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Oxidative Removal of *N*-(4-Methoxybenzyl) Group on 2,5-Piperazinediones with Cerium(IV) Diammonium Nitrate

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It was shown that *N*-(4-methoxybenzyl) group on 2,5-piperazinediones can be oxidatively removed with cerium(IV) diammonium nitrate under mild conditions, and the oxidative removal was performed in some model compounds which have several functional groups.

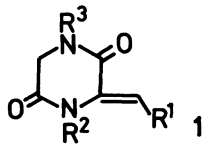
For syntheses of biologically active 2,5-piperazinediones (PDO) having complicated structures such as bicyclomycin,[1] antibiotic 593A,[2] sirodesmin,[3] aspirochlorine[4] *etc.*, the selection of a suitable *N*-protecting group is an important problem. The protecting group should be easily introducible, improvable the solubility of this class of polar compounds, stable under various reaction conditions for conversions, and selectively removable under mild conditions. Up to the present, methylthiomethyl,[5] methoxymethyl,[5,6] and acyl[5,7] groups have been used, but, there are still remaining some problems in stability or conditions for deprotection. In a previous communication,[8] we reported that *N*-(4-methoxybenzyl) group on PDO can be removed by cerium(IV) diammonium nitrate (CAN), and satisfied the aforementioned conditions. This paper describes detailed data of the communication.

The oxidative removal of *O*-benzyl and *O*-(4-methoxybenzyl) groups has been done by the use of DDQ,[9] triphenylmethyl tetrafluoroborate,[10] chromium trioxide[11] and electrolytic oxidation[12] *etc.* For *N*-protecting group of β-lactams, oxidative removal of 2,4-dimethoxybenzyl[13] and 3,4-dimethoxybenzyl[14] groups with potassium peroxodisulfate and of 4-(methoxymethyloxy)phenyl[15] and 4-methoxyphenyl groups[16] with CAN have been reported, but, the introduction of these protecting groups is more or less tedious. Autoxidative removal of *N*-benzyl group in an amino sugar with potassium *t*-butoxide–dimethyl sulfoxide[17] is known, but the strongly alkaline conditions are unsuitable for PDO derivatives. Recently, 4-methoxybenzyl group was actually utilized for the synthesis of bicyclomycin.[18]

Results and Discussion

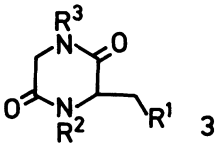
Model compounds (**1i**, **3e—i**, **5a—c**, **6a**) for the examination of oxidative deprotection were synthesized as follows. Condensation of *N*,*N*′-diacetylanhydroglycine with *p*-tolualdehyde in the presence of potassium *t*-butoxide[19] gave the corresponding (*Z*)-1-acetyl-3-(4-methylbenzylidene)-PDO (**1a**) in 87% yield. *N*-Benzylation of the corresponding 3-isobutylidene derivative[19] in *N*,*N*-dimethylformamide (DMF) with sodium hydride and benzyl bromide gave the *N*-benzyl derivative (**1b**) in 73% yield. When benzyl chloride instead of the bromide was used, a 1:1 mixture of **1b** and the corresponding *O*-benzyl derivative (**2**) of the enolate was produced, but the formation of **2** was generally less than 5% in the reaction with the bromide. In a similar way, 3-benzylidene (**1c**) and 3-(4-methylbenzylidene) (**1d**) derivatives were obtained. The formation of **2** may be attributed to the steric hindrance and conjugation of 3-alkylidene group, and also to the soft-hard interrelation between reagents and atoms of the reaction center. A similar reaction of (*Z*)-1-acetyl-3-isobutylidene-PDO[19] with 4-methoxybenzyl bromide gave **1e** in 93% yield. Treatment of **1b—d** with hydrazine gave quantitatively the corresponding *N*-deacetylated derivatives (**1f—h**). Hydrogenation of **1f,g** and the corresponding 6-benzylidene-1-methyl-[20] and 1-benzyl-6-[(ethoxycarbonyl)ethylidene]-PDO[21] in the presence of 10% palladium–carbon gave the corresponding saturated compounds (**3a—d**) in good yields, respectively. *N*-(4-Methoxybenzyl)ation in nonhindered site of **3a—c** proceeded smoothly with sodium hydride and the chloride to give the corresponding 4-(4-methoxybenzyl)-PDO (**3e—g**) in good yields. A similar reaction of **1f—h** and **3d** gave also **1i—k** and **3h**, respectively. Treatment of **1i—k** in methanol with *N*-bromosuccinimide gave the corresponding 6-(1-bromoalkyl)-6-methoxy-PDO (**4a—c**) in good yields. Hydrogenation of **4a—c** in the presence of palladium–carbon gave the corresponding debrominated PDO (**5a—c**) in 47—60% yields.

While, catalytic hydrogenation of **1e** gave 1-acetyl-3-isobutyl-4-(4-methoxybenzyl)-PDO (**3i**) in 94% yield, and a successive treatment of **3e** in tetrahydrofuran with lithium 2,2,6,6-tetramethylpiperidide and allyl bromide at −78 °C gave crystalline 3-allyl-1-benzyl-



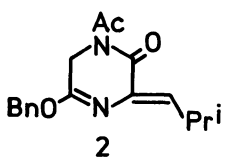
1

	R^1	R^2	R^3
a	Tol	H	Ac
b	i-Pr	Bn	Ac
c	Ph	Bn	Ac
d	Tol	Bn	Ac
e	i-Pr	MBn	Ac
f	i-Pr	Bn	H
g	Ph	Bn	H
h	Tol	Bn	H
i	i-Pr	Bn	MBn
j	Ph	Bn	MBn
k	Tol	Bn	MBn

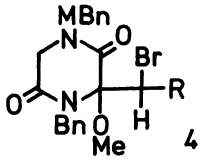


3

	R^1	R^2	R^3
a	i-Pr	Bn	H
b	Ph	Bn	H
c	Ph	Me	H
d	CH_2CO_2Et	H	Bn
e	i-Pr	Bn	MBn
f	Ph	Bn	MBn
g	Ph	Me	MBn
h	CH_2CO_2Et	MBn	Bn
i	i-Pr	MBn	Ac
j	i-Pr	H	Ac

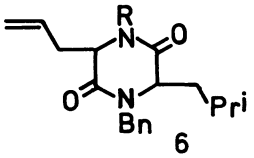


2



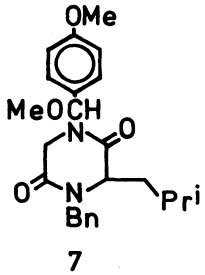
4

	R
a	i-Pr
b	Ph
c	Tol

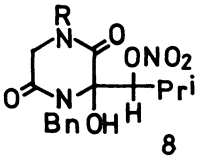


6

	R
a	MBn
b	H

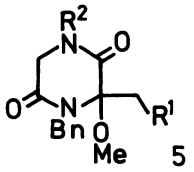


7



8

	R
a	H
b	MBn



5

	R^1	R^2
a	i-Pr	MBn
b	Ph	MBn
c	Tol	MBn
d	i-Pr	H
e	Ph	H
f	Tol	H

6-isobutyl-4-(4-methoxybenzyl)-PDO (**6a**) of *cis*-configuration in 46% yield. Thus, various PDO having different *N*-protecting groups and unsaturated bonds were synthesized.

An attempted oxidation of **3e** with DDQ under various conditions did not proceed, and oxidation with 5 equiv of 0.1 M (1 M=1 mol dm^{-3}) chromium trioxide in acetic acid at room temperature for 1 day gave *N*-de(4-methoxybenzyl)ated product, **3a**, in 41% yield. The results in the similar oxidation with CAN are summarized in Table 1.

The oxidation of **3e** in aqueous acetonitrile with a low concentration of CAN (Run 1) did not proceed even for a longer reaction time, but with 0.17 M solution (Run 2) gave **3a** in 55% yield, indicating the existence of concentration-dependency in this reaction. Thus, the reaction with 0.25 M CAN (Run 3) gave **3e** in quantitative yield. The reaction proceeded smoothly, even in the presence of only small amount of water (Run 4) and also at a lower temperature (Runs 5—6), if a proper concentration of excess CAN is maintained. Methanol can also be used as a solvent (Runs 7—8), but, 1-benzyl-6-isobutyl-4-(α,4-dimethoxybenzyl)-PDO (**7**) was produced as the major product, when absolute methanol was used (Run 9). The formation of **7** indicates that methoxide anion attacks the intermediate iminium cation [$>\overset{+}{N}=CH-C_6H_4-OMe$], which was produced by the direct electron transfer from alkylbenzene moiety to cerium(IV) ion or *via* a benzylic hydrogen abstraction by the metal ligands,[22] in methanol solution. In the presence of water, the attack of hydroxide anion gave the *N*-free PDO and *p*-anisaldehyde, and the latter was actually isolated in the corresponding yield.

As shown in Table 2, a similar oxidation of **3f—h** (Runs 1—3) gave **3b—d**, respectively. No oxidation of *N*-benzyl and terminal alkylbenzene moiety was observed, and an ester function was not affected under the reaction conditions. A lower yield of **3c** may be attributed to its low solubility in ethyl acetate for extraction. Oxidation of **5a—c** and **3i** (Runs 4—7) proceeded smoothly to give **5d—f** and **3j**, respectively. In these cases, 6-*O*-methoxyl and *N*-acetyl groups were not affected. The oxidation of **1i** with 0.5 M CAN (Run 8) was unexpectedly accompanied with an oxidative addition reaction to give 1-benzyl-

Table 1. Oxidative removal of 4-methoxybenzyl group of **3e** with CAN

Run	CAN		Solvent	Temp	Time	Product	Yield
	Molar equivalent	Concentration / mol dm^{-3}	H_2O-CH_3CN(A) H_2O-MeOH(B)	°C	h		%
1	2.0	0.0	(A) 1:9	r.t.	42	—	—
2	2.0	0.17	(A) 1:90	r.t.	12	**3a**	55
3	4.0	0.25	(A) 1:3	r.t.	1	**3a**	96
4	5.0	1.32	(A) 1:100	r.t.	2	**3a**	98
5	2.5	0.33	(A) 1:2	0	12	**3a**	94
6	5.0	0.45	(A) 5:6	0	10	**3a**	95
7	3.8	0.25	(B) 1:1	0	2	**3a**	92
8	3.8	0.25	(B) 1:11	0	2	**3a**	86
9[a)]	3.8	0.25	MeOH	r.t.	3	**3a**	18
						7	67

a) **3e** was recovered in 15% yield.

Table 2. Oxidative removal of 4-methoxybenzyl group of various PDO with CAN

Run	Substrate	CAN		H_2O-CH_3CN	Temp	Time	Product	Yield
		Molar equivalent	Concentration / mol dm^{-3}		°C	h		%
1	**3f**	4.0	0.25	1:3	r.t.	0.5	**3b**	93
2	**3g**	4.0	0.25	1:3	r.t.	1.0	**3c**	48
3	**3h**	2.5	0.33	1:2	r.t.	0.5	**3d**	71
4	**5a**	5.0	0.45	5:6	0	10	**5d**	92
5	**5b**	4.0	0.25	1:3	r.t.	0.5	**5e**	80
6	**5c**	4.0	0.25	1.3	r.t.	0.5	**5f**	83
7	**3i**	3.8	0.29	1:2	r.t.	1.0	**3j**	62
8	**1i**	7.6	0.50	1:1	r.t.	1.0	**8a**	50
9	**1i**	3.8	0.05	1:19	r.t.	3	**8b**	66
10	**6a**	2.5	0.33	1:2	0	12	**6b**	85

6-hydroxy-6-[2-methyl-1-(nitrooxy)propyl]-PDO (**8a**), whereas only oxidative addition product (**8b**) was obtained by the reaction with 0.05 M CAN (Run 9). These results indicate that CAN can not be applied for the selective removal of *N*-(4-methoxybenzyl) group in alkylidene-PDO. However, oxidation of **6a** having an isolated methylene function (Run 10) gave successfully the expected product (**6b**), without accompanying with the addition reaction.

Structures of new compounds were ascertained by ^{1}H NMR spectra (see Experimental). It is characteristic that the H-6 protons of (*Z*)-alkylidene-PDO commonly appeared as a singlet, whereas those of alkyl-PDO as nonequivalent multiplets. The lower chemical shift of methylene protons (δ=5.29s) of *O*-benzyl group of **2** compared with those (δ=4.63s—4.96s) of *N*-benzyl groups of alkylidene-PDO supported its enol ether structure. The α-methoxyl signals of **7** indicated that it is composed of two epimers at the benzylic position. In addition, the chemical shift of H-1′ of **8a** (δ=5.05d) and **8b** (δ=5.00d) supported the assignment of the position of nitrate. This assignment was further confirmed from the δ value of C-1″ of **8b** in ^{13}C NMR (Table 3). Comparison of data for **6a** and **6b** proved the lack of *N*-(4-methoxybenzyl) group in **6b** and its effect was observed in the chemical shifts of C-3, C-6, C-1′, C-2′, and may be C-5.

In conclusion, it was shown that 4-methoxybenzyl group can be easily introduced to PDO skeleton as a suitable *N*-protecting group and also smoothly removed by CAN oxidation under mild conditions, except for alkylidene-PDO.

Experimental

General. Melting points were determined with a Mel-temp apparatus or with a Yanagimoto micro melting-point apparatus, and were not corrected. IR spectra were recorded with a Hitachi EPI-G2 grating spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JMN PS-100 and a JEOL FX-90Q spectrometers, respectively, in $CDCl_3$ solution with tetramethylsilane as the internal standard. Column chromatography was performed on Wakogel C-200 or C-300 (Wako Pure Chemical Industries. Ltd.).

TABLE 3. ^{13}C NMR DATA (δ) OF **6a,b**, AND **8b**

Carbon	6a	6b	8b
C-2	*{ 167.0 s	*{ 169.1 s	*{ 164.2 s
C-5	{ 166.0 s	{ 166.4 s	{ 163.5 s
C-3	56.8 d	52.6 d	49.8 t
C-6	56.8 d	58.2 d	83.6 s
C-1′	34.6 t	36.2 t	—
C-2′	131.1 d	132.6 d	—
C-3′	120.1 t	120.2 t	—
C-1″	40.4 t	40.4 t	87.7 d
C-2″	24.4 d	24.5 d	27.4 d
C-3″	23.4 q	23.2 q	21.5 q
	22.4 q	21.9 q	16.5 q
CH_2 in Bn	46.8 t	47.8 t	49.8 t
CH_2 in MBn	45.4 t	—	44.4 t
C-Aromatic	159.4 s	—	159.3 s
	135.5 s	135.8 s	135.0 s
	127.4 s	—	125.4 s
	129.7 d	—	129.0 d
	128.7 d	128.7 d	127.9 d
	128.5 d	128.1 d	127.8 d
	128.0 d	128.0 d	126.8 d
	114.3 d	—	114.0 d
OMe	55.3 q	—	54.8 q

* The assignment may be reversed.

*(Z)-1-Acetyl-3-(4-methylbenzylidene)-2,5-piperazinedione (**1a**).* To a solution of *N,N′*-diacetylanhydroglycine (4.00 g, 20.6 mmol) and *p*-tolualdehyde (3.71 g, 30.9 mmol) in *N,N*-dimethylformamide (DMF, 54 cm³) was added dropwise 0.5 M potassium *t*-butoxide in *t*-butyl alcohol (43.3 cm³, 21.6 mmol) with stirring at 0 °C. The resulting solution was kept for 1 h at 0 °C and then overnight at room temperature, neutralized with acetic acid, and poured into ice-water. The precipitate formed was filtered, and recrystallized from methanol to give **1a** (4.63 g) as colorless needles in 87% yield. Mp 153—154 °C, ν_{max}^{KBr} (cm⁻¹): 3260 (NH), 1700 (C=O), ^1H NMR δ=8.0 (bs, 1H, NH), 7.28 (s, 4H, Ph), 7.16 (s, 1H, H-1′), 4.49 (s, 2H, H-6), 2.64 (s, 3H, Me), 2.40 (s, 3H, NAc).

Found: C, 65.03; H, 5.51; N, 10.62%. Calcd for $C_{14}H_4N_2O_3$: C, 65.10; H, 5.46; N, 10.85%.

N-Benzylation of (Z)-1-Acetyl-3-alkylidene-2,5-piperazinediones. (*Z*)-1-Acetyl-4-benzyl-3-isobutylidene-2,5-piperazinedione (**1b**) was typically prepared as follows. To a suspension of 50% sodium hydride (2.52 g, 52.5 mmol) in dry DMF (250 cm³) was added a solution of (*Z*)-1-acetyl-3-isobutylidene-2,5-piperazinedione (10.5 g, 50.0 mmol) in dry DMF (50 cm³) with stirring at 0 °C, and after keeping the conditions for 30 min benzyl bromide (9.0 g, 52.5 mmol) was further added dropwise, and stirred for 2 h at 0 °C. The resulting solution was kept at room temperature overnight, neutralized with acetic acid, poured into ice-water, and then extracted with ether. The usual work-up of the extract gave a crude syrup, which was purified on a column of silica gel (hexane–ethyl acetate 7:3) to give colorless syrupy **1b** (10.9 g, 73%) and syrupy (*Z*)-1-acetyl-5-benzyloxy-3-isobutylidene-3,6-dihydro-2(1*H*)-pyrazinone (**2**: 0.75 g, 5.0%).

1b: ^1H NMR δ=7.4—7.1 (m, 5H, Ph), 6.15 (d, 1H, $J_{1',2'}$= 9.0 Hz, H-1′), 4.89 (s, 2H, CH_2 in Bn), 4.42 (s, 2H, H-6), 2.77 (dqq, 1H, H-2′), 2.25 (s, 3H, NAc), 1.04 (d, 6H, $J_{2',3'}$=6.0 Hz, H-3′).

Found: C, 67.86; H, 6.68; N, 9.21%. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33%.

2: ^1H NMR δ=7.5—7.1 (m, 5H, Ph), 6.47 (d, 1H, $J_{1',2'}$= 10.0 Hz, H-1′), 5.29 (s, 2H, CH_2 in Bn), 4.20 (s, 2H, H-6), 3.20 (dsep, 1H, H-2′), 2.61 (s, 3H, NAc), 1.07 (d, 6H, $J_{2',3'}$=6.0 Hz, H-3′).

Found: C, 67.78; H, 6.66; N, 9.32%. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33%.

(*Z*)-1-Acetyl-4-benzyl-3-benzylidene-2,5-piperazinedione (**1c**): yield 65% from (*Z*)-1-acetyl-3-benzylidene-2,5-piperazinedione,[19] mp 132 °C (prisms from carbon tetrachloride), ν_{max}^{KBr} (cm⁻¹): 1700 (C=O), 1640 (C=C), ^1H NMR δ=7.3—6.8 (m, 6H, Ph and H-1′), 7.44 (s, 5H, Ph), 4.70 (s, 2H, CH_2 in Bn), 4.56 (s, 2H, H-6), 2.54 (s, 3H, NAc).

Found: C, 71.89; H, 5.61; N, 8.21%. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38%.

(*Z*)-1-Acetyl-4-benzyl-3-(4-methylbenzylidene)-2,5-piperazinedione (**1d**): yield 93% from **1a**, mp 173—174 °C (prisms from carbon tetrachloride), ν_{max}^{KBr} (cm⁻¹): 1710 (C=O), 1630 (C=C), ^1H NMR δ=7.3—6.8 (m, 5 H, Ph and H-1′), 7.30 (s, 5H, Ph), 4.70 (s, 2H, CH_2 in Bn), 4.53 (s, 2H, H-6), 2.53 (s, 3H, Me), 2.43 (s, 3H, NAc).

Found: C, 72.41; H, 5.88; N, 8.01%. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04%.

*Deacetylation of **1b—d**.* (*Z*)-1-Benzyl-6-isobutylidene-2,5-piperazinedione (**1f**) was typically prepared as follows. To an ice-cooled solution of **1b** (10.0 g, 35.5 mmol) in DMF (50 cm³) was added 70% hydrazine (3.30 g, 66.6 mmol) with stirring at 0 °C. The resulting solution was kept at 0 °C for 3 h, poured into ice-water, and extracted with ethyl acetate. The usual processing of the extract gave the product which was recrystallized from ether–hexane to give **1f** quantitatively as colorless prisms. Mp 124—126 °C, ν_{max}^{KBr} (cm⁻¹): 3180 (NH), 1695 and 1690 (C=O), 1665 (C=C), ^1H NMR δ=7.48 (bd, 1H, NH), 7.4—7.1 (m, 5H, Ph), 6.05 (d, 1H, $J_{1',2'}$=11.0 Hz, H-1′), 4.96 (s, 2H, CH_2 in Bn), 4.02 (d, 2H, $J_{3,NH}$= 2.5 Hz, H-3), 2.69 (dq, 1H, H-2′), 1.00 (d, 6H, $J_{2',3'}$= 6.0 Hz, H-3′).

Found: C, 69.87; H, 6.98; N, 10.79%. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; H, 10.83%.

(*Z*)-1-Benzyl-6-benzylidene-2,5-piperazinedione (**1g**): yield 99% from **1c**, mp 183 °C (prisms from ethanol), ν_{max}^{KBr} (cm⁻¹): 3180 (NH), 1700 (C=O), 1630 (C=C), ^1H NMR δ= 7.88 (bd, 1H, NH), 7.3—6.8 (m, 6H, Ph and H-1′), 7.40 (s, 5H, Ph), 4.71 (s, 2H, CH_2 in Bn), 4.10 (d, 2H, $J_{3,NH}$=2.0 Hz, H-3).

Found: C, 73.92; H, 5.56; N, 9.55%. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58%.

(*Z*)-1-Benzyl-6-(4-methylbenzylidene)-2,5-piperazinedione (**1h**): yield 92% from **1d**, mp 195 °C (prisms from ethanol), ν_{max}^{KBr} (cm⁻¹): 3160 (NH), 1680 (C=O), 1630 (C=C), ^1H NMR δ=7.3—6.8 (m, 5H, Ph and H-1′), 7.27 (s, 5H, Ph), 6.82 (bd, NH), 4.73 (s, 2H, CH_2 in Bn), 4.14 (d, 2H, $J_{3,NH}$=2.0 Hz, H-3), 2.43 (s, 3H, Me).

Found: C, 74.38; H, 5.96; N, 9.09%. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15%.

Catalytic Reduction of Alkylidene-2,5-piperazinediones. The procedure is exemplified by the preparation of 1-benzyl-6-isobutyl-2,5-piperazinedione (**3a**). A solution of **1f** (2.00 g, 7.74 mmol) in ethanol (200 cm^3) was catalytically hydrogenated with 10% palladium-carbon (200 mg) at room temperature for 2 h. The usual processing of the reaction mixture gave the product which was recrystallized from ether–hexane to give **3a** (1.88 g, 93%). Mp 98 °C, ν_{max}^{KBr} (cm^{-1}): 3220 (NH), 1690 (C=O), ^1H NMR δ=7.59 (bd, 1H, NH), 7.45—7.15 (m, 5H, Ph), 5.30 and 3.99 (ABq, 2H, J=15.0 Hz, CH_2 in Bn), 3.89 (dd, 1H, $J_{6,1'a}$=6.0, $J_{6,1'b}$=8.0 Hz, H-6), 3.02 (d, 2H, $J_{3,NH}$=3.0 Hz, H-3), 1.9—1.45 (m, 3H, H-2′ and 1′), 0.91 (d, 6H, $J_{2',3'}$=6.0 Hz, H-3′).

Found: C, 69.35; H, 8.10; N, 10.84%. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20 H, 7.74; N, 10.76%.

1,6-Dibenzyl-2,5-piperazinedione (**3b**): yield 96% from **1g**, mp 183—184 °C (prisms from ethanol), ν_{max}^{KBr} (cm^{-1}): 3250 (NH), 1650 (C=O), ^1H NMR δ=7.5—7.1 (m, 11H, 2×Ph and NH), 5.45 and 3.89 (ABq, 2H, J=15.0 Hz, NCH_2 in Bn), 4.09 (t, 2H, $J_{6,1'}$=4.0 Hz, H-1′), 3.53 (dd, 1H, $J_{3a,NH}$=3.0, $J_{3a,3b}$=17.5 Hz, H-3a), 2.55 (d, 1H, H-3b).

Found: C, 77.08; H, 5.45; N, 8.04%. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18%.

6-Benzyl-1-methyl-2,5-piperazinedione (**3c**): yield 93% from (*Z*)-6-benzylidene-1-methyl-2,5-piperazinedione,[20] mp 169 °C (prisms from ethanol), ν_{max}^{KBr} (cm^{-1}): 3460 (NH), 1650 (C=O), ^1H NMR δ=7.4—7.0 (m, 5H, Ph), 6.80 (bd, 1H, NH), 4.15 (dd, 1H, $J_{6,1'a}$=3.0, $J_{6,1'b}$=2.5 Hz, H-6), 3.45 (dd, 1H, $J_{3a,NH}$=3.5 Hz, H-3a), 3.26 and 3.16 (dABq, 2H, J=14.0 Hz, H-1′), 3.07 (s, 3H, NMe), 2.48 (d, 1H, $J_{3a,3b}$=14.0 Hz, H-3b).

Found: C, 65.98; H, 6.52; N, 12.79%. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84%.

1-Benzyl-3-[2-(ethoxycarbonyl)ethyl]-2,5-piperazinedione (**3d**): yield 93% from (*Z*)-1-benzyl-3-[2-(ethoxycarbonyl)ethylidene]-2,5-piperazinedione,[21] mp 104 °C (prisms from carbon tetrachloride); ν_{max}^{KBr} (cm^{-1}): 3240 (NH), 1740 (ester), 1690 (C=O), 1660 (C=C), ^1H NMR δ=7.55 (bs, 1H, NH), 7.29 (s, 5H, Ph), 4.60 (s, 2H, CH_2 in Bn), 4.3—4.0 (m, 3H, H-3 and CH_2 in Et), 3.85 (s, 2H, H-6), 2.6—2.0 (m, 4H, H-1′ and 2′), 1.24 (t, 3H, Me in Et).

Found: C, 63.09; H, 6.70; N, 9.19%. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62 N, 9.21%.

1-Acetyl-3-isobutyl-4-(4-methoxybenzyl)-2,5-piperazinedione (**3i**): yield 94% from **1e**; mp 114 °C (prisms from diisopropyl ether), ν_{max}^{KBr} (cm^{-1}): 1670 (C=O), ^1H NMR δ=7.16 and 6.85 (each d, 4H, J_{ortho}=8.5 Hz, MBn), 5.08 and 4.01 (ABq, 2H, J=14.5 Hz, CH_2 in MBn), 4.92 and 3.97 (ABq, 2H, J=17.5 Hz, H-6), 3.90 (dd, 1H, $J_{3,1'a}$=5.5, $J_{3,1'b}$=9.0 Hz, H-3), 3.77 (s, 3H, OMe), 2.51 (s, 3H, NAc), 1.9—1.4 (m, 3H, H-1′ and 2′), 0.93 (d, 6H, $J_{2',3'}$=6.0 Hz, H-3′).

Found: C, 64.96; H, 7.33; N, 8.31%. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43%.

N-(4-Methoxybenzyl)ation of 2,5-Piperazinediones. 4-Methoxybenzyl bromide was prepared by an improved method of that for 4-methoxybenzyl chloride[23] as follows. A mixture of 4-methoxybenzyl alcohol (1.00 g, 7.25 mmol) and conc hydrobromic acid (2.0 cm^3) was vigorously stirred at room temperature for 15 min and then extracted with ether (50 cm^3). The extract was washed with saturated sodium hydrogencarbonate and then water, dried over calcium chloride, and then evaporated to give unstable 4-methoxybenzyl bromide (1.45 g) quantitatively as a liquid, which can be used for the next reaction without purification.

The reaction procedure is exemplified by the preparation of (*Z*)-1-benzyl-6-isobutylidene-4-(4-methoxybenzyl)-2,5-piperazinedione (**1i**). To a suspension of 50% sodium hydride (337 mg, 7.01 mmol) in dry DMF (35 cm^3) was added with stirring a solution of **1f** (1.73 g, 6.68 mmol) in dry DMF (5 cm^3) at 0 °C. After keeping the conditions for 30 min, 4-methoxybenzyl bromide (1.61 g, 8.02 mmol) was further added dropwise at 0 °C. The resulting solution was kept at 0 °C for 2 h and then overnight at room temperature, neutralized with acetic acid, poured into ice-water, and then extracted with ethyl acetate. The usual processing of the extract gave a crude syrup which was purified on a column of silica gel (hexane–ethyl acetate 7:3) to give colorless syrup. The syrup was crystallized from ethanol–ether to give **1i** (2.01 g) as colorless prisms in 80% yield. Mp 98.5 °C, ν_{max}^{KBr} (cm^{-1}): 1695, 1675 sh (C=O), 1635 (C=C), ^1H NMR δ=7.4—7.05 (m, 5H, Ph), 7.15 and 6.83 (each d, 4H, J_{ortho}=8.0 Hz, MBn), 6.11 (d, 1H, $J_{1',2'}$=11.0 Hz, H-1′), 4.91 (s, 2H, CH_2 in Bn), 4.56 (s, 2H, CH_2 in MBn), 3.88 (s, 2H, H-3), 3.80 (s, 3H, OMe), 2.67 (dq, 1H, H-2′), 1.02 (d, 6H, $J_{2',3'}$=6.0 Hz, H-3′).

Found: C, 72.68; H, 6.69; N, 7.19%. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.98; H, 6.93; N, 7.40%.

(*Z*)-1-Benzyl-6-benzylidene-4-(4-methoxybenzyl)-2,5-piperazinedione (**1j**): syrup, yield 89% from **1g**, ν_{max}^{KBr} (cm^{-1}): 1690 (C=O), 1630 (C=C), ^1H NMR δ=7.5—6.7 (m, 15H, 2×Ph, MBn and H-1′), 4.66 (s, 2H, CH_2 in Bn), 4.55 (s, 2H, CH_2 in MBn), 3.94 (s, 2H, H-3), 3.72 (s, 3H, OMe).

Found: C, 74.69; H, 6.21; N, 6.81%. Calcd for $C_{26}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00%.

(*Z*)-1-Benzyl-4-(4-methoxybenzyl)-6-(4-methylbenzylidene)-2,5-piperazinedione (**1k**): syrup, yield 85% from **1h**, ν_{max}^{KBr} (cm^{-1}): 1700 (C=O), 1630 (C=C), ^1H NMR δ=7.4—6.7 (m, 14H, 2×Ph, MBn and H-1′), 4.63 (s, 2H, CH_2 in Bn), 4.50 (s, 2H, CH_2 in MBn), 3.88 (s, 2H, H-3), 3.67 (s, 3H, OMe), 2.31 (s, 3H, Me).

Found: C, 75.88; H, 6.21; N, 6.41%. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.15; N, 6.57%.

(*Z*)-1-Acetyl-3-isobutylidene-4-(4-methoxybenzyl)-2,5-piperazinedione (**1e**): yield 94% from (*Z*)-1-acetyl-3-isobutylidene-2,5-piperazinedione,[19] mp 93—94 °C (prisms from ether–hexane), ^1H NMR δ=7.05 and 6.78 (each d, 4H, J_{ortho}=8.5 Hz, Bn), 6.13 (d, 1H, $J_{1',2'}$=11.0 Hz, H-1′), 4.80 (s, 2H, CH_2 in MBn), 4.37 (s, 2H, H-6), 3.75 (s, 3H, OMe), 2.72 (dq, 1H, H-2′), 2.49 (s, 3H, NAc), 1.08 (d, 6H, $J_{2',3'}$=6.0 Hz, H-3′).

Found: C, 65.46; H, 6.86; N, 8.39%. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48%. For the preparation of **3e—g**, 4-methoxybenzyl chloride instead of the bromide was used.

1-benzyl-6-isobutyl-4-(4-methoxybenzyl)-2,5-piperazinedione (**3e**): yield 90% from **3a**, mp 104—105 °C (needles from cyclohexane), ν_{max}^{KBr} (cm^{-1}): 1675, 1665 (C=O), ^1H NMR δ=7.4—7.1 (m, 5H, Ph), 7.12 and 6.82 (each d, 4H, J_{ortho}=8.0 Hz, MBn), 5.22 and 3.94 (ABq, 2H, J=15.0 Hz, CH_2 in MBn), 4.0—3.7 (m, 1H, H-6), 3.87 (s, 2H, H-3), 3.78 (s, 3H, OMe), 1.95—1.4 (m, 3H, H-2′ and 1′), 0.91 (d, 6H, $J_{2',3'}$=6.0 Hz, H-3′).

Found: C, 72.33; H, 7.34; N, 7.27%. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36%.

1,6-Dibenzyl-4-(4-methoxybenzyl)-2,5-piperazinedione (**3f**): yield 90% from **3b**, mp 137 °C (needles from ether–hexane), ν_{max}^{KBr} (cm^{-1}): 1660, 1650 (C=O), ^{1}H NMR δ= 7.25—6.9 (m, 12H, 2×Ph and 1/2×MBn), 6.81 (d, 2H, J_{ortho}=8.0 Hz, 1/2×MBn), 5.44 and 3.92 (ABq, 2H, J=14.5 Hz, CH_2 in Bn), 4.30 and 4.24 (ABq, 2H, J=14.0 Hz, CH_2 in MBn), 4.22 (dd, 1H, $J_{6,1'a}$=4.0, $J_{6,1'b}$=4.5 Hz, H-6), 3.79 (s, 3H, OMe), 3.39 and 2.36 (ABq, 2H, J=17.5 Hz, H-3), 3.20 and 3.14 (dABq, 2H, J=14.0 Hz, H-1').

Found: C, 75.26; H, 6.44; N, 6.63%. Calcd for $C_{26}H_{26}O_3N_2$: C, 75.34; H, 6.32; N, 6.76%.

3-Benzyl-1-(4-methoxybenzyl)-4-methyl-2,5-piperazinedione (**3g**): yield 92% from **3c**; mp 154—155 °C (needles from ether–hexane), ν_{max}^{KBr} (cm^{-1}): 1675, 1665 (C=O), ^{1}H NMR δ=7.3—6.9 (m, 7H, Ph and 1/2×MBn), 6.79 (d, 2H, J_{ortho}=8.0 Hz, 1/2×MBn), 4.34 and 4.22 (ABq, 2H, J=14.0 Hz, CH_2 in MBn), 4.22 (t, 1H, $J_{3,1'}$=4.5 Hz, H-3), 3.77 (s, 3H, OMe), 3.30 and 3.27 (dABq, 2H, J=14.0 Hz, H-1'), 3.01 (s, 3H, NMe), 3.00 and 2.28 (ABq, 2H, J= 17.0 Hz, H-6).

Found: C, 70.81; H, 6.48; N, 8.03%. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28%.

1-Benzyl-3-[2-(ethoxycarbonyl)ethyl]-4-(4-methoxybenzyl)-2,5-piperazinedione (**3h**): syrup, yield 84% from **3d**, ν_{max}^{KBr} (cm^{-1}): 1730 (COOEt), 1660 (C=O), ^{1}H NMR δ=7.3—7.1 (m, 5H, Ph), 7.10 and 6.73 (each d, 4H, J_{ortho}= 8.0 Hz, MBn), 5.10 and 4.31 (ABq, 2H, J=15.0 Hz, CH_2 in Bn), 4.63 (d, 1H, J=14.0 Hz, 1/2×CH_2 in MBn), 4.3—3.7 (m, 4H, H-6, 3 and 1/2×CH_2 in MBn), 4.05 (q, 2H, CH_2 in Et), 3.67 (s, 3H, OMe), 2.5—1.9 (m, 4H, H-1' and 2'), 1.17 (t, 3H, J=6.0 Hz, Me in Et).

Found: C, 67.87; H, 6.71; N, 6.34%. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60%.

6-Alkyl-1-benzyl-6-methoxy-4-(4-methoxybenzyl)-2,5-piperazinediones (5a—c). Compounds **5a—c** were obtained from **1i—k** by successive reactions of NBS and reduction. The procedure is exemplified by the conversion of **1i** into **5a** as follows. To a solution of **1i** (1.90 g, 5.02 mmol) in methanol (80 cm^3) was added NBS (938 mg, 5.27 mmol), and the mixture was stirred at room temperature for 30 min, evaporated, and the residue was extracted with ethyl acetate. The usual processing of the extract gave a crude syrup which was purified on a column of silica gel (hexane–ethyl acetate 7:3) to give 1-benzyl-6-(1-bromo-2-methylpropyl)-6-methoxy-4-(4-methoxybenzyl)-2,5-piperazinedione (**4a**: 2.48 g, 98%) as a colorless syrup. ^{1}H NMR δ=7.5—7.1 (m, 7H, Ph and 1/2×MBn), 6.82 (d, 2H, J_{ortho}=8.0 Hz, 1/2×MBn), 4.65 (s, 2H, CH_2 in Bn), 4.59 (s, 2H, CH_2 in MBn), 4.17 and 3.88 (ABq, 2H, J=16.0 Hz, H-3), 4.08 (d, 1H, $J_{1',2'}$=3.0 Hz, H-1'), 3.79 (s, 3H, OMe), 3.05 (s, 3H, 3-OMe), 2.58 (dqq, 1H, H-2'), 1.01 (d, 6H, $J_{2',3'}$=7.0 Hz, H-3').

Found: C, 56.88; H, 5.66; N, 5.53; Br, 15.60%. Calcd for $C_{24}H_{29}N_2O_5Br$: C, 57.03; H, 5.78; N, 5.54; Br, 15.81%.

The same compound was obtained in 96% yield by treatment of **1i** with a mixture of equimolar bromine and excess methanol.

A solution of **4a** (450 mg, 0.890 mmol) in methanol (50 cm^3) was catalytically hydrogenolyzed in the presence of 10% palladium–carbon (200 mg) and ammonium acetate (343 mg, 4.45 mmol) at room temperature for 24 h. The usual processing of the reaction mixture gave the crude product which was purified on a silica gel column (hexane–ethyl acetate 7:3) to give 1-benzyl-6-methoxy-4-(4-methoxybenzyl)-6-(2-methylpropyl)-2,5-piperazinedione (**5a**: 237 mg, 62%) as a colorless syrup. ^{1}H NMR δ=7.5—7.1 (m, 7H, Ph and 1/2×MBn), 6.83 (d, 2H, J_{ortho}=8.0 Hz, 1/2×MBn), 4.77 and 4.33 (ABq, 2H, J=14.0 Hz, CH_2 in Bn), 4.73 and 4.53 (ABq, 2H, J=14.5 Hz, CH_2 in MBn), 3.99 (s, 2H, H-3), 3.79 (s, 3H, OMe), 2.87 (s, 3H, 3-OMe), 2.13 and 1.86 (dABq, 2H, $J_{1',2'}$=8.0 and 4.5, $J_{A,B}$=15.0 Hz, H-1').

Found: C, 67.38; H, 7.21; N, 6.46%. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.09; N, 6.57%.

Compounds **5b,c** were obtained without characterization of the intermediates, **4b,c**.

1,6-Dibenzyl-6-methoxy-4-(4-methoxybenzyl)-2,5-piperazinedione (**5b**): yield 48% from **1j**, mp 115 °C (prisms from cyclohexane), ^{1}H NMR δ=7.6—6.7 (m, 14H, 2×Ph and MBn), 5.13 and 4.08 (ABq, 2H, J=13.5 Hz, CH_2 in Bn), 4.52 and 4.42 (ABq, 2H, J=14.0 Hz, CH_2 in MBn), 3.74 (s, 3H, OMe), 3.37 and 3.27 (ABq, 2H, J=13.5 Hz, H-1'), 3.28 and 2.36 (ABq, 2H, J=17.5 Hz, H-3), 2.84 (s, 3H, 3-OMe).

Found: C, 72.92; H, 6.29; N, 6.31%. Calcd for $C_{27}H_{28}N_2O_4$: C, 72.95; H, 6.35; N, 6.30%.

1-Benzyl-6-methoxy-4-(4-methoxybenzyl)-6-(4-methylbenzyl)-2,5-piperazinedione (**5c**): yield 56% from **1k**, syrup, ^{1}H NMR δ=7.5—6.6 (m, 13H, Ph, Tol and MBn), 5.10 and 5.37 (ABq, 2H, J=14.0 Hz, CH_2 in Bn), 4.42 and 4.13 (ABq, 2H, J=14.0 Hz, CH_2 in MBn), 3.70 (s, 3H, OMe), 3.42 and 2.41 (ABq, 2H, J=13.5 Hz, H-1'), 2.79 (s, 3H, 3-OMe), 2.19 (s, 3H, Me).

Found: C, 73.26; H, 6.61; N, 6.03%. Calcd for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.59; N, 6.11%.

3-Allyl-1-benzyl-6-isobutyl-4-(4-methoxybenzyl)-2,5-piperazinedione (6a). To a solution of 2,2,6,6-tetramethylpiperazine (508 mg, 3.60 mmol) in tetrahydrofuran (12 cm^3) was successively added dropwise with stirring butyllithium (1.6 M hexane solution, 604 cm^{-3}, 3.60 mmol) and a solution of **3e** (1.14 g, 3.00 mmol) in tetrahydrofuran (7 cm^3) at −78 °C. After keeping the conditions for 15 min, allyl bromide (436 mg, 3.60 mmol) was further added and stirred for 1 h at −78 °C. The temperature of the reaction mixture was raised slowly to room temperature, poured into saturated ammonium chloride solution, and extracted with dichloromethane. The usual processing of the extract gave a crude syrup which was purified on a column of silica gel (hexane–ethyl acetate 7:3) to give a colorless syrup. The syrup was crystallized from ethanol–ether to give **6a** (695 mg, 46%). Mp 123—124 °C, ν_{max}^{KBr} (cm^{-1}): 1650 (C=O), ^{1}H NMR δ=7.22 (s, 5H, Ph), 7.13 and 6.81 (each d, 4H, J_{ortho}=9.0 Hz, MBn), 5.8—5.25 (m, 1H, H-2'), 5.47 and 3.83 (ABq, 2H, J=15.0 Hz, CH_2 in Bn), 5.47 and 3.79 (ABq, 2H, J=15.0 Hz, CH_2 in MBn), 5.40 (dd, 1H, $J_{3'a,3'b}$=2.0, $J_{3'a,2'}$=1.5 Hz, H-3'a), 5.17 (dd, 1H, $J_{3'b,2'}$=8.0 Hz, H-3'b), 4.05—3.6 (m, 2H, H-3 and 6), 3.80 (s, 3H, OMe), 3.1—2.5 (m, 2H, H-1'), 1.9—1.45 (m, 3H, H-1'' and 2''), 0.95 and 0.87 (each d, 6H, $J_{2',3'}$=5.5 Hz, H-3'').

Found: C, 73.96; H, 7.72; N, 6.48%. Calcd for $C_{26}H_{32}N_2O_5$: C, 74.25; H, 7.67; N, 6.66%.

Oxidation of 3e with Chromium Trioxide. A mixture of a solution of **3e** (200 mg, 0.526 mmol) and chromium trioxide (263 mg, 1.58 mmol) in glacial acetic acid (25 cm^3) was stirred for 24 h at room temperature, poured into ice-water, and extracted with ethyl acetate. The usual process-

ing of the extract gave a crude syrup which was purified on a column of silica gel to give **3a** (56 mg) in 41% yield.

Oxidative Removal of ***N*****-(4-Methoxybenzyl) Group of 3e—i,1i,5a—c, and 6a with Cerium(IV) Diammonium Nitrate.** The general procedure is exemplified by the conversion of **3e** into **3a**. A solution of **3e** (95.1 mg, 0.25 mmol) and CAN (548 mg, 1.00 mmol) in acetonitrile (3.0 cm^3) and water (1.0 cm^3) was stirred at room temperature for 2 h, poured into water, and then extracted with ethyl acetate. The extract was successively washed with saturated sodium hydrogencarbonate and water, dried over anhydrous magnesium sulfate, and then evaporated to give crude product, which was purified on a flash column of silica gel (hexane–ethyl acetate 7:3) to give **3a** (62.7 mg) in 96% yield.

A similar oxidation of **3f—h** gave **3b—d**, respectively. Compounds **5a—c**, **3i**, and **6a** were also successfully converted into **5d—f**, **3j**, and **6b**, respectively.

1-Benzyl-6-isobutyl-6-methoxy-2,5-piperazinedione (**5d**): syrup, ν_{max}^{KBr} (cm^{-1}): 3250 (NH), 1680, 1660 (C=O), ^1H NMR δ=8.24 (bs, 1H, NH), 7.5—7.1 (m, 5H, Ph), 4.66 (s, 2H, CH_2 in Bn), 4.24 and 4.08 (ABq, 2H, J=17.5 Hz, H-3), 2.92 (s, 3H, 3-OMe), 2.1—1.5 (m, 3H, H-1′ and 2′), 0.81 and 0.53 (each d, 6H, $J_{2',3'}$=7.0 Hz, H-3′).

Found: C, 66.03; H, 7.47; N, 9.51%. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65%.

1,6-Dibenzyl-6-methoxy-2,5-piperazinedione (**5e**): mp 157 °C (prisms from ethanol–ether), ν_{max}^{KBr} (cm^{-1}): 3320 (NH), 1710 (C=O), ^1H NMR δ=7.72 (bd, 1H, NH), 7.6—6.9 (m, 10H, 2×Ph), 5.18 and 4.35 (ABq, 2H, J=14.0 Hz, CH_2 in Bn), 3.62 (dd, 1H, $J_{3a,NH}$=2.5 Hz, H-3a), 3.29 (s, 2H, H-1′), 2.81 (s, 3H, 3-OMe), 2.48 (d, 1H, $J_{3a,3b}$=17.0 Hz, H-3b).

Found: C, 70.17; H, 6.08; N, 8.41%. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64%.

1-Benzyl-6-methoxy-6-(4-methylbenzyl)-2,5-piperazinedione (**5f**): mp 190 °C (prisms from ethanol–ether), ν_{max}^{KBr} (cm^{-1}): 3290 (NH), 1700 (C=O), ^1H NMR δ=7.80 (bd, 1H, NH), 7.6—6.9 (m, 9H, Ph and Tol), 5.18 and 4.46 (ABq, 2H, J=15.0 Hz, CH_2 in Bn), 3.68 (dd, 1H, $J_{3a,NH}$=5 Hz, H-3a), 3.26 (s, 2H, H-1′), 2.83 (s, 3H, 3-OMe), 2.51 (d, 1H, $J_{3a,3b}$=17.5 Hz, H-3b), 2.26 (s, 3H, Me).

Found: C, 70.81; H, 6.61; N, 8.16%. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28%.

1-Acetyl-3-isobutyl-2,5-piperazinedione (**3j**): mp 136 °C (prisms from ethanol–ether), ν_{max}^{KBr} (cm^{-1}): 3180 (NH), 1710 (C=O), ^1H NMR δ=6.90 (bd, 1H, NH), 4.47 and 4.30 (ABq, 2H, J=17.8 Hz, H-6), 4.04 (dt, 1H, $J_{3,1'}$=7.9, $J_{3,NH}$=2.6 Hz, H-3), 2.58 (s, 3H, NAc), 1.9—1.5 (m, 3H, H-2′ and 3′), 1.01 and 0.98 (each d, 6H, $J_{2',3'}$=5.7 Hz, H-3′).

Found: C, 56.41; H, 7.55; N, 13.01%. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20%.

3-Allyl-1-benzyl-6-isobutyl-2,5-piperazinedione (**6b**): mp 109 °C (prisms from ethanol–ether), ν_{max}^{KBr} (cm^{-1}): 3210 (NH), 1685 (C=O), 1655 (C=C), ^1H NMR δ=7.45—7.1 (m, 5H, Ph), 6.89 (d, 1H, NH), 6.0—5.5 (m, 1H, H-2′), 5.32 and 3.92 (ABq, 2H, J=14.5 Hz, CH_2 in Bn), 5.24 (d, 1H, $J_{3'a,2'}$=12.0 Hz, H-3′a), 5.12 (d, 1H, $J_{3'b,2'}$=1.0 Hz, H-3′b), 4.10 (dd, 1H, $J_{6,1''a}$=4.0, $J_{6,1''b}$=8.0 Hz, H-6), 3.77 (ddd, 1H, $J_{3,1'a}$=4.0, $J_{3,1'b}$=8.0, $J_{3,NH}$=0.5 Hz, H-3), 3.05—2.4 (m, 2H, H-1′), 1.9—1.45 (m, 3H, H-1″ and 2″), 0.96 (d, 6H, $J_{2'',3''}$= 6.0 Hz, H-3″).

Found: C, 71.99; H, 8.00; N, 9.31%. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33%.

A similar oxidation of **1i** was accompanied with an oxidative addition reaction to give **8a** or **8b**, depending on the concentration of oxidant.

1-Benzyl-6-hydroxy-6-(2-methyl-1-nitrooxypropyl)-2,5-piperazinedione (**8a**): mp 137 °C (prisms from ethyl acetate–hexane), ν_{max}^{KBr} (cm^{-1}): 3380 (OH), 3320 (NH), 1700, and 1665 (C=O), 1645, 1275, 840 (ONO_2), ^1H NMR δ=7.68 (d, 1H, NH), 7.5—7.2 (m, 5H, Ph), 5.43 (bs, 1H, OH), 5.05 (d, 1H, $J_{1',2'}$=4.5 Hz, H-1′), 4.78 and 4.48 (ABq, 2H, J=14.0 Hz, CH_2 in Bn), 4.26 (d, 1H, $J_{3a,3b}$=18.0 Hz, H-3a), 3.90 (dd, 1H, $J_{3b,NH}$=6.0 Hz, H-3b), 2.5—2.0 (m, 1H, H-2′), 1.12 and 0.92 (each d, 6H, $J_{2',3'}$=6.5 Hz, H-3′).

Found: C, 53.30; H, 5.68; N, 12.51%. Calcd for $C_{15}H_{19}N_3O_6$: C, 53.40; H, 5.68; N, 12.46%.

1-Benzyl-6-hydroxy-4-(4-methoxybenzyl)-6-(2-methyl-1-nitrooxypropyl)-2,5-piperazinedione (**8b**): syrup, ν_{max}^{KBr} (cm^{-1}): 3380 (OH), 1660 (C=O, ONO_2), 1275, 830 (ONO_2), ^1H NMR δ=7.55—7.05 (m, 7H, Ph and 1/2×MBn), 6.73 (d, 2H, J_{ortho}=8.0 Hz, 1/2×MBn), 5.26 (s, 1H, OH), 5.00 (d, 1H, $J_{1',2'}$=4.0 Hz, H-1′), 4.73 and 4.44 (ABq, 2H, J=15.0 Hz, CH_2 in Bn), 4.60 and 4.49 (ABq, 2H, J=15.0 Hz, CH_2 in MBn), 4.22 and 3.78 (ABq, 2H, J=17.5 Hz, H-3), 3.79 (s, 3H, OMe), 2.5—2.05 (m, 1H, H-2′), 1.11 and 0.88 (each d, 6H, $J_{2',3'}$=7.0 Hz, H-3′).

Found: C, 60.62; H, 5.67; N, 8.98%. Calcd for $C_{23}H_{27}N_3O_7$: C, 60.38; H, 5.95; N, 9.19%.

Oxidation of **3e** with CAN in methanol gave, 1-benzyl-3-isobutyl-4-(α,4-dimethoxybenzyl)-2,5-piperazinedione (**7**); syrup, ν_{max}^{KBr} (cm^{-1}): 1670 (C=O), ^1H NMR δ=7.4—7.05 (m, 7H, Ph and 1/2×MBn), 6.88 (d, 2H, J_{ortho}=8.0 Hz, MBn), 6.59 (s, 1H, CH in MBn), 5.23 and 3.97, 5.22 and 3.99 (each ABq, 2H, each J=15.0 Hz, CH_2 in Bn), 4.0—3.7 (m, 3H, H-3 and 6), 3.83 (s, 3H, OMe), 3.43 and 3.40 (each s, 3H, 3-OMe), 2.0—1.4 (m, 3H, H-2′ and 1′), 0.94 (m, 6H, H-3′).

Found: C, 70.13; H, 7.33; N, 6.65%. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82%.

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