Molecular Structure and Two-Dimensional NMR Spectral Assignment of 2,14-Dimethyl-8aβ-hydroxy-7,10-dioxo-5β,6β-(propano)-6α,8α-(ethanoimino)-trans-perhydroisoquinoline

Shunsaku Shiotani* and Hiroyuki Morita

College of Liberal Arts, University of Toyama, Gofuku 3190,
Toyama 930, Japan

Toshimasa Ishida and Yasuko In

Osaka University of Pharmaceutical Sciences, Kawai 2-10-65, Matsubara,
Osaka 580, Japan

Hitoshi Tatemitsu

The Institute for Scientific and Industrial Research, Osaka University, Ibaraki,
Osaka 567, Japan
Received November 3, 1987

This paper reports the two-dimensional nmr spectral assignment and the X-ray structural determination of 2,14-dimethyl-8aβ-hydroxy-7,10-dioxo-5β,6β-(propano)-6α,8α-(ethanoimino)-trans-perhydroisoquinoline **V** which was obtained from 7,10-dimethyl-2β-hydroxy-14-oxo-2,3-(methanoiminoethano)-3β,4β-(propano)-3,4,5,6,7,8-hexahydro-2H-pyrano[2,3-c]pyridine **IV** by isomerization with hydrochloric acid. Both the compounds **IV** and **V** afforded the same dimethiodide **IV**-2MeI, while the configurational isomer 2,14-dimethyl-8aβ-hydroxy-7,10-dioxo-5α,6β-(propano)-6α,8α-(ethanoimino)-trans-perhydroisoquinoline **III** gave monomethiodide **III**-MeI. The structures of these methiodides were also confirmed by X-ray analysis.

In a recent paper [1], we reported that 6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine afforded, by refluxing with hydrochloric acid, a mixture of several compounds from which four dimerized products, 2,9-dimethyl-1,2,3,4,7,8,9,-10-octahydropyrido[4',3':4,5]furo[3,2-h]isoquinoline (**I**), 3,10-dimethyl-1,2,3,4,8,9,10,11-octahydropyrido[4',3':4,5]-furo[2,3-h]isoquinoline (**II**), 2,14-dimethyl-8aβ-hydroxy-7,10-dioxo-5α,6β-(propano)-6α,8α-(ethanoimino)-trans-perhydroisoquinoline (**III**) and 7,10-dimethyl-2β-hydroxy-14-oxo-2,3-(methanoiminoethano)-3β,4β-(propano)-3,4,5,6,-7,8-hexahydro-2H-pyrano[2,3-c]pyridine (**IV**) were isolated (Chart 1). Among these, the hemiketal compound, **IV**, was expected to be hydrolyzed and recyclized to give an aldol

reaction product **V** through the triketonic intermediate, **IV'**, in aqueous acidic solution. In this paper we report the isomerization of **IV** to **V**, confirmation of the structure of **V** and further stereochemistry of the methiodides of **III**, **IV** and **V**.

Thus, compound **IV** was refluxed with 10% hydrochloric acid for 30 hours. From the reaction mixture a new compound **V**, mp 185-187°, was isolated in 20% yield accompanying recovery of **IV** in 70% yield by column chromatography on silica gel. The elemental analysis and mass spectrum indicated compound **V** to have the molecular formula $C_{16}H_{24}N_2O_3$ (identical to that of compound **III**). The ir spectrum of **V** exhibited an absorption
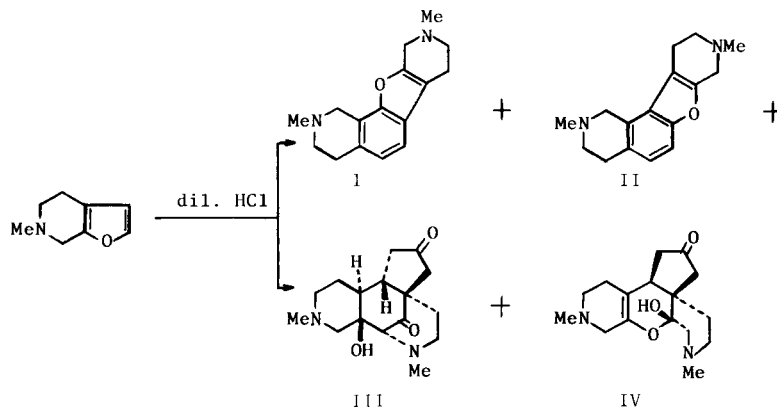

Chart 1

Table I

^{13}C NMR Data for Compound V

Carbon	Chemical shift
C-4	25.611 (t)
C-4a	33.076 (d)
C-12	36.503 (t)
C-9	40.689 (t)
N-Me	45.967 (q)
C-11	46.057 (t)
N'-Me	47.265 (q)
C-13	50.570 (t)
C-6	51.282 (s)
C-5	52.745 (d)
C-3	55.451 (t)
C-1	64.573 (t)
C-8	76.856 (d)
C-8a	79.263 (s)
C=O	210.413 (s)
C=O	215.024 (s)

δ Values in deuteriochloroform. The multiplicities of carbon signals are indicated as, s, d, t and q.

for a hydroxyl group at 3450 cm^{-1} and carbonyl, at 1730 and 1720 cm^{-1}. The ^{1}H nmr spectrum exhibited only resonances of strongly coupled aliphatic proton systems which could not be analyzed even at 400 MHz. The ^{13}C

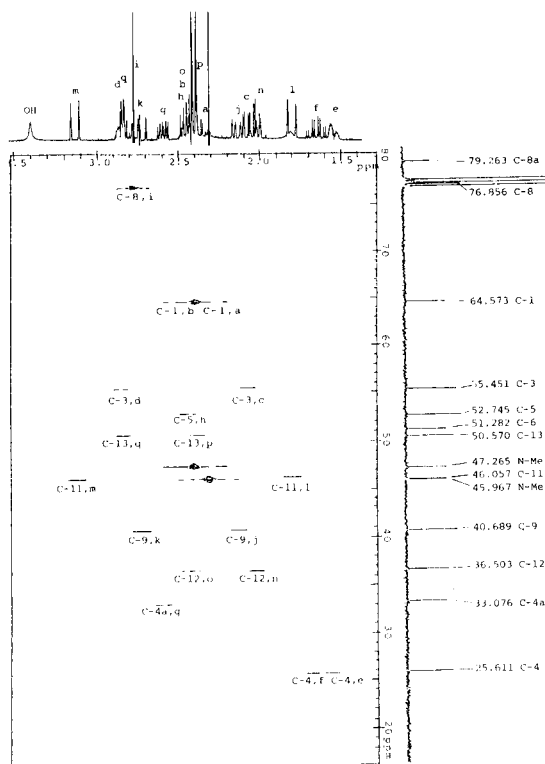nmr spectrum (Table I) showed signals of two carbonyl, two N-methyl, two quaternary, three methine and seven methylene carbons. These data suggested that the compound V could possess a structure resembling that of III. However, the correct structure could not be assigned unless the complex spin systems could be analyzed.

With availability of homonuclear and heteronuclear two-dimensional chemical shift correlation, techniques and data were obtained to assign the structure of V [2]. The heteronuclear shift correlated spectrum (Figure 1) established the carbon-proton connectivity and the unambiguous assignment of the carbon spectrum [3]. The homonuclear shift correlated two-dimensional spectrum (Figure 2) allowed the complex proton-proton coupling network to be analyzed [4].
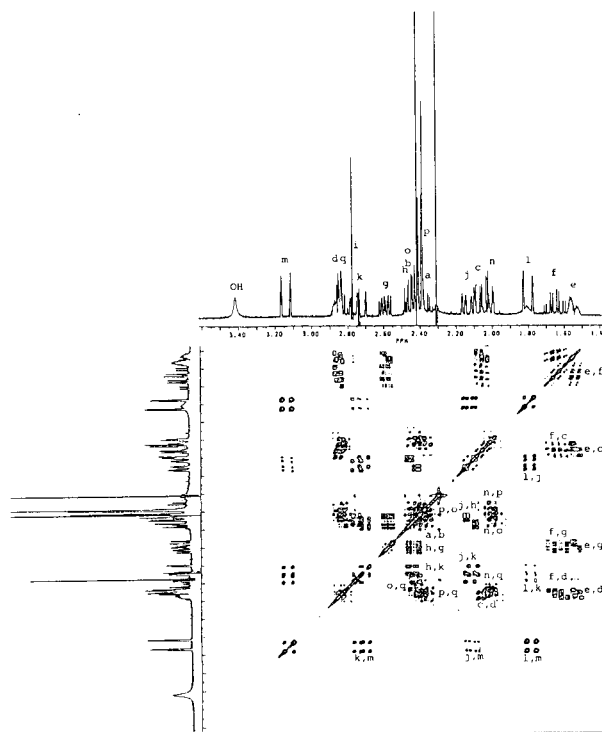

Figure 2. Two-dimensional (360 MHz) homonuclear shift-correlated spectrum of compound V in deuteriochloroform.

The homonuclear spectrum shows that the proton H$_m$ (3.14 ppm) at the furthest downfield couples with the proton H$_l$ (1.81 ppm), which are apparently the geminal protons on the carbon C-11 (46.057 ppm). The chemical shift of C-11 and the coupling pattern of H$_l$ and H$_m$ indicate the methylene carbon is connected with a carbonyl carbon and a quarternary carbon. Judging from the large difference in chemical shift of H$_l$ and H$_m$, the proton H$_m$ should be located in a position greatly deshielded by anisotropic effect of another carbonyl group. The methylene protons H$_l$

Figure 1. Two-dimensional heteronuclear shift-correlated spectrum of compound V [360 (^{1}H) and 90.5 (^{13}C) MHz] in deuteriochloroform (upfield resonances only).

Table II

^{1}H NMR Data for Compound **V**

Proton	Chemical shift	Coupling constants
H_e (m)	1.55	$J_{ef} = 12.8$
H_f (dq)	1.65	$J_{fe} = J_{fc} = J_{fg} = 12.8$, $J_{fd} = 4.5$
H_l (dd)	1.81	$J_{lm} = 18.3$, $J_{lk} = 1.0$
H_n (m)	2.01	
H_c (ddd)	2.07	$J_{cf} = 12.8$, $J_{cd} = 11.3$, $J_{ce} = 3.3$
H_j (ddd)	2.13	$J_{jk} = 18.3$, $J_{jh} = 7.2$, $J_{jm} = 0.5$
N-Me (s)	2.31	
H_a		
H_p (m)		
H_o (m)		2.34-2.48 overlapped
N'-Me (s)	2.42	
H_b		
H_h (m)	2.45	
H_g (ddd)	2.59	$J_{ge} = 4.3$, $J_{gf} = 12.8$, $J_{gh} = 5.8$
H_k (ddd)	2.74	$J_{kj} = 18.3$, $J_{kh} = 13.6$, $J_{kl} = 1.0$
H_i (s)	2.78	
H_q (m)		2.80-2.88 overlapped
H_d (m)	2.86	
H_m (dt)	3.14	$J_{ml} = 18.3$, $J_{mj} = J_{mk} = 0.5$
OH (bs)	3.42	

δ Values in deuteriochloroform and coupling constants in Hz.

and H_m also couple with the protons H_j (2.13 ppm) and H_k (2.74 ppm) respectively through long range coupling which are attached to the carbon C-9 (40.689 ppm). The cross peaks of H_j and H_k indicate that these methylene protons are correlated to the proton H_h (2.45 ppm) whose signal is masked by multiplets of other protons. The heteronuclear spectrum shows the proton H_h is attached to the carbon C-5 (52.745 ppm). The correlation of H_h with another proton, H_g (2.59 ppm), is shown by the cross peaks of H_h in the homonuclear spectrum. The proton H_g is assigned to the methine proton connecting to the carbon C-4a (33.076 ppm), which in turn leads to the assignment of H_e (1.55 ppm), H_f (1.65 ppm), H_c (2.07 ppm) and H_d (2.86 ppm); the former two connecting to the carbon C-4 (25.611 ppm) and the latter two to the carbon C-3 (55.451 ppm), respectively, as evidenced by the cross peaks indicating the coupling between these protons. The chemical shifts of C-3 and C-9 suggests that C-3 connects to an amine-nitrogen and C-9 to a carbonyl carbon.

Though the signals of H_n, H_o, H_p and H_q are overlapped with those of other protons and are difficult to assign completely, the cross peaks of homonuclear spectrum and the heteronuclear correlated spectrum indicate that H_n and H_o are attached to the carbon C-12 (36.503 ppm) and H_p and

Table III

Crystal Data and Intensity Collections for **V**, **III-MeI** and **IV-2MeI**

Compound	**V**	**III-MeI**	**IV-2MeI**
Formula	$C_{16}H_{24}N_2O_3$	$C_{17}H_{27}N_2O_3I$	$C_{18}H_{30}N_2O_3I_2 + \frac{1}{2}H_2O$
Mw	292.368	434.318	585.26
Crystal shape	plate	plate	plate
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1$
Cell constants			
a (Å)	10.209(5)	8.226(1)	9.427(10)
b (Å)	11.802(8)	18.323(3)	10.449(9)
c (Å)	12.769(6)	12.518(2)	12.913(13)
β (Å)	102.74(3)	103.87(1)	109.52(9)
V (Å^3)	1501(1)	1831.9(6)	1199(2)
z	4	4	2
D_x (g cm^{-1})	1.294	1.575	1.621
μ(CuKα) (cm^{-1})	6.859	140.0	209.9
Crystal size (mm)	0.5 x 0.4 x 0.4	0.3 x 0.3 x 0.2	0.3 x 0.3 x 0.2
T (°C)	20	20	20
Data range (deg)	2° < 2θ < 130°	2° < 2θ < 130°	
Scan speed (2θ) (deg min^{-1})	3	3	3
Scan range (θ) (deg)	1.3 + 0.15 tan	1.0 + 0.15 tan	1.9 + 0.15 tan
No of obsd data	2547	3104	2311
No of data with $|Fo| \neq 0.0$	2522	2735	2297
No of variables	279	317	227
Coeff used for refinement			
a	1.2057	0.0	0.0479
b	-0.3409	0.5297	0.3173
c	0.0220	0.0041	-0.0001
R	0.085	0.112	0.080
R_w	0.093	0.132	0.107
S (goodness of fit)	2.134	1.146	1.105

<div style="text-align:center">

Table IV

Atomic Parameters and Equivalent Isotropic Thermal Parameters
for Nonhydrogen Atoms in Compound **V**, **III**-MeI and **IV**-2MeI
(Estimated standard deviations are in parentheses)

</div>

Compound **V**

Atom	X	Y	Z	Beq*
N(2)	0.5206(2)	−0.0737(2)	0.8458(2)	2.91(8)
C(2M)	0.3896(3)	−0.1247(3)	0.8409(3)	4.3(1)
C(3)	0.5143(2)	0.0491(2)	0.8548(2)	3.2(1)
C(4)	0.6540(2)	0.1000(2)	0.8682(2)	2.8(1)
C(4a)	0.7184(2)	0.0655(2)	0.7754(2)	2.23(8)
C(5)	0.8561(2)	0.1183(2)	0.7808(2)	2.33(9)
C(6)	0.9276(2)	0.0727(2)	0.6924(2)	2.34(9)
C(7)	0.9169(2)	−0.0558(2)	0.6898(2)	2.51(9)
O(7)	1.0133(2)	−0.1186(2)	0.7035(2)	4.04(9)
C(8)	0.7738(2)	−0.0981(2)	0.6666(2)	2.49(9)
C(1)	0.5716(2)	−0.1077(2)	0.7523(2)	2.82(9)
O(8a)	0.8017(2)	−0.1192(1)	0.8531(1)	2.73(7)
C(8a)	0.7152(2)	−0.0645(2)	0.7636(2)	2.24(8)
N(14)	0.6967(2)	−0.0456(2)	0.5667(2)	3.00(8)
C(14M)	0.6171(3)	−0.1311(3)	0.4957(2)	4.5(1)
C(13)	0.7828(3)	0.0190(3)	0.5103(2)	3.7(2)
C(12)	0.8574(3)	0.1130(2)	0.5783(2)	3.2(1)
C(11)	1.0722(2)	0.1120(2)	0.7318(2)	2.9(1)
C(10)	1.0953(2)	0.1133(2)	0.8528(2)	2.76(9)
O(10)	1.2038(2)	0.1199(2)	0.9140(2)	3.97(9)
C(9)	0.9624(2)	0.1035(2)	0.8857(2)	2.9(1)

*Beq = $4/3(B_{11}a^2 + B_{22}b^2 + B_{33}c^2 + acB_{13}\cos\beta)$

Compound **III**-MeI

Atom	X	Y	Z	Beq*
C(4a)	0.760(1)	−0.1358(6)	0.1609(9)	1.9(4)
C(5)	0.645(2)	−0.1828(6)	0.0778(9)	2.3(4)
C(6)	0.491(1)	−0.2101(6)	0.1172(9)	2.1(4)
C(7)	0.403(2)	−0.1399(6)	0.134(1)	2.1(4)
C(8)	0.509(1)	−0.0957(6)	0.2297(9)	1.7(4)
C(8a)	0.664(1)	−0.0701(6)	0.1908(8)	1.9(4)
C(1)	0.781(2)	−0.0250(7)	0.2823(9)	2.4(4)
N(2)	0.935(1)	0.0000(6)	0.2501(7)	2.2(4)
C(3)	1.025(1)	−0.0626(7)	0.213(1)	2.6(5)
C(4)	0.911(2)	−0.1079(7)	0.123(1)	2.4(4)
C(9)	0.711(2)	−0.2512(7)	0.035(1)	2.7(5)
C(10)	0.556(2)	−0.2987(7)	−0.004(1)	2.8(5)
C(11)	0.404(2)	−0.2582(7)	0.022(1)	3.0(5)
C(12)	0.530(2)	−0.2526(7)	0.225(1)	2.9(5)
C(13)	0.481(2)	−0.2115(7)	0.318(1)	3.0(5)
N(14)	0.554(1)	−0.1376(6)	0.3333(8)	2.4(4)
O(7)	0.271(1)	−0.1181(5)	0.0783(8)	3.1(4)
O(8a)	0.604(1)	−0.0285(4)	0.0926(6)	2.3(3)
C(2M1)	0.905(2)	0.0613(8)	0.166(1)	3.5(6)
C(2M2)	1.051(2)	0.0303(8)	0.354(1)	3.4(5)
O(10)	0.552(2)	−0.3548(6)	−0.049(1)	4.7(5)
C(14M)	0.510(2)	−0.098(1)	0.423(1)	3.9(6)
I(15)	0.4245(1)	0.13197(5)	0.23583(7)	3.63(4)

*Beq = $4/3(B_{11}a^2 + B_{22}b^2 + B_{33}c^2 + acB_{13}\cos\beta)$

<div style="text-align:center">

Table IV (continued)

</div>

Compound **IV**-2MeI

Atom	X	Y	Z	Beq**
I(A)*	0.2105(1)	0.8801	0.49562(6)	3.23(5)
I(B)	0.2785(1)	0.3853(1)	0.12763(6)	4.20(5)
N(7)	0.8662(2)	0.4803(2)	0.8573(1)	2.6(4)
C(6)	0.8905(2)	0.3365(2)	0.8488(1)	2.6(5)
C(5)	0.7699(2)	0.2597(2)	0.8565(1)	3.4(7)
C(4a)	0.6151(2)	0.3132(2)	0.7832(1)	3.0(6)
C(8a)	0.5999(2)	0.4304(2)	0.7441(1)	2.1(5)
C(8)	0.7314(2)	0.5224(2)	0.7637(1)	2.3(5)
C(4)	0.4757(2)	0.2263(2)	0.7497(2)	3.1(6)
C(3)	0.3463(2)	0.2827(1)	0.6538(1)	1.7(4)
C(2)	0.3339(2)	0.4269(1)	0.6664(1)	2.3(5)
O(1)	0.4778(1)	0.4871(1)	0.6761(7)	1.7(3)
C(12)	0.3664(2)	0.2494(1)	0.5442(1)	1.8(5)
C(11)	0.2350(2)	0.3053(1)	0.4474(1)	2.2(5)
N(10)	0.2443(2)	0.4475(2)	0.4542(1)	3.3(6)
C(9)	0.2196(1)	0.4856(1)	0.5644(1)	1.7(4)
C(15)	0.4089(2)	0.2028(2)	0.8487(1)	3.3(7)
C(14)	0.2450(2)	0.1779(2)	0.7865(2)	3.4(7)
C(13)	0.2064(2)	0.2136(2)	0.6653(1)	2.5(6)
C(7M1)	1.0025(2)	0.5502(2)	0.8522(2)	4.0(8)
C(7M2)	0.8455(3)	0.5140(2)	0.9601(1)	3.9(8)
O(2)	0.2973(1)	0.4578(1)	0.7587(9)	2.8(4)
C(10M1)	0.3659(2)	0.5101(2)	0.4314(1)	2.6(6)
C(10M2)	0.0939(2)	0.4926(2)	0.3614(1)	2.8(6)
O(14)	0.1583(2)	0.1363(2)	0.8280(1)	4.7(6)

*The Y-coordinate of this atom was fixed in order to define the origin.
**Beq = $4/3(B_{11}a^2 + B_{22}b^2 + B_{33}c^2 + acB_{13}\cos\beta)$

H_q to the carbon C-13 (50.570 ppm) and couple with each others. Furthermore, it is evident that the methylene carbon C-1 (64.573 ppm) correlating with protons H_a and H_b is connected to an amine-nitrogen and a quarternary carbon. The chemical shift of the methine carbon at 76.856 ppm (C-8) and the coupling pattern of the singlet at 2.78 ppm (H_i), which is correlated to C-8, indicate that the carbon C-8 is connected to an amine-nitrogen, a carbonyl carbon and a quarternary carbon.

The large coupling constant between H_f and H_g (J = 12.8 Hz) suggests that both the vicinal protons are axial in a rigid piperidine ring. Therefore, this excludes the possibility of compound **V** to be a bicyclo[3.3.1]nonane structure in which C-4a is contained as a bridgehead carbon.
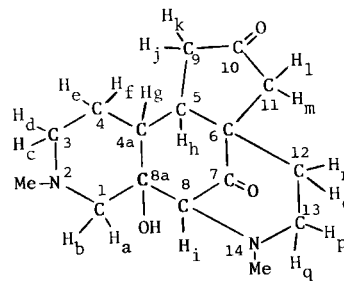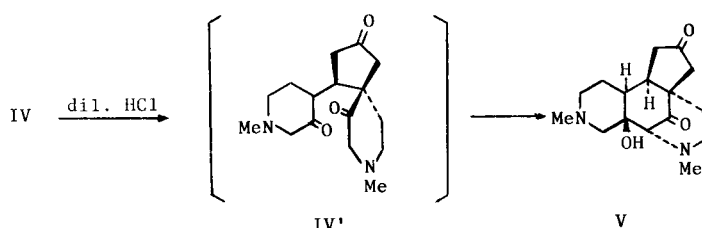

Figure 3

Chart 2

Table V

Bond Length (Å) in Compound **V**, **III**-MeI and **IV**-2MeI
(Estimated standard deviations are in parentheses)

Compound **V**

Bond	Length	Bond	Length
N(2)–C(2M)	1.455(4)	C(7)–O(7)	1.214(3)
N(2)–C(3)	1.456(4)	C(7)–C(8)	1.510(4)
N(2)–C(1)	1.459(3)	C(8)–C(8a)	1.541(3)
C(3)–C(4)	1.522(4)	C(8)–N(14)	1.480(3)
C(4)–C(4a)	1.531(3)	C(1)–C(8a)	1.529(3)
C(4a)–C(5)	1.526(3)	O(8a)–C(8a)	1.434(3)
C(4a)–C(8a)	1.542(3)	N(14)–C(14M)	1.475(4)
C(5)–C(6)	1.568(3)	N(14)–C(13)	1.467(4)
C(5)–C(9)	1.537(4)	C(13)–C(12)	1.508(4)
C(6)–C(7)	1.520(3)	C(11)–C(10)	1.511(4)
C(6)–C(12)	1.549(4)	C(10)–O(10)	1.208(3)
C(6)–C(11)	1.523(4)	C(10)–C(9)	1.511(4)

Compound **III**-MeI

Bond	Length	Bond	Length
C(4a)–C(5)	1.50(2)	C(8a)–O(8a)	1.43(1)
C(4a)–C(8a)	1.53(2)	C(1)–N(2)	1.50(2)
C(4a)–C(4)	1.52(2)	N(2)–C(3)	1.50(2)
C(5)–C(6)	1.55(2)	N(2)–C(2M1)	1.52(2)
C(5)–C(9)	1.51(2)	N(2)–C(2M2)	1.52(2)
C(6)–C(7)	1.52(2)	C(3)–C(4)	1.52(2)
C(6)–C(11)	1.52(2)	C(9)–C(10)	1.52(2)
C(6)–C(12)	1.53(2)	C(10)–C(11)	1.56(2)
C(7)–C(8)	1.53(2)	C(10)–O(10)	1.17(2)
C(7)–O(7)	1.20(2)	C(12)–C(13)	1.52(2)
C(8)–C(8a)	1.55(2)	C(13)–N(14)	1.47(2)
C(8)–N(14)	1.48(2)	N(14)–C(14M)	1.45(2)
C(8a)–C(1)	1.55(2)		

Compound **IV**-2MeI

Bond	Length	Bond	Length
N(7)–C(6)	1.528(2)	N(7)–C(8)	1.498(2)
N(7)–C(7M1)	1.498(3)	N(7)–C(7M2)	1.448(3)
C(6)–C(5)	1.422(3)	C(5)–C(4a)	1.556(3)
C(4a)–C(8a)	1.315(3)	C(4a)–C(4)	1.535(3)
C(8a)–C(8)	1.522(3)	C(8a)–O(1)	1.331(2)
C(4)–C(3)	1.535(3)	C(4)–C(15)	1.622(3)
C(3)–C(2)	1.524(3)	C(3)–C(12)	1.530(2)
C(3)–C(13)	1.553(2)	C(2)–O(1)	1.464(2)
C(2)–C(9)	1.524(3)	C(2)–O(2)	1.386(2)
C(12)–C(11)	1.552(2)	C(11)–N(10)	1.489(2)
N(10)–C(9)	1.568(2)	N(10)–C(10M1)	1.434(3)
N(10)–C(10M2)	1.591(3)	C(15)–C(14)	1.508(3)
C(14)–C(13)	1.531(3)	C(14)–O(14)	1.198(3)

On these bases, the sequence of carbon, nitrogen and oxygen atoms of compound **V** can be drawn as shown in Figure 3.

The steric problem was resolved as follows. It is apparent that the junction between ring B and D in compound **V** should be *cis* and same with that in compound **IV** [1]. The coupling pattern of the geminal protons H_e and H_f apparently indicates that the proton H_e is equatorial and the proton H_f axial in a rigid piperidine ring. It is well known that the signal of an axial proton appears at upper field than that of an equatorial in rigid six-membered ring. Examination with Dreiding model, however, revealed that the reversal in chemical shift of H_e and H_f can be interpreted by the Van der Waals interaction between H_f and H_k [5], when the junction of ring A and B is *trans* and the orientation of H_g and H_h is *cis*. Thus, the final structure of **V** was assigned to 2,14-dimethyl-8aβ-hydroxy-7,10-dioxo-5β,6β-(propano)-6α,8α-(ethanoimino)-*trans*-perhydroisoquinoline.

In order to confirm our results reached by use of the two-dimensional nmr spectroscopic information, the X-ray structural determination of compound **V** was performed by the Osaka group of the authors. The identification of the atoms and the configuration of the molecule are shown in the ORTEP drawing in Figure 4 which shows that the ring A and B are in the chair form and ring C is in the boat form respectively. The *N*-methyl groups are in equatorial relative to each piperidine ring.
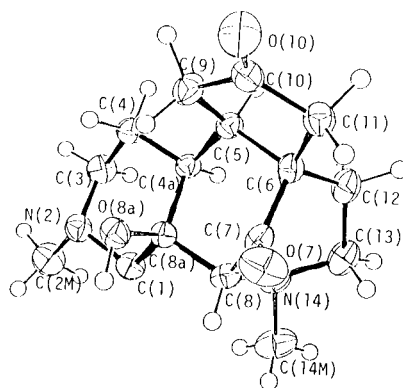

Figure 4.   ORTEP drawing of compound **V**.

In order to see whether compound **V** reversely is changed to compound **IV** or not, compound **V** was refluxed with 10% hydrochloric acid for 20 hours. From the reaction mixture any isomerized compound could not be isolated but only the starting compound **V** in quantitative yield. Therefore, it is evident that compounds **IV** and **V** were formed from the same intermediate **IV′**, and that the reaction step from **IV′** to **IV** is fast and reversible but the step from **IV′** to **V** is slow and irreversible (Chart 3).

Chart 3
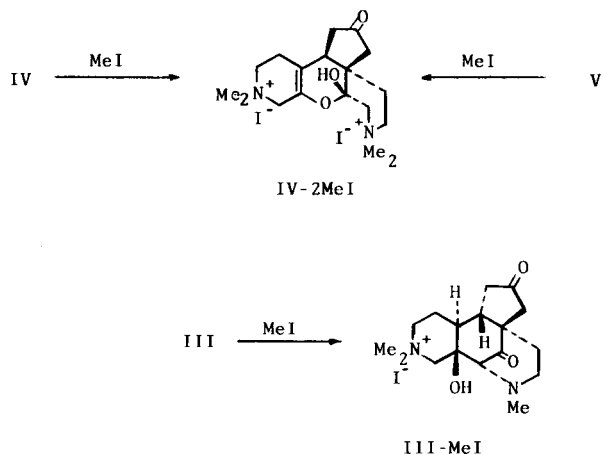
Interestingly, compound **V** was reacted with iodomethane in methanol under reflux to give the dimethiodide **IV**-2MeI identical with that derived from compound **IV**. The single crystal X-ray analysis confirmed the structure of **IV**-

Table VI

Bond Angles (°) in Compound **V**, **III**-MeI and **IV**-2MeI
(Estimated standard deviations are in parentheses)

Compound **V**

Bond	Angle	Bond	Angle
C(2M)–N(2)–C(3)	111.0(2)	C(7)–C(8)–C(8a)	106.7(2)
C(2M)–N(2)–C(1)	109.9(2)	C(7)–C(8)–N(14)	109.8(2)
C(3)–N(2)–C(1)	111.6(2)	C(8a)–C(8)–N(14)	111.0(2)
N(2)–C(3)–C(4)	110.2(2)	N(2)–C(1)–C(8a)	109.8(2)
C(3)–C(4)–C(4a)	111.0(2)	C(4a)–C(8a)–C(8)	109.4(2)
C(4)–C(4a)–C(5)	113.9(2)	C(4a)–C(8a)–C(1)	109.8(2)
C(4)–C(4a)–C(8a)	109.7(2)	C(4a)–C(8a)–O(8a)	111.9(2)
C(5)–C(4a)–C(8a)	114.2(2)	C(8)–C(8a)–C(1)	111.9(2)
C(4a)–C(5)–C(6)	113.5(2)	C(8)–C(8a)–O(8a)	104.2(2)
C(4a)–C(5)–C(9)	117.3(2)	C(1)–C(8a)–O(8a)	109.5(2)
C(6)–C(5)–C(9)	103.7(2)	C(8)–N(14)–C(14M)	111.1(2)
C(5)–C(6)–C(7)	108.4(2)	C(8)–N(14)–C(13)	112.2(2)
C(5)–C(6)–C(12)	112.3(2)	C(14M)–N(14)–C(13)	111.3(2)
C(5)–C(6)–C(11)	103.2(2)	N(14)–C(13)–C(12)	112.4(2)
C(7)–C(6)–C(12)	105.6(2)	C(6)–C(12)–C(13)	112.7(2)
C(7)–C(6)–C(11)	111.8(2)	C(6)–C(11)–C(10)	105.2(2)
C(12)–C(6)–C(11)	115.5(2)	C(11)–C(10)–O(10)	125.2(2)
C(6)–C(7)–O(7)	123.6(2)	C(11)–C(10)–C(9)	109.7(2)
C(6)–C(7)–C(8)	113.3(2)	O(10)–C(10)–C(9)	125.1(2)
O(7)–C(7)–C(8)	123.1(2)	C(5)–C(9)–C(10)	104.7(2)

Table VI (continued)

Compound **III**-MeI

Bond	Angle	Bond	Angle
C(5)–C(4a)–C(8a)	110.3(7)	C(8)–C(8a)–O(8a)	107.1(6)
C(5)–C(4a)–C(4)	113.8(7)	C(1)–C(8a)–O(8a)	112.1(7)
C(8a)–C(4a)–C(4)	108.5(7)	C(8a)–C(1)–N(2)	112.4(6)
C(4a)–C(5)–C(6)	113.1(7)	C(1)–N(2)–C(3)	111.5(8)
C(4a)–C(5)–C(9)	120.0(7)	C(1)–N(2)–C(2M1)	113.9(8)
C(6)–C(5)–C(9)	103.8(7)	C(1)–N(2)–C(2M2)	106.3(8)
C(5)–C(6)–C(7)	103.1(7)	C(3)–N(2)–C(2M1)	111.1(8)
C(5)–C(6)–C(11)	101.8(8)	C(3)–N(2)–C(2M2)	107.1(8)
C(5)–C(6)–C(12)	115.6(8)	C(2M1)–N(2)–C(2M2)	106.5(9)
C(7)–C(6)–C(11)	116.9(8)	N(2)–C(3)–C(4)	112.7(7)
C(7)–C(6)–C(12)	108.4(8)	C(4a)–C(4)–C(3)	111.0(7)
C(11)–C(6)–C(12)	111.0(7)	C(5)–C(9)–C(10)	103.9(8)
C(6)–C(7)–C(8)	110.8(7)	C(9)–C(10)–C(11)	108.3(8)
C(6)–C(7)–O(7)	126.3(7)	C(9)–C(10)–O(10)	125.8(9)
C(8)–C(7)–O(7)	122.8(7)	C(11)–C(10)–O(10)	125.9(9)
C(7)–C(8)–C(8a)	105.9(7)	C(6)–C(11)–C(10)	101.0(8)
C(7)–C(8)–N(14)	112.8(7)	C(6)–C(12)–C(13)	112.9(8)
C(8a)–C(8)–N(14)	112.4(6)	C(12)–C(13)–N(14)	112.3(8)
C(4a)–C(8a)–C(8)	110.5(6)	C(8)–N(14)–C(13)	111.0(8)
C(4a)–C(8a)–C(1)	109.7(7)	C(8)–N(14)–C(14M)	111.3(9)
C(4a)–C(8a)–O(8a)	107.4(6)	C(13)–N(14)–C(14M)	112.7(9)
C(8)–C(8a)–C(1)	110.0(7)		

Compound **IV**-2MeI

Bond	Angle	Bond	Angle
C(6)–N(7)–C(8)	109.8(1)	C(12)–C(3)–C(13)	110.8(1)
C(6)–N(7)–C(7M1)	108.9(1)	C(3)–C(2)–O(1)	109.4(1)
C(6)–N(7)–C(7M2)	112.0(2)	C(3)–C(2)–C(9)	111.3(1)
C(8)–N(7)–C(7M1)	109.2(1)	C(3)–C(2)–O(2)	111.8(2)
C(8)–N(7)–C(7M2)	109.3(2)	O(1)–C(2)–C(9)	105.6(1)
C(7M1)–N(7)–C(7M2)	107.6(2)	O(1)–C(2)–O(2)	108.4(1)
N(7)–C(6)–C(5)	114.1(2)	C(9)–C(2)–O(2)	110.1(1)
C(6)–C(5)–C(4a)	111.3(2)	C(8a)–O(1)–C(2)	115.9(1)
C(5)–C(4a)–C(8a)	121.9(2)	C(3)–C(12)–C(11)	110.3(1)
C(5)–C(4a)–C(4)	120.0(2)	C(12)–C(11)–N(10)	108.3(1)
C(8a)–C(4a)–C(4)	118.0(2)	C(11)–N(10)–C(9)	106.4(1)
C(4a)–C(8a)–C(8)	123.2(2)	C(11)–N(10)–C(10M1)	118.5(1)
C(4a)–C(8a)–O(1)	128.9(2)	C(11)–N(10)–C(10M2)	103.3(1)
C(8)–C(8a)–O(1)	107.7(1)	C(9)–N(10)–C(10M1)	116.3(1)
N(7)–C(8)–C(8a)	111.9(1)	C(9)–N(10)–C(10M2)	104.1(1)
C(4a)–C(4)–C(3)	112.0(2)	C(10M1)–N(10)–C(10M2)	106.5(1)
C(4a)–C(4)–C(15)	112.9(2)	C(2)–C(9)–N(10)	113.9(1)
C(3)–C(4)–C(15)	106.3(2)	C(4)–C(15)–C(14)	101.8(2)
C(4)–C(3)–C(2)	111.3(1)	C(15)–C(14)–C(13)	110.7(2)
C(4)–C(3)–C(12)	110.3(1)	C(15)–C(14)–O(14)	123.7(2)
C(4)–C(3)–C(13)	102.5(1)	C(13)–C(14)–O(14)	125.5(2)
C(2)–C(3)–C(12)	111.2(1)	C(3)–C(13)–C(14)	106.9(1)
C(2)–C(3)–C(13)	110.6(1)		

2MeI to be the dimethiodide of **IV** (Figure 6), which indicate that the frame-work of **V** was changed to that of **IV** in the reaction with iodomethane. While, compound **III** gave the monomethiodide **III**-MeI under the same condition. The X-ray analysis of **III**-MeI showed that the frame work was unchanged and only the nitrogen at 2-position was converted to the quarternary ammonium ion (Figure 5). These facts indicate that the nitrogen at 14-position of
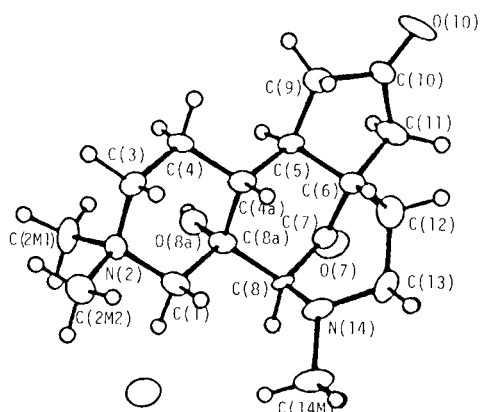
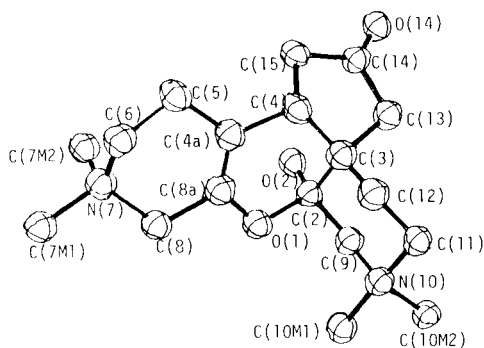Figure 5.   ORTEP drawing of compound **III**-MeI.

Figure 6.   ORTEP drawing of compound **IV**-2MeI.

III can not react with iodomethane because of the steric crowdedness around the nitrogen, and the bond at C_8-C_{8a} of **V** is weakened by the steric crowdedness around the hydroxyl group at C_{8a} and the nitrogen at 14-position.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Ir spectra were recorded on a JASCO A-102 spectrometer. Mass spectra were obtained with a Hitachi RMU-6MG instrument. The ^{1}H nmr and ^{13}C nmr spectra were obtained on a Brucker-WM360 spectrometer operating at 360 MHz for ^{1}H and at 90.5 MHz for ^{13}C spectrum respectively. For the homonuclear ^{1}H nmr two-dimensional chemical shift correlation experiments, an initial data matrix (256 x 256 points) was zero-filled to 1024 x 1024 points. Sine-bell function was used for resolution enhancement. For the heteronuclear ^{1}H-^{13}C shift correlated spectrum, the 90° pulse length for carbon and proton were 8 and 23 μs, respectively. Sine-bell function was used for resolution enhancement.

Conversion of Compound **IV** to **V** with Hydrochloric Acid.

A solution of compound **IV** (1.0 g, 3.42 mmoles) in 10% hydrochloric acid (100 ml) was refluxed for 30 hours. After cooling, the mixture was basified with sodium hydroxide solution, extracted with chloroform and dried over potassium carbonate. The slightly brown residue (0.95 g) of the chloroform solution was chromatographed on a silica gel (Merck

silica gel 60, 30 g) column. The fraction eluted with chloroform-methanol (100:5) gave 200 mg (20%) of compound **V**. The fraction eluted with chloroform-methanol (100:15) gave the starting compound **IV** (700 mg, 79%) which was identified by comparison of the ir spectrum with that of the authentic sample. Recrystallization of the crude **V** from ether afforded pure sample of mp 185-187°; ir (potassium bromide): cm^{-1} 3450 (OH), 1730, 1720 (C=O); ms m/e: 292 (M$^+$), 274, 235, 220.

Anal. Calcd. for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.63; H, 8.19; N, 9.55.

Reaction of **III**, **IV** and **V** with Iodomethane.

(a) Compound **III** (500 mg, 1.7 mmoles) was refluxed with iodomethane (2.85 g, 20 mmoles) in methanol (10 ml) for 5 hours. After evaporation of the excess iodomethane and the solvent, the residual solid was recrystallized from acetone-methanol to give 650 mg (88%) of monomethiodide of **III**, mp 240-245° dec; ir (potassium bromide): cm^{-1} 3400 (OH), 1725 (C=O).

Anal. Calcd. for $C_{17}H_{27}IN_2O_3$: C, 47.01; H, 6.27; N, 6.45. Found: C, 46.75; H, 6.34; N, 6.40.

(b) Compound **IV** (320 mg, 1.1 mmoles) in methanol (10 ml) was refluxed with iodomethane (2.5 g, 17.6 mmoles) for 3 hours. The excess of the iodomethane and the solvent were evaporated to give a solid mass which was recrystallized from methanol-acetone to yield 510 mg (81%) of pure sample of dimethiodide of **IV**, mp 230-235° dec; ir (potassium bromide): cm^{-1} 3450 (OH), 1740, 1710 (C=O).

Anal. Calcd. for $C_8H_{30}I_2N_2O_3 \cdot \frac{1}{2}H_2O$: C, 36.94; H, 5.34; N, 4.79. Found: C, 36.99; H, 5.57; N, 4.58.

(c) Compound **V** (530 mg, 1.82 mmoles) was refluxed with iodomethane (3.0 g, 21 mmoles) in methanol (15 ml) for 6 hours. Evaporation of the excess iodomethane and the solvent afforded a solid mass which was recrystallized from methanol-acetone to give 910 mg (87%) of colorless crystals of mp 231-233° dec. The ir spectrum of this compound was identical with that of the sample obtained from **IV**.

X-Ray Structural Determination of **V**, **III**-MeI and **IV**-2MeI.

Details of crystal data for respective compounds and their intensity collections parameters are summarized in Table III. The unit cell dimensions were determined by a least-squares fit of 2θ reflections (30° $<2\theta<60°$) measured with a graphite-monochromated CuKα radiation (λ = 1.5418 Å) on an automatic Rigaku AFC-5 diffractometer. Intensities for each crystal were collected in a similar manner: a single crystal was mounted on a goniometer, and the intensity data were collected with the same diffractometer at 40kV and 100 mA. The ω-2θ scan technique was employed for the intensity recording, where the background was counted for 5 seconds at both extremes of the peak. Four standard reflections were monitored every 100 reflection interval throughout the data collection and showed a random variation less than 5% with no significant trends. Lorentz and polarization corrections were applied for the intensity. The data for **III**-MeI and **IV**-2MeI were further corrected for absorption effects by using an empirical correction based on ϕ scans.

The structure of **V** was solved by direct method (program MULTAN78 [6]). On the other hand, the structures of **III**-MeI and **IV**-2MeI were solved by heavy-atom method and successive Fourier syntheses. Refinement of each structure was also done in a similar manner: positional parameters of non-hydrogen atoms were refined by a full-matrix least-squares method with isotropic thermal parameters and then by a block-diagonal least-squares method with anisotropic ones. Geometrically reasonable hydrogen atom positions were determined on a difference Fourier map and included in subsequent refinements with isotropic temperature factors; for compounds **III**-MeI and **IV**-2MeI, their hydrogen atoms were fixed at the idealized, calculated positions with common isotopic thermal parameters and included in the calculating of structure factors, but not in the refinement. The function minimized was $\Sigma w(|Fo| - |Fc|)^2$, where $|Fo^{1/2}|$ and $|Fc|$ are the observed and calculated structure factors. The used weighting scheme is as follows: w = a, for Fo = 0.0, and w = $1.0/[\sigma(Fo)^2 + b\ Fo + c\ Fc^2]$ for Fo>0.0, where $\sigma(Fo)^2$ is the standard deviation of the intensity based on counting statistics, and the coefficients, a, b and c, are given in Table III. In the final refinements, none of the positional parameters shifted more than their standard deviations.

Final R ($\Sigma \| Fo | - | Fc \| / \Sigma | Fo |$) and Rw ($[\Sigma w(| Fo | - | Fc |)^2 / \Sigma w | Fo |^2]^{1/2}$), and S ($[\Sigma w(| Fo | - | Fc |)^2 / (M-N)]^{1/2}$, where M and N are the numbers of reflections and variables respectively) are also tabulated. For all crystallographic computations, the UNICS program [7] were used, and the atomic scattering factors and the terms of anomalous dispersion corrections were taken from reference [8]; the measurements of Bijvoet pairs [$| F(hkl) |$ and $| F(\overline{hkl}) |$] clearly demonstrated the absolute configuration of IV-2MeI to be as shown in Figure 6. The numerical calculations were performed on a Micro Vax-II computer at the Computation Center of Osaka University of Pharmaceutical Sciences.

REFERENCES AND NOTES

[1] S. Shiotani, H. Morita, M. Inoue, T. Ishida, M. Doi and Y. In, *J. Heterocyclic Chem.*, **23**, 233 (1986).

[2] A. Bax, "Two-dimensional Nuclear Magnetic Resonances in Liquid", Delft University Press, Delft, Holland, 1984.

[3] A. Bax, G. A. Morris, *J. Magn. Reson.*, **42**, 501 (1981); R. Freeman and G. A. Morris, *J. Chem. Soc. Chem. Commun.*, 684 (1978).

[4] A. Bax and R. Freeman, *J. Magn. Reson.*, **42**, 164 (1981); *ibid.*, **44**, 542 (1981).

[5] S. Winstein, P. Carter, F. A. L. Anet and A. J. R. Brown, *J. Am. Chem. Soc.*, **87**, 5247 (1965); J. E. Baldwin and R. K. Pinschimidt, Jr., *ibid.*, **92**, 5247 (1970); D. F. Evans, *J. Chem. Soc.*, 877 (1960); K. Tori and T. Komeno, *Tetrahedron*, **21**, 309 (1965).

[6] P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, Multan78, A System of Computer Programs for the Automatic Solution of Crystal Structure from X-ray Diffraction Data, University of York, York, England, 1978.

[7] The Universal Crystallographic Computing System-Osaka; The Computation Center, Osaka, Japan, 1979.

[8] International Table for X-ray Crystallography, Kynoch Press, Birmingham England, Vol **14**, 1974.