

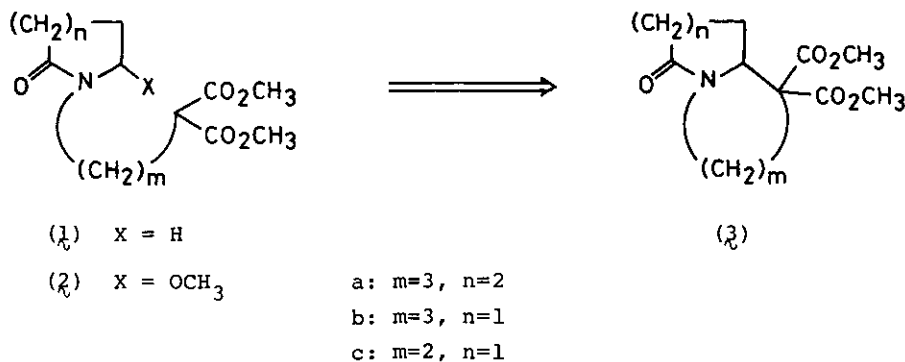
A NEW SYNTHESIS OF (±)-LUPININE, (±)-EPILUPININE, AND THE
RELATED HETEROCYCLES BY APPLICATION OF ANODIC OXIDATION

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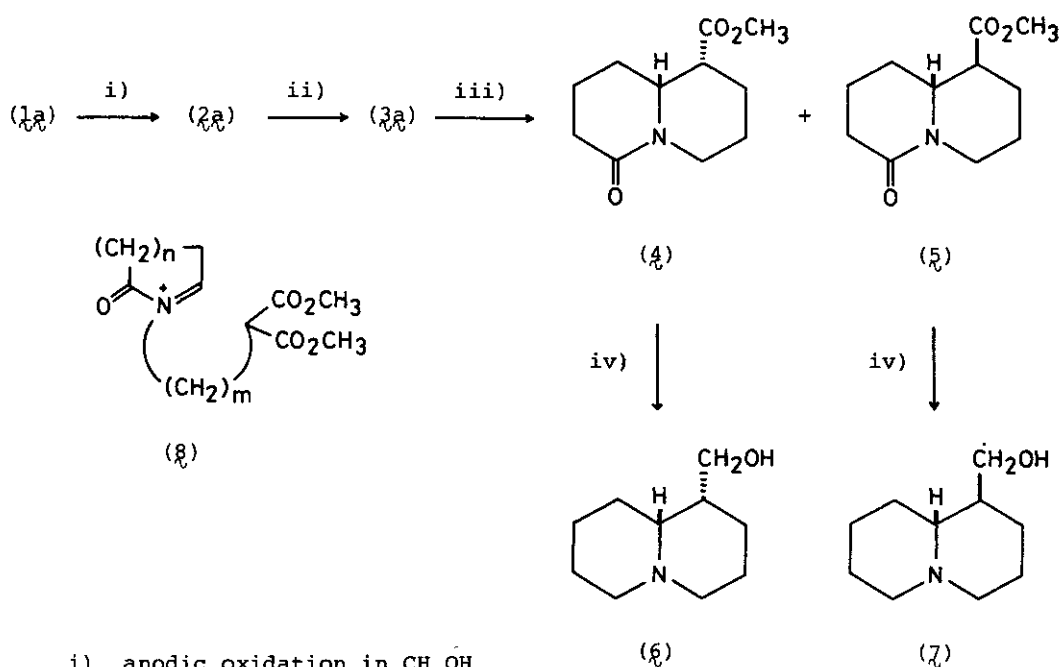
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Abstract — A new synthesis of (±)-lupinine, (±)-epilupinine,
and the related heterocycles has been achieved by utilization
of anodic oxidation of lactams bearing the malonate group at
the terminal position of N-primary alkyl side chain.

It was reported in the previous paper¹ that the anodic oxidation of N-primary-alkyl lactams regioselectively occurred at the endocyclic methylene- α -carbon of nitrogen in five- and six-membered rings to furnish the hydroxylated lactams and imides, and this method was applied to the synthesis of various heterocycles², including the natural alkaloids³. In this communication, we describe a new synthesis of the entitled alkaloids and the related heterobicyclic compounds, by anodic oxidation of lactams (**1**) bearing the malonate group at the terminal position of N-alkyl side chain.



The required lactam ($1a$)⁴ for a synthesis of the entitled alkaloids was prepared from dimethyl 3-iodopropylmalonate by heating with 2-ethoxy-3,4,5,6-tetrahydropyridine, at 110°C in nitrogen atmosphere⁵. A typical procedure of the anodic oxidation in this series is shown as follows : Into an undivided cell equipped with two platinum electrodes (2 X 1 cm²) was added a solution of the lactam ($1a$, 2.7 mM) and Et₄NClO₄ (0.7 mM) in methanol (7 ml), which solution was electrolyzed by constant current (50 mA) at room temperature. After 2.8 F/mol of electricity was passed, the product ($2a$)⁶ was obtained in 71 % yield.



- i) anodic oxidation in CH₃OH
- ii) TiCl₄, CH₂Cl₂, room temp., 3 days, Ar gas
- iii) LiCl, HMPA, 80°C, 24 h, N₂ gas
- iv) LiAlH₄, THF, reflux, 3 h

The methylene chloride solution of this colorless oil ($2a$) was reacted with $TiCl_4$ to give the quinolizidine derivative ($3a$, mp 86.5~88°C)⁷ in 77 % yield, possibly through generation of α -acyliminium cation (8) as a crucial transition state in the intramolecular C-C bond formation⁸. Decarboxylation of the compound ($3a$) gave two products, 4 (mp 49~50.5°C; 19 %)⁹ and 5 (mp 94~95°C; 49 %)¹⁰. The lithium aluminum hydride reduction of 4 afforded (\pm)-lupinine [6 , mp 59~61°C

(lit. 59°C); methiodide mp 285~289°C(decomp.) (lit. 303°C)]¹¹ in 55 % yield. By the same reduction of **5**, (±)-epilupinine [**7**, mp 81~82.5°C (lit. 81°C); methiodide mp 252~257°C(decomp.) (lit. 248°C)]¹¹ was obtained in 93 % yield. The present anodic oxidation, regioselectively effected under a much milder and simpler condition on comparison with the conventional chemical oxidation methods, was also successful with five-membered lactams (**1b**, **1c**), which were followed by intramolecular cyclization to give indolizidine (**3b**, 76 %) and pyrrolizidine (**3c**, 60 %) derivatives. These results will be published in full papers.

REFERENCES AND NOTES

1. M. Okita, T. Wakamatsu, and Y. Ban, J. Chem. Soc. Chem. Comm., 1979, 749; The anodic oxidation of N-primary-alkyl lactams in methanol was also regioselectively carried out in the same way to give methoxylated products., M. Okita, T. Wakamatsu, and Y. Ban, unpublished result; T. Nishitani, H. Horikawa, T. Iwasaki, K. Matsumoto, I. Inoue, and M. Miyoshi, J. Org. Chem., 1982, 47, 1706.
2. M. Okita, T. Wakamatsu, M. Mori, and Y. Ban, Heterocycles, 1980, 14, 1089.
3. K. Irie, M. Okita, T. Wakamatsu, and Y. Ban, Nouveau J. de Chimie, 1980, 4, 275; K. Irie and Y. Ban, Heterocycles, 1981, 15, 201; K. Irie and Y. Ban, ibid., 1982, 18, 225.
4. Compound (**1a**) IR(film) 1750(sh.), 1735, 1635 cm⁻¹; NMR(CDCl₃) δ 1.4~2.1(m, 8H), 2.36(m, 2H), 3.2~3.5(m, 5H), 3.74(s, 6H); MS m/e 271(M⁺), 140(base).
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6. Compound (**2a**) IR(film) 1750(sh.), 1735, 1645 cm⁻¹; NMR(CCl₄) δ 3.31(s, 3H), 3.72(s, 6H), 4.47(m, 1H); MS m/e 301(M⁺), 82(base).
7. Compound (**3a**) IR(nujol) 1740, 1725, 1645, 1635 cm⁻¹; NMR(CDCl₃) δ 1.1~2.6(m, 11H), 3.64(m, 1H), 3.74(s, 3H), 3.76(s, 3H), 4.83(m, 1H); MS m/e 269(M⁺), 213(base); Anal. Calcd: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.09; H, 7.17; N, 5.17.
8. Similar C-C bond forming reaction with malonic diester have been reported; see M. Malmberg and K. Nyberg, J. Chem. Soc. Chem. Comm., 1979, 167; G. A. Kraus and K. Neuenschwander, Tetrahedron Letters, 1980, 21, 3841; T. Shono, Y. Matsumura, and K. Tsubata, J. Am. Chem. Soc., 1981, 103, 1172. references

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9. Compound (4) IR(nujol) 1720, 1635 cm^{-1} ; NMR(CDCl_3) δ 1.4~2.7(m, 12H), 3.44(m, 1H), 3.68(s, 3H), 4.85(m, 1H); MS m/e 211(M^+), 155(base); Anal. Calcd: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.43; H, 8.26; N, 6.56.
10. Compound (5) IR(nujol) 1720, 1635 cm^{-1} ; NMR(CDCl_3) δ 1.3~2.6(m, 12H), 3.48(m, 1H), 3.70(s, 3H), 4.83(m, 1H); MS m/e 211(M^+), 155(base); Anal. Calcd: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.41; H, 8.19; N, 6.69.
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