

Furopyridines. IV. Unexpected Dimerization of 5-Methyl-4,5,6,7-tetrahydrofuro[3,2-c]- and 6-Methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine by Acidic Hydrolysis

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Reaction of 5-methyl-4,5,6,7-tetrahydrofuro[3,2-c]- (**1**) and 6-methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine (**2**) with hydrochloric acid gave novel dimerized compounds **3a-d** and **4a-d**, respectively. The structures of **3a**, **3b**, **4a** and **4b** were determined by spectroscopic method, and **3c**, **3d**, **4c** and **4d** by single crystal X-ray analysis. The reaction courses for the formation of these compounds are proposed.

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Thus, the final structures were determined by a single crystal X-ray analysis performed by the Osaka group of authors. The X-ray data of **3c**-methiodide and **3d** unambiguously established **3c** as 2,10-dimethyl-4 α β -hydroxy-6,13-dioxo-5 α ,7 α -(methanoiminomethano)-7 β ,8 α -(propano)-*trans*-perhydroisoquinoline and **3d** as 2,10-dimethyl-4 α -hydroxy-6,13-dioxo-5 α ,7 α -(methanoiminomethano)-7 β ,8 β -(propano)-*trans*-perhydroisoquinoline, respectively.

Compound **2**, prepared by the reduction of 6-methylfu-

ro[2,3-c]pyridinium iodide [7] with sodium borohydride, was refluxed with 10% hydrochloric acid for 16 hours. The crude reaction product was submitted to column chromatography on silica gel to isolate four colorless crystalline compounds **4a** (mp 77-81°), **4b** (mp 70-73°), **4c** (mp 168-170.5°) and **4d** (mp 148-149°) in 0.75%, 16%, 8.1% and 42%, respectively.

The structures of compounds **4a** and **4b** were determined as 2,9-dimethyl-1,2,3,4,7,8,9,10-octahydropyrido[4',3':4,5]furo[3,2-*h*]isoquinoline and 3,10-dimethyl-1,2,3,4,8,9,10,11-octahydropyrido[4',3':4,5]furo[2,3-*h*]isoquinoline, respectively, from their elemental analyses, mass, ir, ¹H and ¹³C nmr spectral data (Table I and II) and the arguments used for the structural determination of compounds **3a** and **3b**.

The elemental analysis and mass spectrum of **4c** showed the molecular formula C₁₆H₂₄N₂O₃. The ir spectrum showed ν OH at 3420 (broad) cm⁻¹ and ν C=O at 1740 and 1720

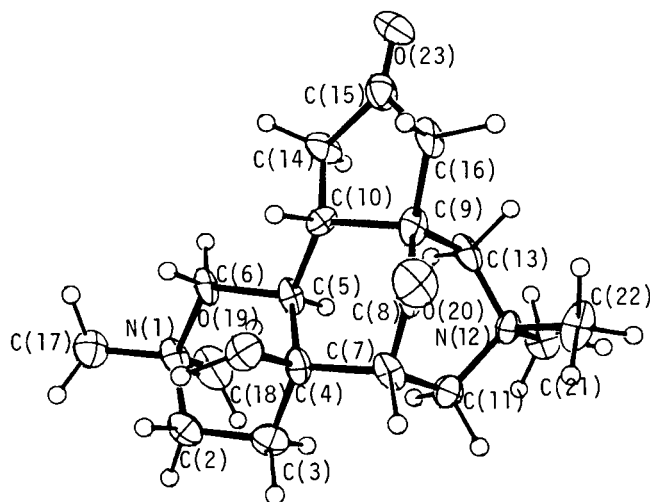
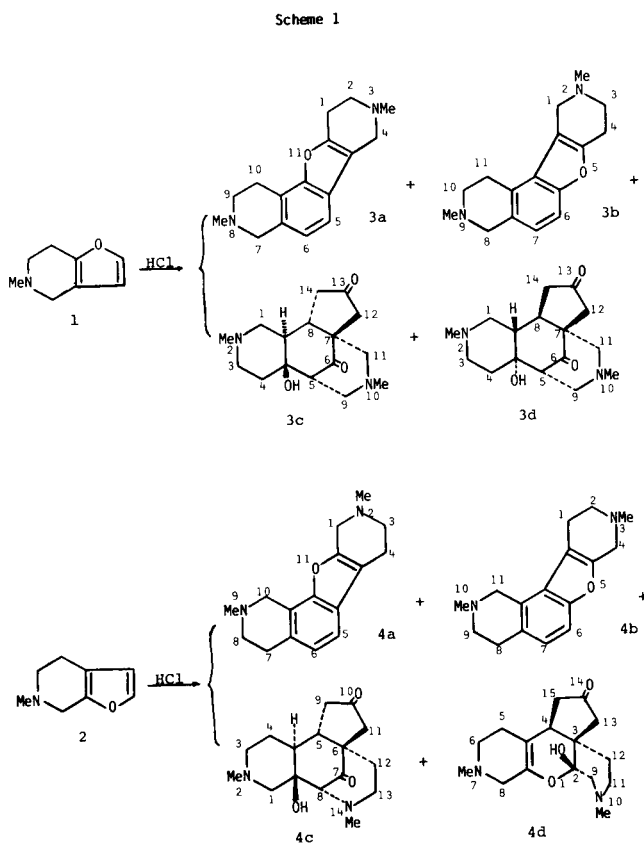
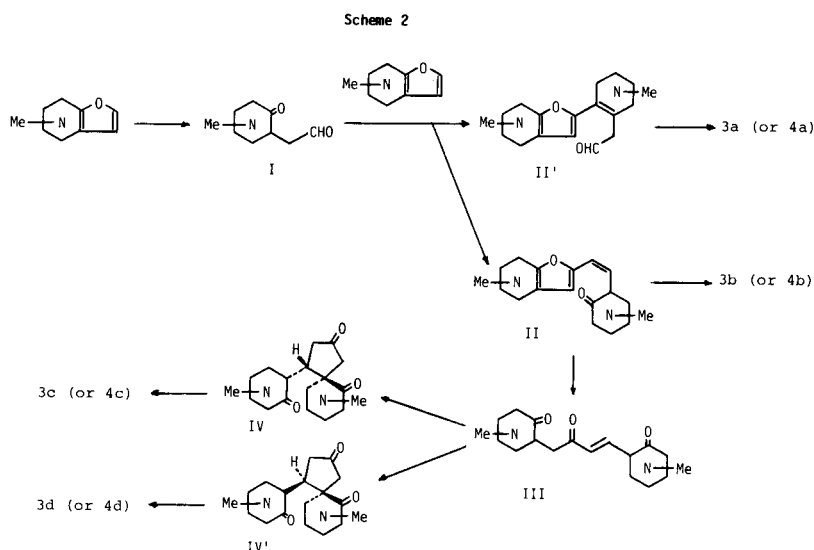


Figure 1. ORTEP drawing of **3c**·2MeI



cm^{-1} . The ^1H nmr spectrum exhibited two *N*-methyl signals at δ 2.30 and 2.39 and complex multiplets at δ 1.40-2.87 (18H). In the ^{13}C nmr spectrum, compound **4c** showed signals of sixteen carbons (two carbonyl, two *N*-methyl, two aliphatic quaternary, three methine and seven methylene) (Table III). While, compound **4d** was found to have the molecular formula $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3 \cdot \frac{1}{2}\text{CH}_3\text{OH}$ from its elemental analysis and mass spectrum. The ir spectrum showed ν OH at 3400 (broad cm^{-1} and ν C=O at 1735 cm^{-1} . The ^1H nmr spectrum exhibited signals of two *N*-methyls at δ 2.29 and 2.32 and a complex multiplet at δ 1.83-2.90. In the ^{13}C nmr spectrum of compound **4d** showed signals of one carbonyl, one aliphatic methine, two *N*-methyls, two olefinic carbons having no hydrogen, two aliphatic quaternary and eight methylene carbons. On the basis of these common

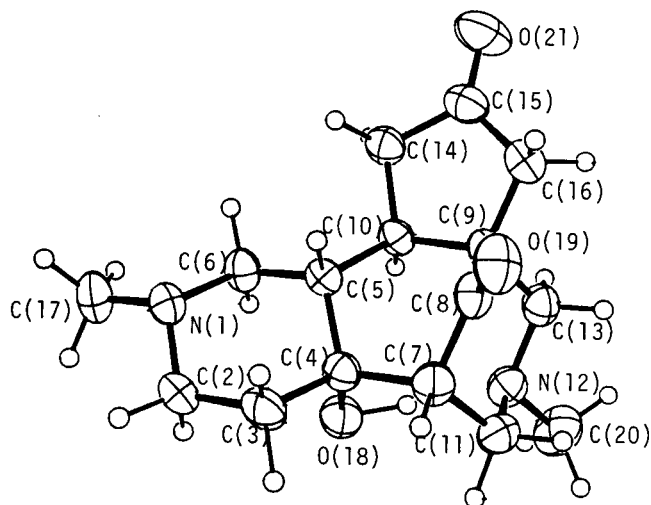


Figure 2. ORTEP drawing of **3d**

Table I

Physical Data for Compounds **3** and **4**

Compound No.	Mp, °C	Solvent	Molecular Formula	Analysis % (Calcd./Found)			IR (cm^{-1})	Mass Spectrum (m/e)
				C	H	N		
3a	117-121	Ether	$\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$	74.96	7.86	10.93	—	256 (M^+), 213, 212, 170
				74.91	7.92	10.95		
3b	90.5-93.5	Ether	$\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$	74.96	7.86	10.93	—	256 (M^+), 213, 212, 170
				74.78	7.70	10.85		
3c	204-209	Methanol-Ether	$\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3$	65.73	8.27	9.58	3400-3200 1735, 1705	292 (M^+), 274, 249, 248
				65.63	8.32	9.58		
3c·2MeI	275-280 dec	Methanol-Water	$\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}_3 \cdot \frac{1}{2}\text{H}_2\text{O}$	36.94	5.34	4.79	—	—
				36.87	5.33	4.57		
3d	154-159	Ether	$\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3$	65.73	8.27	9.58	3450-3250 1735, 1705	—
				65.86	8.39	9.45		
4a	77-81	Ether	$\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$	74.96	7.86	10.93	—	256 (M^+), 213, 212, 170
				74.67	7.78	10.78		
4b	70-73	Ether	$\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}$	74.96	7.86	10.93	—	256 (M^+), 213, 212, 170
				74.59	8.06	10.57		
4c	168-170.5	Ether	$\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3$	65.73	8.27	9.58	3420 (broad) 1740, 1720	292 (M^+), 274, 249, 248
				65.95	8.24	9.56		
4d	148-149	Methanol-Ether	$\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3 \cdot \frac{1}{2}\text{CH}_3\text{OH}$	64.26	8.50	9.08	3400 (broad) 1735	292 (M^+), 274, 249, 248
				64.36	8.58	9.18		

Table II

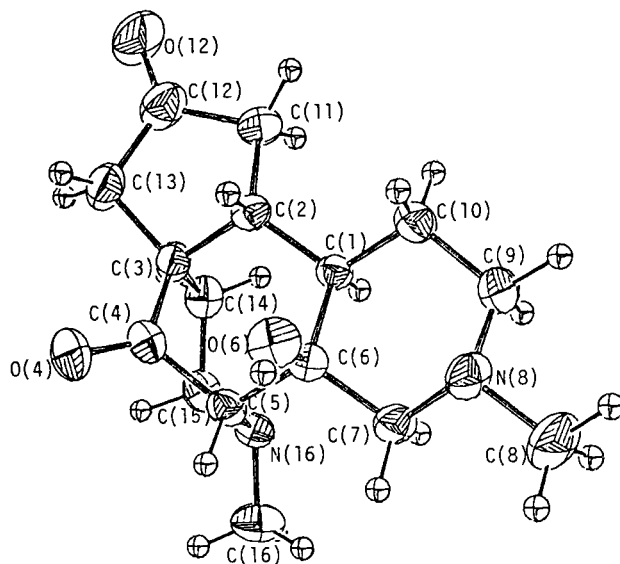
¹H and ¹³C NMR Data for **3a**, **3b**, **4a** and **4b**

Compound No.	3a	3b	4a	4b
¹ H nmr	2.46 (3H, s)	2.46 (3H, s)	2.49 (6H, s)	2.49 (6H, s)
	2.51 (3H, s)	2.54 (3H, s)	2.50-3.10	2.58-3.00
	2.72 (2H, t)	2.72 (2H, t)	(8H, m)	(8H, m)
	(J = 6.0 Hz)	(J = 6.0 Hz)	3.57 (2H, s)	3.58 (2H, s)
	2.83 (4H, s)	2.84 (4H, s)	3.79 (2H, s)	3.87 (2H, s)
	3.07 (2H, t)	3.13 (2H, t)	6.90 (1H)	6.88 (1H)
	(J = 6.0 Hz)	(J = 6.0 Hz)	7.15 (1H) ^{AB-q}	7.16 (1H) ^{AB-q}
	3.52 (2H, s)	3.64 (2H, s)	(J = 8.4 Hz)	(J = 8.6 Hz)
	3.63 (2H, s)	3.77 (2H, s)		
	6.87 (1H)	6.88 (1H)		
7.13 (1H) ^{AB-q}	7.22 (1H) ^{AB-q}			
(J = 8.0 Hz)	(J = 8.0 Hz)			
¹³ C nmr	23.6 (t)	24.3 (t)	19.9 (t)	23.1 (t)
	24.5 (t)	27.1 (t)	28.1 (t)	29.2 (t)
	45.8 (q)	45.7 (q)	44.3 (q)	45.4 (q)
	46.6 (q)	46.4 (q)	45.2 (q)	46.3 (q)
	51.3 (t)	51.9 (t)	51.1 (t)	52.3 (t)
	52.7 (t)	52.5 (t)	(two carbons)	52.5 (t)
	(two carbons)	52.7 (t)	51.3 (t)	52.8 (t)
	58.4 (t)	58.3 (t)	51.9 (t)	55.5 (t)
	112.9 (s)	109.5 (d)	110.0 (s)	109.1 (d)
	116.6 (d)	112.8 (s)	115.2 (d)	110.5 (s)
	118.8 (s)	122.7 (d)	117.6 (s)	124.1 (d)
	122.0 (d)	126.5 (s)	122.0 (d)	124.5 (s)
	125.8 (s)	126.9 (s)	124.2 (s)	127.2 (s)
	131.5 (s)	129.6 (s)	128.3 (s)	127.4 (s)
	152.7 (s)	152.7 (s)	149.3 (s)	150.8 (s)
154.6 (s)	154.4 (s)	150.4 (s)	152.8 (s)	

Table III

¹H and ¹³C NMR Data for **3c**, **3d**, **4c** and **4d**

Compound No.	3c	3d	4c	4d
¹ H nmr	1.25-3.61 (18H)	1.30-3.53 (17H)	1.40-2.87 (18H)	1.83-2.90 (18H)
	(complex m)	(complex m)	(complex m)	(complex m)
	2.13 (3H, s)	2.30 (3H, s)	2.30 (3H, s)	2.29 (3H, s)
	2.17 (3H, s)	2.35 (3H, s)	2.39 (3H, s)	2.32 (3H, s)
		6.55 (1H, s)		3.47 (1.5H, s)
		(-OH)		(½CH₃OH)
¹³ C nmr	34.6 (t)	40.0 (t)	25.5 (t)	27.3 (t)
	39.2 (t)	40.7 (t)	31.8 (t)	35.8 (t)
	43.5 (d & q)	42.6 (t)	36.3 (d)	42.6 (d)
	(two carbons)	42.7 (q)	38.5 (t)	43.3 (t)
	44.6 (q)	43.8 (d)	46.0 (q)	45.4 (q)
	44.9 (t)	45.8 (d)	47.3 (q)	45.9 (q)
	46.5 (d)	49.7 (d)	48.0 (d)	47.7 (t)
	51.8 (t)	51.0 (t)	48.2 (t)	50.5 (s)
	54.1 (t)	53.3 (s)	50.1 (t)	52.3 (t)
	54.4 (s)	53.7 (t)	52.6 (s)	52.5 (t)
	57.5 (t)	55.6 (d)	54.9 (t)	54.6 (t)
	60.7 (d)	58.9 (t)	63.3 (t)	61.7 (t)
	62.0 (t)	67.8 (t)	76.8 (s)	96.6 (s)
	74.5 (s)	72.6 (s)	77.4 (d)	103.7 (s)
	209.3 (s)	212.0 (s)	208.2 (s)	138.5 (s)
	213.6 (s)	213.6 (s)	214.5 (s)	217.1 (s)

Figure 3. ORTEP drawing of **4c**

spectroscopic methods, it is impossible to estimate the real structures of **4c** and **4d**. This question was resolved again by X-ray structural analysis, which showed the structure of **4c** to be 2,9-dimethyl-8 $\alpha\beta$ -hydroxy-7,10-dioxo-5 α ,6 β -(propano)-6 α ,8 α -(ethanoimino)-*trans*-perhydroisoquinoline and **4d** 7,10-dimethyl-2 β -hydroxy-14-oxo-2 α ,3 α -(methanoiminoethano)-3 β ,4 β -(propano)-3,4,5,6,7,8-hexahydro-2H-pyrano[2,3-*c*]pyridine, respectively.

We have presented here quite novel dimerizations of 5-methyl-4,5,6,7-tetrahydrofuro[3,2-*c*] (**1**) and 6-methyl-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine (**2**). Reaction courses for these results may be depicted as follows: At the first stage, the furan ring of **1** or **2** is hydrolyzed to form a keto-aldehyde I. Attack of the aldehyde carbon of I at the 2-position of the Py-tetrahydrofuro-pyridine molecule and the subsequent dehydration gives the intermediate II and attack of ketone carbon another intermediate II' (the former

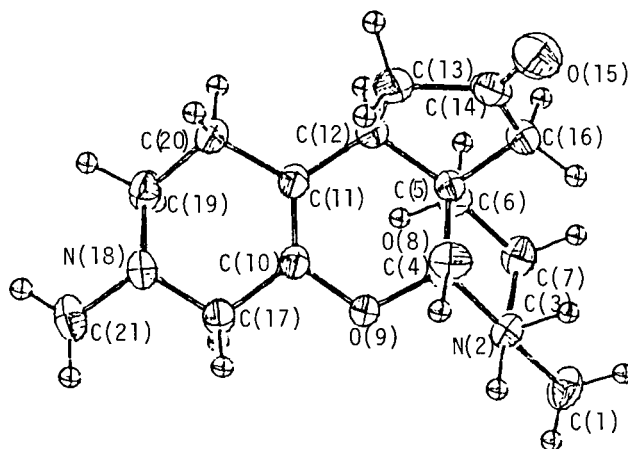
Figure 4. ORTEP drawing of **4d**

Table IV
Crystal Data for **3c·2MeI**, **3d**, **4c** and **4d**

Compound	3c·2MeI	3d	4c	4d
Chemical Mw	C ₁₈ H ₃₀ N ₂ O ₅ I ₂ ·2H ₂ O 612.27	C ₁₆ H ₂₄ N ₂ O ₃ 292.38	C ₁₆ H ₂₄ N ₂ O ₃ 292.38	C ₁₆ H ₂₄ N ₂ O ₃ ·CH ₃ OH 324.44
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group	P2 ₁ /n	P2 ₁ /a	P2 ₁ /c	C2/c
Cell constants				
<i>a</i> (Å)	9.226(6)	24.138(62)	10.11(11)	21.616(6)
<i>b</i> (Å)	14.382(9)	6.311(2)	15.324(6)	8.079(1)
<i>c</i> (Å)	17.827(14)	17.018(44)	11.968(8)	19.883(4)
β (°)	100.40(12)	144.14(10)	124.29(5)	95.07(2)
<i>V</i> (Å ³)	2323(3)	1518(6)	1532(2)	3459(1)
<i>z</i>	4	4	4	8
Independent reflections	3137	2380	2606	2942

Table V

Atomic Parameters ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($\times 10^3$) for Nonhydrogen Atoms in Compound **3c·2MeI**, **3d**, **4c** and **4d** (estimated standard deviations are in parentheses)

Compound 3c·2MeI					Compound 4c				
Atom	X	Y	Z	Beq	Atom	X	Y	Z	Beq
N(1)	2938(17)	645(9)	7039(7)	2.7(5)	C(1)	-102(4)	2501(2)	8589(3)	2.4(1)
C(2)	4321(20)	1163(11)	7400(9)	2.7(6)	C(2)	-907(4)	3050(2)	9101(4)	2.7(1)
C(3)	4999(19)	1729(12)	6840(10)	2.7(6)	C(3)	-2555(4)	2657(2)	8706(4)	2.9(1)
C(4)	3860(19)	2412(11)	6433(8)	2.3(6)	C(4)	-2118(4)	1781(2)	9416(4)	3.0(1)
C(5)	2544(19)	1878(10)	6008(8)	2.1(5)	O(4)	-2272(4)	1578(2)	10307(3)	4.3(1)
C(6)	1850(20)	1307(10)	6571(8)	2.3(6)	C(5)	-1413(4)	1174(2)	8862(3)	2.7(1)
C(7)	4451(19)	3098(10)	5871(8)	2.3(5)	C(6)	163(4)	1575(2)	9193(3)	2.5(1)
C(8)	3235(21)	3732(10)	5546(9)	2.5(6)	O(6)	1182(3)	1607(2)	10641(2)	3.5(1)
C(9)	2072(19)	3209(10)	5010(10)	2.5(6)	C(7)	972(4)	1020(2)	8681(4)	3.1(1)
C(10)	1419(16)	2553(10)	5580(9)	1.9(5)	N(8)	2567(3)	1407(2)	9256(3)	3.4(1)
C(11)	5167(19)	2579(12)	5270(10)	2.8(6)	C(8)	3572(6)	831(3)	9052(6)	5.7(2)
N(12)	4372(14)	2800(9)	4470(7)	2.1(4)	C(9)	2381(5)	2265(3)	8626(4)	3.6(1)
C(13)	2779(22)	2653(10)	4421(10)	3.1(7)	C(10)	1500(5)	2894(2)	8986(4)	3.5(1)
C(14)	18(20)	2167(11)	5070(10)	2.9(6)	C(11)	-1356(5)	4000(2)	8615(5)	3.7(1)
C(15)	-552(20)	2959(12)	4541(10)	3.0(7)	C(12)	-2567(6)	4213(3)	8951(5)	4.3(1)
C(16)	679(21)	3746(11)	4645(10)	3.1(7)	O(12)	-2994(5)	4937(2)	9004(4)	6.6(1)
C(17)	3341(2)	-150(14)	6564(12)	4.2(9)	C(13)	-3141(5)	3372(3)	9235(4)	3.9(1)
C(18)	2280(23)	262(13)	7677(11)	3.4(7)	C(14)	-3763(4)	2486(2)	7162(4)	3.2(1)
O(19)	3330(13)	3000(8)	6973(6)	2.9(4)	C(15)	-4074(4)	1515(3)	6845(4)	3.3(1)
O(20)	3140(16)	4523(8)	5742(7)	3.6(5)	N(16)	-2557(3)	1056(2)	7380(3)	2.8(1)
C(21)	4728(24)	3770(11)	4219(12)	3.5(7)	C(16)	-2847(6)	125(3)	7012(5)	4.5(1)
C(22)	4856(22)	2131(12)	3929(10)	3.1(7)					
O(23)	-1664(15)	3004(11)	4107(8)	4.6(6)					
I(24)	2541(1)	4822(0)	656(0)	3.2(0)					
I(25)	8509(1)	3890(1)	6571(0)	4.5(0)					
O(1)W	3751(21)	3415(17)	2325(11)	7.0(10)					
O(2)W	4104(17)	6277(14)	2169(9)	6.0(8)					
Compound 3d					Compound 4d				
Atom	X	Y	Z	Beq	Atom	X	Y	Z	Beq
N(1)	3419(1)	320(4)	7752(2)	2.4(1)	C(1)	2292(1)	2917(4)	1381(1)	3.9(1)
C(2)	2906(2)	-921(6)	6585(3)	4.0(1)	N(2)	2841(1)	1867(3)	1297(1)	2.8(1)
C(3)	3579(2)	-1952(6)	6765(3)	4.2(1)	C(3)	3082(1)	1204(3)	1956(1)	2.5(1)
C(4)	4200(2)	-285(5)	7091(3)	3.1(1)	C(4)	3652(1)	116(3)	1900(1)	2.3(1)
C(5)	4740(2)	877(4)	8369(3)	2.8(1)	C(5)	3542(1)	-1265(3)	1377(1)	2.3(1)
C(6)	4045(2)	1900(5)	8127(3)	3.5(1)					
C(7)	4906(2)	-1342(5)	7302(3)	3.7(1)					
C(8)	5891(2)	-1005(5)	8711(3)	3.4(1)					

Table V (continued)

C(6)	3246(1)	-531(4)	717(1)
C(7)	2674(1)	514(4)	824(1)
O(8)	3844(1)	-625(2)	2516(1)
O(9)	4121(0)	1270(2)	1713(1)
C(10)	4650(1)	587(3)	1480(1)
C(11)	4696(1)	-949(3)	1272(1)
C(12)	4166(1)	-2148(3)	1270(1)
C(13)	4250(1)	-3515(4)	1815(1)
C(14)	3602(1)	-3806(3)	2035(1)

Table V (continued)

O(15)	3472(1)	-4811(3)	2446(1)	4.7(1)
C(16)	3148(1)	-2650(3)	1658(1)	2.8(1)
C(17)	5146(1)	1886(3)	1484(1)	2.8(1)
N(18)	5752(1)	1158(3)	1369(1)	2.6(0)
C(19)	5687(1)	-70(4)	822(1)	3.1(1)
C(20)	5299(1)	-1523(4)	1017(1)	3.1(1)
C(21)	6189(1)	2470(4)	1220(1)	3.9(1)
C(1)M	8893(1)	1169(5)	5197(1)	4.3(1)
O(1)M	8436(1)	657(3)	5617(1)	4.6(1)

Table VI

Bond Lengths (Å) in Compound **3c·2MeI**, **3d**, **4c** and **4d**
(estimated standard deviations are in parentheses)

Compound **3c·2MeI**

N(1)-C(2)	1.516(25)	C(5)-C(6)	1.524(26)	C(10)-C(14)	1.541(25)
N(1)-C(6)	1.517(25)	C(5)-C(10)	1.520(24)	C(11)-N(12)	1.513(23)
N(1)-C(17)	1.510(31)	C(7)-C(8)	1.479(27)	N(12)-C(13)	1.471(25)
N(1)-C(18)	1.489(27)	C(7)-C(11)	1.548(26)	N(12)-C(21)	1.518(26)
C(2)-C(3)	1.508(26)	C(8)-C(9)	1.502(27)	N(12)-C(22)	1.489(24)
C(3)-C(4)	1.528(25)	C(9)-O(20)	1.198(25)	C(14)-C(15)	1.512(27)
C(4)-C(5)	1.510(25)	C(9)-C(10)	1.583(24)	C(15)-C(16)	1.590(28)
C(4)-C(7)	1.577(25)	C(9)-C(13)	1.553(28)	C(15)-O(23)	1.168(25)
C(4)-O(19)	1.430(22)	C(9)-C(16)	1.539(27)		

Compound **3d**

N(1)-C(2)	1.457(8)	C(5)-C(6)	1.512(8)	C(9)-C(16)	1.525(9)
N(1)-C(6)	1.471(8)	C(5)-C(10)	1.534(8)	C(10)-C(14)	1.532(8)
N(1)-C(17)	1.450(9)	C(7)-C(8)	1.486(9)	C(11)-N(12)	1.474(8)
C(2)-C(3)	1.531(9)	C(7)-C(11)	1.537(9)	N(12)-C(13)	1.464(8)
C(3)-C(4)	1.522(9)	C(8)-C(9)	1.526(9)	N(12)-C(20)	1.460(10)
C(4)-C(5)	1.541(8)	C(8)-O(19)	1.211(8)	C(14)-C(15)	1.509(9)
C(4)-C(7)	1.576(8)	C(9)-C(10)	1.583(8)	C(15)-C(16)	1.498(9)
C(4)-O(18)	1.437(7)	C(9)-C(13)	1.536(9)	C(16)-O(21)	1.207(8)

Compound **4c**

C(1)-C(2)	1.519(7)	C(4)-O(4)	1.201(6)	N(8)-C(9)	1.475(7)
C(1)-C(6)	1.547(6)	C(4)-C(5)	1.531(7)	C(9)-C(10)	1.529(8)
C(1)-C(10)	1.532(7)	C(5)-C(6)	1.538(7)	C(11)-C(12)	1.524(9)
C(2)-C(3)	1.574(7)	C(5)-N(16)	1.484(6)	C(12)-O(12)	1.205(9)
C(2)-C(11)	1.538(8)	C(6)-O(6)	1.433(6)	C(12)-C(13)	1.529(9)
C(3)-C(4)	1.516(7)	C(6)-C(7)	1.527(7)	C(14)-C(15)	1.524(7)
C(3)-C(13)	1.542(8)	C(7)-N(8)	1.475(7)	C(15)-N(16)	1.467(6)
C(3)-C(14)	1.559(7)	N(8)-C(8)	1.467(9)	N(16)-C(16)	1.473(7)

Compound **4d**

C(1)-N(2)	1.479(5)	C(5)-C(16)	1.540(4)	C(14)-O(15)	1.203(4)
N(2)-C(3)	1.469(4)	C(6)-C(7)	1.527(5)	C(14)-C(16)	1.506(5)
N(2)-C(7)	1.466(4)	O(9)-C(10)	1.385(4)	C(17)-N(18)	1.471(4)
C(3)-C(4)	1.524(4)	C(10)-C(11)	1.316(4)	N(18)-C(19)	1.470(4)
C(4)-C(5)	1.530(4)	C(10)-C(17)	1.501(4)	N(18)-C(21)	1.468(5)
C(4)-O(8)	1.394(4)	C(11)-C(12)	1.501(4)	C(19)-C(20)	1.513(5)
C(4)-O(9)	1.450(4)	C(11)-C(20)	1.512(5)	C(1)M-O(1)M	1.411(4)
C(5)-C(6)	1.528(4)	C(12)-C(13)	1.547(5)		
C(5)-C(12)	1.556(4)	C(13)-C(14)	1.522(5)		

Table VII

Bond Angles (°) in Compound **3c**·2MeI, **3d**, **4c**, and **4d**
(estimated standard deviation are in parentheses)

Compound **3c**·2MeI

C(2)-N(1)-C(6)	110.3(14)	C(9)-C(8)-O(20)	125.5(18)
C(2)-N(1)-C(17)	109.6(16)	C(8)-C(9)-C(10)	101.6(14)
C(2)-N(1)-C(18)	106.6(15)	C(8)-C(9)-C(13)	110.4(16)
C(6)-N(1)-C(17)	111.8(16)	C(8)-C(9)-C(16)	117.5(16)
C(6)-N(1)-C(18)	109.4(15)	C(10)-C(9)-C(13)	112.5(15)
C(17)-N(1)-C(18)	108.9(17)	C(10)-C(9)-C(16)	100.7(14)
N(1)-C(2)-C(3)	113.7(15)	C(13)-C(9)-C(16)	113.1(16)
C(2)-C(3)-C(4)	109.0(15)	C(5)-C(10)-C(9)	113.5(14)
C(3)-C(4)-C(5)	109.4(14)	C(5)-C(10)-C(14)	119.2(14)
C(3)-C(4)-C(7)	114.3(14)	C(9)-C(10)-C(14)	102.2(13)
C(3)-C(4)-O(19)	110.4(14)	C(7)-C(11)-N(12)	110.9(14)
C(5)-C(4)-C(7)	109.9(14)	C(11)-N(12)-C(13)	109.4(14)
C(5)-C(4)-O(19)	107.7(14)	C(11)-N(12)-C(21)	112.2(14)
C(7)-C(4)-O(19)	104.9(13)	C(11)-N(12)-C(22)	108.9(14)
C(4)-C(5)-C(6)	109.6(15)	C(13)-N(12)-C(21)	112.4(14)
C(4)-C(5)-C(10)	109.6(14)	C(13)-N(12)-C(22)	106.4(14)
C(6)-C(5)-C(10)	110.2(14)	C(21)-N(12)-C(22)	107.2(14)
N(1)-C(6)-C(5)	112.6(15)	C(9)-C(13)-N(12)	115.0(16)
C(4)-C(7)-C(8)	107.8(15)	C(10)-C(14)-C(15)	104.9(15)
C(4)-C(7)-C(11)	112.4(14)	C(14)-C(15)-C(16)	107.6(15)
C(8)-C(7)-C(11)	114.5(15)	C(14)-C(15)-O(23)	128.3(19)
C(7)-C(8)-C(9)	110.0(16)	C(16)-C(15)-O(23)	124.1(18)
C(7)-C(8)-O(20)	124.2(18)	C(9)-C(16)-C(15)	102.4(15)

Compound **3d**

C(2)-N(1)-C(6)	112.4(5)	C(9)-C(8)-O(19)	124.0(6)
C(2)-N(1)-C(17)	110.1(5)	C(8)-C(9)-C(10)	108.1(5)
C(6)-N(1)-C(17)	109.9(5)	C(8)-C(9)-C(13)	106.4(5)
N(1)-C(2)-C(3)	112.2(5)	C(8)-C(9)-C(16)	112.9(5)
C(3)-C(4)-C(5)	107.4(5)	C(10)-C(9)-C(16)	106.9(5)
C(3)-C(4)-C(7)	110.8(5)	C(13)-C(9)-C(16)	110.3(5)
C(3)-C(4)-O(18)	106.8(5)	C(5)-C(10)-C(9)	111.4(4)
C(5)-C(4)-C(7)	111.0(5)	C(5)-C(10)-C(14)	112.6(5)
C(5)-C(4)-O(18)	110.1(4)	C(9)-C(10)-C(14)	106.7(5)
C(7)-C(4)-O(18)	110.6(4)	C(7)-C(11)-N(12)	109.5(5)
C(4)-C(5)-C(6)	109.7(5)	C(11)-N(12)-C(13)	110.1(5)
C(4)-C(5)-C(10)	112.2(4)	C(11)-N(12)-C(20)	111.0(5)
C(6)-C(5)-C(10)	113.0(5)	C(13)-N(12)-C(20)	110.2(5)
N(1)-C(6)-C(5)	111.4(5)	C(9)-C(13)-N(12)	112.5(5)
C(4)-C(7)-C(8)	109.2(5)	C(10)-C(14)-C(15)	106.9(5)
C(4)-C(7)-C(11)	114.1(5)	C(14)-C(15)-C(16)	110.2(5)
C(8)-C(7)-C(11)	107.1(5)	C(14)-C(15)-O(21)	124.9(6)
C(7)-C(8)-C(9)	111.9(5)	C(16)-C(15)-O(21)	124.8(6)
C(7)-C(8)-O(19)	124.1(6)	C(9)-C(16)-C(15)	107.5(5)

Compound **4c**

C(2)-C(1)-C(6)	108.2(4)	C(1)-C(6)-C(7)	108.4(4)
C(2)-C(1)-C(10)	111.7(4)	C(5)-C(6)-O(6)	105.1(4)
C(6)-C(1)-C(10)	109.9(4)	C(5)-C(6)-C(7)	112.7(4)
C(1)-C(2)-C(3)	112.5(4)	O(6)-C(6)-C(7)	108.8(4)
C(1)-C(2)-C(11)	118.9(4)	C(6)-C(7)-N(8)	106.3(4)
C(3)-C(2)-C(11)	102.3(4)	C(7)-N(8)-C(8)	111.0(5)
C(2)-C(3)-C(4)	104.2(4)	C(7)-N(8)-C(9)	109.2(4)
C(2)-C(3)-C(13)	101.0(4)	C(8)-N(8)-C(9)	110.6(5)
C(2)-C(3)-C(14)	114.3(4)	N(8)-C(9)-C(10)	110.2(5)
C(4)-C(3)-C(13)	117.2(4)	C(1)-C(10)-C(9)	110.3(5)
C(4)-C(3)-C(14)	107.6(4)	C(2)-C(11)-C(12)	102.2(5)
C(13)-C(3)-C(14)	112.4(4)	C(11)-C(12)-O(12)	125.1(6)

Table VII (continued)

C(3)-C(4)-O(4)	125.7(5)	C(11)-C(12)-C(13)	110.0(5)
C(3)-C(4)-C(5)	110.8(4)	O(12)-C(12)-C(13)	124.9(6)
O(4)-C(4)-C(5)	123.5(5)	C(3)-C(13)-C(12)	103.0(5)
C(4)-C(5)-C(6)	108.3(4)	C(3)-C(14)-C(15)	111.9(4)
C(4)-C(5)-N(16)	110.6(4)	C(14)-C(15)-N(16)	110.0(4)
C(6)-C(5)-N(16)	110.7(4)	C(5)-N(16)-C(15)	112.5(4)
C(1)-C(6)-C(5)	111.3(4)	C(5)-N(16)-C(16)	111.5(4)
C(1)-C(6)-O(6)	110.5(4)	C(15)-N(16)-C(16)	110.5(4)

Compound **4d**

C(1)-N(2)-C(3)	109.5(3)	O(9)-C(10)-C(17)	109.3(2)
C(1)-N(2)-C(7)	110.3(3)	C(11)-C(10)-C(17)	126.0(3)
C(3)-N(2)-C(7)	110.4(3)	C(10)-C(11)-C(12)	122.0(3)
N(2)-C(3)-C(4)	111.7(2)	C(10)-C(11)-C(20)	119.1(3)
C(3)-C(4)-C(5)	113.2(2)	C(12)-C(11)-C(20)	118.9(3)
C(3)-C(4)-O(8)	111.3(2)	C(5)-C(12)-C(11)	112.0(2)
C(3)-C(4)-O(9)	103.6(2)	C(5)-C(12)-C(13)	106.4(2)
C(5)-C(4)-O(8)	107.5(2)	C(11)-C(12)-C(13)	114.6(3)
C(5)-C(4)-O(9)	111.4(2)	C(12)-C(13)-C(14)	104.8(3)
O(8)-C(4)-O(9)	109.9(2)	C(13)-C(14)-O(15)	125.1(3)
C(4)-C(5)-C(6)	109.1(2)	C(13)-C(14)-C(16)	109.7(3)
C(4)-C(5)-C(12)	110.1(2)	O(15)-C(14)-C(16)	125.1(3)
C(4)-C(5)-C(16)	109.9(2)	C(5)-C(16)-C(14)	105.9(2)
C(6)-C(5)-C(12)	111.3(2)	C(10)-C(17)-N(18)	111.4(3)
C(6)-C(5)-C(16)	113.0(2)	C(17)-N(18)-C(19)	111.0(2)
C(12)-C(5)-C(16)	103.3(2)	C(17)-N(18)-C(21)	109.9(3)
C(5)-C(6)-C(7)	112.2(3)	C(19)-N(18)-C(21)	111.0(3)
N(2)-C(7)-C(6)	110.3(3)	N(18)-C(19)-C(20)	110.7(3)
C(4)-O(9)-C(10)	116.5(2)	C(11)-C(20)-C(19)	111.2(3)
O(9)-C(10)-C(11)	124.7(3)		

is predominant). Intramolecular cyclization of **II** and **II'** and the successive dehydration yields compound **3b** (or **4b**) and **3a** (or **4a**), respectively. The intermediate **II** takes another course to produce compound **3c** (or **4c**) and **3d** (or **4d**). Hydrolysis of the furan ring of **II** gives an olefinic triketone **III** which cyclizes to give intermediate **IV** or **IV'** through an intramolecular Michael condensation. Cyclization of **IV** and **IV'** through an Aldol reaction gives compound **3c** (or **4c**) and **3d**. An intramolecular hemi-ketalization of **IV'** yields compound **4d**.

As a part of our studies on the chemistry of furopyridines, recently we reported the bromination, nitration and hydrogen exchange of furo[2,3-*b*]-, furo[3,2-*b*]-, furo[2,3-*c*]- and furo[3,2-*c*]pyridine [1]. Now we attempted to investigate the chemical properties of Py-tetrahydro derivatives of furopyridines, some of which are reported to possess biological activities such as blood platelet aggregation inhibition, antiinflammatory activity and others [2]. In this paper we wish to report novel dimerizations of 5-methyl-4,5,6,7-tetrahydrofuro[3,2-*c*] (1) [3] and 6-methyl-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine (2).

Compound **1** was refluxed with 10% hydrochloric acid for five hours to give a slightly brown syrup, from which four colorless crystalline compounds **3a** (mp 117-121°), **3b** (mp 90.5-93.5°), **3c** (mp 204-209°) and **3d** (mp 154-159°)

were isolated in 9%, 40%, 2.1% and 1.9% respectively, after separation by column chromatography on silica gel.

The structures of **3a** and **3b** were determined on the basis of the spectroscopic data. The elemental analyses and mass spectra indicated both the compounds to have the same molecular formula $C_{16}H_{20}N_2O$. The ir spectra showed neither carbonyl nor hydroxyl absorptions. The 1H nmr spectra of **3a** and **3b** exhibited signals of twenty protons, respectively. The AB-type quartet at δ 6.87 and 7.13 (2H, $J = 8.0$ Hz) for **3a** and at δ 6.88 and 7.22 (2H, $J = 8.0$ Hz) for **3b** suggested the presence of a pair of vicinal aromatic protons in each **3a** and **3b**. The values of the chemical shifts and coupling patterns of the triplets at δ 2.72 (2H, $J = 6.0$ Hz) and 3.07 (2H, $J = 6.0$ Hz) and a singlet at δ 3.63 (2H) for compound **3a** and triplets at δ 2.72 (2H, $J = 6.0$ Hz) and 3.13 (2H, $J = 6.0$ Hz) and a singlet at δ 3.64 (2H) for compound **3b** resemble those of the aliphatic protons of Py-tetrahydroisoquinoline [4]. The slightly broad singlets at δ 2.83 (4H) and 3.52 (2H) for **3a** and at δ 2.84 (4H) and 3.77 (2H) for **3b** resemble those of the aliphatic moiety of compound **1** [3]. On this basis, structures of **3a** and **3b** were assigned to the isomeric tetracyclic benzofuran compounds as either 3,8-dimethyl-1,2,3,4,7,8,9,10-octahydropyrido[3',4':4,5]furo[2,3-f]isoquinoline (**A**) or 2,9-dimethyl-1,2,3,4,8,9,10,11-octahydropyrido[3',4':4,5]-furo[3,2-f]isoquinoline (**B**). The final structural assignments were obtained through an analysis of the carbon-13 chemical shifts of the aromatic carbons of **3a** and **3b**. The ^{13}C nmr spectra of **3a** and **3b** exhibited signals of two methyl, six methylene, two aromatic methine and six aromatic quaternary carbons, respectively, which are consistent with the structures **A** and **B**. Arguments based on simple chemical-shift theory using estimation of the carbon-13 chemical shifts in substituted benzene [5] and comparison of the chemical shifts of the aromatic carbons with those of 2,3,4-trimethyl-, 2,3,5-trimethyl- and 2,3,6,7-tetramethylbenzofuran given by Platzer *et al* [6] confirmed the signals at δ 116.6 and 122.0 (both are doublets in the off-resonance decoupled spectrum) of **3a** to be assigned to C-5 and C-6 of **A**, and the signals at δ 109.5 and 122.7 (both are doublets in the off-resonance decoupled spectrum) of **3b** to C-6 and C-7 of **B**, respectively.

On the other hand, the elemental analyses and mass spectra suggested the compounds **3c** and **3d** to have the molecular formula $C_{16}H_{24}N_2O_3$. In the ir spectrum, **3c** showed absorptions assignable to an hydroxyl group at 3400-3200 (broad) cm^{-1} and carbonyl absorptions at 1735 and 1705 cm^{-1} , **3d** showed ν OH at 3450-3250 (broad) cm^{-1} and ν C=O at 1735 and 1705 cm^{-1} . The 1H nmr spectra of **3c** and **3d** exhibited only proton signals of saturated aliphatic compound as complex multiplets and also showed two *N*-methyls. The ^{13}C nmr spectra of **3c** and **3d** showed signals of two carbonyl, two *N*-methyl, two aliphatic qua-

ternary, three methine and seven methylene carbons, respectively (Table III). These data, however, did not give any more information about the structures of **3c** and **3d**.

EXPERIMENTAL

Melting points were determined by using a micro melting point apparatus (Yanagimoto). All melting points are uncorrected. The ir spectra were taken on a JASCO A-102 spectrometer. The 1H nmr spectra were recorded on a JEOL JNM-PMX-60 JEOL MH-100 or Varian XL-200 instrument. The ^{13}C nmr spectra were recorded on a Varian XL-200 or JEOL FX 90Q spectrometer. Chemical shifts are reported in part per million related to tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi RMU-6MG spectrometer.

6-Methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine (2).

To a mixture of 6-methylfuro[2,3-c]pyridinium iodide [7] (10.7 g, 0.041 mole) in methanol (150 ml) was added portionwise sodium borohydride (4.7 g, 0.123 mole) with ice-cooling and stirring. The mixture was stirred at room temperature for 15 hours. After evaporation of the solvent, the residue was treated with water and chloroform. The chloroform solution was evaporated to give a yellow syrup which was refluxed with 10% sodium hydroxide solution (100 ml) for 1.5 hours to decompose the borane-tertiary amine complex (detected by ir and 1H nmr spectra) formed. After cooling, the mixture was extracted with chloroform, washed with water, dried (potassium carbonate) and the solvent evaporated. The residual oil was distilled *in vacuo* to give 4.36 g (78%) of compound **2** as a colorless oil, bp 80-81° (21 mm Hg); ir (liquid film): 3130 (w), 2950 (s), 2860 (m), 2800 (s), 2750 (m), 2700 (w), 1640 (w), 1505 (m), 1465 (m), 1380 (s), 1320 (m), 1285 (m), 1250 (m), 1235 (s), 1190 (m), 1170 (m), 1160 (s), 1125 (m), 1080 (s), 1050 (w), 1040 (m), 1030 (m), 1015 (w), 990 (m), 920 (m), 900 (s), 840 (w), 795 (m), 755 (m), 720 (s) cm^{-1} ; 1H nmr (deuteriochloroform): δ 2.44 (s, 3H, N-CH₃), 2.50-2.77 (poorly split multiplet, 4H, methylene protons at C-4 and C-5), 3.43 (slightly broad s, 2H, methylene protons at C-7), 6.16 (d, $J = 1.8$ Hz, 1H, H-3), 7.15-7.22 (ill-split multiplet, 1H, H-2); ^{13}C nmr (deuteriochloroform): δ 22.4 (t, C-4), 45.4 (q, N-Me), 52.3 (t, C-5 or C-6), 52.7 (t, C-6 or C-5), 109.9 (d, C-3), 114.6 (s, C-3a), 140.7 (d, C-2), 148.1 (s, C-7a).

The picrate had mp 128-130° (yellow prisms from methanol).

Anal. Calcd. for $C_{14}H_{14}N_4O_6$: C, 45.90; H, 3.85; N, 15.30. Found: C, 45.72; H, 3.74; N, 15.56.

Reaction of 5-Methyl-4,5,6,7-tetrahydrofuro[3,2-c]pyridine (**1**) with Hydrochloric Acid.

A solution of compound **1** [3] (6.84 g, 0.05 mole) in 10% hydrochloric acid (300 ml) was refluxed for 5 hours. After cooling, the reaction mixture was made alkaline with 20% sodium hydroxide solution and extracted with ether. The ethereal solution was dried (potassium carbonate) and the solvent evaporated *in vacuo* to give 5.17 g of slightly brown syrup, which was fractionated by silica gel (Merck silica gel 60, 200 g) column chromatography. The fraction eluted with chloroform-methanol (100:3) afforded 0.35 g (9%) of compound **3a**, and the fraction eluted with chloroform-methanol (100:5-100:7) afforded 2.53 g (40%) of compound **3b**.

The aqueous layer after ether extraction was extracted with chloroform. The chloroform extract was dried (potassium carbonate) and evaporated to give 1.88 g of brown syrup, which was chromatographed on a silica gel (Merck silica gel 60, 100 g) column. Elution with chloroform-methanol (100:5) gave a mixture of compound **3c** and **3d** (350 mg). The mixture was fractionated by silica gel (Merck silica gel 60, 15 g) column chromatography. The first fraction eluted with chloroform-methanol (100:2) gave 0.15 g (2.1%) of **3c** and the second fraction 0.14 g (1.9%) of **3d**.

Reaction of Methyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridine (**2**) with Hydrochloric Acid.

A solution of compound **2** (4.26 g, 0.031 mole) in 10% hydrochloric acid (250 ml) was refluxed for 15 hours. After cooling, the mixture was

made alkaline and extracted with chloroform. The chloroform solution was dried (potassium carbonate) and the solvent evaporated *in vacuo* to give 5.26 g of brown syrup, which was fractionated by silica gel (Merck silica gel 60, 200 g) column chromatography. The fractions eluted with chloroform-methanol (100:5-100:7) afforded a mixture of **4a**, **4b** and **4c** (0.87 g). The fraction eluted with chloroform-methanol (100:15) afforded 1.9 g (42%) of **4d**. The mixture of **4a**, **4b** and **4c** (0.87 g) was refractionated by silica gel (Merck silica gel 60, 50 g) column chromatography. The first fraction eluted with chloroform-methanol (100:2) gave 0.14 g (3.1%) of **4c**, the second fraction eluted with chloroform-methanol (100:5) 0.62 g (16%) of **4b** and the third fraction eluted with chloroform-methanol (100:5) 0.03 g (0.75%) of **4a**.

X-Ray Structural Determination of **3c-2MeI**, **3d**, **4c** and **4d**.

Single crystals of **3c-2MeI**, **3d**, **4c** and **4d** were grown from aqueous methanol, ether, ether and methanol-ether solution, respectively. Preliminary oscillation and Weissenberg photographs were taken in each case to establish the crystal symmetries and space groups. Determination of the cell dimensions and collection of the X-ray intensity data were performed on an AFC-5 automatic four-circle monochromated $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$). Numerical calculations for the structure determinations and refinements were carried out using UNICS and AUTO library of Crystallographic Research Center, Institute for Protein Research of Lsaka University. Crystal data are given in Table IV.

The structures of **3c-2MeI**, **3d**, **4c** and **4d** were solved by the direct method using MULTAN 78 program [8]. Electron density maps calculated by the normalized structure factors (E) gave all nonhydrogen atoms, which were computed with the phase set having the highest figure of merit using 200 ($|E| > 1.91$), 300 ($|E| > 1.58$), 240 ($|E| > 1.67$), and 240

reflections ($|E| > 1.74$) for **3c-2MeI**, **3d**, **4c** and **4d**, respectively. The structures were refined by a block-diagonal least squares procedure, minimizing the quantity $\sum w(|F_o| - |F_c|)^2$ with weights w equal to $1/\sigma(F_o)^2$. All heavy atoms were refined with anisotropic temperature factors, while isotropic temperature factors for the hydrogen atoms, calculated in their stereochemically expected position, were used. The final R values were 0.116, 0.096, 0.075 and 0.062 for **3c-2MeI**, **3d**, **4c** and **4d**, respectively. The final atomic parameters of the non-hydrogen atoms, bond lengths and bond angles are listed in Table V, VI and VII.

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