5-ACETOXY-2-PYRROLIDINONE AS A PRECURSOR FOR N-ACYLIMMINIUM ION

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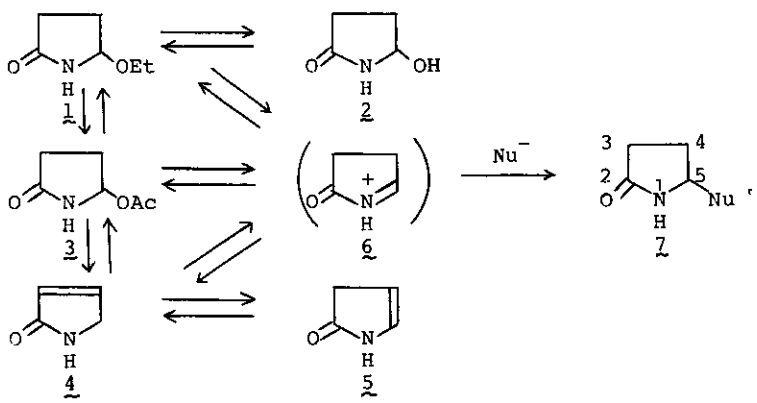
Abstract --- Synthesis of 5-acetoxy-2-pyrrolidinone (3) and its reactions via N-acylimminium ion (6) with nucleophiles are described, especially in comparison with 5-alkoxy-2-pyrrolidinone (1) and 3-pyrrolin-2-one (4).

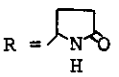
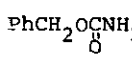
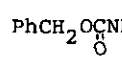
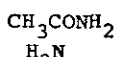
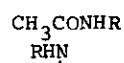
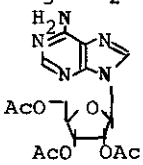
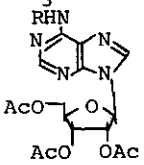
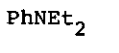
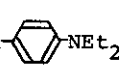
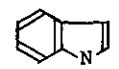
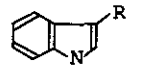
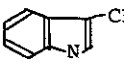
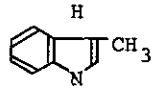
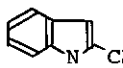
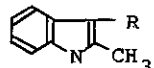
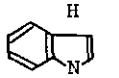
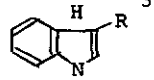
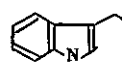
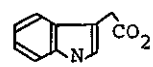
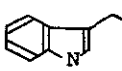
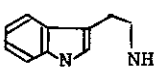
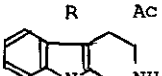
In the previous paper[1] we have described that the reactions of 5-ethoxy-2-pyrrolidinone (1) with nucleophiles such as carbamates, amides, amines, indole, and diethylaniline afford 5-substituted 2-pyrrolidinones (7) in low to moderate yields (7-52%). These results demonstrate the additional examples of the reaction via N-acylimminium ion (6), which is known as a reactive intermediate formed from 5-alkoxy- and 5-hydroxy-2-pyrrolidinones (1, 2)[2] and pyrrolin-2-ones (4, 5)[3]. In this communication we wish to describe the synthesis and reactions of 5-acetoxy-2-pyrrolidinone (3) as a new type of precursors for 6.

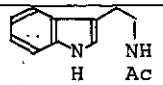
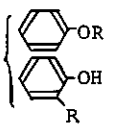
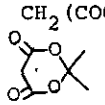


While 4-acetoxy-2-azetidinone performs a very important role in the chemistry of β-lactam antibiotics[4], no experimental data for 5-acetoxy-2-pyrrolidinone (3) have been reported up to date. 3 was easily prepared from 1 as follows: A solution of 1 (300 mg) in acetic acid (10 ml) was stirred at room temperature for 24 h to give

an equilibrium mixture of 1 and 3 (the approximate ratio 1:9). Stirring was continued under slightly reduced pressure till the disappearance of 1 on TLC plate and the successive careful evaporation of excess acetic acid under 40° afforded 3 quantitatively as an unstable oil[5]. The reactions of 3 with several kinds of nucleophiles were examined, especially in comparison with the reactions of 1 and 4. Reaction conditions and results are summarized in Table I and spectral data of new 5-substituted 2-pyrrolidinones (7) are listed in Table II.

Table I. Reactions of 3 with Nucleophiles*1

Run	Nucleophiles	Reaction Conditions*2	Products*3 R = 		Yields (%)	Yields (%) in Literature	
						from 1	from 4
1		A; 90°C, 2h		8	94	51*4	
2		A; 105°C, 1h		9	47.6	52*4	
3		A; 125°C, 2.5h		10	53.2	90.8*5	
4		A; 110°C, 45min		11	72.2	7*4	83*6,#
5		A; 100°C, 1h		12	quant.	22*4	83*6
6		A; 120°C, 1.5h		13	quant.		
7		A; 140°C, 1h		14	quant.		
8		A; 140°C, 2h		15	58.9		
9		A; 110°C, 1h		16	69.1		
10		A; 120°C, 1h		17	81.4		
				18	4.2		

Run	Nucleophiles	Reaction Conditions	Products		Yields (%)	Yields (%) in Literature from 1	Yields (%) in Literature from 4
11		C; 110°C, 1h		17	64		
				18	12.5		75*7
12	PhSH	A; 120°C, 3h	PhSR	19	52.7		
13	PhOH	C; 110°C, 1h		20	37.4		
				21	12.2		58*6
14	$CH_2(COOEt)_2$	B; 120°C, 3h	$RCH(COOEt)_2$	22	19.2	60.5*8	
15		A; 90°C, 2.5h	RCH_2COOH	23	49		

*1 In each run equimolecular quantities of nucleophile and 3 were used.
*2 A; in no solvent, B; in the presence of NaH(equi. mole) in benzene, C; in acetic acid.
*3 Products were purified by column chromatography (silica gel) followed by recrystallization or distillation. All products gave satisfactory analytical results.
*4 Reference 1.
*5 *Unpublished data in our laboratory.*
*6 Reference 3a. #; Yield by the reaction of 4 with N,N-dimethylaniline.
*7 Reference 3b.
*8 Reference 7. Yield by the reaction of 4 with dimethyl malonate.

The significant superiority of 3 to 1 was observed in the reactions of carbamate (Run 1) and strongly nucleophilic aromatic compounds (Run 4,5). Similarly the expected products (13, 14, 15) were obtained in good yields from 3-methyl-, 2-methyl-, and 1-methylindoles (Run 6,7,8). In the case of adenosine-2',3',5'-triacetates (Run 3), 3 was not superior to 1, presumably 3 would gradually decompose at the elevated temperature, which was essential because of the low nucleophilicity of adenosine. Although the reactivity of 3 to dialkylaminobenzene and indole (Run 4,5) seemed to be similar to that of 4 (and 5)[3a], the interesting difference between 3 and 4 was found in Run 6, 9, 10, 11, and 13. Bocchi et al. have reported that the reactions of 4 (and 5) with 3-substituted indoles (skatole and N_b-acetyltryptamine)[3b] in acetic acid afford exclusively the compounds (24, mp 210°C, 82% and 18, mp 223°C, 75%) substituted at the 2-position of the indole nucleus and that the reaction of 4 with phenol[3a] affords only 5-(o-hydroxyphenyl)-2-pyrrolidinone (21, mp 203°C, 58%). However we obtained the compounds (13, 16, 17) substituted at the 1-position of the indole ring in high yields by the

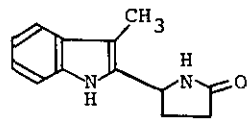


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Table II. Melting Points and Spectral Data of 5-Substituted 2-Pyrrolidinones (7)

Compound [MS(M^+,m/e)]	m.p. [b.p.] (°C)	IR ν max (cm^{-1})	PMR δ (ppm)
10 [476]	100	(KBr) 3370, 3250 (NH), 1750, 1700 (C=O)	($CDCl_3$) 8.28 (1H, d, Ar-H), 7.87 (1H, s, Ar-H), 7.2 (1H, br, NH), 6.82 (1H, br-d, NH), 6.2 (1H, d), 5.86 (1H, t), 5.8 (1H, m, C_5-H), 5.6 (1H, m), 4.33 (2H, s), 2.8-1.8 (4H, m, CH_2CH_2), 2.10 (3H, s, CH_3), 2.06 (3H, s, CH_3), 2.03 (3H, s, CH_3)
12 [200]	177-179	(KBr) 3230 (NH), 1645 (C=O)	($CDCl_3$) 8.5-8.1 (1H, br, NH), 7.7-7.1 (5H, m, Ar-H), 6.0 (1H, br, NH), 5.1 (1H, m, C_5-H), 2.6-2.1 (4H, m, CH_2CH_2)
13 [214]	232-235	(KBr) 3400 (NH), 1700 (C=O)	($CDCl_3$) 7.7-7.0 (5H, m, Ar-H, NH), 6.92 (1H, s, indole C_2-H), 5.85 (1H, m, C_5-H), 2.6-1.8 (4H, m, CH_2-CH_2), 2.26 (3H, s, CH_3)
14 [214]	235	(KBr) 3200 (NH), 1675 (C=O)	(CD_3OD) 7.5-6.9 (4H, m, Ar-H), 5.05 (1H, m, C_5-H), 2.73-2.06 (4H, m, CH_2CH_2), 2.40 (3H, s, CH_3)
15 [214]	170	(KBr) 3150 (NH), 1690 (C=O)	($CDCl_3$) 7.6-7.0 (4H, m, Ar-H), 6.95 (1H, s, indole C_2-H), 5.0 (1H, m, C_5-H), 3.6 (3H, s, CH_3), 2.6-2.0 (4H, m, CH_2CH_2)
16 [258]	164	(KBr) 3200 (NH), 1700 (C=O)	($CDCl_3$) 8.2 (1H, COOH), 7.6-7.0 (6H, m, Ar-H, NHx2), 6.05 (1H, m, C_5-H), 3.67 (2H, s, CH_2COOH), 2.85-2.0 (4H, m, CH_2CH_2)
17 [285]	110-114	(KBr) 3250 (NH), 1690, 1650 (C=O)	(d_6-DMSO) 8.5 (1H, s, NH), 7.9 (1H, br, NH), 7.7-6.9 (5H, m, Ar-H), 6.20 (1H, m, C_5-H), 3.5-3.2 (2H, m, $NHCH_2$), 3.0-2.7 (2H, m, $NHCH_2CH_2$), 2.6-2.0 (4H, m, CH_2CH_2), 2.1 (3H, s, $NHCOCH_3$)
18 [285]	202-203	(KBr) 3250 (NH), 1680 (C=O)	(CD_3OD) 7.6-6.9 (4H, m, Ar-H), 5.2-5.0 (1H, m, C_5-H), 3.5-2.9 (4H, m, CH_2CH_2NHAc), 2.7-2.1 (4H, m, CH_2CH_2) 2.9 (3H, s, $COCH_3$)
19 [193]	81-82	(KBr) 3400 (NH), 1660 (C=O)	($CDCl_3$) 7.6-7.2 (6H, m, Ar-H, NH), 5.0 (1H, d-d, J=3Hz, 7.5Hz, C_5-H), 2.7-1.9 (4H, m, CH_2CH_2)
20 [177]	110-114	(KBr) 3520 (NH), 1700 (C=O)	($CDCl_3$) 7.4 (1H, NH), 7.4-6.8 (5H, m, Ar-H), 5.66 (1H, m, C_5-H), 2.76-1.83 (4H, m, CH_2CH_2)
21 [177]	202-203	(KBr) 3150 (NH, OH), 1670 (C=O)	(d_6-DMSO) 9.5 (1H, br, OH), 7.9 (1H, NH), 7.3-6.7 (4H, m, Ar-H), 4.9 (1H, d-d, J=4.5Hz, 1.6Hz, C_5-H), 2.5-1.5 (4H, m, CH_2CH_2)
22 [243]	48-50 [180(2 mmHg)]	(liq. film) 3200 (NH), 1730, 1700 (C=O)	($CDCl_3$) 6.4 (1H, NH), 4.27 (4H, q, CH_2CH_3), 3.4 (1H, m, C_5-H), 2.5-1.6 (5H, m, CH_2CH_2, $CH(COOEt)_2$), 1.3 (6H, t, CH_2CH_3)
23 [143]	123	(KBr) 3220 (NH), 1725, 1655 (C=O)	($CDCl_3$) 20.2 (1H, s, COOH), 7.8 (1H, NH), 4.03 (1H, m, C_5-H), 2.6-1.5 (6H, m, CH_2CH_2, CH_2COOH)

reactions of 3 with 3-substituted indoles (Run 6,9,10)[6]. No 2-substituted indoles were detected in Run 6 and 9. In Run 10, Bocchi's product (18) was obtained in 4.2% yield and the yield of 18 improved to 12.5% in Run 11 (acetic acid condition) though 17 was a major product in both cases. The reaction of 3 with phenol in neat afforded no product because of the polymerization of 3 in this condition. By the Bocchi's condition (Run 13), 5-phenoxy-2-pyrrolidinone (20) was obtained as a major product accompanying with 21 (Bocchi's product). Transformation of 20 to 21 in acetic acid was attempted but failed. From thiophenol, 5-phenylthio-2-pyrrolidinone (19) was obtained exclusively (Run 12).

From these limited examples we have not been able to realize the reasons why 3 and 4 afforded different products. It should be presumed as one of factors that the characters of nucleophiles such as skatole and phenol are delicately different depending on the reaction conditions.

Active methylene compounds (e. g. diethyl malonate) reacted with 3 in the presence of base (NaH, NaOEt, n-BuLi) (Run 14), but this method was inferior to the method using aluminum chloride[7]. Isopropylidene malonate, a more acidic compound, however, reacted easily with 3 without base to afford 2-pyrrolidinon-5-ylacetic acid (23) directly in the moderate yield (Run 15).

In conclusion 5-acetoxy-2-pyrrolidinone (3) has proved to be easily prepared as mentioned above and to be useful for the synthesis of pyrrolidine derivatives.

REFERENCES AND NOTES

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2. W. N. Speckamp, "Stereoselective Synthesis of Natural Products", Vol. 7, ed. by W. Bartmann and E. Winterfeldt, Excerpta Medica, Amsterdam, 1979, p50.
3. a) V. Bocchi and G. P. Gardini, Org. Prep. Proced., 1969, 1, 271.
   b) V. Bocchi, G. Casnati, and G. P. Gardini, Tetrahedron Lett., 1971, 683.
4. "Recent Advances in the Chemistry of β-Lactam Antibiotics-Second International Symposium", ed. by G. I. Gregory, The Royal Society of Chemistry, London, 1980.
5. Although this material can not be purified by distillation because of its instability, it is sufficiently pure for most purposes. IR ($CHCl_3$) $\nu_{max}^{cm^{-1}}$: 3420 (NH), 1710 (C=O); PMR ($CDCl_3$) δ ppm: 7.25 (1H, br, NH), 5.69 (1H, m, C_5-H), 2.7-2.1 (4H, m, CH_2CH_2), 2.06 (3H, s, $COCH_3$).
6. Structures of 5-(1'-indolyl)-2-pyrrolidinones (13, 16, 17) were confirmed by

their PMR spectra , namely by the chemical shifts at low fields (5.8-6.2 ppm) of the C_5-protons of 2-pyrrolidinones with the presence of the $C_{2'}$-protons of indole nuclei.

7. G. A. Kraus and K. Neunschwander, Tetrahedron Lett., 1980, 21, 3481.

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