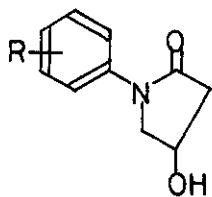
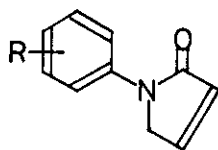
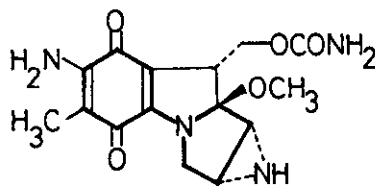


## SYNTHESIS OF 1-ARYL-3-PYRROLIN-2-ONE DERIVATIVES

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Abstract --- 1-Aryl-3-pyrrolin-2-one derivatives (6a-e) were obtained from the corresponding  $\gamma$ -bromoacetoacetanilide derivatives (1a-e) in the overall yields of 31 - 48% through the reduction of the  $\beta$ -carbonyl group, acetylation of the hydroxyl group, and subsequent cyclization and elimination to the 3-pyrrolin-2-one structure.

In the preceeding paper, we reported a new method for the preparation of 1-aryl-4-hydroxypyrrolidin-2-one derivatives (3) from the corresponding  $\gamma$ -bromoacetoacetanilide derivatives (1) via 4-bromo-3-hydroxybutananilide derivatives (2).<sup>1)</sup> In connection with this experiment, we have interested in the structure of these  $\gamma$ -lactams as preliminary intermediate of the synthesis of mitomycin and related compounds, since we can see a similarity between these  $\gamma$ -lactams and certain features of the mitomycin antibiotics.<sup>2)</sup> The present report deals with the synthesis of one of such intermediates, 1-aryl-3-pyrrolin-2-one derivatives (6).

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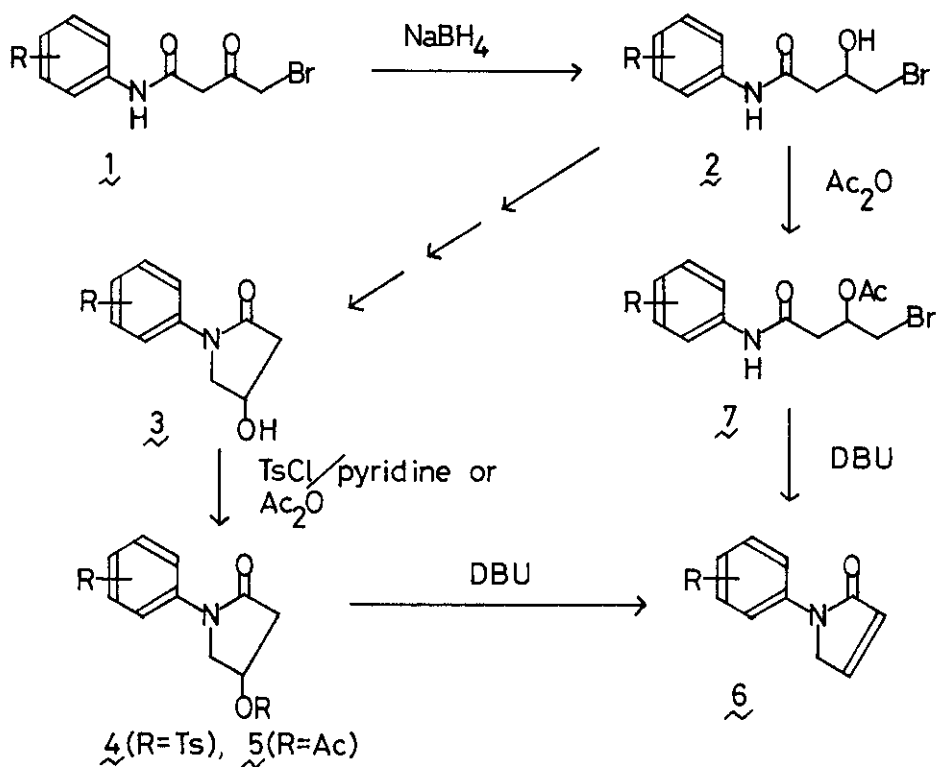
Mitomycin C

It is well known that N-substituted  $\gamma$ -lactams are prepared but in rather low yield from the corresponding N-substituted succinimides through the partial reduction of the carbonyl groups, protection of the hydroxyl group, and subsequent elimination of the ether or ester moiety.<sup>3)</sup>

First we tried the elimination of 4-hydroxy-1-phenylpyrrolidin-2-one (3a) to form 3-pyrrolin-2-one structure. On treatment with *p*-toluenesulfonyl (tosyl) chloride in dry pyridine at room temperature, compound 3a did not give the objective 3-pyrrolin-2-one derivative but gave its O-tosylate, 1-phenyl-4-tosyloxypyrrolidin-2-one (4a),  $C_{17}H_{17}NO_4S$ ,<sup>4,5</sup> as colorless needles (from benzene) of mp 96° in 85% yield. When acetic anhydride was used as acylating agent, compound 3a afforded 4-acetoxy-1-phenylpyrrolidin-2-one (5a),  $C_{12}H_{13}NO_3$ ,<sup>6</sup> as colorless viscous oil in 92% yield.

Compounds 4a and 5a were treated with 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) in dry THF at room temperature giving 1-phenyl-3-pyrrolin-2-one (6a),  $C_{10}H_9NO$ ,<sup>7</sup> as colorless needles (from ethanol) of mp 86° in 95% and 82% yields, respectively.

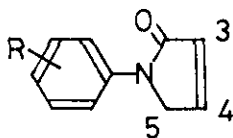
In the similar manner, 4-hydroxy-1-(2,5-dimethoxyphenyl)pyrrolidin-2-one (3e) was treated with acetic anhydride and subsequently with DBU to afford 1-(2,5-dimethoxyphenyl)pyrrolin-2-one (6e),  $C_{12}H_{13}NO_3$ ,<sup>8</sup> as colorless needles (from benzene) of mp 90° in 63% yield.



Since compound 3a was obtained in about 50% yield from 1a following the method mentioned in our previous report, the overall yield of 6a from 1a is estimated to be 38 - 40%. Therefore, we tried direct cyclization of 3-acetoxy-4-bromobutan-anilide (7a) in order to improve the synthetic process. However, cyclization of 2-(3-acetoxy-4-bromobutanamido)pyridine was unsuccessful under treatment with DBU.

4-Bromo-3-hydroxybutananilide (2a) which was derived from compound 1a in 70% yield was treated with acetic anhydride giving 3-acetoxy-4-bromobutan-anilide (7a),  $C_{12}H_{13}BrNO_3$ ,<sup>8)</sup> as colorless viscous oil in 95% yield. Compound 7a was treated with DBU in dry THF at room temperature for 4 hrs affording 6a in 69% yield. Four kinds of 1-aryl-3-pyrrolin-2-one derivatives (6b-e) were also prepared from the corresponding  $\gamma$ -bromoacetoacetanilide derivatives (1b-e) by the similar manner as described above in the overall yields of 31 - 48%. The mps, yields, and spectral data are listed in Table I.

Table I. Mps, Yields, and Spectral Data of 6a-e



<u>6</u>	R	Mp (°C)	Yield <sup>a)</sup> (%)	IR $\nu$ (KBr) $cm^{-1}$ (amide C=O)	NMR $\delta$ ( $CDCl_3$ ) ppm		
					H-3 <sup>b)</sup>	H-4 <sup>b)</sup>	H-5 <sup>c)</sup>
a	H	86	48.3	1690	6.20	7.09	4.18
b	<u>p</u> -OCH <sub>3</sub>	103	32.9	1678	6.20	7.10	4.35
c	<u>p</u> -CH <sub>3</sub>	95	41.5	1682	6.20	7.08	4.35
d	<u>m</u> -CH <sub>3</sub>	91	31.0	1678	6.20	7.04	4.39
e	2,5-di OCH <sub>3</sub>	90	46.6	1670	6.25	7.17	4.40

a) based on  $\gamma$ -bromoacetoacetanilide derivatives (1a-e)

b) 1H, multiplet

c) 2H, multiplet

From the above results, the present method involving cyclization of 3-acetoxy-4-bromobutanilide derivatives (7) was found to be more favourable for the preparation of 1-aryl-3-pyrrolin-2-one derivatives (6). The synthetic approach to mitomycin structure from compound 6 is now in progress.

#### References and Notes

- 1) K. Tabei, H. Ito, and T. Takada, Heterocycles, 14, 1779 (1980).
- 2) R. W. Franck and J. Auerbach, J. Org. Chem., 36, 31 (1971).
- 3) J. B. P. A. Wijnberg, J. J. J. de Boer, and W. N. Speckamp, Recueil. J of the Royal Netherland Chem. Soc., 97, 227 (1978) and the literature cited therein.
- 4) All new compounds reported herein gave satisfactory elemental analyses and the mass numbers (m/e) of the parent peaks in agreement with the proposed structure.
- 5) IR  $\nu$  (KBr)  $\text{cm}^{-1}$ : 1698 (C=O). NMR  $\delta$  (DMSO- $d_6$ ) ppm: 2.47 (3H, s, tosyl  $\text{CH}_3$ ), 2.50 - 3.00 (2H, ABX-octet, H-3), 3.90 - 4.24 (2H, ABX-octet, H-5), 5.23 (1H, m, H-4), 7.1 - 7.8 (9H, m, aromatic H). Mass (m/e): 331 ( $\text{M}^+$ ), 159, 130, 106
- 6) IR  $\nu$  ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 1735 (acetyl C=O), 1705 (amide C=O). NMR  $\delta$  ( $\text{CDCl}_3$ ) ppm: 2.10 (3H, s, acetyl  $\text{CH}_3$ ), 2.50 - 3.10 (2H, ABX-octet, H-3), 3.70 - 4.30 (2H, ABX-octet, H-5), 5.35 (1H, m, H-4), 7.10 - 7.65 (5H, m, aromatic H). Mass (m/e): 219 ( $\text{M}^+$ ), 159, 130, 106.
- 7) Lit. mp 89 - 90°; J. B. P. A. Wijnberg et al., Recueil. J. of the Royal Netherland Chem. Soc., 97, 227 (1978).
- 8) IR  $\nu$  (KBr)  $\text{cm}^{-1}$ : 1735 (acetyl C=O), 1670 (amide C=O). NMR  $\delta$  ( $\text{CDCl}_3$ ) ppm: 2.08 (3H, s, acetyl  $\text{CH}_3$ ), 2.78 (2H, d,  $J = 8$  Hz, changed to singlet at 2.72 ppm on irradiation at 5.35 ppm, H-4), 3.60 (2H, m, changed to AB-quartet centred at 3.45 and 3.65 ppm on irradiation at 5.35 ppm, H-2), 5.35 (1H, m, H-3), 7.00 - 7.50 (5H, m, aromatic H), 7.80 (1H, broad s, disappeared by addition of  $\text{D}_2\text{O}$ , NH). Mass (m/e): 299 ( $\text{M}^+$ ), 159, 130.

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