obtain a colorless gum. Purification by chromatography on a silica gel (5 g) column with AcOEt–methanol (8:1) as the eluent gave a solid (45.5 mg, 99%). Recrystallization from AcOEt–ether gave **16** as colorless prisms, mp $117\text{--}118^\circ\text{C}$ (lit.¹⁸⁾ mp $115\text{--}116^\circ\text{C}$). Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_6$: C, 63.72; H, 7.55; N, 8.74. Found: C, 63.49; H, 7.68; N, 8.66. MS m/z (%): 320 (M^+ , 19), 249 (20), 248 (100), 218 (18). IR (KBr): 1655 cm^{-1} . UV λ_{max} nm (log ϵ): 208 (4.43), 224 sh (4.03), 272 (3.02), 278 (3.04). $^1\text{H-NMR}$ δ : 2.187 (3H, s, ArCH_3), 2.494 (3H, s, NCH_3), 2.856 (3H, s, NCH_3), 2.920 (1H, dd, $J=17.6, 1.2\text{ Hz}$, 6-H β), 3.037 (1H, dd, $J=17.6, 6.6\text{ Hz}$, 6-H α), 3.091 (1H, dd, $J=11.7, 0.7\text{ Hz}$, 2-H β), 3.641 (1H, ddd, $J=6.6, 1.2, 0.5\text{ Hz}$, 5-H), 3.678 (3H, s, OCH_3), 3.801 (3H, s, OCH_3), 3.878 (3H, s, OCH_3), 3.942 (1H, dd, $J=11.7, 4.9\text{ Hz}$, 2-H α), 4.112 (1H, ddd, $J=4.9, 0.7, 0.5\text{ Hz}$, 1-H). $^{13}\text{C-NMR}$ δ : 9.3 (q, ArCH_3), 23.7 (t, 6- CH_2), 33.9 (q, NCH_3), 40.1 (q, NCH_3), 51.1 (d, 5-CH), 53.3 (t, 2- CH_2), 58.8 (d, 1-CH), 59.8 (q, OCH_3), 60.0 (q, OCH_3), 60.2 (q, OCH_3), 122.1 (s), 124.5 (s), 126.3 (s), 146.1 (s), 149.8 (s), 152.3 (s), 170.1 (s, CO).

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