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The Formation of the Main Skelton of Bicyclomycin by the Cyclization of 6-Hydroxy-3-(3-hydroxypropyl)-2,5-piperazinedione Derivatives

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This paper describes the synthesis of 3-(3-*t*-butoxypropyl)-6-hydroxy-2,5-piperazinedione derivatives by the hydroxylation of the corresponding 2,5-piperazinedione with *N*-bromosuccinimide (NBS) in the presence of water and the subsequent cyclization to 2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione derivatives (**11**). The reversible interconversion between the spiro[oxolane-2,2′-piperazine]-3′,6′-dione prepared previously and the bicyclo compound **11** was established. The formation mechanisms and the structural confirmation of **11** and the other products are discussed.

Bicyclomycin, produced by *Streptomyces (St.) sapporonensis*[1] and *St. aizunensis*,[2] is found to have an interesting bicyclostructure and a marked bioactivity.[3-6] The very interesting and important investigation on the correlation between the structure and the bioactivity attracked and prompted us to synthesize the bicyclomycin and its analogs. Many workers have attempted the synthesis of bicyclomycin,[7-12] more recently, it has been reported that Nakatsuka *et al.* have succeeded in the total synthesis.[13] We also reported briefly the facile conversion of 1-benzyl-3-(3-hydroxypropyl)-2,5-piperazinedione (**3**) (2,5-piperazinedione=PDO) derivative to the corresponding bicyclo compound.[10]

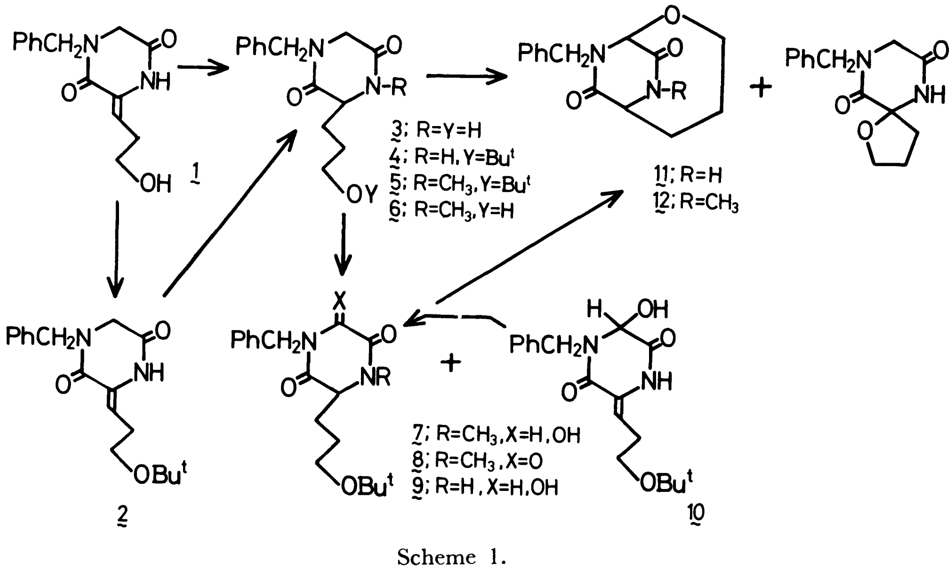
In the present paper, we wish to report in detail the synthesis of the main framework of bicyclomycin. The structural determination and the formation mechanisms are discussed.

Results and Discussion

Synthesis of 3,6-Bridged PDO. The starting 1-benzyl-3-(3-hydroxypropylidene)–PDO (**1**), derived by the cyclization of diethyl (*Z*)-2-chloroacetylamino-2-pentendioate[14,15] with benzylamine and the reduction of the resulting 3-[2-(ethoxycarbonyl)ethylidene]-PDO derivative with $LiAlH_4$,[14] was treated with isobutene to give 1-benzyl-3-(3-*t*-butoxypropylidene)–PDO (**2**). The subsequent hydrogenation of **2** with 10% Pd/C gave 1-benzyl-3-(3-*t*-butoxypropyl)–PDO (**4**) in a good yield.

According to the method for the selective hydroxylation of 6-position of PDO derivative reported recently,[14] the compound **4** was treated with *N*-bromosuccinimide (NBS) in a mixture of chloroform and water to give reaction products as a mixture. The crude mixture thus obtained was chromatographed on a silica-gel column to give three fractions, from which the compounds **2**, **10**, and **9** were in turn obtained in 28, 21, and 29% yields respectively. The latter two were identified as 1-benzyl-3-(3-*t*-butoxypropylidene)-6-hydroxy–PDO (**10**) and 3-(3-*t*-butoxypropyl)-6-hydroxy–PDO (**9**). In addition, the compound **9** separated above and newly obtained by the catalytic hydrogenation of **10** with 10% Pd/C was found to be comprised of two stereoisomers, which could be separated purely to give **9a** and **9b** (*ca.* 1:1 ratio).

On the other hand, in order to block the 4-position,



Scheme 1.

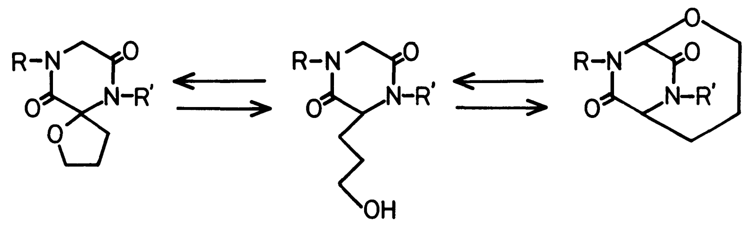


Fig. 1.

according to the method reported previously,[16] the compound **4** was subjected to the methylation with methyl iodide, followed by the reaction of the resulting 1-benzyl-3-(3-*t*-butoxypropyl)-4-methyl–PDO (**5**) with NBS in the presence of water. The reaction products thus obtained as a mixture were separated on a silica-gel column to give two kinds of colorless crystals, which were identified as 1-benzyl-5-(3-*t*-butoxypropyl)-4-methyl-2,3,6-piperazinetrione (**8**) and the corresponding 6-hydroxy–PDO (**7**) obtained in a 26% and a 40% yield respectively.

In order to examine whether or not the *N*-unmasked **3**[14] can be hydroxylated at the 6-position, the substrate **3** was also made to react with NBS in the presence of water. As a result, the expected hydroxylation of **3** took place. The resulting product, yielded as an intermediate, was cyclized to give the 3,6-bridged PDO and spiro-PDO derivatives. The two products thus obtained were readily characterized to be 9-benzyl-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione (**11**) and 4'-benzylspiro[oxolane-2,2'-piperazine]-3',6'-dione[14] in a 28% and a 38% yield respectively.

On the other hand, the similar reaction of **3** with NBS in chloroform in the absence of water gave an oily product, which was assigned to be a mixture of 3-, 6-bromo, and 3,6-dibromo derivatives of **3** based on the spectroscopic analyses. However, the attempts to separate the above mixture purely have been unsuccessful so far. Consequently, the hydroxylation mechanism is supposed to be the bromination of **3** in the first step and then the substitution of bromine with hydroxyl group at 3- and 6-positions. Furthermore, from the above results and the fact that the spiro compound easily converted into **3**,[14] the reversible interconversion route between the spiro and 3,6-bridged compounds (**11**) *via* **3** was first ascertained and established here, as is illustrated in Fig. 1.

In addition, in order to obtain **11** in a higher yield, the cyclization of 1-benzyl-6-hydroxy-3-(3-hydroxypropyl)–PDO *in situ*, formed as an intermediate by the treatment of **9** with trifluoroacetic acid, was successful. **11** was obtained in a 95% yield from **9a** and in a 90% yield from **9b**. **7** was similarly worked up to give 7-methyl derivative of **11** (**12**) in a quantitative yield. Therefore, the formation mechanisms of **11** and **12** could be unambiguously concluded to be the decomposition of *t*-butoxyl group of **7** and **9** with trifluoroacetic acid to hydroxyl group, followed by the immediate cyclization by the intramolecular dehydration between 3-(3-hydroxypropyl) and 6-hydroxyl groups.

The yields, physical constants, and spectral data of **4**—**8** and **9** are summarized in Table 1.

In the NMR spectrum of **11**, the signal of the proton at the 1-position appeared in the δ 4.20 as a multiplet and the signal at δ 5.01 is attributable to 6-proton, which is splitting as a doublet (J=1.2 Hz) of the long range coupling due to the *W*-letter relationship between NH and 1-proton. In consequence, the 3,6-bridged PDO (**11** and **12**) thus obtained was found to have a boat structure, as in the corresponding spiro derivative;[14] this is illustrated in Fig. 2.

Synthesis of 3-Methoxy-3,6-bridged PDO. To

TABLE 1. 3-ALKYL-2,5-PIPERAZINEDIONE DERIVATIVES (**4**—**9**)

Compound No.	Yield %	Mp θ_m/°C	Formula	Found (Calcd) (%) C	H	N	NMR spectrum, δ in $CDCl_3$ 3-H J/Hz	6-H J/Hz	OH	NH (N-CH_3)
4	92	120—122[a)]	$C_{18}H_{26}N_2O_3$	68.01 (67.90	8.45 8.23	8.86 8.80)	4.00 m	3.77 s		7.74
5	98	97—98[b)]	$C_{19}H_{28}N_2O_3$	68.70 (68.64	8.74 8.49	8.48 8.43)	4.03 dd (5.0, 6.0)	3.84 q[g)] (18.0)		(2.98)
6	92	73—75[c)]	$C_{15}H_{20}N_2O_3$	65.23 (65.19	7.34 7.30	9.89 10.14)	4.04 t (5.0)	3.84 s	4.40 s	(2.96)
7	40	134—135[d)]	$C_{19}H_{28}N_2O_4$	65.35 (65.49	8.19 8.10	8.08 8.04)	3.95 dd (5.0, 6.0)	5.03 d	6.53 d (5.5)	(2.96)
8	26	59—60[a)]	$C_{19}H_{26}N_2O_4$	65.61 (65.87	7.66 7.57	7.83 8.09)	4.28 dd (4.0, 5.5)			(3.04)
9a	29	204—206[e),f)]	$C_{18}H_{26}N_2O_4$	64.38 (64.65	7.88 7.84	8.31 8.38)	4.06 m	4.96 d	5.90 d (5.0)	7.64
9b		Syrup					4.16 m	4.96 bs	5.8—6.4 bs	7.96

a) Colorless needles from dibutyl ether. b) Colorless needles from hexane. c) Colorless prisms from benzene-hexane. d) Colorless needles from CCl_4. e) Decomposition. f) Colorless needles from benzene. g) AB quartet.

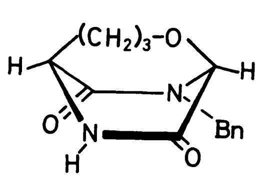


Fig. 2.

generalize the synthesis of the 3,6-bridged PDO, 3-alkoxy- and 3-hydroxy-3-(3-*t*-butoxypropyl)-PDO derivatives newly synthesized here were made to undergo the cyclization reaction. According to the method reported previously,[17] the compound **2** was treated with NBS in a mixture of dioxane and water to give colorless crystals, which were identified as 1-benzyl-3-(1-bromo-3-*t*-butoxypropyl)-3-hydroxy-PDO (**14**) in a 97% yield. In this case, the hydroxylation at the both 3- and 6-positions of **2** did not take place, but only **14** was obtained selectively. The subsequent hydrogenolysis of bromine on **14** with 10% Pd/C gave the corresponding 3-(3-*t*-butoxypropyl)-3-hydroxy-PDO derivative (**16**) in a 94% yield.

On the other hand, the methoxylation of **2** with NBS in methanol was also achieved, followed by the similar hydrogenolysis of the resulting 3-(1-bromo-3-*t*-butoxypropyl)-3-methoxy-PDO derivative (**13**) gave 1-benzyl-3-(3-*t*-butoxypropyl)-3-methoxy-PDO (**15**) in a 95% yield. For the purpose of the conversion of *t*-butoxyl group, **15** was treated with organic acid such as glacial acetic acid; the unexpected elimination of methanol readily occurred to give the starting material **2** quantitatively. Hence, to prevent the methoxyl group from being eliminated it is necessary to protect the 4-position of **15**.[14] The methylation of **15** with methyl iodide[16] gave the corresponding 4-methyl-PDO derivative of **15** (**17**) in a 71% yield.

Next, the reaction of **17** with NBS in a mixture of chloroform and water was performed to obtain a crystalline product as a mixture. Subsequently, by the usual column chromatograph method, the crude mixture was separated purely to give two fractions: The first fraction gave colorless crystals, identified as the corresponding 2,3,6-piperazinetrione derivative of **17** (**18**) in a 23% yield, while the second one gave a colorless syrup, which was also identified as the corresponding 6-hydroxy-PDO derivative of **17** (**19**) in a 40% yield. Although the compounds **17** and **19** thus obtained did not give satisfactory elemental analyses because of the difficulty of purification, their structures could be exactly confirmed by the further transformation to **18** and to the 6-acetoxy derivative of **19** (**20**) respectively.

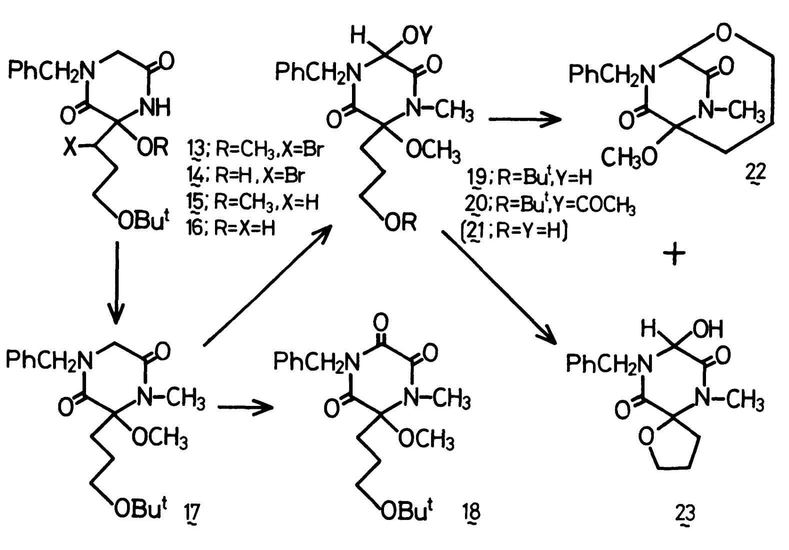
In order to activate the 6-hydroxyl group, the compound **19** was acetylated by the usual method, followed by the treatment of **20** obtained with trifluoroacetic acid. As a result, the cyclization proceeded quickly to give the reaction products as a mixture. The subsequent separation of the mixture on a silica-gel column gave a syrup from the first fraction and colorless crystals from the second one. These compounds were characterized to be 9-benzyl-6-methoxy-7-methyl-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione (**22**) in a 54% yield and the authentic 4'-benzyl-5'-hydroxy-1'-methylspiro[oxolane-2,2'-piperazine]-3',6'-dione (**23**)[14] in a 32% yield respectively.

From the above results, interestingly, even if both 3- and 4-positions were protected with methoxyl and methyl groups respectively, it was found that the spiro formation reaction could be carried out to give **23**.

The yields, physical constants, and spectral data of **13**—**19**, and **20** are summarized in Table 2.

From the NMR spectral data of **22**, the disappearance of the signals due to *t*-butyl of 3-*t*-butoxypropyl at the 3-position and those due to methyl of acetoxyl groups at the 6-position, and the appearance of methylene protons at δ 2.95 (dd, J=5.0 Hz, J=7.5 Hz), 4-methyl protons at δ 2.95 (s), 3-methyl group at δ 3.32 (s), and 6-proton at δ 5.07 (s) indicate unambiguously the formation of the expected bicyclo compound (**23**).

Further work including the cyclization of **16** and **21** is now in progress and the results will be published later.



Scheme 2.

Table 2. 3-Substituted 3-alkyl-2,5-piperazinedione derivatives (**13**—**20**)

Compound No.	Yield %	Mp θ_m/°C	Formula	Found (Calcd) (%)			NMR spectrum, δ in $CDCl_3$		
				C	H	N	6-H J/Hz	OCH_3 (OH), s	NCH_3 (NH), s
13	96	138[a)]	$C_{19}H_{27}N_2O_4Br$	53.47 (53.40	6.47 6.37	6.39 6.56)	3.94 d (1.5)	3.30	(8.54)
14	97	141—142[b)]	$C_{18}H_{25}N_2O_4Br$	52.17 (52.31	6.17 6.10	6.64 6.78)	3.85 s	(7.20)	(8.90)[g)]
15	95	Syrup	$C_{19}H_{28}N_2O_4$	65.30 (65.49	8.12 8.10	8.06 8.04)	3.88 q[f)] (17.5)	3.18	(8.34)
16	94	149—150[c)]	$C_{18}H_{26}N_2O_4$	64.61 (64.65	7.91 7.84	8.15 8.38)	3.86 q[f)] (18.0)	(5.82)	(7.92)
17	71	Syrup					3.90 s	3.12	2.90
18	28	111—112[d)]	$C_{20}H_{28}N_2O_5$	63.28 (63.81	7.51 7.50	7.23 7.44)		3.05	3.01
19	40	Syrup					5.06 s 5.12 s	2.90 2.98	3.04
20	89	102—103[e)]	$C_{22}H_{32}N_2O_6$	62.57 (62.84	7.80 7.67	6.54 6.66)	6.42 s	3.04	2.88

a) Colorless needles from benzene-hexane. b) Colorless needles from CCl_4. c) Colorless needles from benzene. d) Colorless needles from dibutyl ether. e) Colorless needles from hexane. f) AB quartet. g) Measured in DMDO-d_6.

Experimental

All the boiling and melting points are uncorrected. The IR spectra were recorded with a Hitachi EPI-G3 Spectrometer. The NMR spectra were measured with a JNM-PS-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd), using tetramethylsilane as an internal standard.

Preparation of 2. Into a solution of **1** (3.0 g, 11.54 mmol) in CH_2Cl_2 (250 ml), we stirred concentrated H_2SO_4 (1.2 ml). Isobutene gas was then introduced into the resultant solution under cooling, till the volume of the solution became about 350 ml. After the mixture was allowed to stand at room temperature overnight, an aqueous solution of $NaHCO_3$ (100 ml) was added with vigorous stirring. The organic layer was washed with water and then dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 gave crystals, which were recrystallized from dibutyl ether to give colorless prisms. Yield 88%, mp 123—125 °C. IR (KBr): 3180 (NH), 1680, 1635 (CO) cm^{-1}. NMR ($CDCl_3$): δ=1.24 (s, Bu^t), 6.28 (t, -CH=, J=8.0 Hz), 9.56 (bs, NH). Found: C, 67.82; H, 7.84; N, 8.78%. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85%.

Preparation of 4. A solution of **2** (1.2 g, 3.80 mmol) in methanol (60 ml) was hydrogenated catalytically with 10% Pd/C (120 mg) at room temperature for 30 min. After filtering off Pd/C, the methanol solution was concentrated to give crude crystals, which were recrystallized from dibutyl ether to give colorless needles. IR (KBr): 3240 (NH), 1695, 1660 (CO) cm^{-1}.

Preparation of 5. Into a solution of **4** (450 mg, 1.41 mmol) in DMF (5 ml), we stirred 55% NaH (74 mg, 1.70 mmol) at room temperature. After the evolution of hydrogen ceased, methyl iodide (240 mg, 1.69 mmol) was added to the resulting solution, with stirring for 15 min. Into the reaction solution was added ice water (20 ml) and then the resulting solution was extracted twice with benzene (30 ml). The benzene layer was washed twice with water and then dried over anhydrous Na_2SO_4. Removal of benzene gave crystals, which were recrystallized from hexane to give colorless needles. IR (KBr): 1650 (CO) cm^{-1}.

Preparation of 6. After a solution of **5** (400 mg, 1.20 mmol) in trifluoroacetic acid (3 ml) was allowed to stand at room temperature for 2 h, the resulting solution was concentrated under reduced pressure to give a residual product. The residue thus obtained was purified on a silica-gel column using a mixture of chloroform and acetone (5:1 v/v) as the eluent. Concentration of the fraction obtained gave crude crystals, which were recrystallized from benzene-hexane to give colorless prisms. IR (KBr): 3350 (OH), 1660 (CO) cm^{-1}.

Reaction of 4 with NBS-Water. Into a solution of **4** (2.0 g, 6.29 mmol) in chloroform (200 ml) was added water (20 ml) and NBS (1.34 g, 7.55 mmol) at room temperature. After stirring for 2 h, the organic layer which separated was washed with water and then dried over anhydrous Na_2SO_4. After removal of chloroform, the residue was chromatographed on a silica-gel column using a mixture of chloroform and acetone (10:1 v/v) as the eluent. Four fractions thus obtained were concentrated under reduced pressure and each resulting product was purified by means of the recrystallization or on the silica-gel column to give **2**, **10**, **9a**, and **9b** respectively. **2**; Yield 28%. **9a**; IR (KBr): 3200, 1705, 1670, 1665, and 1630 cm^{-1}. **9b**; IR: 3250, 1680 cm^{-1}. **10**; Yield 21%, mp 134—136 °C (colorless prisms from benzene-hexane). IR (KBr): 3300 (OH), 3200 (NH), 1690 (CO), 1620 (C=C) cm^{-1}. NMR ($CDCl_3$): δ=1.22 (s, 9H, Bu^t), 5.06 (bs, 1H, 6-H), 5.7—6.0 (OH), 6.30 (t, -CH=, J=8.0 Hz), 9.70 (bs, NH). Found: C, 65.08; H, 7.22; N, 8.49%. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43%.

Hydrogenation of 10. A solution of **10** (225 mg, 0.678 mmol) in methanol (20 ml) was catalytically hydrogenated with 10% Pd/C (30 mg) at room temperature for 30 min to give a mixture of **9a** and **9b** (*ca.* 1:1) in a 93% yield.

Reaction of 5 with NBS-Water. Into a solution of **5** (1.0 g, 3.01 mmol) in a mixture of chloroform (20 ml) and water (5 ml), we stirred NBS (643 mg, 3.61 mmol) at room temperature for 6 h. The resulting chloroform layer was washed with water and then dried over anhydrous Na_2SO_4. After removal of chloroform, the residue obtained was chromatographed on a silica-gel column using a mixture of chloroform and acetone (20:1 v/v) as the eluent. The two fractions thus obtained were concentrated to give **8** and **9** respectively. **8**; IR (KBr): 1720, 1690 (CO) cm^{-1}. **9**; IR: 3170 (OH), 1675, 1650 (CO) cm^{-1}.

*Reaction of **3** with NBS–Water.* In a similar manner, the treatment of **3** (800 mg, 3.05 mmol) with a solution of NBS (600 mg, 3.37 mmol) in a mixture of chloroform (30 ml) and water (3 ml) was worked up for 3 h to give two kinds of products, **11** and the corresponding spiro derivative[14] in a 28 and a 38% yield respectively. **11**; Mp 200—202 °C (colorless prisms from benzene–hexane). IR (KBr): 3230 (NH), 1800 1670 (CO) cm^{-1}. NMR ($CDCl_3$): δ=1.7—2.3 (m, 4H, $-CH_2-$), 3.4—4.0 (m, 2H, $-O-CH_2-$), 4.20 (m, 1H, $-C\underline{H}-CH_2-$, 6-H), 5.01 (d, 1H, $-C\underline{H}-OCH_2-$, $J_{3\text{-H,NH}}=1.2$ Hz, 3-H), 7.68 (s, NH). Found: C, 65.01; H, 6.34; N, 10.66%. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76%.

*Cyclization of **9a** and **9b**.* A solution of **9** (300 mg, 0.898 mmol) in CF_3COOH (2 ml) was allowed to stand at room temperature for 2 h. After removal of CF_3COOH, the residual product was dissolved in benzene (20 ml) and the resulting solution was washed with water and then dried over anhydrous Na_2SO_4. Concentration of the solution gave **11** in a 95% yield from **9a** and in a 90% yield from **9b**.

*Preparation of **12**.* *From **6***: The treatment of **6** (110 mg, 3.99 mmol) with NBS (71 mg, 3.99 mmol) in chloroform (10 ml) was carried out under reflux for 1 h to give **12** as an unstable colorless crystals. Yield 48%. IR (KBr): 1670 (CO) cm^{-1}. NMR ($CDCl_3$): δ=1.5—2.4 (m, 4H, $-CH_2-$), 2.96 (s, 3H, $N-CH_3$), 3.3—3.9 (m, 2H, $-O-CH_2-$), 4.12 (dd, 1H, $-C\underline{H}-CH_2-$, J=3.0, 4.5 6-H), 5.12 (s, 1H, $-C\underline{H}-OCH_2-$, 3-H).

*From **7***: Treatment of **7** (240 mg, 6.89 mmol) in CF_3COOH (2 ml) at room temperature for 2 h gave **12** in a 98% yield.

*Preparation of **13**.* Into a mixture of **2** (900 mg, 2.85 mmol) in methanol (10 ml), we stirred NBS (507 mg, 2.85 mmol) at room temperature for 10 min. After removal of methanol, the residue was dissolved in chloroform (20 ml) and the resulting solution was washed twice with water and then dried oved anhydrous Na_2SO_4. Concentration of the solution gave crystals, which were recrystallized from benzene–hexane to give colorless needles. IR (KBr): 3160 (NH), 1680 (CO) cm^{-1}.

*Preparation of **14**.* Similarly, the treatment of **2** (900 mg, 2.85 mmol) with NBS (507 mg, 2.85 mmol) in a mixture of dioxane (10 ml) and water (5 ml) was worked up to give **14** as colorless needles from CCl_4. IR (KBr): 3200 (NH, CO), 1660 (CO) cm^{-1}.

*Preparation of **15**.* A solution of **13** (900 mg, 2.11 mmol) in methanol (50 ml) was catalytically hydrogenated with 10% Pd/C (100 mg) in the presence of triethylamine (220 mg, 2.18 mmol) at room temperature for 15 min. After the Pd/C was filtered off, the methanol solution was concentrated. The residue was dissolved in CH_2Cl_2 (50 ml) and the resulting solution was washed twice with water and then dried over anhydrous Na_2SO_4. After removal of CH_2Cl_2, the residual syrup thus obtained was purified on a silica-gel column using a mixture of chloroform and acetone (10:1 v/v) as the eluent. Evaporation of the solvent gave **15** as a colorless syrup. IR (KBr): 3220 (NH), 1680 (CO) cm^{-1}.

*Preparation of **16**.* Similarly, the hydrogenation of **14** (1.1 g, 2.66 mmol) with 10% Pd/C (100 mg) in methanol (60 ml) in the presence of triethylamine (270 mg, 2.66 mmol) was performed to give **16** as colorless needles from benzene. IR (KBr): 3240 (OH, NH), 1690, 1640 (CO) cm^{-1}.

*Preparaation of **17**.* Into a solution of **15** (1.2 g, 3.45 mmol) in THF (40 ml), we stirred 55% NaH (150 mg, 3.45 mmol) at room temperature. After the evolution of hydrogen ceased, methyl iodide (580 mg, 4.08 mmol) was added to the resulting solution with stirring. After continuing the stirring for 1 h, the reaction solution was neutralized with acetic acid. After removal of THF, the residue obtained was dissolved in ethyl acetate (30 ml) and the resulting solution was washed twice with water and then dried over anhydrous Na_2SO_4. Concentration of the solution gave the residual syrup, which was purified on a silica-gel column using a mixture of chloroform and acetone (30:1 v/v) to give **17** as a colorless syrup. IR (KBr): 1660 (CO) cm^{-1}.

*Reaction of **17** with NBS–Water.* Into a solution of **17** (850 mg, 2.35 mmol) in a mixture of chloroform (20 ml) and water (5 ml), we stirred NBS (460 mg, 2.58 mmol) at room temperature overnight. The resulting organic layer was washed with water and dried over anhydrous Na_2SO_4 and finally concentrated. The residue thus obtained was chromatographed on a silica-gel column using a mixture of chloroform and acetone (20:1 v/v) as the eluent. The first fraction gave trione derivative **18**, and the second one gave 6-hydroxy derivative **19**. **18**; IR (KBr): 1745, 1685 (CO) cm^{-1}. **19**; IR: 3300 (OH), 1660 (CO) cm^{-1}.

*Acetylation of **19**.* A solution of **19** (700 mg, 1.85 mmol) in acetic anhydride (5 ml) in the presence of sodium acetate (3 mg) was heated at 100 °C for 1 h. After removal of acetic anhydride under reduced pressure, the residue was purified on a silica-gel column using a mixtuie of chloroform and acetone (30:1 v/v) as the eluent. The fraction was concentrated under reduced pressure to give the corresponding acetyl derivative (**20**). IR (KBr): 1760, 1690 (CO) cm^{-1}.

*Cyclization of **20**.* A solution of **20** (650 mg, 1.55 mmol) in CF_3COOH (5 ml) was allowed to stand at room temperature for 2 h. The reaction solution was concentrated under reduced pressure and the residue was chromatographed on a silica-gel column using a mixture of chloroform and acetone (10:1 v/v) as the eluent. The first fraction gave bicyclo compound **22** and the second one gave the spiro compound **23** in a 32% yield. **22**: Yield 54%, syrup. IR (KBr): 1680 (CO) cm^{-1}. NMR ($CDCl_3$): δ=1.3—1.9 (m, 2H, $-CH_2-$), 2.16 (dd, 2H, $-CH_2-$, J=5.0, 7.5 Hz), 2.95 (s, 3H, $N-CH_3$), 3.32 (s, 3H, OCH_3), 3.3—4.0 (m, 2H, $-OCH_2-$), 5.07 (s, 1H, $-C\underline{H}-OCH_2-$, 3-H). Found: N, 9.20%. Calcd for $C_{16}H_{20}N_2O_4$: N, 8.98%.

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