ALKALOID SYNTHESIS USING FUROPYRIDONE AS SYNTON
-SYNTHESIS OF KEY INTERMEDIATES FOR THE SYNTHESSES OF
(±)-QUININE, (±)-AJMALICINE, AND (±)-7-DEMETHYLTECOMANINE-

Takeaki Naito, Okiko Miyata, and Ichiya Ninomiya*
Kobe Women's College of Pharmacy, Motoyamakita, Higashinada,
Kobe 658, Japan

Abstract—Furopyridones (4a, b, and c) have been proved as the potential synthons for alkaloid synthesis from their facile conversion to the key intermediates (9e), (10e), and (13) for the synthesis of quinine, ajmalicine, and 7-demethyltecomanine.

Biogenetically loganin and secologanin stand as key intermediates in the biosynthetic pathway of monoterpenoid alkaloids. Considering this, we have now explored a general and divergent synthetic route for a large number of monoterpenoid alkaloids employing unnatural heterocycle, furopyridones, as common synthons which were prepared via the route involving reductive photocyclization of enamides substituted with α-alkylthio group which can be removed at a later step.

N-Benzylthioacetamide (1a) and N-methylthiopropionamide (1b) were alkylated with dimethyl sulfate to give respective thioimidates (2a) and (2b) in quantitative yields which were then acylated with either 3-furoyl or 5-methyl-3-furoyl chloride to afford two enamides (3a) or (3b) both quantitatively. The latter enamide (3b) was found to be a 1:2 separable mixture of two geometrical isomers, though their stereochemistries remained unclarified. Reductive photocyclization of the enamides (3a) and (3b) in the presence of sodium borohydride in acetonitrile-methanol proceeded smoothly to give the hydrogenated lactams (4a) [55% from (3a)] and (4b) [41% and 48% from (3b)].

[Synthesis of the Key Intermediates (9e) and (10e) for (±)-Quinine, (±)-Akuammigine, and (±)-Ajmalicine]

Reduction of 6-methylthiofuropyridone (4a) with tributyltinhydride and 2,2'-azo-bisisobutyronitrile followed by catalytic hydrogenation of the resulting 6-
unsubstituted furopyridone (5a) over platinum dioxide under hydrogen atmosphere afforded the tetrahydrofuran (5b) in 71% yield which was also prepared by catalytic reduction of the 6-methylthiofuropyridone (4a) in the presence of Raney-Ni as catalyst in 51% yield. In order to introduce two carbon unit at the 4-position of the piperidone ring, the furopyridone (5b) was subjected to the elimination-addition reaction which consists of opening reaction of the furan ring in (5b) by lithiation with lithium diisopropylamide followed by addition of the 2-lithioacetate to give the desired adduct (6a) and (6b) as a 1:1 diastereomeric mixture at the 3-position in 69% yield. Phenylselenylation of a mixture of the ethylols (6a) and (6b) with o-nitrophenylselenocyanate-tributylphosphine followed by oxidation with hydrogen peroxide gave a 1:1 mixture of the vinyl esters (7) and (8) in 64% yield which was separated by column chromatography. The cis-lactam (7) was converted into the known key intermediate (9e) for (+)-quinine, (±)-akuammigine, and (±)-tetrahydroalstonine by the following reaction sequence. Chemoselective reduction of the lactam carbonyl group (AlH₃ at -50°C), transesterification (MeOH-H₂SO₄), carbamoylation (ClCOOCH₂CCl₃-NaHCO₃), reductive decarbamoylation (Zn-AcOH), and finally benzylation (PhCOCl-Et₃N) afforded the desired cis-N-benzoate (9e) in almost quantitative yield. Similarly, the trans-lactam (8) was also converted into the known synthetic intermediate (10e) of (±)-ajmalicine quantitatively.

[Synthesis of the Key Intermediate (13) for (±)-7-Demethyltecomamine]

Tecomanine (14a) is a monoterpenoid alkaloid having hypoglycemic activity and has been recently synthesized by two groups. The furopyridones (4b) and (4c) were converted into the known synthetic intermediate (13) of 7-demethyltecomamine (14b). Reduction of the 6-methylthiolactams (4b) and (4c) with lithium aluminum hydride by refluxing in tetrahydrofuran gave the desulfurized amines (11a) and (11b) in 91 and 88% yields which were hydrolyzed with 10% hydrochloric acid to give the hydroxyketones (12a) and (12b) in 82 and 94% yields, respectively. Jones oxidation of the hydroxyketone (12b) gave the diketone (13) in quantitative yield which was also prepared by the same reaction of the another hydroxyketone (12a) in 55% yield via presumable isomerization at the 3- or 5-position of the resulting thermodynamically unstable 3,5-trans-diketone. The cis-diketone (13) had been utilized as a key intermediate for the synthesis of (±)-7-demethyltecomamine.14
ACKNOWLEDGEMENTS

We are grateful to the Ministry of Education, Science, and Culture (Japan) for research grant and Misses T. Kato, N. Kitade, M. Fukui, and S. Hira for technical assistance.

REFERENCES AND NOTES


3 α-Unsubstituted enamides were known to resist to photocyclization as shown in the following reports. (a) A. Couture, R. Dubiez, and A. Lablache-Combier, J. Chem. Soc., Chem. Commun., 1982, 842. (b) A. Couture, R. Dubier, and A. Lablache-Combier, Tetrahedron, 1984, 40, 1835.


5 All new compounds reported herein gave ir, nmr, and mass spectral data consistent with the assigned structures.

6 Intermediates (9e), (10e), and (13) prepared herein gave identical spectral data with those of the respective authentic samples.9-11


14 T. Momose, M. Kinoshita, and T. Imanishi, Heterocycles, 1979, 12, 243.

Received, 12th February, 1988

—1324—