Convenient Alkylation of 6,7-Dihydro-7-phenyl-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones in a Phase Transfer System. Synthesis of Novel Cyclic Nicotinamide Analogs

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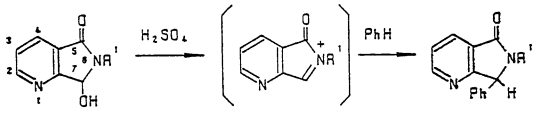
Synopsis. The title reaction is readily achieved with alkyl halides in the presence of sodium hydroxide and a phase transfer catalyst to afford 7-alkylated derivatives in good yields. The present reaction involving intramolecular double-alkylation at C-7 and N-6 with dihalides leads to novel fused heterocyclic systems.

Although 7-substituted 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones and related compounds have received increased attention as biologically active compounds such as herbicides[1a] and central nervous system agents,[1b] we find only few studies on general synthetic approach to the 7-substituted derivatives in the literature. In the course of our studies on the synthesis of cyclic nicotinamide analogs having some functionality, we have developed an efficient method for the preparation of the 7-hydroxy derivative **1** as a precursor for various pyrrolopyridinone derivatives.[2] This prompted us to synthesize new type of compounds derived from **1**. Here we wish to report the synthesis of novel heterocyclic systems by the alkylation of 7-phenyl derivative **2** which is readily available from **1**.

Results and Discussion

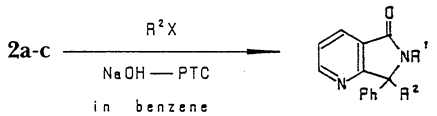
Hydroxylactam **1** can be regarded as an α-amidoalkylating reagent which is well known to react with a variety of nucleophiles.[3] In fact, **1a—c** cleanly reacted with benzene in conc sulfuric acid at room temperature to furnish novel 7-phenyl derivatives **2a—c** quantitatively (Eq. 1). During further attempts to expand the scope of the synthetic methods for the pyrrolopyridinone derivatives, our attention was directed toward the introduction of a substituent at the 7-position of the pyrrolopyridinone ring system with an electrophile. As far as we know, there has been no study from such a standpoint in the literature, although it is easily envisaged that **2** can undergo the substitution reaction at the 7-position with an electrophile in the presence of a base. Thus, **2** was found to be alkylated easily with alkyl halides in a phase transfer system affording new pyrrolopyridinone derivatives which have a tertiary unsymmetrical carbon atom in the lactam ring (Eq. 2). These results are listed in Table 1.



(1)

1a: R^1=Me
1b: R^1=Ph
1c: R^1=H

2a-c



(2)

3a: R^1=R^2=Me
3ba: R^1=Ph, R^2=Me
3bb: R^1=Ph, R^2=CH_2Ph
3bc: R^1=Ph, R^2=$CH_2CH{=}CH_2$
3bd: R^1=Ph, R^2=CH_2CO_2Et
3be: R^1=Ph, R^2=$CH_2CH_2CO_2Et$
3c: R^1=H, R^2=Me

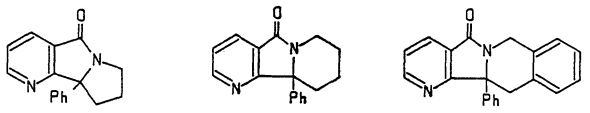
Table 1. Alkylation of **2** with Alkyl Halide in Phase Transfer System[a]

Run	Lactam	Halide (mmol)	PTC (mmol)	Base	React. time/h	Product (yield/%)[b]
1	**2a**	MeI(20)	Bu_4NI(1)	aq NaOH	52	**3a**(77)
2	**2a**	MeI(20)	TOMAC(1)	aq NaOH	9	**3a**(79)
3	**2a**	MeI(20)	TOMAC(1.5)	aq NaOH	2	**3a**(92)
4	**2a**	MeI(20)	TOMAC(1.5)	NaOH	3.5	**3a**(89)
5	**2b**	MeI(20)	TOMAC(1.5)	NaOH	0.08	**3ba**(98)
6	**2b**	$PhCH_2Cl$(1.5)	TOMAC(1.5)	NaOH	3	**3bb**(93)
7	**2b**	$CH_2{=}CHCH_2Br$(1.5)	TOMAC(1.5)	NaOH	0.2	**3bc**(97)
8	**2b**	$BrCH_2CO_2Et$(3)	TOMAC(3)	NaOH	0.7	**3bd**(74)
9	**2b**	$BrCH_2CH_2CO_2Et$(1.5)	TOMAC(1.5)	NaOH	0.08	**3be**(90)
10	**2c**	MeI(20)	TOMAC(1.5)	NaOH	1	**3a**(84)
11	**2c**	MeI(1)	TOMAC(1.5)	NaOH	0.5	**3a**(40)[c] **3c**(19)[c] **2a**(9)[c]
12	**2c**	$ClCH_2CH_2CH_2Br$(1.3)	TOMAC(3)	NaOH	0.5	**4**(69)
13	**2c**	$BrCH_2CH_2CH_2CH_2Br$(1.3)	TOMAC(3)	NaOH	0.5	**5**(80)
14	**2c**	*o*-$Ph(CH_2Br)_2$(1.3)	TOMAC(3)	NaOH	0.5	**6**(92)

a) Substrate: 1 mmol; react. temp: r.t.; solvent: benzene(10 ml); aq NaOH: 50% (10 ml); NaOH: powder(0.5 g). b) Isolated yield. c) Determined by ^1H NMR.

The methylation of **2a** to **3a** with MeI in benzene depended on both kind and amount of the phase transfer catalyst(PTC) used (Runs 1—3). The best result was obtained when an excess amount of trioctylmethylammonium chloride(TOMAC) was employed (Run 3). Since a satisfactory yield was obtained with NaOH-powder (Run 4), the use of NaOH-powder instead of aq NaOH is a better choice for simplified experimental procedure. In order to establish the utility and generality of the present reaction, 6-phenylated **2b** was subjected to the reaction with various types of alkyl halides to give desirable results (Runs 5—9). Especially, it is noteworthy that **2b** was smoothly ethoxycarbonylmethylated and ethoxycarbonylethylated without considerable hydrolysis of ester moiety to afford **3bd** and **3be**, respectively, which have a structure related to an anxiolytic compound.[1b,4]

The methylation of 6-unsubstituted lactam **2c** with an excess amount of MeI led to the formation of **3a** in which lactam nitrogen(N-6) was also methylated (Run 10).[5] When an equimolar amount of MeI was employed, a mixture of **3a**, **3c**, and **2a** along with recovered **2c** was obtained (Run 11). The result in Run 11 indicated that two kinds of anions(N-6 and C-7) would exist in the reaction system, and the rate of the latter alkylation is considerably fast. On the basis of these results, the intramolecular double-alkylation of **2c** with dihalides was examined. Indeed, **2c** reacted uneventfully with 1-bromo-3-chloropropane (Run 12), 1,4-dibromobutane (Run 13), and α,α'-dibromo-*o*-xylene (Run 14) to produce the corresponding fused heterocyclic compounds **4**, **5**, and **6** in good yields, respectively (Chart 1). It deserves emphasis that these novel tricyclic and tetracyclic compounds contain pyrrolizidine or indolizidine ring system analogous to 1-azabicyclic alkaloids.[6]



4 **5** **6**

Chart 1.

Experimental

Measurements. Melting points were uncorrected. ^{1}H NMR spectra were recorded at 90 MHz with Hitachi R-22. IR spectra were recorded with Hitachi 295. Mass spectra were recorded with Hitachi M-2000. Elemental analyses were determined with Yanagimoto MT-3.

6-Substituted and Unsubstituted 6,7-Dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones (1a—c). These were prepared according to a procedure in the literature.[2]

6-Substituted and Unsubstituted 6,7-Dihydro-7-phenyl-5*H*-pyrrolo[3,4-*b*]pyridin-5-ones (2a—c). As a general procedure, into a solution of **1** (1 mmol) in conc H_2SO_4 (2 ml) was added benzene (1 ml) under argon and then the mixture was vigorously stirred for 30 min. The reaction mixture was neutralized with Na_2CO_3 and extracted with $CHCl_3$ (10 ml×3). After evaporation, the residue was purified on a short silica-gel columun (Wako-Gel C-200, $CHCl_3$).

2a: Mp 141—142 °C (from AcOEt-hexane); ^{1}H NMR ($CDCl_3$) δ=3.03 (3H, s, CH_3), 5.42 (1H, s, H-7), 7.1—7.4 (6H, m, arom+H-3), 8.16 (1H, dd, J=7 and 1 Hz, H-4), 8.65 (1H, dd, J=5 and 1 Hz, H-2); IR (KBr) 1690 (C=O) cm^{-1}; MS (70 eV) m/z 224 (M^+). Found: C, 75.20; H, 5.36; N, 12.51%. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49%.

2b: Mp 199 °C (from EtOH) ; ^{1}H NMR ($CDCl_3$) δ=6.17 (1H, s, H-7), 7.0—7.8 (11H m, arom+H-3), 8.25 (1H, dd, J=7 and 1Hz, H-4), 8.74 (1H, dd, J=5 and 1 Hz, H-2); IR (KBr) 1700 (C=O) cm^{-1}; MS (70 eV) m/z 286 (M^+). Found: C, 79.87; H, 4.89; N, 9.61%. Calcd for : $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78%.

2c: Mp 221—222 °C (from EtOH); ^{1}H NMR ($CDCl_3$) δ=5.67 (1H, s, H-7), 7.2—7.5 (7H, m, arom+H-3+NH), 8.15 (1H, dd, J=7 and 1 Hz, H-4), 8.69 (1H, dd, J=5 and 1 Hz, H-2); IR (KBr) 3160, 3060 (N-H), 1690 (C=O) cm^{-1}; MS (70 eV) m/z 210 (M^+). Found: C, 74.45; H, 4.72, N, 13.30%. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32%.

Alkylation of 2 in a Phase Transfer System. Typical procedure (Run 4): Into a mixture of **2a** (1 mmol),TOMAC (1.5 mmol) and benzene (10 ml) were added NaOH-powder (0.5 g) under argon with vigorous stirring. MeI (20 mmol) in benzene (2 ml) was added to the dark blue suspension. After 3.5 h, dichloromethane (20 ml) was added to the reaction mixture and the resulting mixture was filtered, and evaporated. The residue was purified through a short silica-gel column (Wako-gel C-200, AcOEt) to give **3a** as colorless crystals.

3a: Mp 103—104 °C (from AcOEt-hexane); ^{1}H NMR ($CDCl_3$) δ=1.94 (3H, s, CH_3), 2.91 (3H, s, CH_3), 7.0—7.6 (6H, m, arom+H-3), 8.14 (1H, dd, J=9 and 2 Hz, H-4), 8.60 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1690 (C=O) cm^{-1}; MS (70 eV) m/z 238 (M^+). Found: C, 75.65; H, 5.90; N, 11.47%. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76%.

3ba: Mp 174—175 °C (from AcOEt); ^{1}H NMR ($CDCl_3$) δ=2.00 (3H, s, CH_3), 7.0—7.6 (11H, m, arom+H-3), 8.25 (1H, dd, J=9 and 2 Hz , H-4), 8. 69 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1710 (C=O) cm^{-1}; MS (70 eV) m/z 300 (M^+). Found: C, 80.21; H, 5.34; N, 9.19%. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33%.

3bb: Mp 144—145 °C (from AcOEt-hexane); ^{1}H NMR ($CDCl_3$) δ=3.76 and 4.40 (2H, d+d, J_{gem}=14Hz, CH_2Ph), 6.2—7.6 (16H, m, arom+H-3), 8.00 (1H, dd, J=9 and 2 Hz, H-4), 8.73 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1710 (C=O) cm^{-1}; MS (70 eV) m/z 376 (M^+). Found:C, 83.19; H, 5.29; N, 7.34%. Calcd for $C_{26}H_{20}N_2O$: C, 82.95; H, 5.35; N, 7.44%.

3bc: Mp 97—98 °C (from AcOEt-hexane); ^{1}H NMR ($CDCl_3$) δ=3.16 and 3.68 (2H, dd+dd, J=15 and 7 Hz, CH_2), 4.5—5.5 (3H, m, CH=CH_2), 6.9—7.6 (11H, m, arom+H-3), 8.22 (1H, dd, J=9 and 2 Hz , H-4), 8.70 (1H , dd, J=5 and 2 Hz, H-2); IR (KBr) 1700 (C=O) cm^{-1}; MS (70 eV) m/z 285 (M^+−41). Found: C, 81.26; H, 5.52; N, 8.55%. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58%.

3bd: Mp 116—117 °C (from AcOEt-hexane); ^{1}H NMR ($CDCl_3$) δ=0.89 (3H, t, J=8 Hz, CH_3), 3.79 (2H, q, J=8 Hz, CH_2), 3.33 and 3.97 (2H, d+d, J_{gem}=16 Hz, CH_2), 7.0—7.5 (6H, m, arom+H-3), 8.29 (1H, dd, J=9 and 2 Hz, H-4), 8.74 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1750, 1723 (C=O) cm^{-1}; MS (70 eV) m/z 372 (M^+). Found: C, 74.35; H, 5.42; N, 7.58%. Calcd for $C_{23}H_{20}N_2O_3$; C, 74.18; H, 5.41; N, 7.52%.

3be: Mp 123—124 °C (from AcOEt-hexane); ^{1}H NMR ($CDCl_3$) δ=1.17 (3H, t, J=8 Hz, CH_3), 4.02 (2H, q, J=8 Hz, CH_2), 1.5—3.5 (4H, m, CH_2×2), 7.0—7.5 (6H, m, arom+H-3), 8.26 (1H, dd, J=9 and 2 Hz, H-4), 8.72 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1700 (C=O) cm^{-1}; MS (70 eV) m/z 386 (M^+). Found: C, 74.53; H, 5.77; N, 7.06%. Calcd for $C_{24}H_{22}N_2O_3$; C, 74.59; H, 5.74; N, 7.25%.

4: Mp 150—151 °C (from AcOEt); ^{1}H NMR ($CDCl_3$) δ=1.3—2.9 (4H, m, CH_2×2), 3.3—4.2 (2H, m, CH_2), 7.2—7.8

(6H, m, arom+H-3), 8.04 (1H, dd, J=9 and 2 Hz, H-4), 8.64 (1H, dd, J=5 and 2 Hz H-2); IR (KBr) 1670 (C=O) cm^{-1}; MS (70 eV) m/z 250 (M^+). Found: C, 77.00; H, 5.62; N, 10.94%. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19%.

5: Mp 186—187 °C (from AcOEt); ^1H NMR ($CDCl_3$) δ=1.2—4.7 (8H, m, CH_2×4), 7.2—7.5 (6H, m, arom+H-3), 8.15 (1H, dd, J=9 and 2 Hz , H-4), 8.61 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1700 (C=O) cm^{-1}; MS (70 eV) m/z 264 (M^+). Found: C, 77.53; H, 6.09; N, 10.45%. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60%.

6: Mp 213—214 °C (from AcOEt); ^1H NMR ($CDCl_3$) δ=3.04 and 4.20 (2H, d+d, J_{gem}=17 Hz, CH_2), 4.30 and 5.45 (2H, d+d, J_{gem}=17 Hz, CH_2), 6.8—7.5 (10H, m, arom+H-3), 8.22 (1H, dd, J=9 and 2 Hz, H-4), 8.68 (1H, dd, J=5 and 2 Hz, H-2); IR (KBr) 1690 (C=O) cm^{-1}; MS (70 eV) m/z 312 (M^+). Found: C, 81.00; H, 5.12; N, 8.75%. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N,8.79%.

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