The Synthesis and Reaction of Spiro[oxolane-2,2′-piperazine]-3′,6′-diones with *N*-Bromosuccinimide in the Presence or Absence of Water

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The compound 3-(3-hydroxy)propylidene-piperazine-2,5-dione, derived from ethyl 4-ethoxycarbonyl-2-chloroacetylamino-2-butenoate, was treated with *N*-bromosuccinimide (NBS) in chloroform to give the spiro-[oxolane-2,2′-piperazine]-3′,6′-dione derivative. The spiro compound was further treated with NBS in water to give the corresponding spiro[oxolane-2,2′-piperazine]-3′,5′,6′-trione and -3′,6′-dione-5′-ol. The latter compound and a new spiro-5′,6′-dione-3′-ol derivative were also obtained by the reduction of the spiro-3′,5′,6′-trione. The structural confirmation of all the new products is discussed.

Bicyclomycin, which has been produced by *Streptomyces (St.) sapporonensis*[1] and *St. aizunenensis*,[2] was degraded with various acids by heating to give the dispiropiperazinedione derivatives.[3] Although the total synthesis of bicyclomycin is very attractive and much attention has by now been devoted to the bioactivity, the chemistry of the degradation products, spiro- or dispiro-piperazinedione derivatives, are also very interesting. There have been a few reports on the synthesis of the spiro derivatives by three routes,[3–5] but the synthesis and the reaction have not been investigated in detail.

Previously, we reported briefly the synthesis of 3-(3-hydroxy)propylidene-piperazine-2,5-dione (**3a**) and its conversion into the corresponding spiro[oxolane-2,2′-piperazine]-3′,6′-dione {[oxolane-2,2′-piperazine]-3′,6′-dione=PDO} derivatives.[6] Here, we wish to report in detail the synthesis of the various spiro-PDO derivatives by the reaction of **3a** with NBS, followed by the hydrogenolysis and further reaction with NBS, in water. Moreover, the structural confirmation of the spiro-PDO is discussed.

Results and Discussion

Synthesis of 3-Alkylidene-piperazine-2,5-dione. According to the method reported previously,[7] ethyl 4-ethoxycarbonyl-2-oxobutanoate was condensed with chloroacetamide in benzene in the presence of a mixture of $POCl_3$ and concentrated H_2SO_4 under reflux to give the starting ethyl 4-ethoxycarbonyl-(*Z*)-2-chloroacetylamino-2-butenoate (**1**) in a 57% yield. After the halogen-exchange reaction of **1** with potassium iodide,[8,9] the resulting 2-iodoacetylamino derivative was immediately cyclized with benzylamine to give 1-benzyl-3-(2-ethoxycarbonyl)ethylidene-piperazine-2,5-dione (**2**) in an 80% yield. By the usual method, the subsequent selective reduction of exocyclic 2-ethoxycarbonyl group of **2** with $LiAlH_4$ in THF was achieved to give the expected **3a** in a 60% yield.

In order to ascertain and to protect the 3-hydroxyl group, the **3a** compound was subjected to acylation and alkylation, followed by the addition of methanol to the exocyclic carbon-carbon double bond. The acetylation and the benzoylation of **3a** with acetic anhydride and with benzoyl chloride, in the usual ways, gave 1-benzyl-3-(3-acetoxy)- and -(3-benzoyloxy) propylidene-piperazine-2,5-diones (**3b** and **3c**) in 82 and 86% yields respectively. On the other hand, the alkylation of **3a** with 2,3-dihydropyrane gave 1-benzyl-3-(3-tetrahydropyrane-2-yloxy)propylidene-piperazine-2,5-dione (**3d**) in an 82% yield. Furthermore, the **3a**,**b**,**d** compounds thus obtained were treated with methanol in the presence of NBS to give the corresponding 1-benzyl-3-(1-bromo)alkyl-3-methoxy-piperazine-2,5-dione derivatives (**4a**,**b**,**d**) in *ca.* an 88% yield. Subsequently, the catalytic hydrogenolysis of **4b**,**d** with 10% Pd/C in the presence of triethylamine was carried out to give the corresponding 1-benzyl-3-alkyl-3-methyl-piperazine-2,5-dione derivatives (**5b**,**d**) in *ca.* a 78% yield.

The characteristic absorption of the IR spectra, the chemical shifts, and the coupling constants of **2** and **3** were assigned as is shown in Table 1. In the NMR spectra, the signals of the olefinic protons appeared in the δ 6.30 and δ 6.18—6.26 regions as a triplet, while the β-alkyl protons were shifted to the δ 3.26 and δ 2.40—2.64 regions. From the comparison of the NMR spectral data of **2** and **3** with that of the *E*-isomer of the α-dehydroamino acid ester and its cyclic dipeptide derivative prepared by us,[10] Compounds **1**, **2**, and **3** could be readily confirmed to have a *(Z)*- geometric structure. In addition, the IR and NMR spectral data of **4** and **5** are summarized in Table 2.

Synthesis of Spiro-PDO Derivatives. In order to synthesize the desired spiro-PDO derivatives, Compound **3a** was led to cyclization by the intramolecular addition of the 3-hydroxylpropylidene group to the exocyclic carbon-carbon double bond. The treatment of **3a** with NBS in chloroform gave a viscous syrup, which was found to consist of two stereoisomers. From the spectral data and the satisfactory elemental analysis of the two kinds of crystals separated, the new products were identified as 4′-benzyl-3-bromospiro-PDO (**6a** and **6b**) as diastereomers in an 86% total yield. The catalytic hydrogenolysis of each isomer with 10% Pd/C in methanol gave exactly the same crystals as these identified as 4′-benzyl-spiro-PDO (**7**) in a 91% yield from **6a** and in a 90% yield from **6b**. Subsequently, the prolonged catalytic redution of **7** for 24 h was found to give 1-benzyl-3-(3-hydroxy) propyl-

Table 1. 4-Benzyl-3-alkylidene-piperazine-2,5-dione derivatives (**2** and **3**)

Compd No.	Yield %	Mp θ_m/°C	Formula	Found (Calcd) (%) C	H	N	IR, $\tilde{\nu}$/cm^{-1} in KBr NH	C=C	NMR, δ in $CDCl_3$ -CH= (J_{Hz})	NH
2	79	131—132[a]	$C_{16}H_{18}N_2O_4$	63.74 (63.56	5.88 6.00	9.05 9.26)	3200,	1635	6.30 (7.5),	9.76
3a	60	130—131[b]	$C_{14}H_{16}N_2O_3$	64.66 (64.60	6.14 6.20	10.68 10.76)	3200,	1630	6.25 (8.0),	9.62
3b	82	127—128[c]	$C_{16}H_{18}N_2O_4$	63.56 (63.56	5.99 6.00	9.21 9.26)	3190,	1640	6.18 (8.0),	9.56
3c	86	146—147[c]	$C_{21}H_{20}N_2O_4$	69.32 (69.21	5.57 5.53	7.46 7.69)	3180,	1640	6.26 (8.0),	9.76
3d	83	90— 91[d]	$C_{19}H_{24}N_2O_4$	66.20 (66.26	7.14 7.02	8.13 8.13)	3230,	1620	6.25 (8.0),	9.22

a) Colorless needles from ethanol. b) Colorless prisms from ethyl acetate. c) Colorless needles from ethyl acetate. d) Colorless needles from dibutyl ether.

Table 2. 3-Alkyl-4-benzyl-piperazine-2,5-dione derivatives (**4** and **5**)

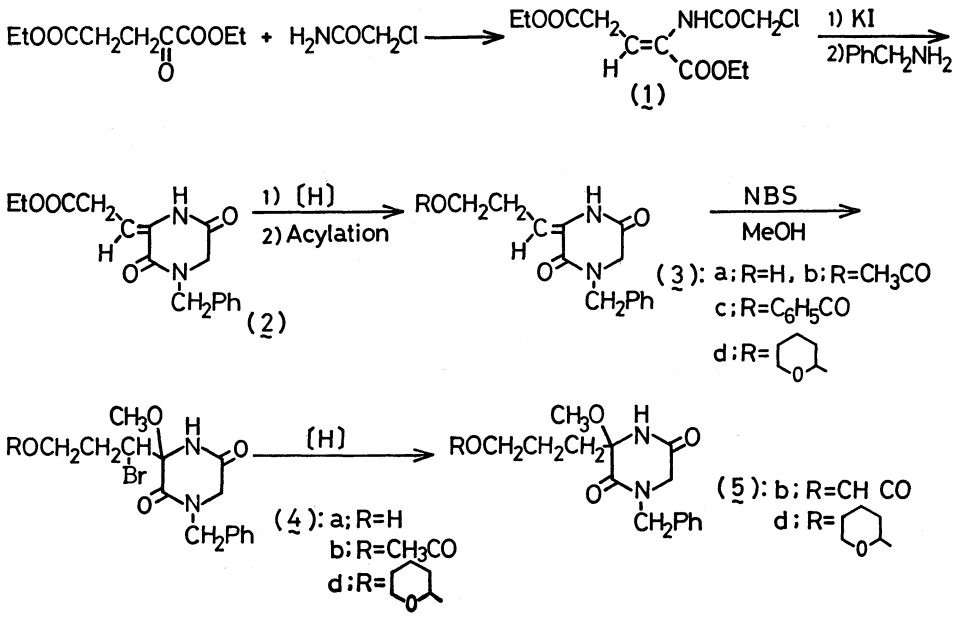
Compd No.	Yield %	Mp θ_m/°C	Formula	Found (Calcd) (%) C	H	N	IR, $\tilde{\nu}$/cm^{-1} [d] NH (OH)	NMR, δ in $CDCl_3$ -CH- (-CH_2-) (J_{Hz})	NH
4a	85	173—174[a]	$C_{15}H_{19}N_2O_4Br$	48.63 (48.53	5.06 5.16	7.61 7.55)	3170 (3380)	4.70 dd (2.0, 11.0)	9.05
4b	96	syrup	$C_{17}H_{21}N_2O_5Br$	49.71 (49.40	4.98 5.12	6.89 6.78)	3200	4.60 m	8.24
4d	81	syrup	$C_{20}H_{27}N_2O_5Br$	52.98 (52.75	6.11 5.98	6.35 6.15)	3200	4.82 m	8.04 8.11
5b	94	syrup	$C_{17}H_{22}N_2O_5$	61.32 (61.06	6.85 6·63	8.13 8.38)	3200	(1.6—2.3)[b]	8.00
5c	87	syrup	$C_{20}H_{28}N_2O_5$	64.02 (63.81	7.38 7.50	7.74 7.44)	3200	(1.4—2.3)[c]	7.90

a) Colorless needles from methanol. b) 4H. c) 10H. d) Measured in KBr.

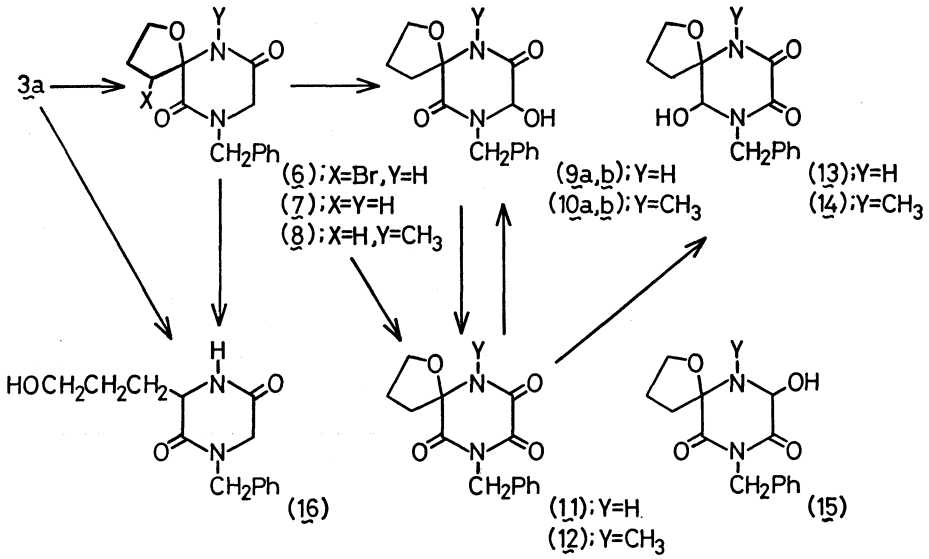
Table 3. 4′-Benzylspiro[oxolane-2,2′-piperazine]-3′,6′-dione derivatives (**6—14**)

Compd No.	Yield %	Mp θ_m/°C	Formula	Found (Calcd) (%) C	H	N	IR, $\tilde{\nu}$/cm^{-1} [e] NH OH	NMR, δ in $CDCl_3$ -CHBr- [-CHOH-] (J_{Hz})	OH
6a	61	142—143	$C_{14}H_{15}N_2O_3Br$	49.49 (49.57	4.39 4.46	8.24 8.26)	3270	5.05 dd (7.5, 8.0)	
6b	25	150—151	$C_{14}H_{15}N_2O_3Br$	49.56 (49.57	4.50 4.46	8.17 8.26)	3180	4.28 dd (3.0, 9.5)	
7	91[a] 90[b]	94—95	$C_{14}H_{16}N_2O_3$	64.51 (64.60	6.25 6.20	10.59 10.76)	3200	—	
8	80	68—69	$C_{15}H_{18}N_2O_3$	65.74 (65.67	6.62 6.61	10.12 10.21)	—	—	
9a	56	139—140	$C_{14}H_{16}N_2O_3$	60.69 (60.86	5.79 5.84	10.03 10.14)	3230	[4.86 dd] (1.0, 11.0)	4.50 d
9b	9	135—136	$C_{14}H_{16}N_2O_4$	60.98 (60.86	5.88 5.84	9.92 10.14)	3220	[5.07 d] (4.0)	5.15 d
10a	20[c] 19[d]	134—135	$C_{15}H_{18}N_2O_4$	62.02 (62.05	6.28 6.25	9.68 9.65)	3130	[4.93 d] (9.0)	4.83 d
10b	28	123—124	$C_{15}H_{18}N_2O_4$	62.03 (62.05	6.25 6.25	9.42 9.65)	3270	[4.98 d] (5.0)	6.41 d
11	34	156—157	$C_{14}H_{14}N_2O_4$	61.22 (61.31	5.13 5.15	9.93 10.21)	3230	—	
12	40	129—130	$C_{15}H_{16}N_2O_4$	62.70 (62.49	5.61 5.59	9.73 9.72)	—	—	
13	86	209—210	$C_{14}H_{16}N_2O_4$	60.52 (60.86	5.80 5.84	10.07 10.14)	3350	[4.58 d] (7.0)	7.00 d
14	68	222—223	$C_{15}H_{18}N_2O_4$	62.17 (62.05	6.24 6.25	9.48 9.65)	3300	[4.60 d] (6.0)	6.63 d

a) Yield from **6a**. b) Yield from **6b**. c) Yield from **8**. d) Yield from **12**. e) Measured in KBr.



Scheme 1.



Scheme 2.

piperazine-2,5-dione (**16**) in a 64% yield, by the carbon-oxygen bond fission of the spiro ring. Compound **16** was entirely in agreement with the product prepared independently by the hydrogenation of **3a** with 10% Pd/C.

When Compound **7** was further treated with NBS in a mixture of water and chloroform, three kinds of products were obtained in fairly good yields. Based on the NMR spectral data, the compound from the first fraction was confirmed to be 4′-benzyl-spiro [oxolane-2,2′-piperazine]-3′,5′,6′-trione (**11**) in a 31% yield; the other two kinds of compounds, which were stereoisomers with each other, were obtained from the second and the final fractions in 51% and 10% yields respectively. The two stereoisomers separated were also characterized as 4′-benzyl-spiro[oxolane-2,2′-piperazine]-3′,6′-dione-5′-ol (**9a** and **9b**).

In order to generalize the above reactions, after the methylation of the 1′-position of **7** with methyl iodide, according to a method previously reported by us,[9] the resulting 4′-benzyl-1′-methylspiro-PDO (**8**) was similarly treated with NBS in water. The expected corresponding 1′-methylspiro-3′,5′,6′-trione derivative (**12**) was obtained in a 40% yield, while 1′-methylspiro-3′,6′-dione-5′-ol derivatives (**10a** and **10b**) as diastereomers were also obtained in 20 and 28% yields respectively. The subsequent reduction of the 1′-methyl trione derivative (**12**) with $NaBH_4$ in methanol was carried out to give another new compound (**14**) with **10a** in a 19% yield. Moreover, the similar reduction of **11** was worked up to also give a new compound (**13**) alone.

The structural assignment and the conformational analysis of **6**—**13** and **14** have also been elucidated

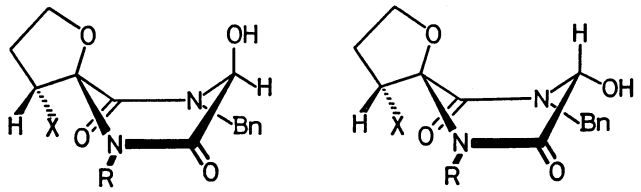


Fig. 1.

from their spectroscopic data and satisfactory elemental analyses (see Table 3). Consequently, the two new compounds could be readily identified as 4′-benzyl- and 4′-benzyl-1′-methylspiro[oxolane-2,2′-piperazine]-5′,6′-dione-3′-ol (**13** and **14**) in 86 and 68% yields respectively, not the spiro[oxolane-2,2′-piperazine]-3′,5′-dione-6′-ol derivative (**15**).

In the NMR spectrum of **6**, the chemical shift of the 3-proton on the spiro ring is in the δ 5.05 (**6a**; J=7.5 Hz) and δ 4.28 (**6b**; J=3.0 Hz, J=7.5 Hz) regions as a double doublet. On the other hand, the 3-proton signals on the spiro ring of **7**, derived from both **6a** and **6b**, also appeared in the δ 2.7—3.1 and δ 1.7—2.3 regions as splitting multiplets. This fact indicates that the spiro-PDO structure is maintained during the hydrogenolysis. From the above results, it may be supposed that one proton of the 3-position on the spiro ring of **6a** and **7** resonating in the lower magnetic field is due to the coplanar interaction between the 3-proton and the 3′-carbonyl groups on the boat structural piperazine-2,5-dione ring. Accordingly, it is assumed that all the spiro compounds obtained here have the boat structure, as is illustrated in Fig. 1. In fact, the Dreiding model of the spiro-PDO structure and the following facts further support the above presumption. In addition, the NMR spectrum of **9a** showed a long-range coupling at δ 4.86 (6-H, $J_{4,6}$=1.0 Hz, $J_{6,OH}$=11.0 Hz) as a double doublet, due to the *W*-letter relationship between two protons at the 3- and 5′-positions. On the other hand, in the NMR spectrum of **9b**, the signal at δ 5.05 (6-H, $J_{6,OH}$= 4.0Hz), appearing as only a doublet, is attributable to the two protons between 5′-H and the hydroxyl group. By a comparison of the chemical shifts and the coupling constants, the orientation of the hydroxyl group of **9a** appearing at an upper magnetic field was determined to be axial and that of **9b** at a lower field, to be equatorial, as is illustrated in Fig. 1. Similarly, based on the above results, the orientation of the hydroxyl group of **10a** appearing at a comparatively high field (δ 4.93, d, J=9.0 Hz) was also confirmed to be axial, and that of **10b** at a lower field (δ 4.94, d, J=6.0 Hz and J=7.0 Hz), to be equatorial. Furthermore, since the NMR spectrum of **13** showed a long-range coupling (J=1.0Hz) at δ 4.58 between 3′- and 1′-protons, the orientation of the hydroxyl group at the 3′-position could be unambiguously inferred to be axial.

Consequently, even if the spiro-PDO derivatives were transformed to the piperazine-3′,5′,6′-trione and -3′,6′-dione-5′-ol, the spiro and the boat conformational structures were found to be maintained.

Experimental

All the melting and boiling 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 the internal standard.

Starting Material. Compound **1** was prepared by the condensation of ethyl 4-ethoxycarbonyl-2-oxobutanoate (70 g, 347 mmol) with chloroacetamide (36 g, 385 mmol) in the presence of $POCl_3$ (7 ml) and concentrated H_2SO_4 (3 ml), according to the method reported previously.[7] Yield, 57%; bp 162—164 °C/2 mmHg (1 mmHg≈133.322 Pa). IR (KBr): 3280, 1730, 1690, 1515 cm^{-1}. NMR ($CDCl_3$): δ 6.94 t, 7.36 t (-CH=, J=7.0 Hz), 8.28 and 8.68 (NH), Found: C, 47.78; H, 6.02; N, 4.88%. Calcd for $C_{11}H_{16}NO_5Cl$: C, 47.57; H, 5.81; N, 5.04%.

Preparation of 2. After the halogen exchange of **1** (3.0 g, 10.81 mmol) with potassium iodide,[8,9] into the resulting solution in ethanol (40 ml), we stirred benzylamine (2.9 g, 27.03 mmol) in, drop by drop, at room temperature for 2 h. The crystals thus precipitated were collected and recrystallized from ethanol to give **2** as colorless needles.

Preparation of 3a. Into a mixture of $LiAlH_4$ (200 mg, 5.3 mmol) in THF (30 ml), we stirred a solution of **2** (1.0 g, 3.3 mmol) in THF (30 ml) at −10 °C. After treating the excess $LiAlH_4$ in the solution with 1 M HCl (1M= 1 mol dm^{-3}), the insoluble substance was filtered off, and then the filtrate was concentrated. The crude residual syrup was purified on a silica-gel column, using a mixture of $CHCl_3$ and ethanol (30 : 1 v/v) as the eluent. After the eluted fraction had been concentrated, the crystalline residue was recrystallized from ethyl acetate to give **3a** as colorless prisms.

Preparation of 3b—d. Into a solution of **3a** (200 mg, 0.769 mmol) in pyridine (3 ml), we stirred acetic anhydride (100 mg, 0.980 mmol) at room temperature for 3 h. The resulting solution was poured into CH_2Cl_2 (30 ml) and washed successively with 3 M HCl and water, and then dried over anhydrous Na_2SO_4. The removal of the solvent gave crude crystals, which were recrystallized from ethyl acetate to give **3b** as colorless needles.

In a similar manner, a solution of **3a** (1.0 g, 3.85 mmol) and benzoyl chloride (650 mg, 4.62 mmol) in pyridine (3 ml) was worked up under cooling for 1 h to give crystals. The subsequent recrystallization of the crystals from ethyl acetate gave **3c** as colorless needles.

Similarly, a mixture of **3a** (520 mg, 2.0 mmol), 3,4-dihydro-2*H*-pyran (346 mg, 4.0 ml), and *p*-toluenesulfonic acid (4 mg) in CH_2Cl_2 (10 ml) was worked up at room temperature for 6 h to give crystals. Recrystallization from dibutyl ether gave **3d** as colorless needles.

Preparation of 4a, 4b, and 4d. Into a solution of **3d** (770 mg, 2.23 mmol) in methanol (30 ml), we stirred NBS (438 mg, 2.46 mmol) at room temperature for 10 min. The subsequent removal of the solvent gave crude crystals, which were collected and then washed with water. The recrystallization of the crystals from methanol gave **4a** as colorless needles.

In a similar manner, a mixture of **3b** (1.6 g, 5.30 mmol) and NBS (943 mg, 530 mmol) in methanol (40 ml) was worked up to give a syrupy residue. The residue was dissolved in $CHCl_3$ (30 ml), and the resulting solution was washed twice with water and then dried over anhydrous Na_2SO_4. The removal of the solvent gave a viscous oil,

which was purified on a silica-gel column, using a mixture of $CHCl_3$ and acetone (20 : 1 v/v), to give **4b** as a viscous syrup.

Similarly, a mixture of **3d** (600 mg, 1.74 mmol) and NBS (310 mg, 1.74 mmol) in methanol (30 ml) gave **4c** as a viscous syrup.

*Preparation of **5b** and **5c**.* A solution of **4b** (1.9 g, 4.60 mmol) in methanol (50 ml) in the presence of triethylamine (500 mg, 4.95 mmol) was hydrogenolyzed with 10% Pd/C (200 mg) at room temperature for 15 min. After the Pd/C had been filtered off, the resulting solution was concentrated to give residual syrupy crystals, which were dissolved in CH_2Cl_2 (50 ml). The solution was washed twice with water and then dried over anhydrous Na_2SO_4. After the removal of the solvent, the residual oil was purified on a silica-gel column, using a mixture of $CHCl_3$ and acetone (15 : 1 v/v) as the eluent. The fraction thus obtained was concentrated to give **5b** as a viscous syrup.

In a similar manner, a solution of **4d** (900 mg, 1.98 mmol) and potassium *t*-butoxide (244 mg, 2.18 mmol) in methanol (50 ml) was worked up to give **5d** as a viscous syrup.

*Preparation of **6**.* Into a solution of **3a** (800 mg, 3.08 mmol) in $CHCl_3$ (20 ml), we stirred NBS (548 mg, 3.08 mmol) at room temperature for 10 min. The resulting solution was washed twice with water, dried over anhydrous Na_2SO_4, and then concentrated. The residual syrup thus obtained was chromatographed on a silica-gel column, using a mixture of $CHCl_3$ and acetone (25 : 1 v/v) as the eluent. From the two fractions thus separated, two diastereomeric isomers, **6a**,**b**, were obtained. The first fraction was concentrated to give crude crystals, which were then recrystallized from ethanol to give **6a** as colorless needles. Similarly, the second fraction gave **6b** as colorless needles from benzene.

*Preparation of **7**.* A solution of **6a** and **6b** (560 mg, 1.65 mmol) in methanol (50 ml) in the presence of triethylamine (170 mg, 1.68 mmol) was hydrogenolyzed with 10% Pd/C (60 mg) at room temperature for 20 min. After the removal of the Pd/C, the reaction solution was concentrated and the residue thus obtained was dissolved in CH_2Cl_2 (20 ml). The resulting solution was washed twice with water and then dried over anhydrous Na_2SO_4. The evaporation of CH_2Cl_2 gave crystals, which were subsequently recrystallized from diethyl ether to give **7** as colorless needles.

*Preparation of **8**.* Into a solution of **7** (500 mg, 1.92 mmol) in THF (20 ml), we stirred 55% NaH (84 mg, 1.92 mmol) at room temperature. After the evolution of hydrogen had ceased in a few minutes, we stirred methyl iodide into the resulting solution at room temperature for 6 h. The reaction solution was neutralized with acetic acid and then concentrated. The residue thus obtained was dissolved in $CHCl_3$ (30 ml), and the resulting solution was washed with water and then dried over anhydrous Na_2SO_4. After the removal of the $CHCl_3$, the residue was purified on a silica-gel column, using a mixture of $CHCl_3$ and acetone (15 : 1 v/v) as the eluent. The concentration of the fraction gave crystals, which were subsequently recrystallized from diethyl ether to give **8** as colorless needles.

*Preparation of **9** and **11**.* Into a solution of **7** (1.0 g, 3.85 mmol) in $CHCl_3$ (30 ml) and water (3 ml), we stirred NBS (690 mg, 3.85 mmol) at room temperature for 3 h. The $CHCl_3$ layer was separated, washed with water, and finally dried over anhydrous Na_2SO_4. After the removal of the $CHCl_3$, the residue was chromatographed on a silica-gel column, using a mixture of $CHCl_3$ and acetone (15 : 1 v/v) as the eluent. Three fractions were obtained, and then each fraction was concentrated. The first fraction gave **11** as colorless prisms from a mixture of benzene and hexane, while the second and third fractions gave **9a** as colorless needles from CCl_4 and **9b** as colorless prisms from benzene respectively.

*Preparation of **10** and **12**.* In a similar manner, the treatment of **8** (820 mg, 2.99 mmol) in a mixture of $CHCl_3$ (30 ml) and water (5 ml) with bromine (580 mg, 3.62mmol) was worked up for 6 h to give three fractions. The first fraction gave colorless needles **12** from a mixture of benzene and hexane. The second and the third fractions gave colorless needles **10a** and **10b** from benzene-hexane.

Moreover, similarly, in the case of the reaction of **8** (1.35 g, 4.93 mmol) with *ca.* two moles of NBS (1.8 g). Compound **12** alone was obtained in *ca.* a 92% yield.

*Reduction of **11**.* Into a mixture of **11** (1.2 g, 4.17 mmol) in methanol (50 ml), we stirred $NaBH_4$ (160 mg, 4.21 mmol), portion by portion, under cooling for 10 min. After a few drops of acetic acid had been added and the methanol evaporated, the residue thus obtained was chromatographed on a silica-gel column, using a mixture of $CHCl_3$ and ethanol (15 : 1 v/v) as the eluent. From the first fraction, Compound **9a** was obtained, while the second fraction gave **13** as colorless prisms from ethanol.

*Reduction of **12**.* A similar hydrogenation of **12** was worked up to give **10a** and **14**.

*Preparation of **16**.* *From **7***: The catalytic reduction of **7** (360 mg, 1.38 mmol) with 10% Pd/C (70 mg) in methanol (50 ml) at room temperature overnight, and the concentration of the resulting solution, gave **16** as colorless needles from ethyl acetate. Yield, 64%; mp 103—104 °C. IR (KBr): 3500, 3200, 1670, 1640 cm^{-1}. NMR ($CDCl_3$): δ 1.4—1.2 m (-CH_2-, 4H), 4.10 m (3-H), 3.82 (OH), 8.12 (NH). Found: C, 64.20; H, 6.99; N, 10.58%. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68%.

*From **3a***: In a similar manner, the reduction of **3a** (500 mg, 1.93 mmol) with 10% Pd/C (50 mg) in methanol (50 mg) was worked up for 20 min to give **16** in a 93% yield.

References

1) T. Miyoshi, N. Miyairi, H. Aoki, M. Kohsaka, H. Sakai, and H. Imanaka, *J. Antibiot.*, **25**, 569 (1972).

2) S. Miyamura, N. Ogasawara, H. Otsuka, S. Niwayama, H. Tanaka, T. Take, T. Uchiyama, H. Ochiai, K. Abe, K. Koizumi, K. Asao, K. Mitsuki, and T. Hoshino, *J. Antibiot.*, **25**, 610 (1972); S. Miyamura, N. Ogasawara, H. Otsuka, S. Niwayama, H. Tanaka, T. Take, T. Uchiyama, and H. Ochiai, *ibid.*, **26**, 479 (1973).

3) H. Maag, J. F. Blount, D. L. Coffen, T. V. Steppe, and F. Wong, *J. Am. Chem. Soc.*, **100**, 6786 (1978).

4) S. Nakatsuka, K. Yoshida, and T. Goto, *Tetrahedron Lett.*, **22**, 2009 (1981).

5) T. Fukuyama, B. D. Robins, and R. A. Sachleben, *Tetrahedron Lett.*, **22**, 4155 (1981).

6) C. Shin, Y. Sato, and J. Yoshimura, *Tetrahedron Lett.*, **22**, 2401 (1981).

7) C. Shin, M. Fujii, and J. Yoshimura, *Tetrahedron Lett.*, **1971**, 2499; C. Shin, K. Sato, A. Ohtsuka, K. Mikami, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **46**, 3876 (1973).

8) C. Shin, Y. Sato, H. Ohmatsu, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **54**, 1137 (1981).

9) C. Shin, Y. Sato, M. Hayakawa, M. Kondo, and J. Yoshimura, *Heterocycles*, **16**, 1573 (1981).

10) C. Shin, M. Hayakawa, T. Suzuki, A. Ohtsuka, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **51**, 550 (1978).