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

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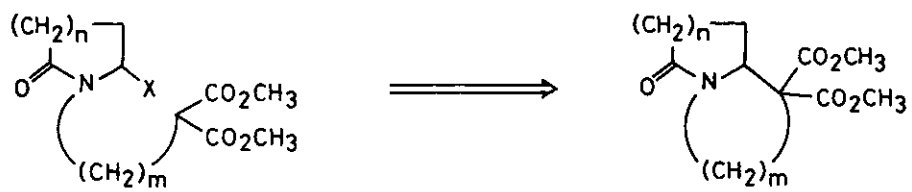
Abstract —— A new synthesis of (±)-lupinine, (±)-epilupinine, and the related heterocycles has been achieved by utilization of anodic oxidation of lactams bearing the malonate group at the terminal position of N-primary alkyl side chain.

It was reported in the previous paper[1] 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 heterocycles[2], including the natural alkaloids[3]. 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.

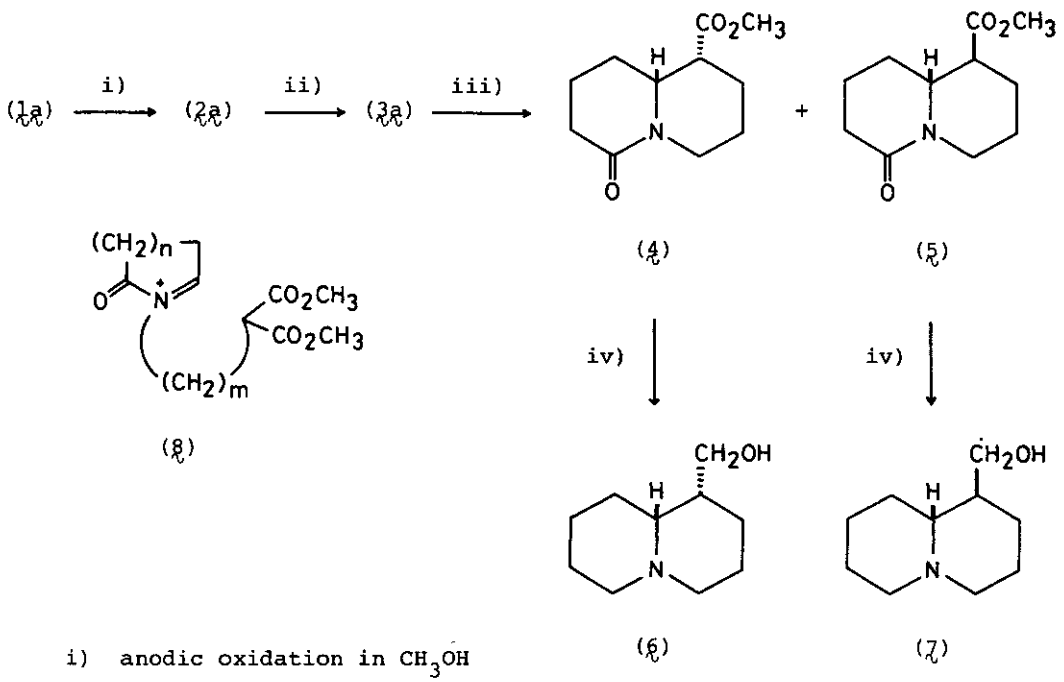


(1) X = H
(2) X = OCH_3

(3)

a: m=3, n=2
b: m=3, n=1
c: m=2, n=1

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 atmosphere[5]. 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 cm^2) was added a solution of the lactam (1a, 2.7 mM) and Et_4NClO_4 (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 CH_3OH

ii) $TiCl_4$, CH_2Cl_2, room temp., 3 days, Ar gas

iii) LiCl, HMPA, 80°C, 24 h, N_2 gas

iv) $LiAlH_4$, 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 formation[8]. 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 (±)-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

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4. Compound (1a) IR(film) 1750(sh.), 1735, 1635 cm^{-1}; NMR($CDCl_3$) 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(CCl_4) 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($CDCl_3$) 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

cited herein.

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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