[Chem. Pharm. Bull.
25(11)3120—3121(1977)]

UDC 547.837.2.02.04 : 547.94.02.04

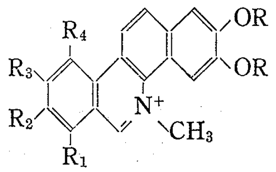
Structural Establishment of Chelilutine Due to the Chemical Correlation with Nitidine and Isoarnottianamide[1]

Chelilutine (2) was chemically correlated with nitidine (6) and isoarnottianamide (5). The practical method for synthesis of the fully aromatized O_5-benzo[*c*]phenanthridine alkaloid was established.

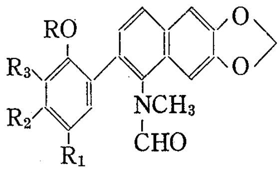
Keywords——chelilutine; isoarnottianamide; nitidine; O_5-benzo[*c*]phenanthridine; Bischler-Napieralski reaction

The natural occurrence[2] of fully aromatized O_5-benzo[*c*]phenanthridine alkaloids has been known in *Papaveraceous* plants. In the previous paper,[3] we reported the structural establishment of chelirubine (bocconine) (1) and tentatively proposed the formulae (2), (3), and (4) for chelilutine, sanguirubine, and sanguilutine, respectively. In this proposal, however, there was no reasoning for determination of the species of alkoxy groups at C_2 and C_3 and at C_8 and C_9 on the structures[4] of chelilutine (2) and sanguirubine (3), because the reported physical data[2b] for these alkaloids gave no decisive answer on this matter. In this communication, we wish to show definite chemical evidences for their structures due to chemical correlation of chelilutine (2) with isoaronottianamide[5] (5) and nitidine (6).

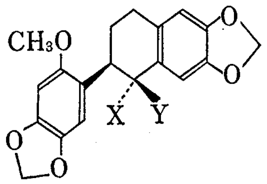
In the course of studies on the chemical constituents of *Rutaceous* plants, we[6] recently isolated some new amides from several plants (*Xanthoxylum*). These new amides were suppos-



1: $2R=CH_2$, $R_1+R_2=OCH_2O$, $R_3=H$, $R_4=OCH_3$
2: $2R=CH_2$, $R_1=R_2=R_4=OCH_3$, $R_3=H$
3: $R=CH_3$, $R_1+R_2=OCH_2O$, $R_3=H$, $R_4=OCH_3$
4: $R=CH_3$, $R_1=R_2=R_4=OCH_3$, $R_3=H$
6: $2R=CH_2$, $R_1=R_4=H$, $R_2=R_3=OCH_3$
7: $2R=CH_2$, $R_1=R_2=OCH_3$, $R_3=R_4=H$



5: $R=H$, $R_1=R_2=OCH_3$, $R_3=H$
8: $R=H$, $R_1=H$, $R_2=R_3=OCH_3$
10: $R=CH_3$, $R_1=R_2=CH_3$, $R_3=H$
14: $R=CH_3$, $R_1+R_2=OCH_2O$, $R_3=H$



9: X or Y=NHCHO or H
11: $X=H$, $Y=N(CH_3)CHO$
12: $X+Y=O$
13: $X=H$, $Y=NHCH_3$

Chart 1

---

[1] This paper forms Part XXXIV of "Studies on the Chemical Constituents of *Rutaceous* Plants" by H. Ishii. Part XXXIII; H. Ishii, T. Ishikawa, and J. Haginiwa, *Yakugaku Zasshi*, **97**, 890 (1977).

[2] *a*) J. Slavík and L. Slaviková, *Collect. Czech. Chem. Commun.*, **20**, 21 (1955); **25**, 1667 (1960); J. Slavík, L. Slaviková, and K. Haisová, *ibid.*, **32**, 4420 (1967); J. Slavík and F. Šantavý, *ibid.*, **37**, 2804 (1972); *b*) J. Slavík, L. Dolejš, V. Hanuš, and A.D. Cross, *ibid.*, **33**, 1619 (1968).

[3] H. Ishii, K.-I. Harada, T. Ishida, E. Ueda, K. Nakajima, I. Ninomiya, T. Naito, and T. Kiguchi, *Tetrahedron Lett.*, **1975**, 319.

[4] Recently, Kessar, *et al.* reported the validity of our proposal by photochemical synthesis of chelilutine (2). [S.V. Kessar, Y.P. Gupta, K. Dhingra, G.S. Sharma, and S. Narula, *Tetrahedron Lett.*, **1977**, 1459].

[5] H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *Tetrahedron Lett.*, **1976**, 1203.

[6] H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, *Yakugaku Zasshi*, **96**, 1458 (1976); H. Ishii, T. Ishikawa, and J. Haginiwa, *ibid.*, **97**, 890 (1977).

ed to be formed by Baeyer–Villiger like oxidation of the immonium group of quaternary O_4-benzo[*c*]phenanthridine alkaloids in a plant. According to this assumption, we[5] treated nitidine (**6**) and chelerythrine (**7**) sulfate with *m*-chloroperbenzoic acid (*m*-CPBA) in hexamethylphosphoric triamide (HMPA) and obtained the corresponding amides which were identified with the sample of naturally occurring isoarnottianamide (**5**) and arnottianamide (**8**), respectively. At this stage of our studies, we were interested in examination of Bischler–Napieralski reaction of these new amides, though all trials[7] to Bischler–Napieralski reaction of the aliphatic formamide (**9**) were failed.

Treatment of **5** derived from **6** by the reported method[5] with Rodionow reagent[8] gave the trimethoxy formamide (**10**), colourless prisms, mp 212—214°, $C_{22}H_{21}NO_6$[9] [IR ν (Nujol) cm^{-1}: 1670 (C=O); NMR ($CDCl_3$) δ: 2.94 (3H, s, NCH_3), 3.68, 3.79, and 3.92 (each 3H, s, OCH_3), 8.08 (1H, s, NCHO)], in 79.3% yield.

Refluxing this formamide (**10**) with $POCl_3$ in CH_3CN for 1 hr afforded a cyclized product as chloride, orange fine needles, mp 184—186°, in 55.9% yield. This compound was identified with an authentic sample of chelilutine (**2**) chloride, mp 186—192° (lit.[2a] mp 197—198°), by direct comparison.

The success of the Bischler–Napieralski cyclization of isoarnottianamide (**5**) would offer a promising prospect of synthesizing the fully aromatized O_5-benzo[*c*]phenanthridine alkaloids, if the dehydrogenation of the formamide[10] (**9**) or its N-methyl derivative (**11**) were successfully achieved. Treatment of the ketone (**12**) with CH_3NH_2 and $TiCl_4$[2,11] followed by reduction with $NaBH_4$ in DMF–MeOH gave the *cis*-secondary amine (**13**), colourless prisms, mp 156—158°, $C_{20}H_{21}NO_5$[9] in 82.4% yield. The secondary amine (**13**) was treated with chloral to give the *cis*-NCH_3-formamide (**11**) as colourless prisms, mp 236.5—239°, $C_{21}H_{21}NO_6$[9] [IR ν (Nujol) cm^{-1}: 1655 (C=O); NMR ($CDCl_3$) δ: 2.46 (3H, s, NCH_3), 7.64 (1H, s, CHO)], in 86.6% yield.

The NCH_3-formamide (**11**) was dehydrogenated with DDQ in benzene to give the desired formamide (**14**) as colourless prisms, mp 238—240°, $C_{21}H_{17}NO_6$[9] in 74.7% yield.

The aromatized formamide (**14**) was treated with $POCl_3$ in CH_3CN gave red purple needles, mp 299—302° (lit.[2a] mp 282—283°), in 30.3% yield. This material was completely identical with an authentic sample of chelirubine[3] (**1**). These results provide us a practical method for synthesis of the fully aromatized O_5-benzo[*c*]phenanthridine alkaloid which has an interesting pharmacological activity.[12]

Acknowledgement We wish to thank Prof. J. Slavík, Purkyne University, for the gift of the sample of chelilutine (1) chloride, and Dr. A. Brossi, National Institutes of Health, for his heartful discussion on the condition of Bischler–Napieralski reaction.

Faculty of Pharmaceutical Sciences,
Chiba University,
1-33, Yayoi-cho,
Chiba, 280, Japan.

HISASHI ISHII
TSUTOMU ISHIKAWA
YUH-ICHIRO ICHIKAWA
MITSUGI SAKAMOTO

Received June 27, 1977

---

[7] H. Ishii, T. Deushi, and K.-I. Harada, Symposium Papers, 16th, Symposium on the Chemistry of Natural Products, Osaka, Japan, October, 1972, pp. 327—333; H. Ishii, T. Deushi, T. Ishida, M. Sakamoto, K.-I. Harada, and K. Takizawa, *Chem. Pharm. Bull.* (Tokyo), in preparation.

[8] W. Rodionow, *Bull. Soc. Chim. Fr.*, **39**, 305 (1926); H.R. Synder, H.F. Strohmayer, and R.A. Mooney, *J. Am. Chem. Soc.*, **80**, 3708 (1958).

[9] The compound gave satisfactory elemental analysis for the formula given.

[10] We succeeded in dehydrogenating the NH formamide (9). The Bischler–Napieralski reaction of the dehydrogenated NH formamide afforded norchelirubine. We will describe on this matter in the full paper in detail.

[11] H. Weingarten, J.P. Chupp, and W.A. White, *J. Org. Chem.*, **32**, 3246 (1967).

[12] H. Ishii, T. Ishikawa, A. Hoshi, and K. Kuretani, *J. Med. Chem.*, in preparation.