

1,3-DIPOLAR CYCLOADDITION REACTION OF 6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINE *N*-OXIDE WITH DIKETENE: A NOVEL CONSECUTIVE REARRANGEMENT TO HEXAHYDROPYRROLO[2,1-*a*]ISOQUINOLINES

Bao-Xiang Zhao and Shoji Eguchi*

*Department of Molecular Design and Engineering, Graduate School of Engineering,
Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-01, Japan*

ABSTRACT: A new kind of hexahydropyrrolo[2,1-*a*]isoquinolines, 1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-2-one-3-carboxylic acid **3**, and 3-acetoacetyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-2-one **4**, were obtained by 1,3-dipolar cycloaddition reaction of 5,6-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1** with diketene. These products could be interpreted to be derivable via an initial cycloaddition reaction of the nitron to the exocyclic double bond of diketene followed by a novel consecutive rearrangement involving N-O bond cleavage rather than elimination of carbon dioxide. The fact that the cycloaddition reaction of **1** with allene afforded 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-oxopropylidene)isoquinoline **5** supported also this mechanism. These compounds would be expected to be useful alkaloid analogues. Thus, the esterification of **3** with methanol afforded methyl 1,2,3,5,6,10b-hexahydro-2-hydroxy-2,8,9-trimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate **7** and methyl 1,2,3,5,6,10b-hexahydro-2,2-dihydroxy-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate **8**, while thermal decarboxylation of **3** gave a vinylogous amide derivative **5** exclusively.

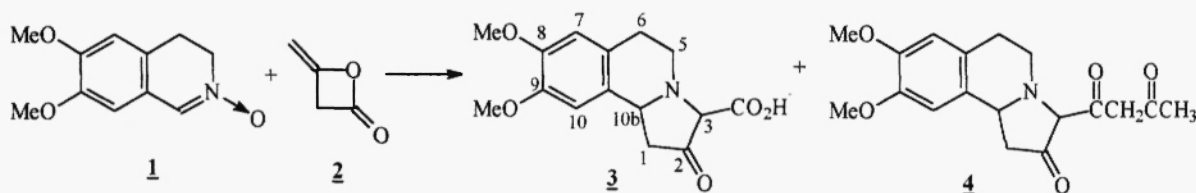
INTRODUCTION

The 1,3-dipolar cycloaddition reaction of nitrones has attracted considerable attention as a convenient tool for constructing various five-membered heterocycles and synthesizing a wide variety of natural products (1). We were interested in the use of 3,4-dihydroisoquinoline *N*-oxide and their cycloaddition reactions to synthesize new heterocyclic compounds, analogues of isoquinoline alkaloids, because of isoquinoline alkaloids are abundant in plant products and many exhibit interesting biological activity (2). We have reported that isoquinoline-fused pyrroles can be obtained by rearrangement of 3,4-dihydroisoquinoline-fused 4-isoxazolines and 5-methyleneisoxazolidines generated from 1,3-dipolar cycloaddition reactions of 3,4-dihydroisoquinoline *N*-oxide with alkynes and electron-deficient allenes (3). In continuation of our

work in this area, we have examined the 1,3-dipolar cycloaddition reaction of 5,6-dimethoxy-3,4-dihydroisoquinoline *N*-oxide with diketene, considering the fact that only a few reports concerning 1,3-dipolar cycloaddition with diketene have been reported up to now (4). Unexpectedly, we found that the cycloaddition reaction affords a new kind of hexahydropyrrolo[2,1-*a*]isoquinoline by a novel rearrangement, which would be expected to be useful precursors of some modified alkaloid products.

RESULTS AND DISCUSSION

The cycloaddition reaction of 5,6-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1** with diketene **2** produced 1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-2-one-3-carboxylic acid **3** and 3-acetoacetyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-2-one **4** as depicted in Scheme 1. The mixture of **3** and **4** were readily separated by silica gel chromatography using ethyl acetate-hexane (2:1) mixture as the eluent and **3** was recrystallized from acetone giving a colorless crystal. The structure of these compounds was confirmed by spectral inspections. The IR spectrum of **3** showed two carbonyl absorptions in 1759 and 1701 cm^{-1} . The mass spectrum (m/z 291, M^+) and elemental analysis of **3** showed that it has the molecular formula $\text{C}_{15}\text{H}_{17}\text{NO}_5$. Moreover, the Fischer esterification and formation of hemiacetal as well as the hydrate with methanol supported also the assigned structure as discussed later.



Scheme 1

The structure assignment of **4** was also made tentatively on the basis of spectroscopic evidence as well as elemental analyses. The IR spectrum of **4** showed carbonyl absorptions at 1761 and 1716 cm^{-1} . In ^1H NMR spectrum, **4** had peaks at δ 2.24 (3 H, s, $-\text{COCH}_3$), 2.26 (2 H, s, $\text{COCH}_2\text{COCH}_3$), 2.80 (1 H, dd, J 17.2 and 6.0, CHHCO), 2.92 (2 H, t, J 6.2, ArCH_2), 3.08 (1 H, dd, J 17.2 and 6.0, CHHCO), 3.44 (2 H, t, J 6.2, $\text{ArCH}_2\text{CH}_2\text{N}$), 3.47 (1 H, s, NCHCO), 3.82 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 4.79 (1 H, t, J 6.0, ArCHN), 6.54 (1 H, s, ArH) and 6.58 (1 H, s, ArH) ppm. Furthermore, the ^{13}C NMR spectrum showed three carbonyl peaks at δ 207.1, 200.6 and 166.2 ppm.

It is reported that diketene reacted with nitrile oxides to yield spiro bis-isoxazoline compounds with loss of carbon dioxide and when a five-fold excess of diketene was allowed to react with *C*-benzoyl-*N*-phenylazomethine oxide in anhydrous benzene, 2-acetoacetyl-5-benzoyl-1-

phenyl-pyrrolidin-3-one was obtained (**4**). These results have been interpreted as an initial cycloaddition reaction of the dipole to the exocyclic double bond of diketene was followed by elimination of carbon dioxide to give the intermediate methyleneisoxazolidine, which rearranged to 5-benzoyl-1-phenylpyrrolidin-3-one, however, because of the acetoacetylation is a faster reaction than the initial cycloaddition, the reaction afforded acetoacetylation product. Obviously, in the present case, the cycloaddition reaction of 5,6-dimethoxy-3,4-dihydroisoquinoline *N*-oxide with diketene proceeded in a novel pathway that is different from previously reported one. A reasonable mechanism for the present reaction is depicted in Scheme 2, in which the attack of diketene occurs initially as the dipolarophile in the 1,3-dipolar cycloaddition reaction to give **9**. The nitrogen-oxygen bond of the heterocyclic ring is expected to be readily cleaved since such heteroatom-heteroatom bonds are known to be relatively weak (5), furthermore, in the present case, N-O bond polarization by the influence of an adjacent polar bond in **9** may ascend the cleavage of weak N-O bond to give **10** rather than elimination of carbon dioxide, and **10** rearranged to **11**, which underwent elimination of carbon dioxide to **13** and hydrogen abstraction to **12** and/or **14**, respectively (6). These intermediates underwent two competitive consecutive reactions, i.e., giving **3** by the radical coupling of **12** or by the cyclocondensation of **14**, and **4** by the acetoacetylation of intermediately formed product **15**.

Table 1. Influence of the reaction conditions on the yields of products **3** and **4**

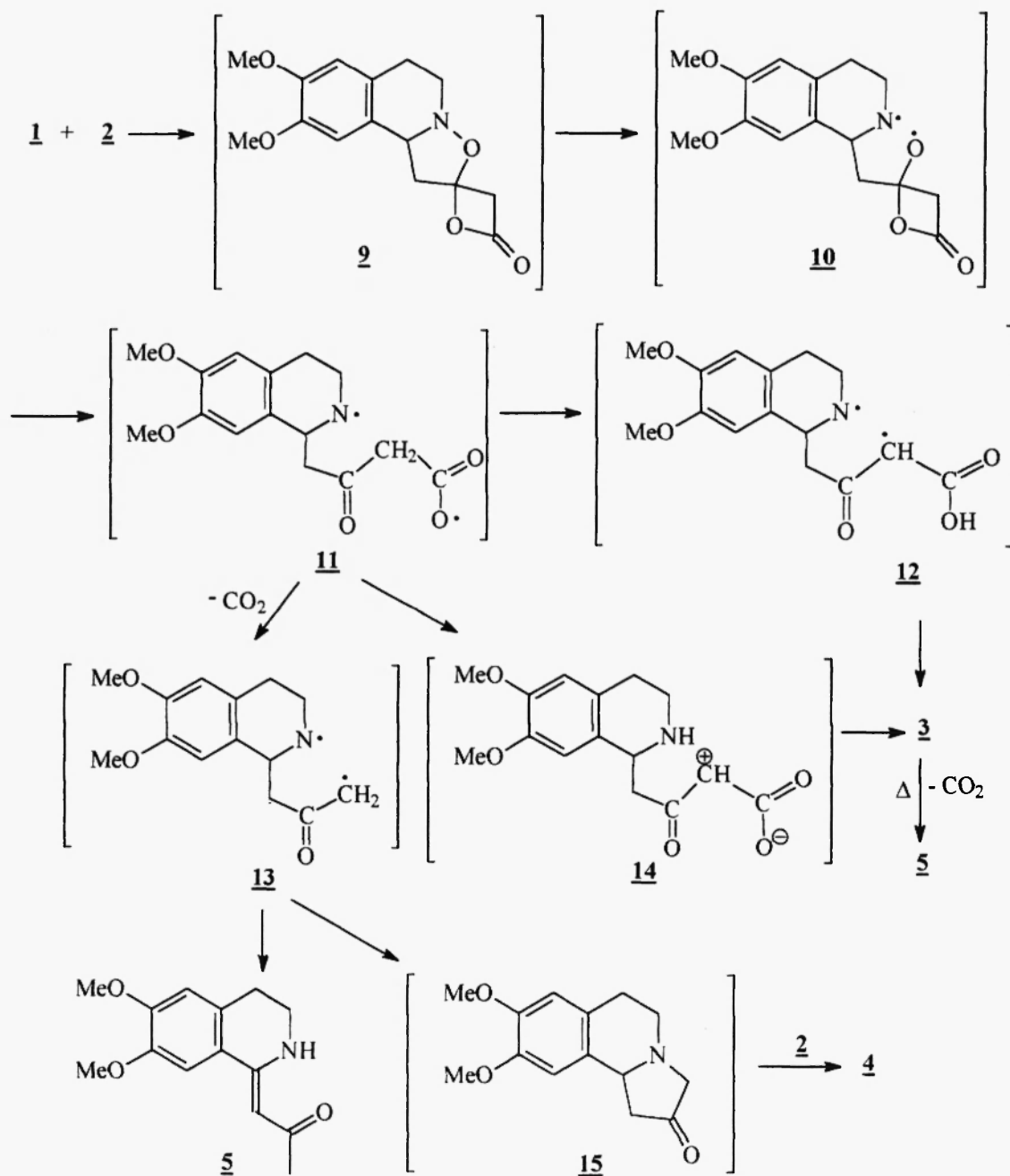
entry	solvent	molar ratio 2:1	temp. ^a	yield ^b	
				3	4
1	CH ₂ Cl ₂	10:1	reflux	33	39
2		10:1	rt.	31	23
3		1:1	reflux	37	5
4		1:1	82 °C ^d	50	8
5	CH ₃ CN	10:1	rt.	45	16
6		1:1	rt.	38	9
7 ^c		1:1	reflux	-	-
8	THF	1:1	82 °C ^d	48	5

^a) the reaction time is 2 h. ^b) isolated yield. ^c) only **5** was obtained in 53 %.

^d) in a sealed tube.

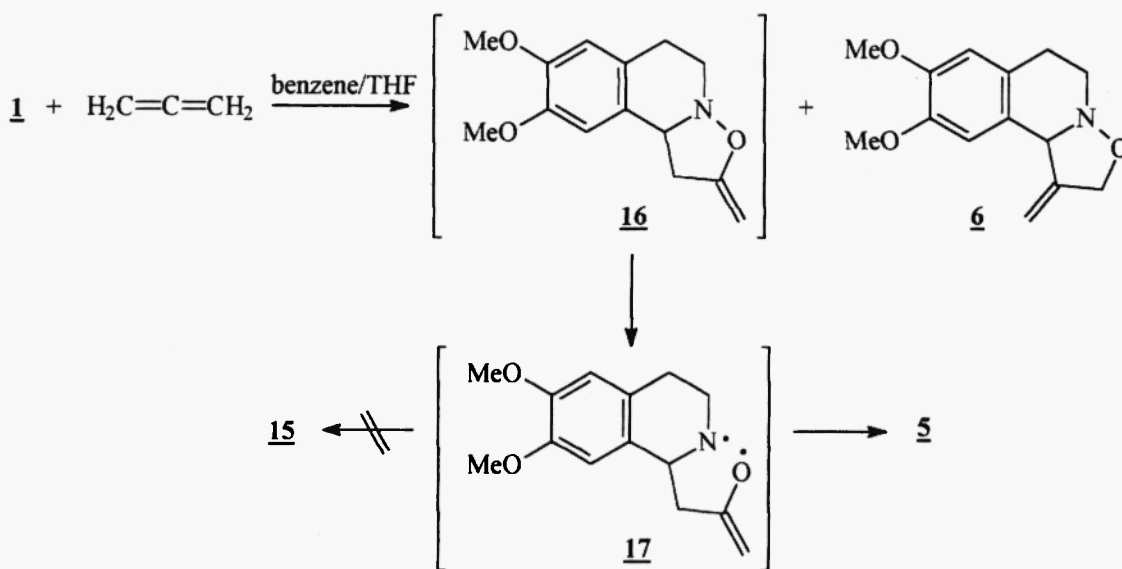
We have examined the influence of the reaction conditions, such as molar ratio, solvent and temperature, on the products ratio and yields. The results are summarized in Table 1. We found that as the molar ratio of diketene **2** vs. nitron **1** was increased, the products ratio of **3** vs. **4** was decreased, on the other hand, at lower temperature, the formation of **3** was favourable due to diminished decarboxylation. In the case of entry 7, **3** and **4** were not obtained, however, a vinylogous amide, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-oxopropylidene)isoquinoline **5** was

obtained in 53% yield. The ^1H NMR spectrum of **5** showed peaks at δ 2.16 (3 H, s, COCH_3), 2.85 (2 H, t, J 6.6, $\text{ArCH}_2\text{CH}_2\text{NH}$), 3.46 (2 H, td, J 6.6 and 3.2, $\text{ArCH}_2\text{CH}_2\text{NH}$), 3.83 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 5.53 (1 H, s, $\text{C}=\text{CHCOCH}_3$), 6.69 (1 H, s, ArH), 7.14 (1 H, s, ArH), 11.25 (1 H, br s, NH) ppm. The IR spectrum exhibited absorptions at 1605 and 1562 cm^{-1} . These spectral properties closely resemble those of reported for analogues of **5**, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-oxobutylidene)isoquinoline formed by the rearrangement of tetrahydroisoxazole-5-spirocyclopropane (**7**). Other vinylogous amides can also become valuable comparison (**8**).



Scheme 2

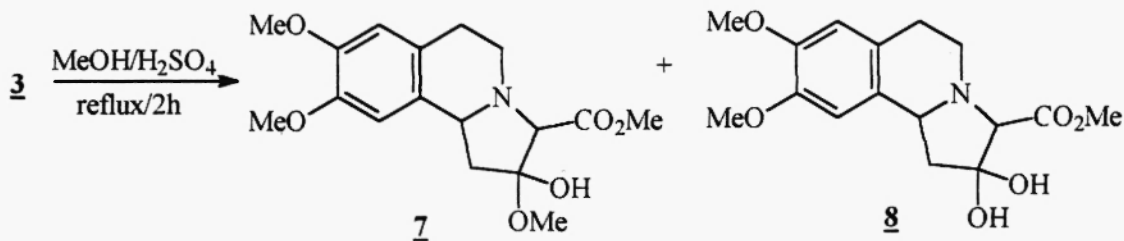
In our previous paper, we reported that the 5-methyleneisoxazolidines generated from 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline *N*-oxides with electron-deficient allenes were considerably stable (9). It is also known that the reactions of *N*-arylnitrones, *N*-alkylnitrones and *C,N*-diphenylnitron with allene afford 3-pyrrolidinones, 4-piperidinones and tetrahydrobenzazepinone (10). We examined the cycloaddition reaction of the nitron **1** with simple allene. A solution of **1** and excess allene, prepared freshly from 2,3-dichloropropene by the literature method (11), in dry benzene and THF in a sealed tube was heated at 85 °C for 6 h leading to the formation of two products. These products were purified by chromatography on silica gel to afford two adducts, **5** and **6**. One of these (i.e., **6**) derived from one regiochemical mode of cycloaddition, while the other (i.e., **5**) derived from the alternative mode of addition followed by a novel rearrangement (Scheme 3). Adduct **6**, formed in 19% yield, displayed significant absorptions at 1610 (C=C stretch) and 1018 cm⁻¹(C=CH₂) in the IR spectrum. In the ¹H NMR spectrum, **6** exhibited peaks at δ 2.71-3.24 (4 H, m, ArCH₂CH₂), 3.87 (3 H, s, OCH₃), 3.90 (3 H, s, OCH₃), 4.64 (2 H, m, OCH₂C=CH₂), 4.77 (1 H, s, ArCH), 5.04 (1 H, q, *J* 2.6, C=CHH), 5.18 (1 H, q, *J* 2.4, C=CHH), 6.64 (1 H, s, ArH) and 6.68 (1 H, s, ArH) ppm. The 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-oxopropylidene)isoquinoline **5**, formed in 27 % yield, was readily characterized by its identical spectral properties with **5** obtained from the reaction with diketene as mentioned above. The fact that the 5-methyleneisoxazolidine rearranged to the vinylogous amide **5** rather than pyrrolidinone **15** supports the proposed N-O bond cleavage as the key step in the mechanism for the reaction with diketene, that is related indirectly with methyleneisoxazolidine described above.



Scheme 3

It should be noted that heterocycle-fused isoquinolines would be attractive for their potential biological activities (12). The synthesis of **3** and **4** are of some interest since the synthesis of these

compounds have not been reported, and they would be expected to become convenient precursors to modify alkaloid skeletons due to multifunctional groups. Thus, we carried out the esterification of **3** with methanol by refluxing for 2 h in the presence of concentrated sulfuric acid catalyst and obtained methyl 1,2,3,5,6,10b-hexahydro-2-hydroxy-2,8,9-trimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate **7** in 66% yield as the major product accompanied with a minor product **8**, in 6% yield. Under the conditions of lower temperature, e.g., when dichloromethane was employed as the solvent, after reflux for 2 h, only the hydrate **8** was obtained in 77% yield. It was easily recrystallized from ethyl acetate to give a colorless crystal, mp. 162-163 °C. It is very interesting that the stable hydrate was isolated because it is well known that the hydrates of most aldehydes and ketones cannot be isolable except for compounds with special structural features such as strained rings or strongly electron-deficient nature. In the present case, the reason may be decreasing ring strain along with the forming intramolecular hydrogen bond. The hydrolysis reaction of the hemiacetal **7** gave the hydrate **8** rather than methyl 1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-2-one-3-carboxylate.



Scheme 4

Recently, syntheses of the hexahydropyrroloisoquinoline rings, such as **18** and **19** (Chart 1), have appeared in the literature (13). A popular method for the synthesis of these alkaloids involves *N*-acyliminium ion cyclizations (14), therefore, 2-oxohexahydropyrrolo[2,1-*a*]isoquinoline **15** which can be also a precursor of **19** has not been reported. Taking into consideration of this fact, we examined the decarboxylation of **3**, expecting to obtain **15**. Thus, a mixture of **3** and xylene was heated under reflux for 6 h to afford a product in 81% yield, however, the product was assigned to be **5** rather than expected **15** based on the spectral properties.

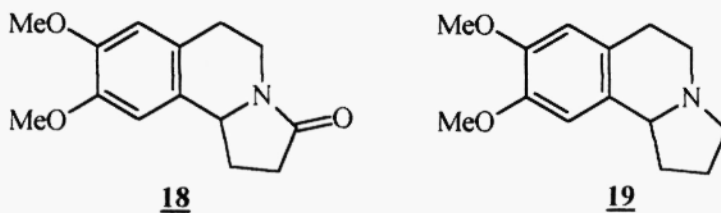


Chart 1

In conclusion, we have found a novel reaction behavior of 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide with diketene and simple allene. 1,2,3,5,6,10b-Hexahydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-2-one-3-carboxylic acid **3**, 3-acetoacetyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-2-one **4** and 1,2,3,4-tetrahydro-6,7-dimethoxy-1(2-oxopropylidene)isoquinoline **5** were obtained by 1,3-dipolar cycloaddition reaction of 5,6-dimethoxy-3,4-dihydroisoquinoline *N*-oxide with diketene, depending on the reaction conditions, and it can be interpreted as an initial cycloaddition reaction of the nitron to the exocyclic double bond of diketene followed by a novel consecutive rearrangement involving N-O bond cleavage rather than consecutive elimination of carbon dioxide. The cycloaddition reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide with allene produced also 1,2,3,4-tetrahydro-6,7-dimethoxy-1(2-oxopropylidene)isoquinoline **5**. Furthermore, the esterification of **3** afforded methyl 1,2,3,5,6,10b-hexahydro-2-hydroxy-2,8,9-trimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate **7**, and methyl 1,2,3,5,6,10b-hexahydro-2,2-dihydroxy-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate **8**, depending on the reaction conditions.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra of liquids were measured as films on sodium chloride plates and those of solids were measured in pressed potassium bromide discs on a JASCO FT/IR 5300 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian GEMINI 200 spectrometer at 200 and at 50 MHz, respectively. Chemical shifts are recorded in parts per million (ppm) for samples in CDCl_3 solution with Me_4Si as an internal standard. Coupling constants J are reported in Hz. Elemental analyses were carried out on a Perkin-Elmer 2400S elemental analyzer. Mass spectra (EI) were obtained using a JEOL JMS-AX505 HA mass spectrometer at 70 eV. The thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F₂₅₄.

Reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline *N*-oxide **1** with diketene **2**

To a solution of **1** (0.207 g, 1.0 mmol) in dry dichloromethane (10 mL), diketene **2** (0.840 g, 10.0 mmol) was added and stirred for 2 h at room temperature, then the solvent was evaporated under reduced pressure. Column chromatography of the residue on silica gel eluted with ethyl acetate-hexane (2 : 1) afforded product **3** with R_f 0.48, 90 mg (31% yield), followed by the product **4**, R_f 0.21, 75 mg (23% yield). In the case of acetonitrile employed as the solvent and under the conditions of reflux, only one product **5**, 1,2,3,4-tetrahydro-6,7-dimethoxy-1(2-oxopropylidene)isoquinoline rather than **3** and **4**, was obtained, R_f 0.17, 130 mg, 53% yield.

1,2,3,5,6,10b-Hexahydro-8,9-dimethoxypyrrolo[2,1-a]isoquinolin-2-one-3-carboxylic acid 3

A white solid, mp 143-145 °C (Found: C, 61.82; H, 5.91; N, 4.77. $C_{15}H_{17}NO_5$ requires C, 61.85; H, 5.84; N, 4.81 %); $\nu_{\max}$ (KBr)/ cm^{-1} 3443(br), 2964, 2868, 1759, 1701, 1606, 1521, 1467, 1369, 1255, 1149, 1103, 1011, 968 and 872; δ_H 2.57(1 H, dd, J 6.4 and 1.6), 2.80-3.06 (2 H, m), 3.22-3.38 (4 H, m), 3.83 (3 H, s), 3.88 (3 H, s), 4.04 (1 H, d, J 7.6), 4.60-4.64 (1 H, m), 6.45 (1 H, s), 6.63 (1 H, s); δ_C 22.6, 46.2, 49.3, 51.6, 56.1, 56.3, 61.8, 108.3, 111.9, 124.8, 125.8, 148.6, 149.0, 172.6 and 200.9; m/z 291 (M^+ , 14%), 274 (7), 247 (65), 232 (100), 207 (70) and 191 (20).

3-Acetoacetyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-one 4

An oil (Found: C, 65.20; H, 6.46; N, 4.19; $C_{18}H_{21}NO_5$ requires C, 65.24; H, 6.39; N, 4.23%); $\nu_{\max}$ (Neat)/ cm^{-1} 2938, 2837, 1761, 1716, 1611, 1516, 1464, 1408, 1362, 1315, 1252, 1227, 1125, 1022, 935, 862, 802 and 764; δ_H 2.24 (3 H, s), 2.26 (2 H, s), 2.80 (1 H, dd, J 17.2 and 6.0), 2.92 (2 H, t, J 6.2), 3.08 (1 H, dd, J 17.2 and 6.0), 3.44 (2 H, t, J 6.2), 3.47 (1 H, s), 3.82 (3 H, s), 3.85 (3 H, s), 4.79 (1 H, t, J 6.0), 6.54 (1 H, s) and 6.58 (1 H, s); δ_C 14.2, 24.9, 30.2, 30.6, 48.9, 49.4, 56.0, 56.1, 60.4, 109.7, 111.3, 125.1, 127.6, 148.2, 148.5, 166.2, 200.6 and 207.1; m/z 311 (45 %) and 296 (100).

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-oxopropylidene)isoquinoline 5

A pale yellowish solid, mp 134-136 °C (Found: C, 68.09; H, 7.03; N, 5.53; $C_{14}H_{17}NO_3$ requires C, 67.98; H, 6.93; N, 5.67%); $\nu_{\max}$ (KBr)/ cm^{-1} 2939, 2841, 1605, 1562, 1506, 1464, 1410, 1348, 1267, 1219, 1167, 1121, 1045, 986, 920, 877, 818, 760 and 704; δ_H 2.16 (3 H, s), 2.85 (2 H, t, J 6.6), 3.46 (2 H, td, J 6.6 and 3.2), 3.93 (3 H, s), 3.94 (3 H, s), 5.53 (1 H, s), 6.69 (1 H, s), 7.14 (1 H, s) and 11.25 (1 H, br s); δ_C 28.1, 29.5, 38.7, 56.2, 56.4, 89.5, 108.6, 111.0, 121.5, 130.9, 148.3, 151.9, 157.4 and 195.8; m/z 247 (M^+ , 48 %), 232 (100), 216 (7) and 188 (6).

Reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide 1 with allene

A mixture of 1 (0.207g, 1.0 mmol) and excess allene, prepared freshly from 2,3-dichloropropene (9 g, 78.6 mmol) by the literature method (11), in dry benzene (10 mL) and THF (6 mL) was heated in a sealed tube to 85 °C for 5 h, and then the solvent was evaporated under a reduced pressure. The residue was chromatographed on a silica gel column with ethyl acetate to give 1,5,6,10b-tetrahydro-8,9-dimethoxy-1-methylene-1*H*-isoxazolo[3,2-*a*]isoquinoline 6, R_f 0.45, 50 mg, 19% yield and 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-oxopropylidene)isoquinoline 5, R_f 0.27, 70 mg, 27 % yield.

1,5,6,10b-Tetrahydro-8,9-dimethoxy-1-methylene-1*H*-isoxazolo[3,2-*a*]isoquinoline 6

An oil (Found: C, 67.84; H, 7.04; N, 5.56. $C_{14}H_{17}NO_3$ requires C, 67.98; H, 6.93; N, 5.67%); $\nu_{\max}$ (Neat)/ cm^{-1} 2932, 2831, 1610, 1517, 1462, 1358, 1256, 1222, 1112, 1018, 891 and 771; δ_H 2.71-3.24 (4 H, m), 3.87 (3 H, s), 3.90 (3 H, s), 4.64 (2 H, m), 4.77 (1 H, s), 5.04 (1 H, q, J 2.6),

5.18 (1 H, q, J 2.4), 6.64 (1 H, s) and 6.68 (1 H, s); δ_C 28.5, 48.1, 56.1, 56.4, 66.3, 69.4, 106.3, 111.4, 111.6, 124.6, 125.7, 148.1, 148.7 and 151.7; m/z 247 (M^+ , 34%), 207 (100), 203 (23) and 192 (12).

Esterification of **3**

To anhydrous methanol (30 mL), concentrated sulfuric acid (60 mg) was added, and then **3** (90 mg, 0.3 mmol) was added. Then the mixture was heated and reflux for 2 h. After about a half of solvent was evaporated under reduced pressure, water (15 mL) was added. The residue was extracted with dichloromethane (10 mL) three times. The dichloromethane layer was washed with 10% sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. After removal of the solvent under a reduced pressure, the residue was chromatographed on a silica gel column with a mixture of ethyl acetate and hexane (2:1) to afford methyl 1,2,3,5,6,10b-hexahydro-2-hydroxy-2,8,9-trimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate **7**, R_f 0.21, 60 mg, 66% yield, and methyl 1,2,3,5,6,10b-hexahydro-2,2-dihydroxy-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate **8**, R_f 0.10, 5 mg, 6% yield. The starting substrate **3** was recovered in 10%.

Similarly, to a mixture of anhydrous methanol (4 mL) and dichloromethane (10 mL), concentrated sulfuric acid (40 mg) was added, and then **3** (60 mg, 0.20 mmol) was added. Then the mixture was heated and reflux for 2 h. After cooling to room temperature, water (15 mL) was added, and the dichloromethane layer was separated, washed with 10% sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. After removal of the solvent under a reduced pressure, a colorless solid was obtained, 50 mg, yield 77%, which was identified as **8** on the basis of spectral data.

Methyl 1,2,3,5,6,10b-hexahydro-2-hydroxy-2,8,9-trimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate **7**

A colorless solid, mp 119-120 °C (Found: C, 60.40; H, 6.95; N, 3.98; $C_{17}H_{23}NO_6$ requires C, 60.53; H, 6.82; N, 4.15%); ν_{max} (KBr)/ cm^{-1} 3490 (br), 2936, 2835, 1729, 1611, 1517, 1466, 1348, 1260, 1222, 1120, 1026, 884, 854 and 763; δ_H 2.58 (1 H, d, J 14.2), 2.66-2.91 (4 H, m), 3.04 (1 H, d, J 14.2), 3.27 (2 H, t, J 7.8), 3.40 (3 H, s), 3.62 (3 H, s), 3.85 (3 H, s), 3.86 (3 H, s), 4.79 (1 H, t, J 7.8), 6.57 (1 H, s) and 6.58 (1 H, s); δ_C 26.3, 40.0, 47.3, 49.3, 49.9, 52.0, 56.0, 56.1, 61.2, 105.6 (C-2), 110.0, 111.1, 126.0, 127.4, 148.1, 148.3 and 169.9; m/z 337 (M^+ , 8), 232 (8), 207 (100) and 192 (6).

Methyl 1,2,3,5,6,10b-hexahydro-2,2-dihydroxy-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline-3-carboxylate **8**

A colorless crystal from ethyl acetate, mp 162-163 °C (Found: C, 59.46; H, 6.60; N, 4.24; $C_{16}H_{21}NO_6$ requires C, 59.42; H, 6.55; N, 4.33%); ν_{max} (KBr)/ cm^{-1} 3453 (br), 2997, 2843, 1729, 1615, 1519, 1450, 1365, 1325, 1254, 1125, 1019, 887, 841 and 761; δ_H 2.35- 2.45 (1 H, m), 2.64-

2.90 (6 H, m), 3.25-3.40 (2 H, m), 3.72 (3 H, s), 3.85 (3 H, s), 3.89 (3 H, s), 4.85 (1 H, t, J 7.8), 6.56 (1 H, s), 6.59 (1 H, s); δ_C 25.9, 43.7, 48.4, 49.6, 52.3, 56.1, 56.2, 61.0, 102.8 (C-2), 110.0, 111.2, 126.2, 127.3, 148.2, 148.4 and 171.8; m/z 323 (M^+ , 3%), 305 (2), 208 (84), 207 (100), 191 (29) and 176 (14).

Hydrolysis reaction of the hemiacetal 7

A solution of 7 (20 mg, 0.06 mmol) in acetic acid (2 mL) and water (1 mL) was heated to 50 °C for 3 h. The cooled solution was then neutralized by solid sodium hydrogen carbonate and extracted with dichloromethane (30 mL). The combined extracts was washed with a saturated solution of sodium chloride and dried on magnesium sulfate. After removal of the solvent under a reduced pressure, a colorless solid (15 mg) was obtained, which was identified as 8 on the basis of spectral data.

Decarboxylation of 3

A solution of 3 (30 mg, 0.10 mmol) in dry xylene (10 mL) was heated to reflux for 6 h under an atmosphere of argon. After evaporation of the solvent under a reduced pressure, the residue was chromatographed on silica gel with ethyl acetate to give 1,2,3,4-tetrahydro-6,7-dimethoxy-1(2-oxopropylidene)isoquinoline 5, 20 mg, 81% yield.

ACKNOWLEDGMENT

This work was partially supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.

REFERENCE

- (1) a) M. Frederickson, *Tetrahedron*, **53**, 403 (1997).
b) J. J. Tufariello, *Acc. Chem. Res.*, **12**, 396 (1979).
- (2) a) W. K. Anderson, A. R. Heider, N. Raju and J. A. Yucht, *J. Med. Chem.*, **31**, 2097 (1988).
b) W. K. Anderson, H. L. McPherson, Jr. J. S. New and A. C. Rick, *J. Med. Chem.*, **27**, 1321 (1984).
- (3) a) B.-X. Zhao Y. Yu and S. Eguchi, *Tetrahedron*, **52**, 12049 (1996).
b) B.-X. Zhao and S. Eguchi, *J. Chem. Soc., Perkin Trans. 1*, 2973 (1997).
- (4) M. C. Aversa, G. Cum, G. Stagno d'Alcontres and N. Uccella, *J. Chem. Soc., Perkin Trans. 1*, 222 (1972).

- (5) J. E. Baldwin, R. G. Pudussery, A. K. Qureshi and B. B. Sklarz, *J. Am. Chem. Soc.*, **90**, 5325 (1968).
- (6) For a general review on radical reaction, see J. Fossey, D. Lefort and J. Sorba, "Free Radicals in Organic Chemistry", John Wiley and Sons, New York, 1995.
- (7) A. Brandi, S. Garro, A. Guarna, A. Goti, F. Cordero and F. De Sarlo, *J. Org. Chem.*, **53**, 2430 (1988).
- (8) a) S. Eguchi, I. Ogura and Y. Terada, *Heterocyclic Commun.*, **1**, 365 (1995).
b) S. Eguchi, K. Asai, H. Takeuchi and T. Sasaki, *J. Chem. Soc., Perkin Trans. 1*, 1171 (1987).
- (9) B.-X. Zhao and S. Eguchi, *Tetrahedron*, **53**, 9575 (1997).
- (10) a) M. C. Aversa, G. Cum and N. Uccella, *J. Chem. Soc., Chem. Commun.*, 156 (1971).
b) G. Cum, G. Sindona and N. Uccella, *J. Chem. Soc., Perkin Trans. 1*, 719 (1976).
c) J. J. Tufariello, Sk. A. Ali and H. O. Klingele, *J. Org. Chem.*, **44**, 4213 (1979).
- (11) H. N. Cripps and E. F. Kiefer, *Org. Synth.*, **42**, 12 (1962).
- (12) a) B. Lal, A. N. Dohadwalla, N. K. Dadkar, A. D'Sa and N. J. de Souza, *J. Med. Chem.*, **27**, 1470 (1984).
b) B. E. Maryanoff, D. F. McComsey, M. J. Costanzo, P. E. Setler, J. F. Gardocki, R. P. Shank and C. R. Schneider, *J. Med. Chem.*, **27**, 943 (1984).
c) K. L. Sorgi, C. A. Maryanoff, D. F. McComsey, D. W. Graden and B. E. Maryanoff, *J. Am. Chem. Soc.*, **112**, 3567 (1990).
- (13) a) K. Orito, T. Matsuzaki and H. Sugimoto, *Heterocycles*, **27**, 2403 (1988).
b) B. E. Maryanoff, D. F. McComsey and B. A. Duhl-Emswiler, *J. Org. Chem.*, **48**, 5062 (1983).
c) E. Lete, A. Eguiarte, N. Sotomayor, T. Vicente and M. J. Villa, *Synlett*, 41 (1993).
d) M. I. Collado, I. Manteca, N. Sotomayor, M.-J. Villa and E. Lete, *J. Org. Chem.*, **62**, 2080 (1997).
- (14) a) Y. S. Lee, S. H. Kim, S. H. Jung, S. J. Lee and H. Park, *Heterocycles*, **37**, 303 (1994).
b) Y. S. Lee, C. S. Kim, S. H. and H. Park, *Heterocycles*, **38**, 2605 (1994).
c) Y. S. Lee, D. W. Kang, S. J. Lee and H. Park, *J. Org. Chem.*, **60**, 7149 (1995).
d) B. E. Maryanoff, D. F. McComsey, H. R. Almond, Jr. and M. S. Mutter, *J. Org. Chem.*, **51**, 1341 (1986).
e) W. N. Speckamp and H. Hiemstra, *Tetrahedron*, **41**, 4367 (1985).

Received on January 20, 1998

