Synthesis of 7-Substituted 6,7-Dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones. Reaction of 7-Hydroxy Derivatives with Nucleophiles

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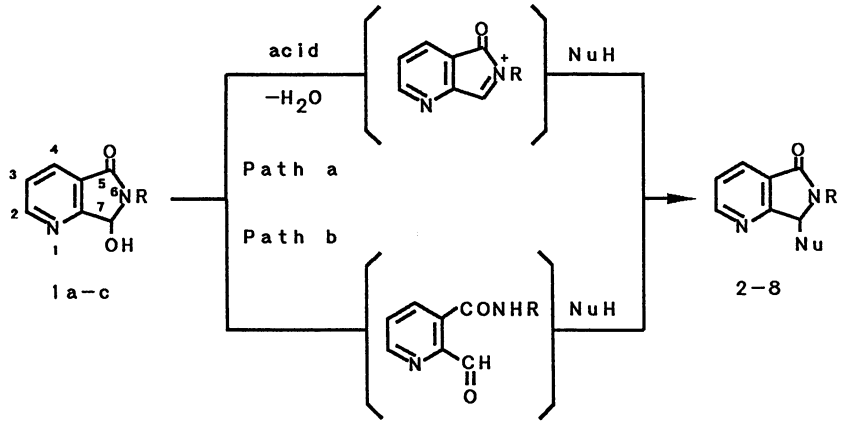
Various 7-substituted 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones are synthesized by the reaction of the corresponding 7-hydroxy derivatives with nucleophiles involving active methylene compounds, aromatics, alcohols, *p*-toluenethiol, benzenesulfinic acid, triethyl phosphite, ammonia, and amines under acidic or basic conditions. Some synthetic applications of the products obtained are demonstrated to give a 7-methylene derivative and fused tricyclic derivatives.

Much effort has been devoted to the investigation of 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones and their derivatives as cyclic nicotinamide analogs or aza-analogs of phthalimidines,[1–6] some of which are known to be biologically active compounds such as antidiabetic agents,[2] central nervous agents,[3,4] and herbicides.[5] In connection with our studies of novel functionalized isoindoles,[7] we planned the synthesis of their aza-analogs and concentrated our attention on 7-substituted 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones. Though some 7-substituted derivatives are known to be interesting pharmacologically active compounds such as non-benzodiazepine anxiolytic agents,[3,4] there have been few studies on general synthetic approach to 7-substituted derivatives in the literature, partially because unsymmetrically substituted cyclic compounds pose the problem of regiochemistry. Recently, we have performed the efficient regioselective synthesis of 7-hydroxy derivative[8a] and preliminarily reported some transformations of the hydroxyl group to other substituents.[8b,c] In this paper, we describe the synthesis of a wide variety of 7-substituted derivatives **2**—**8** from 7-hydroxy derivative **1** in detail and discuss the scope and limitation of the present methodology.

Results and Discussion

In principle, hydroxylactam **1** can be considered as (a) a source of acyliminium cation which is well known to react with various types of nucleophiles[9] and (b) a masked aldehyde which is expected to react with anionic species[4,10,11] as depicted in Scheme 1. On the basis of such viewpoints, we examined the reaction of **1** with nucleophiles under various reaction conditions and



1a: R=H
1b: R=CH_3
1c: R=C_6H_5

2: Nu=active methylene
3: Nu=aryl
4: Nu=alkoxy
5: Nu=*p*-tolylthio
6: Nu=phenylsulfonyl
7: Nu=diethoxyphosphoryl
8: Nu=amino and alkylamino

Scheme 1.

† This paper is dedicated to an emeritus professor of University of Iwate, the late Minoru Saito.

Table 1. 7-Substituted Derivatives **2**—**8** Prepared

Product	R	Nu	Method[a]	React. temp °C	React. time h	Yield[b] %	mp/°C (solvent)	Molecular formula (FW)	MS (70 eV) *m/z*
2a	H	$CH(CO_2Et)(COMe)$	A	73	3	95[c]	125—127 (AcOEt/hexane)	$C_{13}H_{14}N_2O_4$ (262.3)	219(M^+−43)
2b	Me	$CH(CO_2Et)(COMe)$	A	73	6	95[c]	101—102 (AcOEt/hexane)	$C_{14}H_{16}N_2O_4$ (276.3)	233(M^+−43)
2c	Me	$CH(COMe)_2$	A	73	2.5	95	142—143 (AcOEt)	$C_{13}H_{14}N_2O_3$ (246.3)	246(M^+)
2d	Me	$CH(COPh)_2$	A	73	0.5	100	167—168 (AcOEt)	$C_{23}H_{18}N_2O_3$ (370.4)	265(M^+−105)
2e	Ph	$CH(COPh)_2$	A	73	2.5	100	166 (AcOEt/hexane)	$C_{28}H_{20}N_2O_3$ (432.5)	432(M^+)
3a	H	2,5-$(MeO)_2C_6H_3$	A	73	1	97	187—188 (EtOH)	$C_{15}H_{14}N_2O_3$ (270.3)	270(M^+)
3b	Me	2,5-$(MeO)_2C_6H_3$	A	73	1	100	115—116 (AcOEt)	$C_{16}H_{16}N_2O_3$ (284.3)	284(M^+)
3c	Ph	2,5-$(MeO)_2C_6H_3$	A	73	3	96	175 (EtOH)	$C_{21}H_{18}N_2O_3$ (346.4)	346(M^+)
3d	H	3,4-$(MeO)_2C_6H_3$	A	73	1	95	194—195 (EtOH)	$C_{15}H_{14}N_2O_3$ (270.3)	270(M^+)
3e	Ph	3,4-$(MeO)_2C_6H_3$	A	73	12	96	145 (EtOH)	$C_{21}H_{18}N_2O_3$ (346.4)	346(M^+)
3f	H	4-$MeOC_6H_4$	A	73	0.5	55	204—206 (EtOH)	$C_{14}H_{12}N_2O_2$ (240.3)	240(M^+)
3g	H	2-BrC_6H_4	B	R.T.	1	36	169—170 (EtOH)	$C_{13}H_9N_2OBr$ (289.1)	289(M^+)
3h	H	4-BrC_6H_4				53	187 (EtOH)	$C_{13}H_9N_2OBr$ (289.1)	289(M^+)
3i	Ph	2-BrC_6H_4	B	R.T.	3	28	173 (AcOEt/hexane)	$C_{19}H_{13}N_2OBr$ (365.2)	365(M^+)
3j	Ph	4-BrC_6H_4				54	207 (EtOH)	$C_{19}H_{13}N_2OBr$ (365.2)	365(M^+)
4a	Me	OMe	C	65	8	95	91 (CCl_4/hexane)	$C_9H_{10}N_2O_2$ (178.2)	178(M^+)
4b	Me	OEt	C	78	6	97	47—48 (CCl_4/hexane)	$C_{10}H_{12}N_2O_2$ (192.2)	147(M^+−45)
4c	H	OCH_2CH_2OH	C	80	5	90	106—107 (EtOH)	$C_9H_{10}N_2O_3$ (194.2)	133(M^+−61)
4d	H	OCH_2CH_2Cl	C	80	0.2	92	141 (EtOH)	$C_9H_9N_2O_2Cl$ (212.6)	212(M^+)
4e	H	$OCH_2CH_2CH_2Cl$	C	80	0.5	100	128 (EtOH)	$C_{10}H_{11}N_2O_2Cl$ (226.7)	147(M^+−79)
4f	Me	$OCH_2CH(CH_3)_2$	C	108	3	100	70—71 (CCl_4/hexane)	$C_{12}H_{16}N_2O_2$ (220.3)	147(M^+−73)
4g	Me	$OCH(CH_3)_2$	C	82	7	96	48—52 (CCl_4/hexane)	$C_{11}H_{14}N_2O_2$ (206.2)	147(M^+−59)
4h	Me	1-menthyl	C	110	6	45	138 (Et_2O/hexane)	$C_{18}H_{26}N_2O_2$ (302.4)	302(M^+)
4i	Me	1-menthyl				43	145—146 (Et_2O/hexane)	$C_{18}H_{26}N_2O_2$ (302.4)	302(M^+)
4j	H	O-*t*-Bu	F	R.T.	0.1	91	157 (AcOEt)	$C_{11}H_{14}N_2O_2$ (206.2)	206(M^+)
4k	Me	O-*t*-Bu	F	R.T.	0.1	97	106 (Et_2O/hexane)	$C_{12}H_{16}N_2O_2$ (220.3)	220(M^+)
4l	Ph	O-*t*-Bu	F	R.T.	0.1	85	133 (AcOEt)	$C_{17}H_{18}N_2O_2$ (282.3)	282(M^+)
5a	H	S(*p*-Tol)	D	82	3.5	95	185—186 (AcOEt)	$C_{14}H_{12}N_2OS$ (256.3)	256(M^+)
6a	H	$SO_2C_6H_5$	E	82	5	69	190—191 (EtOH)	$C_{13}H_{10}N_2O_3S$ (274.3)	274(M^+)
6b	Me	$SO_2C_6H_5$	E	82	5	76	153—154 (AcOEt)	$C_{14}H_{12}N_2O_3S$ (288.3)	288(M^+)

Table 1. (Continued)

Product	R	Nu	Method[a]	React. temp °C	React. time h	Yield[b] %	mp/°C (solvent)	Molecular formula (FW)	MS (70 eV) *m/z*
7a	H	$P(O)(OEt)_2$	G	R.T.	5	57	147—148 (AcOEt)	$C_{11}H_{15}N_2O_4P$ (270.2)	270(M^+)
7b	Me	$P(O)(OEt)_2$	G	R.T.	4	73	73—74 (AcOEt)	$C_{12}H_{17}N_2O_4P$ (284.3)	284(M^+)
8a	Ph	NH_2	H	110	12	99	130 (AcOEt)	$C_{13}H_{11}N_3O$ (225.3)	225(M^+)
8b	H	NH-*n*-Pr	I	101	32	98	116 ($CHCl_3$/hexane)	$C_{10}H_{13}N_3O$ (191.2)	133(M^+−58)
			J	101	1	98			
8c	Me	NH-*n*-Pr	J	101	24	96	105 (Et_2O/hexane)	$C_{11}H_{15}N_3O$ (205.3)	147(M^+−58)
8d	Ph	NH-*n*-Pr	I	101	12	84	96 ($CHCl_3$/hexane)	$C_{16}H_{17}N_3O$ (267.3)	267(M^+)
			J	101	3	91			
8e	Me	NH-*n*-Bu	J	101	18	96	116—117 (Et_2O/hexane)	$C_{12}H_{17}N_3O$ (219.3)	147(M^+−72)
8f	Me	Piperidino	J	101	24	95	122—123 (Et_2O/$CHCl_3$)	$C_{13}H_{17}N_3O$ (231.3)	147(M^+−84)
8g	Me	NH-*t*-Bu	K	R.T.	0.1	90	143—144 (EtOH)	$C_{12}H_{17}N_3O$ (219.3)	204(M^+−15)
8h	Me	NEt_2	K	R.T.	0.1	95	89 (Et_2O/hexane)	$C_{12}H_{17}N_3O$ (219.3)	147(M^+−72)

a) For Methods A—K, see Experimental section. b) Yield of the isolated product based on **1**. c) Yield of the mixture of two diastereomers.

Table 2. Spectral and Analytical Data of Compounds **2**—**8** Prepared

Compound	IR (KBr) $\nu_{C=O}$/cm^{-1}	^{1}H NMR ($CDCl_3$/TMS) δ/ppm, J/Hz	Found Calcd/% C	H	N
2a	1720, 3180 (NH)	1.03 (3H, t, J=7, $OCH_2C\underline{H}_3$); 2.02 (3H, s, $COCH_3$); 4.06 (2H, q, J=7, $OC\underline{H}_2CH_3$); 4.23 (1H, d, J=5, H-7); 5.20 (1H, d, J=5, $COCHCO_2$); 6.92 (1H, br s H-6); 7.41 (1H, dd, J=8 and 5, H-3); 8.14 (1H, dd J=8 and 2, H-4); 8.75 (1H, dd, J=5 and 2, H-2)	59.42 59.54	5.37 5.38	10.71 10.68
2b	1720, 1740	1.17 (3H, t, J=6, $OCH_2C\underline{H}_3$); 2.09 (1H, s, $COCH_3$); 3.15 (3H, s, N-CH_3); 4.15 (2H, q, J=6, $OC\underline{H}_2CH_3$); 4.31 (1H, d, J=4, H-7); 5.18 (1H, d, J=4, $COCHCO_2$); 7.39 (1H, dd, J=8 and 5, H-3); 8.09 (1H, dd, J=8 and 2, H-4); 8.70 (1H, dd, J=5 and 2, H-2)	60.80 60.86	5.83 5.84	10.09 10.14
2c	1710, 1730	1.78 (3H, 5, $COCH_3$); 2.26 (3H, s, $COCH_3$); 3.06 (s, 3H, N-CH_3); 4.52 (1H, d, J=4, H-7); 5.33 (1H, d, J=4, COCHCO); 7.45 (1H, dd, J=8 and 5, H-3); 8.12 (1H, dd, J=8 and 2, H-4); 8.75 (1H, dd, J=5 and 2, H-2)	63.15 63.40	5.76 5.73	11.45 11.38
2d	1700	3.22 (3H, s, N-CH_3); 5.63 (1H, d, J=3, H-7); 6.21 (1H, d, J=3, COCHCO); 7.0—7.7 (m, 12H, arom+H-3+ H-4); 8.72 (1H, dd, J=5 and 2, H-2)	74.70 74.58	4.86 4.90	7.66 7.56
2e	1690, 1700	1.89 (3H, s, $COCH_3$); 3.16 (3H, s, N-CH_3); 5.38 (2H, s, H-7+COCHCO); 7.3—8.0 (6H, m, arom+H-3+H-4); 8.71(1H, dd, J=5 and 2, H-2)	78.01 77.76	4.58 4.66	6.47 6.48
3a	1710, 3310 (NH)	3.66 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); 6.03 (1H, s, H-7); 6.55 (1H, s, arom); 6.82 (2H, s, J=2H, arom), 6.94 (1H, br s, H-6); 7.37 (1H, dd, J=8 and 5, H-3); 8.17 (1H, dd, J=8 and 2, H-4); 8.74(1H, dd, J=5 and 2, H-2)	66.83 66.66	5.22 5.22	10.17 10.36
3b	1710	3.00 (3H, s, N-CH_3); 3.67 (3H, s, OCH_3); 3.78 (3H, s, OCH_3); 5.91 (1H, s, H-7); 6.36 (1H, s, arom); 6.86(2H, d, J=2, arom); 7.35 (1H, dd, J=8 and 5, H-3); 8.15 (1H, dd, J=8 and 2, H-4); 8.66 (1H, dd, J=5 and 2, H-2)	67.65 67.59	5.68 5.67	9.98 9.85
3c	1700	3.59 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 6.62 (1H, s, H-7); 6.4—7.8 (9H, m, arom+H-3); 8.26 (1H, dd, J=8 and 2, H-4); 8.73 (1H, dd, J=5 and 2, H-2)	72.69 72.82	5.22 5.24	7.91 8.09

Table 2. (Continued)

Compound	IR (KBr) $\nu_{C=O}$/cm^{-1}	^{1}H NMR ($CDCl_3$/TMS) δ/ppm, J/Hz	Found / Calcd/% C	H	N
3d	1720, 3300 (NH)	3.85 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 5.66 (1H, s, H-7); 6.8—7.0 (3H, m, arom); 7.43 (1H, dd, J=8 and 5, H-3); 7.47 (1H, br s, H-6); 8.20 (1H, dd, J=8 and 2, H-4); 8.75 (dd, 1H, J=5 and 2, H-2)	66.62 66.66	5.17 5.22	10.22 10.36
3e	1690	3.75 (3H, s, OCH_3); 3.81 (3H, s, OCH_3); 6.09 (1H, s, H-7); 6.6—7.8 (9H, m, arom+H-3); 8.23 (1H, dd, J=8 and 2, H-4); 8.73 (1H, dd, J=5 and 2, H-2)	72.68 72.82	5.19 5.24	7.91 8.09
3f	1690, 3180 (NH)	3.78 (3H, s, OCH_3); 5.63 (1H, s, H-7); 6.87 (2H, d, arom); 7.17 (1H, br s, H-6); 7.24 (2H, d, arom); 7.36 (1H, dd, J=8 and 5, H-3); 8.15 (1H, dd, J=8 and 2, H-4); 8.71 (1H, dd, J=5 and 2, H-2)	70.02 69.99	5.07 5.03	11.70 11.66
3g	1690, 3250 (NH)	6.23 (1H, s, H-7); 6.9—7.7 (6H, m, arom+H-3+H-6); 8.15 (1H, dd, J=8 and 2, H-4); 8.74 (1H, dd, J=5 and 2, H-2)	54.17 54.00	3.08 3.14	9.64 9.69
3h	1730, 3220 (NH)	5.64 (1H, s, H-7); 7.25 (2H, d, J=7, arom); 7.40 (1H, dd, J=8 and 5, H-3); 7.48 (2H, d, J=7, arom); 8.13 (1H, dd, J=8 and 2, H-4); 8.34 (1H, br s, H-6); 8.70 (1H, dd, J=5 and 2, H-2)	54.27 54.00	3.09 3.14	9.72 9.69
3i	1700	6.87 (1H, s, H-7); 7.0—7.5 (9H, m, arom); 7.67 (1H, dd, J=8 and 5, H-3); 8.25 (1H, dd, J=8 and 2, H-4); 8.74 (1H, dd, J=5 and 2, H-2)	62.67 62.48	3.59 3.59	7.62 7.67
3j	1700	6.17 (1H, s, H-7); 7.1—7.6 (5H, m, arom); 7.24 (2H, d, J=7, arom); 7.49 (2H, d, J=7, arom); 7.71 (1H, dd, J=8 and 5, H-3); 8.34 (1H, dd, J=8 and 2, H-4); 8.82 (1H, dd, J=5 and 2, H-2)	62.70 62.48	3.54 3.59	7.51 7.67
4a	1720	3.14 (3H, s, N-CH_3); 3.15 (3H, s, OCH_3); 7.43 (1H, dd, J=8 and 5, H-3); 5.65 (1H, s, H-7); 8.07 (1H, dd, J=8 and 2, H-4); 8.76 (1H, dd, J=5 and 2, H-2)	60.56 60.66	5.86 5.66	15.91 15.72
4b	1700	1.22 (3H, t, J=7, $OCH_2C\underline{H}_3$); 3.13 (3H, s, N-CH_3); 3.35 (2H, m, $OC\underline{H}_2CH_3$); 5.65 (1H, s, H-7); 7.39 (1H, dd, J=8 and 5, H-3); 8.05 (1H, dd, J=8 and 2, H-4); 8.71 (1H, dd, J=5 and 2, H-2)	62.45 62.48	6.34 6.29	14.82 14.57
4c	1710, 3100 (NH and OH)	3.5—4.0 (4H, m, $OC\underline{H}_2C\underline{H}_2O$); 4.24 (1H, br s, OH); 5.95 (1H, s, H-7); 7.50 (1H, dd, J=8 and 5, H-3); 7.78 (1H, br s, H-6); 8.12 (1H, dd, J=8 and 2, H-4); 8.75 (1H, dd, J=5 and 2, H-2)	55.58 55.67	5.17 5.19	14.50 14.43
4d	1670, 1720, 3200 (NH)	3.6—4.2 (4H, m, $OC\underline{H}_2C\underline{H}_2Cl$); 6.02 (1H, s, H-7); 7.55 (1H, br s, H-6); 7.55 (1H, dd, J=8 and 5, H-3); 8.17 (1H, dd, J=8 and 2, H-4); 8.85 (1H, dd, J=5 and 2, H-2)	50.87 50.84	4.30 4.27	13.26 13.17
4e	1710, 3150 (NH)	(DMSO-d_6) 1.98 (2H, quintet, J=6, $OCH_2C\underline{H}_2CH_2Cl$); 3.4—4.0 (4H, m, $OC\underline{H}_2CH_2C\underline{H}_2Cl$); 5.87 (1H, s, H-7); 7.56 (1H, dd, J=8 and 5, H-3); 8.08 (1H, dd, J=8 and 2, H-4); 8.77 (1H, dd, J=5 and 2, H-2); 9.33 (1H, br s, H-6)	53.10 52.99	4.96 4.89	12.37 12.36
4f	1700	0.88 and 0.91 [6H, d+d, J=7, $CH(C\underline{H}_3)_2$]; 1.7—2.0 [1H, m, $C\underline{H}(CH_3)_2$]; 2.7—3.2 (m, 2H, OCH_2); 3.12 (s, 3H, N-CH_3); 5.64 (1H, s, H-7); 7.38 (1H, dd, J=8 and 5, H-3); 8.03 (1H, dd, J=8 and 2, H-4), 8.73 (1H, dd, J=5 and 2, H-2)	65.10 65.43	7.37 7.32	12.89 12.72
4g	1710	1.22 and 1.28 [6H, d+d, J=7, $CH(C\underline{H}_3)_2$]; 3.12 (3H, s, N-CH_3); 4.00 [1H, septet, J=6, $C\underline{H}(CH_3)_2$]; 5.60 (1H, s, H-7); 7.37 (1H, dd, J=8 and 5, H-3); 8.04 (1H, dd, J=8 and 2, H-4), 8.72 (1H, dd, J=5 and 2, H-2)	63.79 64.06	6.87 6.84	13.81 13.58
4h	1700	0.6—4.2 (19H, m, menthyl); 3.11 (3H, s, N-CH_3); 5.60 (1H, s, H-7); 7.36 (1H, dd, J=8 and 5, H-3); 8.03 (1H, dd, J=8 and 2, H-4); 8.66 (1H, dd J=5 and 2, H-2)	71.43 71.49	8.77 8.67	9.19 9.26
	$[\alpha]_D^{24}$=−37.9° (c=0.715, $CHCl_3$)				
4i	1710	0.6—3.7 (19H, m, menthyl); 3.16 (3H, s, N-CH_3); 5.66 (1H, s, H-7); 7.37 (1H, dd, J=8 and 5, H-3); 8.04 (1H, dd, J=6 and 2, H-4); 8.75 (1H, dd, J=5 and 2, H-2)	71.26 71.49	8.82 8.67	9.31 9.26
	$[\alpha]_D^{24}$=−91.1° (c=0.610, $CHCl_3$)				
4j	1720, 3180 (NH)	1.50 (9H, s, $C(CH_3)_3$); 6.01 (1H, s, H-7); 7.43 (1H, dd, J=8 and 5, H-3); 8.10 (1H, dd, J=8 and 2, H-4); 8.35 (1H, br, s, H-6); 8.81 (1H, dd, J=5 and 2, H-2)	64.36 64.06	6.79 6.84	13.55 13.58

Table 2. (Continued)

Compound	IR (KBr) $\nu_{C=O}$/cm^{-1}	^{1}H NMR ($CDCl_3$/TMS) δ/ppm, J/Hz	Found Calcd/% C	H	N
4k	1710	1.49 (9H, s, $C(CH_3)_3$); 3.08 (3H, s, N-CH_3); 5.71 (1H, s, H-7); 7.33 (1H, dd, J=8 and 5, H-3); 7.98 (1H, dd, J=8 and 2, H-4); 8.68 (1H, dd, J=5 and 2, H-2)	65.30 65.43	7.44 7.32	12.80 12.72
4l	1720	1.20 (9H, s, $C(CH_3)_3$); 6.16 (1H, s, H-7); 7.3—7.6 (6H, m, arom+H-3); 8.28 (1H, dd, J=8 and 2, H-4); 8.76 (1H, dd, J=5 and 2, H-2)	72.53 72.32	6.51 6.43	9.71 9.92
5a	1720	2.23 (3H, s, CH_3); 5.89 (1H, s, H-7); 6.9—7.6 (6H, m, arom+NH+H-3); 7.95 (1H, dd, J=8 and 2, H-4); 8.87 (1H, dd, J=5 and 2, H-2)	65.84 65.60	4.75 4.72	10.64 10.93
6a	1710, 3400 (NH), 1130 (S=O), 1320 (S=O)	(DMSO-d_6) 6.39 (1H, s, H-7); 7.4—7.7 (6H, m, arom+H-3), 7.94 (1H, dd, J=8 and 2, H-4); 8.82 (1H, dd, J=5 and 2, H-2); 9.96 (1H, br s, NH)	57.07 56.93	3.69 3.67	10.22 10.21
6b	1710, 1160 (S=O), 1330 (S=O)	3.46 (3H, s, CH_3), 5.62(1H, s, H-7); 7.2—7.6 (6H, m, arom+H-3); 7.80 (dd, 1H, J=8 and 2, H-4); 8.81 (1H, dd, J=5 and 2, H-2)	58.35 58.32	4.14 4.19	9.71 9.72
7a	1250 (P=O), 1710	1.28 (6H, dt, J=8 and 2, CH_3×2); 3.9—4.5 (4H, m, CH_2×2); 5.19 (1H, d, J=15, H-7); 7.50 (1H, dd, J=8 and 5, H-3); 8.24 (1H, dd, J=8 and 1, H-4); 8.76 (1H, br s, NH); 8.88 (1H, dd, J=5 and 1, H-2)	48.79 48.89	5.63 5.60	10.60 10.37
7b	1250 (P=O), 1720	1.30 (6H, dt, J=8 and 8, CH_3×2); 3.39 (3H, s, CH_3), 4.0—4.5 (4H, m, CH_2×2); 4.88 (1H, d, J=15, H-7); 7.43 (1H, dd, J=8 and 5, H-3); 8.18 (1H, dd, J=8 and 1, H-4); 8.82 (1H, dd, J=5 and 1, H-2)	50.64 50.71	6.08 6.03	10.07 9.86
8a	1690, 3320 (NH)	2.15 (2H, br s, NH_2); 5.92 (1H, s, H-7); 7.1—7.7 (6H, m, arom+H-3); 8.12 (1H, dd, J=8 and 2, H-4); 8.77 (1H, dd, J=5 and 2, H-2)	69.43 69.32	5.05 4.92	18.33 18.65
8b	1720, 3180 (NH)	0.90 (3H, t, J=7, $NCH_2CH_2C\underline{H}_3$); 1.2—1.8 (2H, m, $NCH_2C\underline{H}_2CH_3$); 2.08 (1H, br s, NH); 2.4—2.9 (2H, m, $NC\underline{H}_2CH_2CH_3$), 5.56 (1H, s, H-7); 7.48 (1H, dd, J=8 and 2, H-3); 7.93 (1H, br s, H-6); 8.17 (1H, dd, J=8 and 2, H-4); 8.83 (1H, dd, J=5 and 2, H-2)	62.77 62.80	6.85 6.85	22.22 21.97
8c	1680, 3400 (NH)	0.85 (3H, t, J=6, $NCH_2C\underline{H}_2CH_3$); 1.45 (2H, sextet, J=6, $NCH_2C\underline{H}_2CH_3$); 2.0—2.5 (3H, m, NH+$NC\underline{H}_2CH_2CH_3$); 3.13 (3H, s, N-$CH_3$); 5.23 (1H, s, H-7); 7.37 (1H, dd, J=8 and 5, H-3); 8.06 (1H, dd, J=8 and 2, H-4); 8.72 (1H, dd, J=5 and 2, H-2)	64.38 64.37	7.49 7.37	20.31 29.47
8d	1700, 3320 (NH)	0.4—3.0 (8H, m, $NHCH_2CH_2CH_3$); 6.04 (1H, s, H-7), 7.1—7.8 (6H, m, arom+H-3); 8.16 (1H, dd, J=8 and 2, H-4); 8.81 (1H, dd, J=5 and 2, H-2)	72.23 71.89	6.45 6.41	15.54 15.72
8e	1680, 3300 (NH)	0.7—1.0 (3H, m, $NCH_2CH_2CH_2C\underline{H}_3$); 1.1—1.6 (4H, m, $NCH_2C\underline{H}_2C\underline{H}_2CH_3$); 2.18 (1H, br s, NH); 2.2—2.5 (2H, m, $NC\underline{H}_2CH_2CH_2CH_3$), 3.14 (3H, s, N-$CH_3$); 5.24 (1H, s, H-7); 7.38 (1H, dd, J=8 and 5, H-3); 8.08 (1H, dd, J=8 and 2, H-4); 8.74 (1H, dd, J=5 and 2, H-2)	65.61 65.73	7.93 7.81	19.50 19.16
8f	1690	1.3—1.7 [6H, m, CH_2×3(piperidino)]; 2.3—3.0 [4H, m, CH_2×2(piperidino)]; 3.13 (3H, s, NCH_3); 5.01 (1H, s, H-7); 7.36 (1H, dd, J=8 and 5, H-3); 8.06 (1H, dd, J=8 and 2, H-4); 9.71 (1H, dd, J=5 and 2, H-2)	67.59 67.51	7.49 7.41	18.50 18.17
8g	1680, 3300 (NH)	1.34 (9H, s, $C(CH_3)_3$); 3.11 (3H, s, N-CH_3); 5.22 (1H, s, H-7); 7.34 (1H, dd, J=8 and 5, H-3); 8.02 (1H, dd, J=8 and 2); 8.70 (1H, dd, J=5 and 2, H-2, H-4)	65.53 65.73	7.84 7.81	19.34 19.16
8h	1690	1.08 [6H, t, $N(CH_2C\underline{H}_3)_2$]; 2.4—3.0 [4H, m, $N(C\underline{H}_2CH_3)_2$]; 3.11 (3H, s, N-$CH_3$), 5.22 (1H, s, H-7); 7.36 (1H, dd, J=8 and 5, H-3); 8.07 (1H, dd, J=8 and 2, H-4); 8.71(1H, dd, J=5 and 2, H-2)	65.41 65.73	7.87 7.81	19.44 19.16

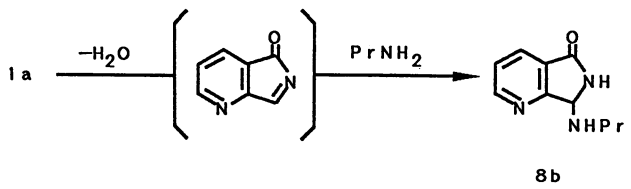
representative results are shown in Tables 1 and 2.

Acyliminium cations generated from **1a**—**c** in boiling trifluoroacetic acid (Method A) smoothly reacted with active methylene compounds such as a keto ester and diketones to yield the corresponding 7-substituted derivatives **2a**—**e** quantitatively. In the case of the keto ester (ethyl acetoacetate), the ^{1}H NMR of the crude product indicated existence of two diastereomers, but only one diastereomer was obtained after recrystallization and characterized. In contrast with the diketone and keto ester, diethyl malonate was inactive under the reaction condition, probably due to the lower concentration of the enol-form compared to the keto ester and diketone. Unfortunately, our further attempts to cause the substitution reaction under severer acidic conditions with sulfuric acid[9] or aluminum trichloride[9] and a basic condition with the enolate anion[10] of diethyl malonate resulted in the formation of a complex mixture.

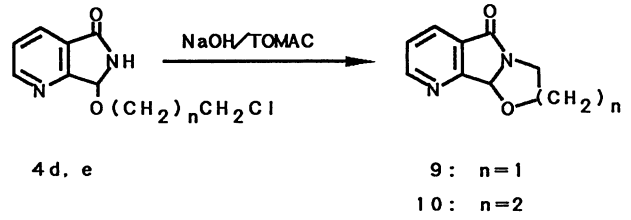
Although our effort to introduce a 7-alkenyl substituent by the reaction of alkenes with the acyliminium cation resulted in the formation of a complex mixture, aromatic compounds cleanly underwent an electrophilic substitution reaction with the acyliminium cation to furnish the corresponding 7-aryl substituted product **3**. Thus, when dimethoxybenzenes and anisole which are activated for the electrophilic substitution reaction were treated with **1a**—**c** under the reaction condition of Method A, the corresponding products **3a**—**f** were obtained in reasonable to excellent yields. On the other hand, a deactivated aromatics, bromobenzene required a strong acid such as concd sulfuric acid (Method B) for the preparation of products **3g**—**j** as well as the case of benzene itself.[8c] In contrast to the completely regioselective formation of the 3,4-isomer with 1,2-dimethoxybenzene, anisole, and bromobenzene afforded a mixture of ortho and para isomers. These isomers were separated by recrystallization and column chromatography and their regiochemistries were determined by ^{1}H NMR.[12]

The reaction of **1** with primary and secondary alcohols in the presence of a catalytic amount of *p*-toluenesulfonic acid (Method C) gave the corresponding 7-alkoxy products **4a**—**g** in quantitative yields. In the case of an optically active alcohol, *l*-menthol, a mixture of the corresponding diastereomers (**4h** and **4i**, diastereomeric excess=0), which was separable by column chromatography, was produced in a high chemical yield. Some 7-sulfur-atom-substituted derivatives were also prepared by the acid-catalyzed reaction in good yields. Thus, the reaction of **1** with *p*-toluenethiol in the presence of catalytic amount of *p*-toluenesulfonic acid in boiling acetonitrile (Method D) gave **5a**. Furthermore, a similar treatment with benzenesulfinic acid which was generated with sodium benzenesulfinate and *p*-toluenesulfonic acid (Method E) led to the formation of **6a,b**. However, the acid-catalyzed reaction with *t*-butyl alcohol gave only a low yield (20%) of the corresponding product because of the equilibrium between the substrate and the product in the presence of water. We could overcome this problem by the conversion of the hydroxyl group of the lactam to an excellent leaving group such as trifluoroacetate in the absence of water. Thus, the treatment of **1a**—**c** with trifluoroacetic anhydride followed by the addition of *t*-butyl alcohol (Method F) led to the formation of **4j**—**l** in high yields. This improved method was also effective for an Arbuzov type of reaction of **1a,b** with triethyl phosphite (Method G) to give the corresponding products **7a,b** which could not be obtained by the *p*-toluenesulfonic acid-catalyzed or non-catalyzed reaction. Even though the trifluoroacetylated intermediate could not be isolated due to its lability, the trifluoroacetylation procedure complements existing methods for the generation of the acyliminium cation.

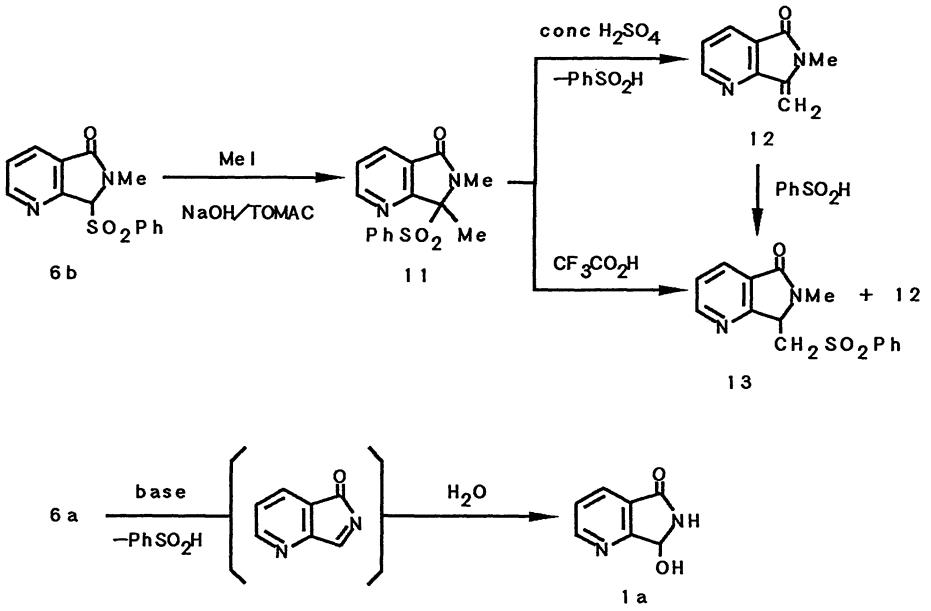
N-Phenylated lactam **1c** was cleanly aminated to **8a** by heating in liquid ammonia (Method H) as shown in the previous report with *N*-unsubstituted **1a**,[8b] while *N*-methylated **1b** gave only a trace amount of the corresponding product under the same reaction conditions. Similarly, treatment of **1a**—**c** with propylamine in boiling dioxane (Method I) led to **8b**—**d** but almost all amount of **1b** was again recovered under these reaction conditions. This remarkable substituent effect suggests that an electron-donating group such as methyl group at N-6 position precludes the ring opening of the hydroxylactam depicted in Scheme 1 (Path b). The electronic effect of substituents (H, Me, and Ph) at N-6 position is consistent with chemical shifts of H-7 of **1a**—**c**; in DMSO-d_6 δ=5.72 (**1b**), 5.82 (**1a**), and 6.44 (**1c**). However, the present data can not exclude a possibility that *N*-unsubstituted lactam **1a** undergoes the elimination of water instead of the ring opening, followed by the addition of an amine (Scheme 2). As also expected from the reaction mechanism in Path b which would involve the formation of a Schiff base, secondary amines



Scheme 2.



Scheme 3.



Scheme 4.

were inactive for the hydroxylactam under the basic reaction condition of Method I. Interestingly, the addition of a catalytic amount of *p*-toluenesulfonic acid in the reaction system (Method J) remarkably accelerated the rate of the reaction with primary and secondary amines to give **8b**—**f** in excellent yields, probably due to the generation of the acyliminium cation. As far as we know, it is the first example of acid-catalyzed amination of hydroxylactams. However, Method J was unsatisfactory for bulky amines such as diethylamine and *t*-butylamine resulting in low yields of the products (<36%). After examining reaction conditions, we found an effective way similar to Method G, that is the treatment of the bulky amine with the solution of **1b** in trifluoroacetic anhydride (Method K) affording **8g**,**h**, quantitatively. It is noteworthy that Methods J and K might be the fruitful methods for the preparation of alkylaminolactam **8** from hydroxylactam **1**.

Since various types of novel 7-substituted derivatives **2**—**8** have become available, we are now attracted to the synthetic application of these compounds. Previously, we reported a convenient alkylation of the 7-phenyl derivative at the 7-position in a phase transfer system, which involved synthesis of some fused cyclic derivatives, to demonstrate a synthetic utility of the 7-substituted derivative.[8b] Thus, we preliminarily tried to expand this methodology as follows: Compounds **4d** and **4e** having a terminal electrophilic carbon cleanly cyclized intramolecularly in the presence of NaOH-powder and trioctylmethylammonium chloride (TOMAC) to tricyclic products **9** and **10**, respectively (Scheme 3). 7-Sulfonylated **6b** having an active methine proton (H-7) was smoothly reacted with methyl iodide in the liquid–solid phase transfer system to give the 7-methylated product **11** in a good yield. Interestingly, compound **11** underwent the elimination of sulfinic acid in concd sulfuric acid to produce 7-methylene derivative **12** (Scheme 4). Recently, a similar elimination reaction has been observed by Hitching and Vernon with a 7-benzyl-7-hydroxy derivative.[6] Although this unstable and strongly fluorescent product could not be purified for the elemental analysis, spectroscopic data support the structure **12** and this method seems to be a useful way for the synthesis of 7-alkylidene derivatives. When compound **11** was treated with trifluoroacetic acid, 7-sulfonylmethyl derivative **13** was isolated (42%) along with **12** (36%) (Scheme 4). It is easily envisaged that this rearrangement product **13** was produced via elimination product **12**. In fact, **12** underwent the addition reaction with benzenesulfinic acid in trifluoroacetic acid to provide **13**. In contrast with 6-substituted **6b**, 6-unsubstituted **6a** could not be alkylated due to the elimination of sulfinic acid in the presence of NaOH followed by the addition of water resulting the 7-hydroxy derivative **1a** (Scheme 4).

In summary, novel 7-substituted derivatives **2**—**8** were obtained from 7-hydroxy derivative **1** by Methods A—K and some synthetic applications of the products were demonstrated.

Experimental

Measurements. Melting points are uncorrected. ^1H NMR spectra at 90 MHz were recorded with Hitachi R-22. IR spectra were recorded with Hitachi 295. Mass spectra were recorded with Hitachi M-2000. Optical rotations were measured with JASCO DPI-181. Elemental analysis were determined with Yanagimoto MT-3.

Materials. All reagents were obtained from Nacalai Tesque, Inc., Wako Pure Chemical Industries Ltd., Tokyo Kasei Co., Ltd., or Aldrich Chemical Co. The reagents were

used without further purification.

6-Substituted and Unsubstituted 6,7-Dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones (1a—c). These compounds were prepared according to an earlier reported procedure.[8a)]

Ethyl 2-(6-Substituted and Unsubstituted 6,7-Dihydro-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridin-7-yl)-3-oxobutanoates (2a—b), 3-(6,7-Dihydro-6-methyl-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridin-7-yl)-2,4-pentanedione (2c), 2-(6-Substituted 6,7-Dihydro-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridin-7-yl)-1,3-diphenyl-1,3-propanediones (2d—f), and 6-Substituted and Unsubstituted 7-Aryl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones (3a—f). General Procedure, Method A: A solution of **1** (1 mmol) and an active methylene compound or an aromatic compound (20 mmol) in trifluoroacetic acid (1 ml) was refluxed with stirring for 0.5—6 h. The reaction mixture was poured into ice-water, neutralized with solid Na_2CO_3 to pH 8 and extracted with $CHCl_3$ (10 ml×3). The organic layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was further purified over a silica-gel column (Wako-gel C-200, $CHCl_3$ as eluent) to afford the product which was purified by recrystallization (Table 1). Recrystallization of a mixture of ortho and para isomers obtained by using anisole gave the pure para isomer **3f**. The ortho isomer was not isolated.

3g—3j General Procedure, Method B: To a solution of **1** (1 mmol) in concd sulfuric acid (1 ml), bromobenzene (20 mmol) was added under argon. The heterogeneous mixture was vigorously stirred at r. t. for 1—3 h. After a work-up similar to that in Method A, the mixture of the corresponding para and ortho isomer was separated by column chromatography (Wako-Gel C-200, AcOEt as eluent) to isomerically pure product which was further purified by recrystallization (Table 1).

6-Substituted and Unsbstituted 6,7-Dihydro-7-alkoxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones (4a—i). General Procedure, Method C: A mixture of **1** (1 mmol), *p*-toluenesulfonic acid monohydrate (0.1 mmol), and an alcohol (20 mmol) was heated at 65—110 °C, if necessary under reflux, for 0.2—8 h. After evaporation of the excess alcohol under reduced pressure, water (10 ml) was added to the residue. The resulting mixture was basified with solid $NaHCO_3$ to pH 9 and extracted with $CHCl_3$ (10 ml×3). The organic layer was washed with water, dried over Na_2SO_4 and evaporated to give the product which was purified by recrystallization (Table 1). Optically pure diastereomers were obtained from the mixture of diastereomers, which were produced by the reaction with *l*-menthol, by column chromatography [Wako-gel C-200, hexane–AcOEt (5 : 4 v/v) as eluent] and recrystallization.

4j—l. General Procedure, Method F: A mixture of **1** (1 mmol) and trifluoroacetic anhydride (0.5 ml) was stirred for 20 min under nitrogen. The excess trifluoroacetic anhydride and the resulting trifluoroacetic acid were removed under reduced pressure, followed by addition of *t*-butyl alcohol (2 ml). After 5 min, the mixture was quenched with aqueous $NaHCO_3$ (saturated, 5 ml) and extracted with $CHCl_3$ (10 ml×3). The organic layer was washed with water, dried over Na_2SO_4, and evaporated to give the product which was purified by recrystallization (Table 1).

6,7-Dihydro-7-(*p*-tolythio)-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (5a). Method D: A solution of **1a** (1 mmol), *p*-toluenethiol (1.1 mmol) and *p*-toluenesulfonic acid (0.05 mmol) in CH_3CN (10 ml) was refluxed for 3.5 h. After $NaHCO_3$ (0.5 g) had been added to the reaction mixture, the solvent was evaporated. The residue was treated with water (10 ml) and extracted with $CHCl_3$ (10 ml×3). The organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed (Wako-gel C-200, $CHCl_3$ as eluent) to give the product which was purified by recrystallization (Table 1).

6-Substituted and Unsubstituted 6,7-Dihydro-7-phenylsulfonyl-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones (6a,b). General Procedure, Method E: Hydroxylactam **1** (1 mmol) was added to benzenesulfinic acid generated from sodium benzenesulfinate (1 mmol) and *p*-toluenesulfonic acid (1 mmol) in acetonitrile (10 ml). The resulting mixture was heated under reflux in the reaction flask connected with a dehydration column involving Na_2SO_4. After 2 h, an additional amount of benzenesulfinic acid (0.5 mmol) was supplied and further heating was continued for 3 h. After cooling to r. t., the reaction mixture was basified with $NaHCO_3$ (0.2 g) and evaporated. The residue was treated with water (10 ml) and extracted with $CHCl_3$ (10 ml×3). The combined extract was washed with water, dried (Ns_2SO_4), and evaporated. The residue was chromatographed (Wako-gel C-200, AcOEt) to give the product which was purified by recrystallization (Table 1).

6-Substituted and Unsubstituted Diethyl 6,7-Dihydro-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridin-7-ylphosphonate (7a,b). General Procedure, Method G: A mixture of **1** (1 mmol) and trifluoroacetic anhydride (2 ml) was stirred for 20 min under nitrogen. After the excess trifluoroacetic anhydride and the resulting trifluoroacetic acid were removed under reduced pressure, triethyl phosphite (2 mmol) in $CHCl_3$ (3 ml) was added to the residue and the resulting mixture was stirred for 4 h. The reaction mixture was quenched with aqueous $NaHCO_3$ (saturated, 20 ml) and extracted with $CHCl_3$ (10 ml×3). The organic layer was washed with water, dried over Na_2SO_4, and evaporated. The residue obtained was chromatographed (Wako-gel C-200, AcOEt as eluent) to give the product which was purified by recrystallization (Table 1).

7-Amino-6,7-dihydro-6-phenyl-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (8a). Method H: A solution of **1c** (1 mmol) in liquid ammonia (20 ml) was heated in an autoclave at 110 °C for 12 h. After the evaporation of ammonia at r. t., the residue was chromatographed (Wako-gel C-200, $CHCl_3$ as eluent) to give the product which was purified by recrystallization (Table 1).

6-Substituted and Unsubstituted 7-Alkylamino-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones (8b—f). General Procedure, Methods I and J: A solution of **1** (1 mmol), an amine (1.5 ml), and *p*-toluenesulfonic acid [none (Method I) or 0.2 mmol (Method J)] in dioxane (3 ml) was refluxed for 3—24 h. After addition of water (5 ml), the resulting mixture was extracted with $CHCl_3$ (10 ml×3). The organic layer was washed with water and dried over Na_2SO_4. Evaporation of organic solvent from the extract gave the product which was purified by recrystallization (Table 1).

8g—h. General Procedure, Method K: To a solution of **1b** (1 mmol) in trifluoroacetic anhydride (1 ml), an amine (2 ml) was added at 0 °C under nitrogen. A work-up similar to that in Method I afforded the product which was purified by recrystallization (Table 1).

2,3,5,9b-Tetrahydro[1,3]oxazolo[3′,2′:1,2]pyrrolo[3,4-*b*]-pyridin-5-one (9) and 3,4,6,10b-Tetrahydro-2*H*-pyrido[2′,3′:3,4]pyrrolo[2,1-*b*][1,3]oxazin-6-one (10). A mixture of **4d** (0.5 mmol), trioctylmethylammonium chloride (0.05 mmol), and NaOH-powder (0.25 g) in benzene (10 ml) was stirred under nitrogen at r. t. for 40 min. After addition of dichloromethane (10 ml) and filtration, the organic layer was dried over Na_2SO_4 and evaporated to yield **9** (96%) as colorless crystals. Similar

reaction with **4e** for 5 h gave **10** (90%) as colorless crystals.

9: Mp 102 °C (from EtOH); ^{1}H NMR ($CDCl_3$) δ=3.3—4.5 (4H, m, CH_2CH_2), 5.81 (1H, s, H-7), 7.45 (1H, dd, J=8 and 5 Hz, H-3), 8.08 (1H, dd, J=8 and 2 Hz, H-4), 8.80 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1720 cm^{-1} (C=O); MS (70 eV) m/z 176(M^+). Found: C, 61.30; H, 4.55; N, 16.14%. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.57; N, 15.90%.

10: Mp 104—105 °C (from AcOEt); ^{1}H NMR ($CDCl_3$) δ=1.5—2.2 (2H, m, CH_2), 3.1—4.7 (4H, m, CH_2×2), 5.60 (1H, s, H-7), 7.48 (1H, dd, J=8 and 5 Hz, H-3), 8.17 (1H, dd, J=8 and 2 Hz, H-4), 8.80 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1690 cm^{-1} (C=O); MS (20 eV) m/z 176 (M^+−14). Found: C, 63.01; H, 5.35; N, 14.79%. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.31; N, 14.73%.

6,7-Dihydro-6,7-dimethyl-7-phenylsulfonyl-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (11). Into a mixture of **6b** (2 mmol), trioctylmethylammonium chloride (3 mmol), and benzene (10 ml, saturated with argon) was added NaOH-powder (1 g) under argon with vigorous stirring. When MeI (10 mmol) was added to the resulting dark red suspension, the color disappeared and the stirring was continued for 30 min. After addition of dichloromethane (20 ml), the reaction mixture was filtered and evaporated. The residue was recrystallized from AcOEt to yield **11** (89%) as colorless crystals: Mp 145—146 °C (from AcOEt); ^{1}H NMR ($CDCl_3$) δ=2.13 (3H, s, CH_3), 3.32 (3H, s, CH_3), 7.1—7.5 (6H, m, arom+H-3), 7.70 (1H, dd, J=8 and 2 Hz, H-4), 8.80 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1150 (S=O), 1300 (S=O), and 1720 cm^{-1} (C=O); MS (70 eV) m/z 161 (M^+−141). Found: C, 59.69; H, 4.66; N, 9.05%. Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27%.

6,7-Dihydro-6-methyl-7-methylene-5*H*-pyrrolo[3,4-*b*]-pyridin-5-one (12). A mixture of **11** (1 mmol) and concd sulfuric acid was stirred at r. t. for 30 min. The reaction mixture was poured into ice-water, neutralized with solid Na_2CO_3 to pH 9, and extracted with $CHCl_3$ (10 ml×3). The extracts were washed with water, dried over Na_2SO_4 and evaporated. The residue obtained was chromatographed (Wako-gel C-200, AcOEt as eluent) to give the product **12** (86%): Mp 77 °C (decomp); ^{1}H NMR ($CDCl_3$) δ=3.31 (3H, s, CH_3), 4.94 and 5.67 (2H, d+d, J=2 Hz, =CH_2), 7.39 (1H, dd, J=8 and 5 Hz, H-3), 8.08 (1H, dd, J=8 and 2 Hz, H-4), 8.73 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1650 (C=C) and 1720 cm^{-1} (C=O); MS (70 eV) m/z 160 (M^+).

6,7-Dihydro-6-methyl-7-phenylsulfonyl-5*H*-pyrrolo[3,4-*b*]-pyridin-5-one (13). A solution of **1b** (0.5 mmol) in trifluoroacetic acid (2 ml) was stirred at r. t. for 1 d. The reaction mixture was quenched with ice-water, neutralized with solid Na_2CO_3, and extracted with $CHCl_3$ (10 ml×3). The organic layer was washed with water, dried over Na_2SO_4 and evaporated. The residue obtained was chromatographed (Wako-gel C-200, AcOEt as eluent) to give **12** (36%) and **13** (42%) as colorless crystals. Alternatively, into a solution of **12** (0.5 mmol) in trifluoroacetic acid (2 ml) was added sodium benzenesulfinate (4 mmol). After 4 h, a similar work-up gave **13** (62%) as colorless crystals: Mp 132—133 °C; ^{1}H NMR ($CDCl_3$) δ=3.19 (3H, s, CH_3), 3.66 (1H, dd, J=16 and 6 Hz, SO_2CH), 4.02 (1H, dd, J=16 and 5 Hz, SO_2CH), 5.93 (1H, dd, J=6 and 5 Hz, H-7), 7.5—7.9 (6H, m, H-3+arom), 8.02 (1H, dd, J=8 and 2 Hz, H-4), 8.60 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1140 (S=O), 1300 (S=O), and 1700 cm^{-1} (C=O); MS (20 eV) m/z 225 (M^+−77). Found: C, 59.55; H, 4.64; N, 9.35%. Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27%.

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