$$\text{6-methylaminoquinoline} \xrightarrow[81\%]{NO_2^+} \text{5-nitro-6-methylaminoquinoline}$$

$$\xrightarrow[78\%]{Pd/C,\ H_2} \text{5-amino-6-methylaminoquinoline} \xrightarrow[59\%]{BrCN} \text{IQ (29\% from 6-aminoquinoline)}$$

6) F.F. Kadlubar, J.A. Miller, and E.C. Miller, *Cancer Res.*, **36**, 2350 (1976).
7) Y. Hashimoto, K. Takeda, K. Shudo, and T. Okamoto, T. Sugimura, *Chem.-Biol. Interactions*, **23**, 137 (1978).

Faculty of Pharmaceutical Sciences
University of Tokyo
Hongo, Tokyo, Japan

Toshihiko Okamoto*
Koichi Shudo
Yuichi Hashimoto
Takuo Kosuge

Shizuoka College of Pharmacy
Oshika, Shizuoka, Japan
National Cancer Center Research Institute
Tsukiji, Tokyo, Japan

Takashi Sugimura
Susumu Nishimura

Received December 2, 1980

[Chem. Pharm. Bull. 29(2) 593—595 (1981)]

1,2-Dihydrocyclobuta[*c*]quinoline[1)]

Using 1,2-dihydrocyclobuta[*c*]quinolin-3(4H)-one (III) obtained through the photoaddition of 4-methoxy-2-quinolone (I) to ethylene and subsequent base treatment of the resulted cycloadduct (II) as a key intermediate, 1,2-dihydrocyclobuta[*c*]quinoline (V), a new aza-analogue of naphthocyclobutene, was synthesized.

Keywords——photochemical synthesis; photochemical 2+2 cycloaddition; 3-chloro-1,2-dihydrocyclobuta[*c*]quinoline; 1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline; aza-analogue of naphthocyclobutene; 1,2-dihydrocyclobuta[*c*]quinolin-3(4H)-one

1,2-Dihydrocyclobuta[*b*]quinoline, one of the possible heterocyclic analogues of naphthocyclobutene, has been synthesized previously either from a sealed tube reaction of anthranil with cyclobutanone in the presence of mercuric sulphate,[2)] or *via* a Friedlander synthesis using cyclobutanone and *o*-aminobenzaldehyde.[3)] In this paper, we describe the synthesis and characterization of 1,2-dihydrocyclobuta[*c*]quinoline (V), a new heterocyclic analogue of naphthocyclobutene.

Irradiation of 4-methoxyquinolin-2(1H)-one (I) in a mixture of methanol and acetone (2: 3 v/v) under bubbling of ethylene by high pressure mercury lamp (Toshiba 400P) through a Pyrex filter afforded a 2+2 cycloadduct (II, mp 172.5—173.5°) in 90% yield as a sole isolable product. The adduct (II) was treated with potassium hydroxide in methanol at reflux to give 1,2-dihydrocyclobuta[*c*]quinolin-3(4H)-one (III, mp 223.5—224.5°) in a quantitative yield. Comparison of the spectral data of II and III with those of the cycloadducts of I with substituted olefins and their methanol elimination products[4)] confirmed correctness of the assigned structures. Chlorination of III (reflux in phosphorous oxychloride) led to 3-chloro-1,2-dihydrocyclobuta[*c*]quinoline (IV, mp 115.5—116.5°) in a quantitative yield. The structure of IV was established on the basis of combustion analysis,[5)] UV spectrum [λ_{max}^{MeOH} nm (log ε): 210 (4.60), 229.5 (4.67), 234 (4.68), 277.5 (3.63), 306 (3.60), and 319 (3.66)] which is quite similar to that of 2-chloro-4-methylquinoline [λ_{max}^{MeOH} nm (log ε): 208 (4.59), 229 (4.65), 277 (3.65), 304 (3.54), and 317.5 (3.59)], and finally of its pmr spectrum.[6)] Thus, the four methylene

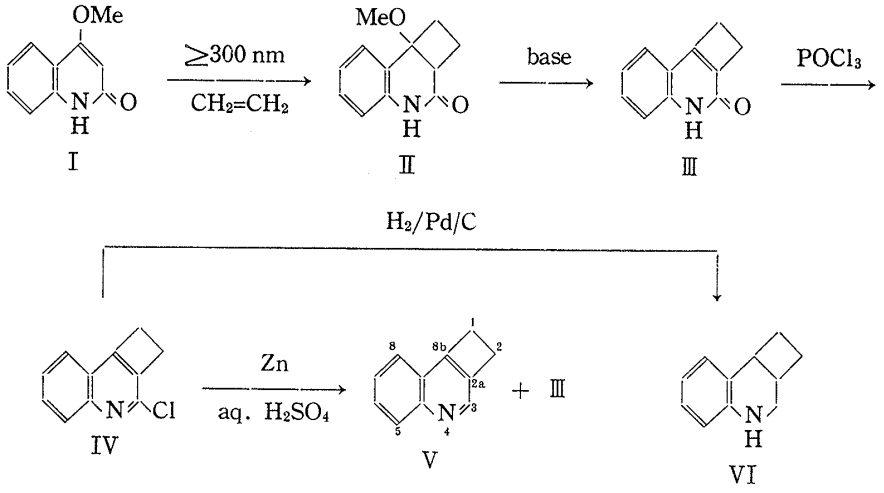

Chart 1

protons appeared as a singlet at δ 3.35 and the aromatic ones as multiplets between 7.35 and 8.1.

Though reductive dehalogenation of 2- and 4-halogenopyridines and -quinolines is generally achieved by catalytic hydrogenation over palladium on charcoal (1 atm, room temp.),[7] attempted reductive dechlorination of IV to the title compound (V) by this method was failed and gave 1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline[8] (VI, oil) as the major product. Since the fused four membered ring was known to enhance susceptibility of the aromatic ring to catalytic hydrogenation,[9] an alternative method for this reductive dechlorination step was examined. Thus, the reduction of IV with zinc in aq. sulfuric acid (reflux) was found to give the desired 1,2-dihydrocyclobuta[*c*]quinoline (V, mp 46.0—47.0°); picrate, mp 208.0—211.0°, decomp.) in 25.5% yield. In this case, III (the simple hydrolysis product of IV) was obtained in 52.5% yield.[10]

1,2-Dihydrocyclobuta[*c*]quinoline (V) was characterized by its pmr spectrum (δ: methylene protons; 3.38 s, H_3; 8.53 s, H_5; 8.0 m, H_6, H_7, and H_8; 7.15—7.75) and UV spectrum [λ_{max}^{MeOH} nm (log ε): 222 (4.73), 277.5 (3.63), 306.5 (3.43), and 319.5 (3.49)] which is almost the same with those of alkylated quinolines.

Since 4-alkoxy-2-quinolones and -pyridones have no tendency to photodimerize but selectively add to a variety of olefins and the resulted cycloadducts eliminate an alcohol to give 1,2-dihydrocyclobuta[*c*]quinolin-3(4H)-ones and -pyridin-3(4H)-ones[11] by base, the present route to the title compound (V) may have wide applicability for the syntheses of this class of heterocyclic compounds.

References and Notes

1) Part V of "Cycloadditions in Syntheses." Part IV: T. Naito and C. Kaneko, *Chem. Pharm. Bull.*, **28**, 3150 (1980).
2) M. Wilk, H. Schwab, and J. Rochlitz, *Annalen*, **698**, 149 (1966).
3) J.H. Markgraf and W.L. Scott, *J. Chem. Soc. Chem. Comm.*, **1967**, 296.
4) C. Kaneko and T. Naito, *Chem. Pharm. Bull.*, **27**, 2254 (1979). See also, C. Kaneko, T. Naito, and M. Somei, *J. Chem. Soc., Chem. Comm.*, **1979**, 804.
5) Satisfactory analyses and mass spectra were obtained for all new crystalline compounds.
6) Throughout the present work, PMR spectra were measured in $CDCl_3$.
7) J.P. Stevens, P.H. Beutel, and E. Chamberlin, *J. Am. Chem. Soc.*, **64**, 1093 (1942); J.P. Wibaut and E.C. Kooyman, *Rec. Trav. Chim.*, **63**, 236 (1944).
8) The compound (VI) and its acetate showed the corresponding molecular ions in their mass spectra and their UV spectra resembled to those of aniline and acetanilide, respectively.
9) R.P. Thummel and D.K. Kohli, *J. Org. Chem.*, **43**, 4882 (1978); D.J. Haywood, R.G. Hunt, C.J. Potter, and S.T. Reid, *J. Chem. Soc. Perkin I*, 2458 (1977).

10) Optimization of the yield of V has not been made.
11) H. Fujii, K. Shiba, and C. Kaneko, *J. Chem. Soc. Chem. Comm.*, **1980**, 537.

Faculty of Pharmaceutical Sciences,
Kanazawa University, Takara-machi,
Kanazawa, 920, Japan

CHIKARA KANEKO*
TOSHIHIKO NAITO
NAYOMI NAKAYAMA

Received December 11, 1980

[Chem. Pharm. Bull. 29(2)595—596 (1981)]

Synthesis of Renierone, Antimicrobial Metabolite from a Marine Sponge *Reniera* sp.

Renierone, a unique isoquinolinequinone antimicrobial metabolite produced from a marine sponge *Reniera* sp., was synthesized.

Keywords——renierone; antimicrobial metabolite; *Reniera* sp.; marine sponge; isoquinolinequinone; synthesis

Renierone, isolated from the ethanolic extracts of an intense blue sponge *Reniera* sp., has been characterized as 1-(7-methoxy-6-methyl-5,8-dioxoisoquinolyl)carbinyl angelate (**2**) by an X-ray crystallographic study. It shows strong antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Candida albicans*.[1)]

Recently we have reported the structure determination and synthesis of mimocin (**1**), a new isoquinolinequinone antibiotic, from the fermentation broth of *Streptomyces lavendulae*.[2)]

Their structural feature and antimicrobial activities led us to undertake the synthesis of **2** and its isomer **3**.

7-Methoxy-6-methyl-8-nitroisoquinoline (**4**) [mp 84—86°][3,4)] was converted to the Reissert compound (**5**) [mp 160—161°; MS *m/e*: 349 (M^+), 105; ^1H NMR ($CDCl_3$, 100 MHz) δ: 2.40 (3H, s, C_6–CH_3), 3.95 (3H, s, C_7–OCH_3), 6.11 (1H, d, J=8 Hz, C_4–H), 6.54 (1H, s, C_1–H), 6.71 (1H, d, J=8 Hz, C_3–H), 7.24 (1H, s, C_5–H), 7.3—7.6 (5H, br s)] in 40% yield by Uff's procedure.[5)]

The lithium salt of **5**, prepared by treatment with phenyllithium in dioxane–ether at −20°, was treated with gaseous formaldehyde[6)] [−20°——5°, 30 min; then 10°, 30 min] to yield 1-(7-methoxy-6-methyl-8-nitroisoquinolyl)carbinyl benzoate (**6**) [mp 128—129°; MS *m/e*: 352 (M^+), 247, 105; ^1H NMR ($CDCl_3$) δ: 2.54 (3H, s, C_6–CH_3), 3.96 (3H, s, C_7–OCH_3), 5.75 (2H, s, CH_2O), 7.53 (1H, d, J=6 Hz, C_4–H), 7.76 (1H, s, C_5–H), 8.45 (1H, d, J=6 Hz, C_3–H)] in 61% yield.

Upon hydrolysis[2% NaOH–EtOH, 45°, 5 min], **6** gave in 90.3% yield 1-(7-methoxy-6-methyl-8-nitroisoquinolyl)carbinol (**7**) [mp 148—149°; MS *m/e*: 248 (M^+), 231, 201; ^1H NMR ($CDCl_3$) δ: 2.56 (3H, s, C_6–CH_3), 3.97 (3H, s, C_7–OCH_3), 4.96 (2H, s, CH_2O), 7.56 (1H, d, J= 6 Hz, C_4–H), 7.81 (1H, s, C_5–H), 8.44 (1H, d, J=6 Hz, C_3–H); IR (KBr) 3340 cm^{-1}].

The Fremy's salt oxidation of 1-(8-amino-7-methoxy-6-methylisoquinolyl)carbinol (**8**) [mp 150—151° (dec); MS *m/e*: 218 (M^+); IR (KBr) 3390, 3320 cm^{-1}], obtained in 92.1% yield by catalytic reduction of **7**, provided 1-(7-methoxy-6-methyl-5,8-dioxoisoquinolyl)carbionl (**9**) [mp 131—133°; MS *m/e*: 233 (M^+); ^1H NMR ($CDCl_3$) δ: 2.12 (3H, s, C_6–CH_3), 4.24 (3H, s, C_7–OCH_3), 5.24 (2H, s, CH_2O), 7.86 (1H, d, J=5 Hz, C_4–H), 8.84 (1H, d, J=5 Hz, C_3–H); IR (KBr) 3400, 1670 cm^{-1}] in 63.7% yield.

The compound **9** was treated with phenyllithium in dioxane-ether at −20° followed by addition of angeloyl chloride to afford **2** [mp 92.0—92.5°][7)] in 37% yield, which was identified with the natural renierone by comparison of IR, ^1H and ^{13}C NMR spectra.