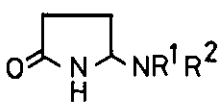
SYNTHESIS OF 5-AMINO-2-PYRROLIDINONE AND ITS DERIVATIVES

Yoshiyuki Kosugi*, Humiko Hamaguchi, Tatsuo Nagasaka, Naganori Ozawa, and Sadao Ohki

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

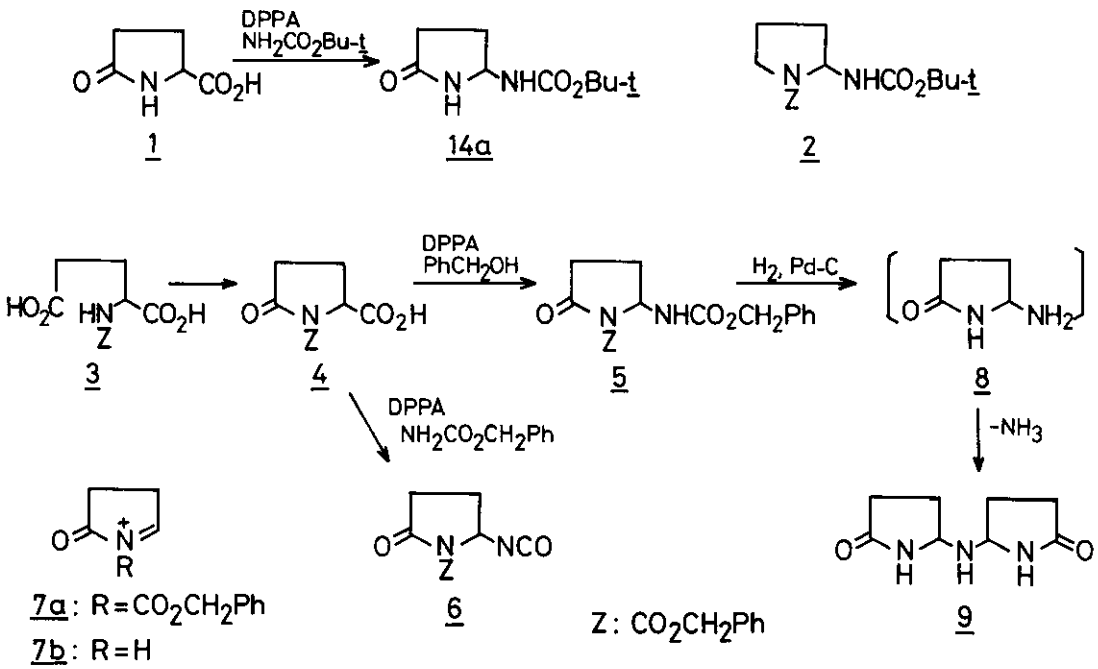
Abstract —— Two routes to a new type of 2-pyrrolidinones having various nitrogen functions at the 5-position were described. The modified Curtius reaction of pyroglutamic acid derivatives(1 and 4) with diphenylphosphoryl azide(DPPA) gave 5-alkoxycarbonylamino-2-pyrrolidinones(5 and 14a) in one step. Furthermore, the substitution reaction of 5-ethoxy-2-pyrrolidinone(12) with nucleophiles(amines, carbamates, amide, indole, and diethylaniline) was found to be a preferable synthetic method to 5-substituted-2-pyrrolidinones(13, 14, 15, and 16). The synthesis of 5-amino-2-pyrrolidinone(8), a simple one, was also mentioned.

As a series of studies on the chemistry of 2-pyrrolidinones[1], we are now interested in the synthesis of 2-pyrrolidinones having nitrogen functions such as amino, amide, or carbamate groups at the 5-position, since few attempts to synthesize 5-amino-2-pyrrolidinones, especially having no substituent at the 1-position (naked NH), have been reported, and 5-amino-2-pyrrolidinones would be expected to have pharmacological activities. In this paper, we wish to report a convenient synthesis of 5-amino-2-pyrrolidinones starting with pyroglutamic acid derivatives or with succinimide.

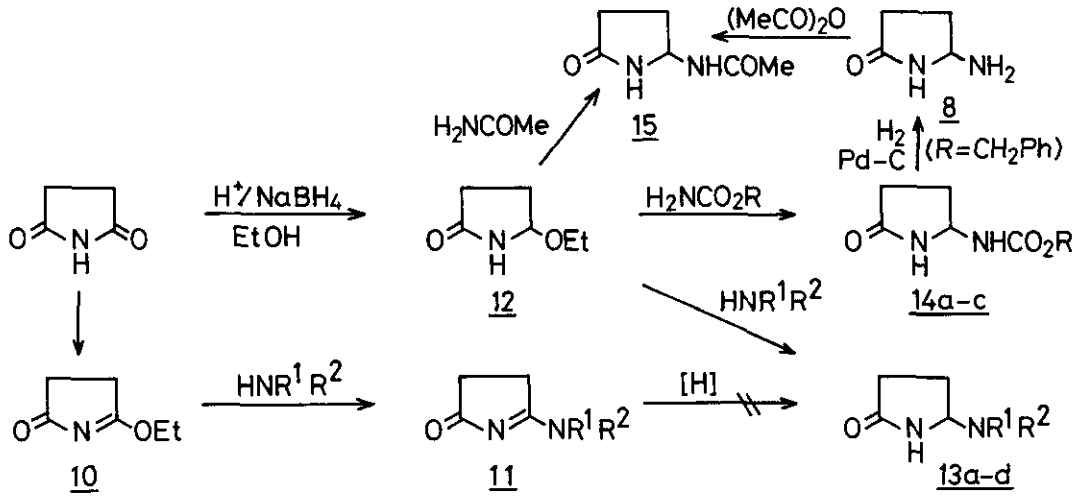


5-Amino-2-pyrrolidinones

Our initial studies were with the Curtius type rearrangement of pyroglutamic acid derivatives. Shioiri et al.[2] reported that the reaction of N-benzoxycarbonylproline with diphenylphosphoryl azide(DPPA) in the presence of carbamate gave the rearrangement product(2) in good yield. This modified Curtius reaction involved



the elimination of cyanate anion and the nucleophilic addition of carbamate. We applied this method to pyroglutamic acid(1)[reflux, 5hr, in C_6H_6], and the corresponding carbamate(14a) was afforded in 24% yield. To improve the yield of the rearrangement product, N-protected substance(4), prepared from N-benzoxycarbonylglutamic acid(3) by Gibian's procedure[3], was used under the same conditions described above, but the product isolated was only an unexpected isocyanate(6). This result suggested that the isocyanate(6) was stabilized by the electron withdrawing effect of two carbonyl functions adjacent to the nitrogen atom and that the iminium ion(7a) could not be formed. The treatment of 4 by the same procedure as above, but in the presence of benzyl alcohol[reflux, 4hr, in dioxane], gave the carbamate(5)[4] in 75% yield. Though it was one of our purposes to synthesize 5-amino-2-pyrrolidinone(8), the catalytic hydrogenation of 5 with Pd-C did not afford the expected amine(8), but furnished the secondary amine(9)[5] instead. Next attempts were made to find another general route to the 5-amino-2-pyrrolidinones. It seemed that the reduction of the keto-amidines(11), which were formed by the reaction of O-ethylsuccinimide(10) with amines as reported in our previous communication[1a], could afford the 2-pyrrolidinones having various amino groups at the 5-position. Unfortunately, this process failed to yield the expected products,

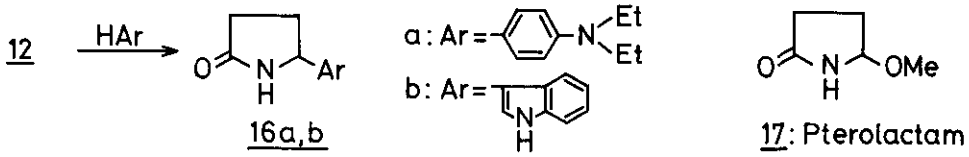


because of the resisting ability of keto-amidines to the usual reducing agents. However, 5-ethoxy-2-pyrrolidinone(12), which had been prepared by Speckamp et al.[6] by pH controlled $NaBH_4$ reduction of succinimide, was found to be a useful intermediate for the synthesis of 5-amino-2-pyrrolidinones, because of the reactivity of 12 with nucleophiles. As shown in Table 1, a series of 5-amino-2-pyrrolidinones(13a-d) were obtained in moderate yields by heating 12 at 120-150° with several amines without solvent.

Because the reaction of 12 seemed to proceed via the iminium intermediate(7b) as described by Speckamp et al.[6], 12 would also react with the less active nucleophiles such as carbamates, in the same way as the isocyanate did in the modified Curtius reaction[2]. Thus, 12 was treated with tert-butyl, ethyl and benzyl carbamate and acetamide in the same manner to give the carbamate(14a-c) and the amide (15), respectively(see Table 1). The catalytic hydrogenation of 14c with Pd-C in ethanol followed by careful evaporation of the solvent gave the amine(8)[7] quantitatively. This primary amine(8) was stable enough to be recrystallized from C_6H_6, but when in polar solvent or at elevated temperature(>105°), it was readily converted to the secondary amine(9) which was identical with the amine obtained by the catalytic hydrogenation of 5. The compound obtained in a small amount by the reaction of 12 with ammonium carbonate[120°, 4hr] was properly not 8 but 9.

In order to extend this reaction, some other nucleophiles were examined. The treatment with diethylaniline[150°, 1hr] and indole[135°, 1.5hr] formed the C-C bond to give 16a[8] and 16b[9] in 7% and 22% yield, respectively. When methanol containing a trace amount of HCl was used as nucleophile[reflux, 1hr], pterolactam

(17), which was the natural product isolated from bracken by Takatori et al.[10], was obtained. 17 was also obtained by Yamazaki's procedure[11], namely, by O-methylation of succinimide followed by reduction with $NaBH_4$. The reactivity of 17 with nucleophiles will be similar to that of 12.



The results presented here show that two routes are possible for the synthesis of 5-amino-2-pyrrolidinones, and especially that the route via 12 is better than the other in view of steps, yields and applicability. Because the compound 12 seems to react with weak nucleophiles according to our results, the reaction of the biological substances having nucleophilic amino acids or nucleosides with 12 will be investigated in the near future. The studies on the biological activities of a series of 5-amino-2-pyrrolidinones obtained here are under investigation.

Table 1. 5-Amino-2-pyrrolidinones(13a-d, 14a-c, 15).

	R^1	R^2	Yield(%)	mp(°C)	Spectral Data[IR(KBr,cm^{-1}), NMR($CDCl_3$,δ), MS(m/e)]
13a	$-(CH_2)_4-$		51	85	IR 3150(NH), 1685(C=O); NMR 8.1(1H,NH), 4.55(1H,m,CH), 2.6(4H,m,NCH_2), 1.9-2.3(4H,m,CH_2), 1.7(4H,m,CH_2); MS 154(M^+).
13b	$-(CH_2)_2O(CH_2)_2-$		33	143-5	IR 3145(NH), 1675(C=O); NMR 7.9(1H,NH), 4.45(1H,m,CH), 3.7(4H,m,OCH_2), 2.55(4H,m,NCH_2), 1.9-2.3(4H,m,CH_2); MS 170(M^+).
13c	H	Ph	35	144-6	IR 3325(NH), 3150(NH), 1690(C=O); NMR 6.5-7.2(5H,m,Ar-H), 5.8(1H,NH), 5.20(1H,m,CH), 1.7-2.7(4H,m,CH_2); MS 176(M^+).
13d	H	CH_2Ph	27	103-5	IR 3250(NH), 3120(NH), 1675(C=O); NMR 7.7(1H,NH), 7.2(5H,s,Ar-H), 4.5(1H,m,CH), 3.8(2H,s,CH_2Ar), 2.5(1H,NH), 1.6-2.4(4H,m,CH_2); MS 190(M^+).
14a	H	CO_2Bu-t	19	144	IR 3315(NH), 3170(NH), 1680(C=O); NMR 7.1-6.6(2H,NH), 5.25(1H,m,CH), 2.5-1.8(4H,m,CH_2), 1.40(9H,s,CH_3); MS 143(M^+-Bu-t).
14b	H	CO_2Et	30	114	IR 3230(NH), 1710(C=O), 1675(C=O); NMR 5.95(2H,NH), 5.3(1H,m,CH), 4.0(2H,d of q,CH_2CH_3), 2.8-1.8(4H,m,CH_2), 1.15(3H,t,CH_2CH_3); MS 172(M^+).
14c	H	CO_2CH_2Ph	51	101	IR 3330(NH), 3210(NH), 1740(C=O), 1685(C=O); NMR 7.2(5H,s,Ar-H), 7.15(1H,NH), 6.4(1H,NH), 5.2(1H,m,CH), 5.0(2H,s,CH_2), 2.6-1.6(4H,m,CH_2); MS 234(M^+).
15	H	COMe	52	146-8	IR 3270(NH), 3220(NH), 1670(C=O); NMR 7.75(1H,NH), 7.4(1H,NH), 5.55(1H,m,CH), 1.8-2.7(4H,m,CH_2), 2.00(3H,s,CH_3); MS 142(M^+).

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4) mp 154-7°; IR(KBr)cm^{-1}: 3260(NH), 1795(C=O), 1705(C=O); NMR($CDCl_3$)δ: 7.25(10H, m, Ar-H), 5.36-6.12(2H, NH, CH), 5.15(2H, s, CH_2Ar), 4.98(2H, s, CH_2Ar), 1.83-2.56(4H, m, CH_2).

5) mp 189-192°; IR(KBr)cm^{-1}: 3260(NH), 3180(NH), 1720(C=O), 1675(C=O); NMR(D_2O)δ: 4.7(5H, m, CH, NH), 2.7-1.6(8H, m, CH_2); MS m/e: 100(The molecular ion peak was not obserbed); Anal. Calcd. for $C_8H_{13}N_3O_2$: C, 52.44; H, 7.15; N, 22.94. Found: C, 52.44; H, 7.06; N, 23.06.

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7) mp 103-5°(decomp.); IR(KBr)cm^{-1}: 3300(NH), 3250(NH), 1675(C=O); NMR($CDCl_3$)δ: 7.55(1H, NH), 4.75(1H, m, CH), 2.7-1.6(4H, m, CH_2), 1.95(2H, NH_2); MS m/e: 100 (M^+). Acetylation of 8 with acetic anhydride gave 15, quantitatively. During our investigation, Willson's report including the synthesis of 8 was abstracted in the Chemical Abstracts, but no data could be known about its physical constants, yield and detailed procedure for synthesis. C. G. Willson, M. Goodman, J. Rivier and W. Vale, Pept., Proc. Am. Pept. Symp., 5th, 1977, 579; C. A., 1978, 88, 191455b.

8) mp 112-3°; IR(KBr)cm^{-1}: 3170(NH), 1655(C=O); NMR($CDCl_3$)δ: 7.1(2H, d, J 8, Ar-H), 6.6(2H, d, J 8, Ar-H), 6.25(1H, NH), 4.55(1H, m, CH), 3.3(4H, q, J 7, CH_2CH_3), 2.6-1.6(4H, m, CH_2), 1.1(6H, t, J 7, CH_2CH_3); MS m/e: 232(M^+).

9) mp 177-9°; IR(KBr)cm^{-1}: 3270(NH), 1655(C=O); NMR($CDCl_3$)δ: 9.1(1H, NH), 7.6-6.8 (5H, m, Ar-H), 7.0(1H, NH), 4.95(1H, m, CH), 2.6-1.6(4H, m, CH_2); MS m/e: 200 (M^+).

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