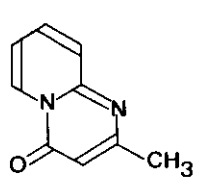
CYCLIZATION OF 2-(Γ-BROMOACETOACETAMIDO)PYRIDINE DERIVATIVES: FORMATION OF N-ARYL-Γ-LACTAM DERIVATIVES

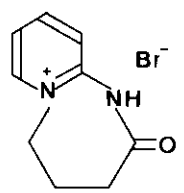
Katsumi Tabei*, Hideharu Ito, and Toyozo Takada
Tokyo College of Pharmacy, Horinouchi 1432-1, Hachioji City,
Tokyo 192-03, Japan

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)



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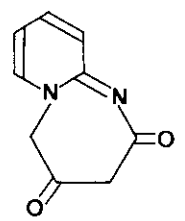

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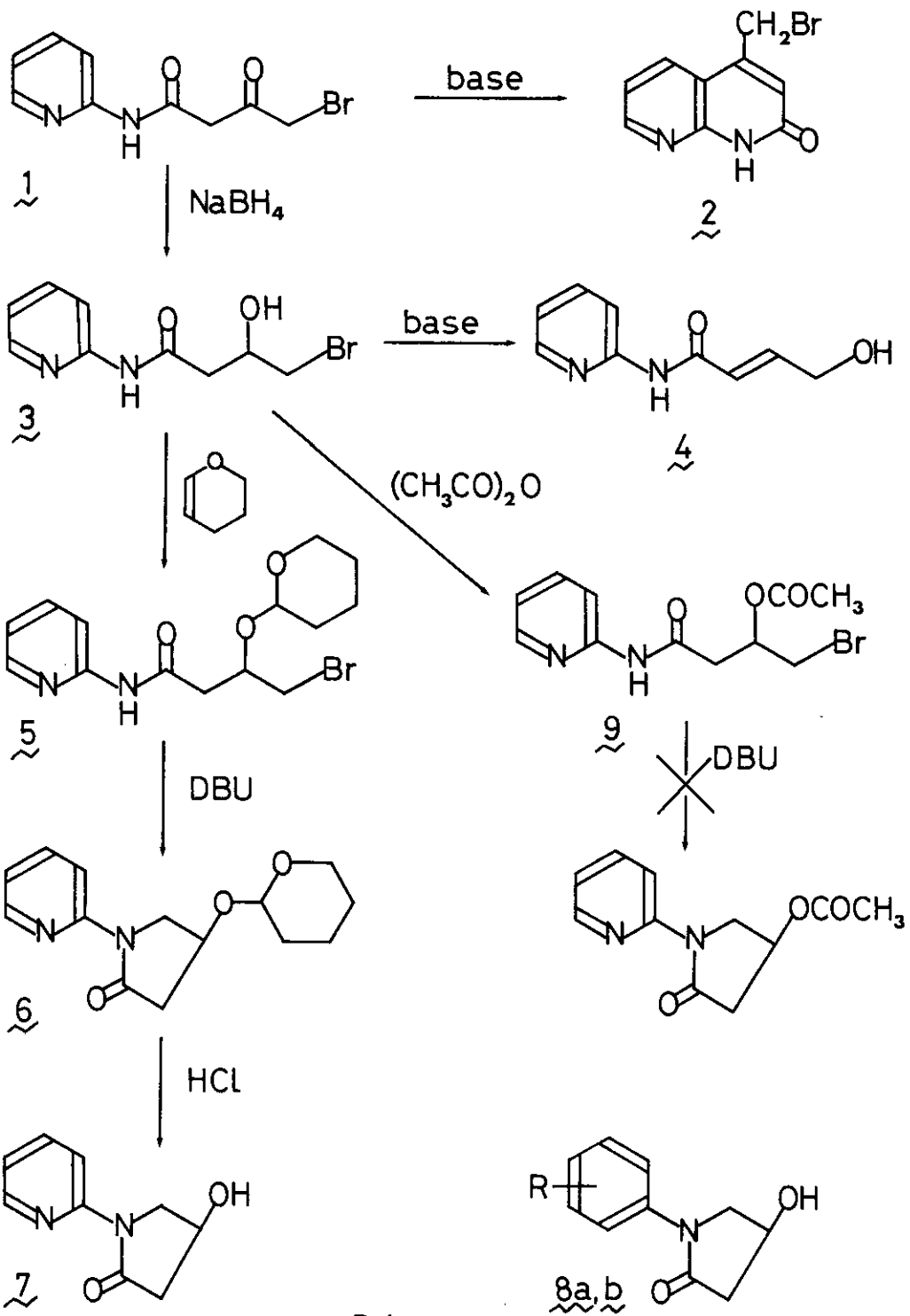

Scheme 1

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-methylcarbostyril.[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-bromobutananilide with 1N sodium hydroxide yields 4-hydroxy-2-butenanilide 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 λmax (EtOH) at 242nm (ε = 9200) and 278nm (ε = 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-acetoacetanisidide, 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 (8b, R = p-OCH_3)($C_{11}H_{13}NO_3$,[17] colorless needles from benzene, mp 125°), were obtained in the over-all yields of 48 and 26%, respectively.

Contrary to compound 5, 2-(3-acetoxy-4-bromobutanamido)pyridine (9) ($C_{11}H_{13}BrN_2O_3$,[18] colorless scales from $CHCl_3$, 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 to 7 through 3, 5, and 6 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($CDCl_3$) ppm: 4.36 (2H, s, CH_2Br), 6.55 (1H, s, 3-H), 7.15 - 7.85 (3H, m, aromatic H), 9.00 (1H, m, disappeared by addition of D_2O, 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($CDCl_3$) 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 D_2O, 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-d_6) ppm: 4.15 (2H, m, CH_2OH), 5.1 (1H, m, disappeared by addition of D_2O, OH), 6.28 (1H, m, CO-CH=), 6.55 (1H, m, =CH-CH_2), 7.0 - 8.3 (4H, m, pyridyl H), 8.5 (1H, b, disappeared by addition of D_2O, 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 $\nu(CHCl_3)$ cm^{-1}: 3300 (NH), 2950 (CH), 1695 (C=O). ^1H NMR $\delta(CDCl_3)$ 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 $\nu(CHCl_3)$ cm^{-1}: 2950 (CH), 1705 (C=O). ^1H NMR $\delta(CDCl_3)$ 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, Philla., Pennsylvania 19104, (1979), pp. 705.

15) IR ν(KBr) cm^{-1}: 3400 (OH), 1680 (C=O). ^1H NMR $\delta(CDCl_3)$ 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 ν(KBr) cm^{-1}: 3370 (OH), 1685 (C=O). ^1H NMR $\delta(CDCl_3)$ 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 ν(KBr) cm^{-1}: 3310 (OH), 1680 (C=O). ^1H NMR $\delta(CDCl_3)$ 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, $\underline{J}$ = 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 ($CDCl_3$) ppm: 2.08 (3H, s, acetyl CH_3), 2.81 (2H, d, $\underline{J}$ = 6 Hz, $CO-CH_2$), 3.62 (2H, m, changed to AB-quartet centred at 3.55 and 3.70 ppm on irradiation at 5.41 ppm, CH_2Br), 5.41 (1H, m, CH-OAc), 6.95 - 8.5 (4H, m, pyridyl H), 9.50 (1H, b, disappeared by addition of D_2O, NH). MS (m/e): 302, 300 (M^+).

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