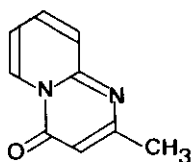


CYCLIZATION OF 2-(γ -BROMOACETOACETAMIDO)PYRIDINE DERIVATIVES:
FORMATION OF N-ARYL- γ -LACTAM DERIVATIVES

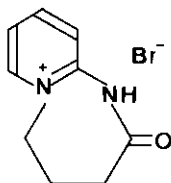
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Abstract -- 1-(2-Pyridyl)-4-hydroxy-2-pyrrolidone (**7**) was obtained from 2-(γ -bromoacetoacetamido)pyridine (**1**) through the reduction of the β -carbonyl group with NaBH_4 , protection of the hydroxyl group by tetrahydropyranyl group, cyclization of the ether to a γ -lactam by using DBU, and subsequent hydrolysis of the ether. According to the similar synthetic process, 1-phenyl-4-hydroxy-2-pyrrolidone (**8a**) and 1-(*p*-methoxyphenyl)-4-hydroxy-2-pyrrolidone (**8b**) were derived from the corresponding γ -bromoacetoacetanilide derivatives.

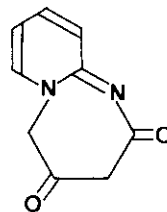
It is known that 2-aminopyridine is one of the useful synthon for the preparation of 1,3-diazabicyclo compounds. For instance, Kato *et al.* have reported that the reaction of 2-aminopyridine with diketene affords 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (**A**)¹⁾, and Fozard and Jones described that a small amount of 2-oxo-2,3,4,5-tetrahydro-1H-pyrido[1,2-a]-1,3-diazepinium bromide (**B**) is formed from the reaction with γ -bromobutyryl bromide.²⁾ We were interested in the preparation of a 1,3-diazepine derivative (**C**) by dehydrobromination of 2-(γ -bromoacetoacetamido)-pyridine (**1**) which is readily prepared from 2-aminopyridine and γ -bromoacetoacetyl



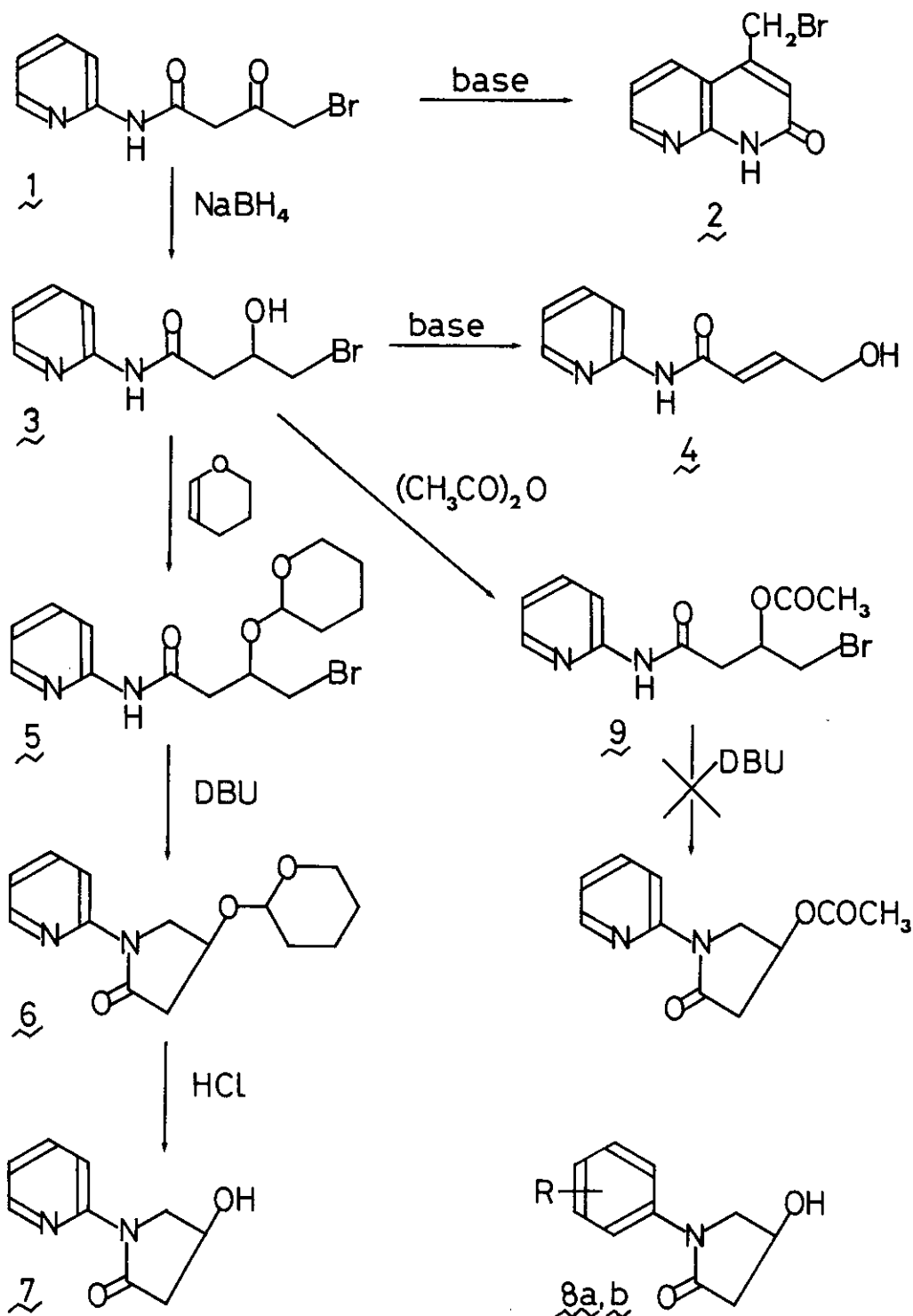
(A)



(B)



(C)



Scheme 1

bromide. However, attempted cyclization of **1** and its derivatives by means of an organic base gave not any seven-membered products but instead γ -lactam derivatives (Scheme 1).

Treatment of compound **1** with triethylamine or 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) at room temperature gave a large amount of resinous substance and a small amount of 1,2-dihydro-4-bromomethyl-1,8-naphthyridin-2-one (**2**), $C_9H_7BrN_2O$,^{3,4} as colorless needles (from $CHCl_3$, mp 147° , 7%).⁵ Chick and Wilsmore have observed a similar cyclization of acetoacetanilide to 4-methylcarbostyryl.⁶

Therefore, compound **1** was reduced with sodium borohydride in EtOH to give 2-(3-hydroxy-4-bromobutanamido)pyridine (**3**), $C_9H_{11}BrN_2O_2$,⁷ as colorless needles (from MeOH, mp 112° , 49%). Treatment of compound **3** with triethylamine or DBU in dry THF at room temperature gave 2-(4-hydroxy-2-butenamido)pyridine (**4**), $C_9H_{10}N_2O_2$,⁸ as colorless needles (from $CHCl_3$, mp 137° , 80%), no 1,3-diazepine derivative being noticed also in this case. Miyamoto *et al.* have recently reported that dehydrobromination of 3-hydroxy-4-bromobutanilide with $1N$ sodium hydroxide yields 4-hydroxy-2-butenilide *via* 3,4-epoxybutananilide.⁹

In order to prevent epoxidation of the bromohydrin moiety, the hydroxyl function of **3** was protected as a tetrahydropyranyl derivative. Thus compound **3** was treated with 2,3-dihydro-4H-pyran in dry dioxan at room temperature in the presence of boron trifluoride-etherate to give 2-[3-(tetrahydropyran-2-yloxy)-4-bromobutanamido]pyridine (**5**),¹⁰ $C_{14}H_{19}BrN_2O_3$,¹¹ as fairly unstable pale yellow viscous oil (73.2%). The ether (**5**) was then treated with DBU in dry THF at room temperature for 8 hr to afford the dehydrobrominated product (**6**),¹² $C_{14}H_{18}N_2O_3$,¹³ as colorless viscous oil (82%). However, it was confirmed that compound **6** was not a 1,3-diazepine derivative but a γ -lactam derivative. The UV spectrum of compound **6** showed λ_{max} (EtOH) at 242nm ($\epsilon = 9200$) and 278nm ($\epsilon = 7000$) and was very similar to that of 2-acetamidopyridine derivatives,¹⁴ and the mass spectrum exhibited the fragment ion of the pyridyl moiety at m/e 78. Thus compound **6** was determined to be 1-(2-pyridyl)-4-(tetrahydropyran-2-yloxy)-2-pyrrolidone.

When compound **6** was refluxed with 5% hydrochloric acid in aqueous EtOH for 2 hr, 1-(2-pyridyl)-4-hydroxy-2-pyrrolidone (**7**), $C_9H_{10}N_2O_2$,¹⁵ was obtained as colorless needles (from $CHCl_3$, mp 104° , 55%).

A similar synthetic process was applied to γ -bromoacetoacetanilide and γ -bromo-*p*-acetoacetanilide, and 1-phenyl-4-hydroxy-2-pyrrolidone (**8a**, R = H) ($C_{10}H_{11}NO_2$,¹⁶

colorless needles from benzene, mp 88°) and 1-(p-methoxyphenyl)-4-hydroxy-2-pyrrolidone (8_k, R = p-OCH₃) (C₁₁H₁₃NO₃,¹⁷) colorless needles from benzene, mp 125°), were obtained in the over-all yields of 48 and 26%, respectively.

Contrary to compound 5_k, 2-(3-acetoxy-4-bromobutanamido)pyridine (9_k) (C₁₁H₁₃BrN₂O₃,¹⁸) colorless scales from CHCl₃, mp 112°), which was prepared by the action of acetic anhydride in 95% yield, gave only a resinous substance upon treatment with DBU in dry THF at room temperature.

While we were not able to obtain the desired 1,3-diazepine derivative, the reaction sequence from 1_k to 7_k through 3_k, 5_k, and 6_k is apparently a convenient method for the preparation of N-aryl-γ-lactam derivatives. Research on the scope and limitation of the present method is currently investigated.

REFERENCES AND NOTES

- 1) T. Kato, Y. Yamanaka, T. Niitsuma, K. Wagatsuma, and M. Oizumi, Chem. Pharm. Bull. (Tokyo), 12, 910 (1964).
- 2) A. Fozard and G. Jones, J. Chem. Soc., 1964, 2763.
- 3) All new compounds reported herein gave the analytical values and the mass numbers (m/e) of the parent peaks in full agreement with the proposed structures. The IR, NMR, and UV spectral data were also consistent with the assigned structures.
- 4) IR ν(KBr) cm⁻¹: 3100 (NH), 1695 (C=O). ¹H NMR δ(CDCl₃) ppm: 4.36 (2H, s, CH₂Br), 6.55 (1H, s, 3-H), 7.15 - 7.85 (3H, m, aromatic H), 9.00 (1H, m, disappeared by addition of D₂O, NH). MS (m/e): 240, 238 (M⁺).
- 5) Melting points are uncorrected.
- 6) F. Chick and N. Wilsmore, J. Chem. Soc., 97, 1978 (1910).
- 7) IR ν(KBr) cm⁻¹: 3420 (OH), 3200 (NH), 1675 (C=O). ¹H NMR δ(CDCl₃) ppm: 2.61 (2H, d, J = 5 Hz, 2-H), 3.51 (2H, d, J = 5 Hz, 4-H), 4.18 (1H, m, 3-H), 3.7 - 4.5 (2H, b, disappeared by addition of D₂O, OH and NH), 7.0 - 8.3 (4H, m, pyridyl H). MS (m/e): 260, 258 (M⁺).
- 8) IR ν(KBr) cm⁻¹: 3450 (OH), 3200 (NH), 1680 (C=O). ¹H NMR δ(DMSO-d₆) ppm: 4.15 (2H, m, CH₂OH), 5.1 (1H, m, disappeared by addition of D₂O, OH), 6.28 (1H, m, CO-CH=), 6.55 (1H, m, =CH-CH₂), 7.0 - 8.3 (4H, m, pyridyl H), 8.5 (1H, b, disappeared by addition of D₂O, NH). MS (m/e): 178 (M⁺).
- 9) S. Miyamoto, S. Shigeoka, K. Imai, and M. Kurono, Yakugaku Zasshi, 99, 633

(1979).

- 10) The product was a mixture of diastereoisomers and showed very closely located two spots on its Thin-layer chromatogram.
- 11) IR $\nu(\text{CHCl}_3)$ cm^{-1} : 3300 (NH), 2950 (CH), 1695 (C=O). $^1\text{H NMR } \delta(\text{CDCl}_3)$ ppm: 2.75 (2H, m, changed to broad singlet centred at about 2.84 ppm on irradiation at 5.4 ppm, 2-H), 3.68 (2H, m, changed to AB-quartet centred at 3.56 and 3.70 ppm on irradiation at 5.4 ppm, 4-H), 5.42 (1H, m, 3-H), 1.6, 3.5, 3.7 and 4.2 (9H, each m, tetrahydropyranyl H), 9.5 (1H, b, disappeared by addition of D_2O , NH). MS (m/e): 344, 342 (M^+).
- 12) The product was a mixture of diastereoisomers and showed very closely located two spots on its Thin-layer chromatogram.
- 13) IR $\nu(\text{CHCl}_3)$ cm^{-1} : 2950 (CH), 1705 (C=O). $^1\text{H NMR } \delta(\text{CDCl}_3)$ ppm: 2.58 - 3.00 (2H, m, changed to AB-quartet centred at 2.65 and 2.89 ppm on irradiation at 4.50 ppm, 3-H), 4.25 (2H, d, $J = 5$ Hz, 5-H), 4.50 (1H, m, 4-H), 6.9 - 8.3 (4H, m, pyridyl H), 1.6, 3.5, 3.7, and 3.8 (9H, each m, tetrahydropyranyl H). MS (m/e): 262 (M^+).
- 14) "The Sadtler Handbook of Ultraviolet Spectra", Sadtler Research Lab., Dic., of Bio-Rad Lab., Inc., 3316, Spring Garden Street, Phila., Pennsylvania 19104, (1979), pp. 705.
- 15) IR $\nu(\text{KBr})$ cm^{-1} : 3400 (OH), 1680 (C=O). $^1\text{H NMR } \delta(\text{CDCl}_3)$ ppm: 2.50 - 3.05 (2H, m, changed to AB-quartet centred at 2.65 and 2.92 ppm on irradiation at 4.50 ppm, 3-H), 3.30 (1H, b, disappeared by addition of D_2O , OH), 4.18 (2H, m, 5-H), 4.50 (1H, m, 4-H), 6.8 - 8.3 (4H, m, pyridyl H). MS (m/e): 178 (M^+).
- 16) IR $\nu(\text{KBr})$ cm^{-1} : 3370 (OH), 1685 (C=O). $^1\text{H NMR } \delta(\text{CDCl}_3)$ ppm: 2.37 - 2.85 (2H, m, changed to AB-quartet centred at 2.50 and 2.78 ppm on irradiation at 4.4 ppm, 3-H), 3.5 - 4.0 (2H, m, changed to AB-quartet centred at 3.65 and 3.90 ppm on irradiation at 4.4 ppm, 5-H), 4.1 (1H, b, disappeared by addition of D_2O , OH), 4.43 (1H, m, 4-H), 7.0 - 7.5 (5H, m, aromatic H). MS (m/e): 177 (M^+).
- 17) IR $\nu(\text{KBr})$ cm^{-1} : 3310 (OH), 1680 (C=O). $^1\text{H NMR } \delta(\text{CDCl}_3)$ ppm: 2.40 - 2.98 (2H, ABX-octet, changed to AB-quartet centred at 2.52 and 2.81 ppm on irradiation at 4.45 ppm, 3-H), 3.6 - 4.1 (2H, ABX-octet, changed to AB-quartet centred at 3.74 and 3.92 ppm on irradiation at 4.45 ppm, 5-H), 3.76 (3H, s, OCH_3), 3.9 (1H, b, disappeared by addition of D_2O , OH), 4.45 (1H, m, 4-H),

6.82 and 7.39 (4H, AB-q, $J = 6$ Hz, aromatic H). MS (m/e): 207 (M^+).

18) IR ν (KBr) cm^{-1} : 3200 (NH), 1740 (acetyl C=O), 1690 (amido C=O). ^1H NMR δ (CDCl₃) ppm: 2.08 (3H, s, acetyl CH₃), 2.81 (2H, d, $J = 6$ Hz, CO-CH₂), 3.62 (2H, m, changed to AB-quartet centred at 3.55 and 3.70 ppm on irradiation at 5.41 ppm, CH₂Br), 5.41 (1H, m, CH-OAc), 6.95 - 8.5 (4H, m, pyridyl H), 9.50 (1H, b, disappeared by addition of D₂O, NH). MS (m/e): 302, 300 (M^+).

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