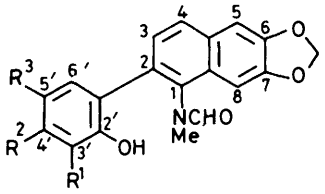
Baeyer–Villiger-type Oxidation of an Immonium Group: The Structural Establishment of Naturally Occurring Amides Related to Benzo[*c*]phenanthridine Alkaloids[1]†

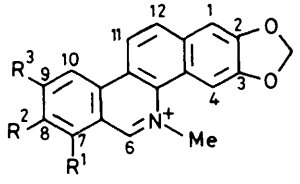
Hisashi Ishii* and Tsutomu Ishikawa
Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Chiba, 260, Japan
Sheng-Teh Lu and Ih-Sheng Chen
School of Pharmacy, Kaohsiung, Medical College, No. 100, Shih-chuan 1st. Road, Kaohsiung, Taiwan

Structures of four new amide-alkaloids, arnottianamide (**1**), isoarnottianamide (**2**), integriamide (**3**), and iwamide (**4**), which occur naturally in *Xanthoxylum* plants, were established by derivation from the known benzo[*c*]phenanthridine alkaloids chelerythrine (**5**), nitidine (**6**), avicine (**7**), and decarine (**8**). In these transformations, the novel Baeyer–Villiger-type oxidation of an immonium group was applied.

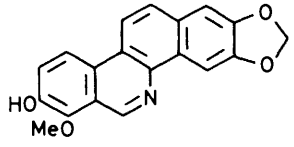
In the course of our studies on the chemical constituents of Rutaceous plants, we isolated four new amide alkaloids, arnottianamide[2] (**1**), isoarnottianamide[2a] (**2**), integriamide[2b] (**3**), and iwamide[2c] (**4**). In several short communications,[3] we have reported the structural establishment of these amide alkaloids by chemical conversion of three known quaternary tetraoxygenated benzo[*c*]phenanthridine alkaloids,[4] chelerythrine (**5**), nitidine (**6**), and avicine (**7**), into the first three, (**1**), (**2**), and (**3**), respectively, through the novel Baeyer–Villiger-type oxidation of an immonium group. Moreover, iwamide (**4**) was derived from decarine (**8**), the known phenolic tertiary base, also *via* the oxidative process. In this paper, we give a full account of our work on these reactions.



(**1**) $R^1 = R^2 = OMe$, $R^3 = H$
(**2**) $R^1 = H$, $R^2 = R^3 = OMe$
(**3**) $R^1 = H$, $R^2R^3 = OCH_2O$
(**4**) $R^1 = OMe$, $R^2 = OH$, $R^3 = H$



(**5**) $R^1 = R^2 = OMe$, $R^3 = H$
(**6**) $R^1 = H$, $R^2 = R^3 = OMe$
(**7**) $R^1 = H$, $R^2R^3 = OCH_2O$



(**8**)

Arnottianamide[3a] (**1**) was isolated from *Xanthoxylum arnottianum* Maxim.[2c] as a major component, but from *X. integrifoliolum* (Merr.) Merr. (*Fagara integrifoliola* Merr.)[2b] and *X. cuspidatum* Champ. (*F. cuspidata* Engl.)[2a] as a minor component. On the other hand, isoarnottianamide[3a] (**2**), integriamide[3b] (**3**), and iwamide[3c] (**4**) were obtained as minor components of *X. cuspidatum*,[2a] *X. integrifoliolum*,[2b] and *X. arnottianum*,[2c] respectively. All four alkaloids have a common feature that, in the i.r. spectrum, an amide band [$\nu_{max.}$ 1 663 (**1**), 1 670 (**2**), 1 657 (**3**), and 1 646 cm^{-1} (**4**)] was observed and, in the ^1H n.m.r. spectrum, one doublet and two singlets ascribable to aromatic protons, and signals due to an *N*-methyl amide group and a formyl proton [δ 8.50 (**1**), 8.50 (**2**), 8.10 (**3**), and 8.07 (**4**)] along with those due to four oxygen functions, methoxy and/or methylenedioxy groups, appeared (see Table).

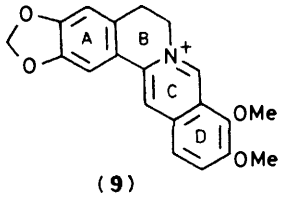
The same molecular formula, $C_{21}H_{19}NO_6$, was established for arnottianamide (**1**) and isoarnottianamide (**2**) on the basis of elemental analyses and mass spectral measurements. In the ^1H n.m.r. spectrum, arnottianamide (**1**) has a pair of 1 H doublets due to aromatic protons, while isoarnottianamide (**2**) two 1 H singlets as characteristic signals other than common ones of these alkaloids, indicating that two aromatic protons of the former (**1**) should be located at *ortho*-positions to each other, but that those of the latter (**2**) should be isolated ones. It is well known that such pairs of positional isomers in a variety of types of benzylisoquinoline alkaloids occur naturally in Rutaceous plants, for example, chelerythrine–nitidine[4] [(**5**) and (**6**): the ring A of benzo[*c*]phenanthridine], berberine–xylopinine[5] [(**9**) and (**10**): the ring D of protoberberine], magnoflorine–xanthoplanine[6] [(**11**) and (**12**): the ring D of aporphine].

On the other hand, treatment of arnottianamide (**1**) with lithium aluminium hydride gave deoxoarnottianamide (**13**). Its

Table. ^1H N.m.r. data at 100 MHz for arnottianamide (**1**) and isoarnottianamide (**2**) in CF_3CO_2H

Proton		Arnottianamide (**1**)	Isoarnottianamide (**2**)
Common signals	NMe	3.27 (3 H, s)	3.26 (3 H, s)
	NCHO	8.50 (1 H, s)	8.50 (1 H, s)
	ArH	7.03 (1 H, s), 7.28 (1 H, s), 7.36 (1 H, d, *J* 8.5 Hz), 7.87 (1 H, d, *J* 8.5 Hz)	7.02 (1 H, s), 7.27 (1 H, s), 7.35 (1 H, d, *J* 9.0 Hz), 7.88 (1 H, d, *J* 9.0 Hz)
Oxygen functions	OMe	4.04 (3 H, s), 4.09 (3 H, s)	3.97 (6 H, s)
	OCH_2O	6.09 (2 H, s)	6.08 (2 H, s)
Characteristic signals	ArH	6.81 (1 H, d, *J* 8.5 Hz), 7.06 (1 H, d, *J* 8.5 Hz)	6.78 (1 H, s), 6.88 (1 H, s)

† This paper forms Part 57 of the series 'Studies on the Chemical Constituents of Rutaceous Plants. Development of a Versatile Method for Synthesis of the Antitumor Benzo[*c*]phenanthridine Alkaloids' by H. Ishii.



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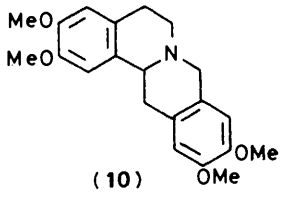

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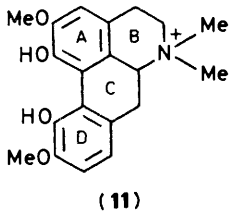

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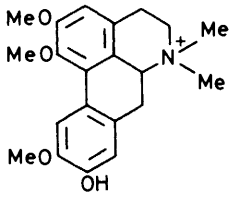


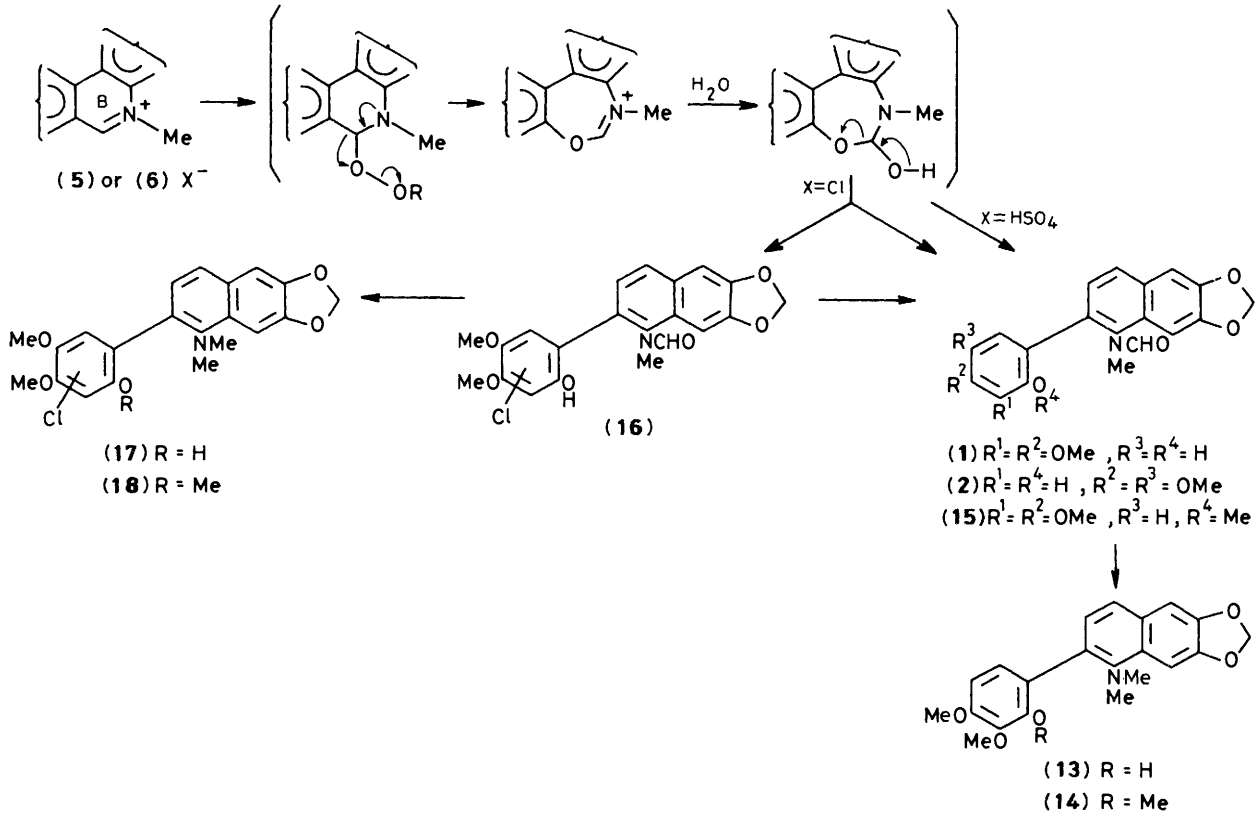
(12)

^{1}H n.m.r. spectrum shows no signals due to a formyl and an *N*-methylamide group, which were present in the starting arnottianamide (**1**), but instead a new 6-H singlet which was assignable to an *NN*-dimethyl group, demonstrating that an *N*-methylformamide groups in the former compound (**1**) was transformed into an *NN*-dimethyl group in the latter (**13**). Treatment of deoxoarnottianamide (**13**) with Rodionow's reagent[7] gave methyl deoxo-*O*-methylarnottianamide (**14**) which has an additional methoxy group in addition to the two methoxy groups present in the parent material (**13**), indicating that this latter compound has a phenolic group in the molecule. Moreover, the original arnottianamide (**1**) gave also *O*-methylarnottianamide (**15**) when a solution of it in hexamethylphosphoric triamide (HMPA) was treated with an ethereal solution of diazomethane.

Taking into account the difference in the characteristic signal patterns of aromatic protons between arnottianamide (**1**) and isoarnottianamide (**2**), the existence of an *N*-methylformamide and a phenolic group in the molecule of arnottianamide (**1**) allowed us to speculate on the biogenetical pathway for formation of arnottianamide (**1**) and isoarnottianamide (**2**) from chelerythrine (**5**) and nitidine (**6**), respectively. Although the Baeyer–Villiger-type oxidation of an immonium group was unknown before, it is possible that in plants arnottianamide (**1**) and isoarnottianamide (**2**) could be biogenetically derived by such an oxidative cleavage of the ring B of chelerythrine (**5**) and of nitidine (**6**) as shown in Scheme 1. Therefore, we undertook an investigation of the possibility of this type of reaction *in vitro*.

Treatment of chelerythrine (**5**) chloride with *m*-chloroperbenzoic acid (*m*CPBA) in HMPA at 40 °C gave arnottianamide (**1**) in 39.1% yield. This synthetic evidence is enough to establish the structure of arnottianamide as (**1**).

However, in the case of nitidine (**6**) chloride, we obtained a chlorinated derivative (**16**) as the main product in 33.6% yield along with the desired isoarnottianamide (**2**) in 3.8% yield. The chlorinated derivative (**16**) could be transformed into the corresponding chloro-deoxo-derivative (**17**) by treatment with lithium aluminium hydride, similarly to arnottianamide (**1**). Treatment of the chloro-deoxo-derivative with Rodionow's reagent[7] gave the corresponding methylated derivative (**18**). Moreover, catalytic hydrogenation of the original chloro-derivative (**16**) with Raney nickel gave the desired isoarnottianamide (**2**) in 27.3% yield. This chemical evidence showed that the structure of isoarnottianamide should be depicted as (**2**). It should be added here that the introduced chlorine atom should be located on ring A of the benzo[*c*]phenanthridine skeleton, because, in the ^{1}H n.m.r. spectrum, these chlorinated products showed only one signal assignable to an aromatic proton of ring A.



Scheme 1.

From the above experimental result on nitidine (**6**) chloride, we doubted if chlorination could also occur in the Baeyer–Villiger-type oxidation of chelerythrine (**5**). Actually, in the mass spectrum, the crude material obtained from the mother liquor of recrystallization of the synthetic arnottianamide (**1**) shows a small peak at both *m/z* 415 and at *m/z* 417 corresponding to the M^+ and the $(M^+ + 2)$ ions of $C_{21}H_{18}ClNO_6$, respectively. This fact shows strongly the common occurrence of chlorination in the oxidation, when a quaternary base chloride was used as a starting material. Moreover, the chlorination would be explained by supposing that a chloride anion, a counterpart of the quaternary base, was oxidized with *m*CPBA to give a chloro-radical or a chloro-cation either of which attacked ring A of the amide alkaloid. Therefore, we achieved the oxidation of quaternary base sulphates with *m*CPBA,* resulting in an improved yield from 39.1 to 70.6% in the case of chelerythrine (**5**) and from 3.8 to 55.8% in the case of nitidine (**6**).

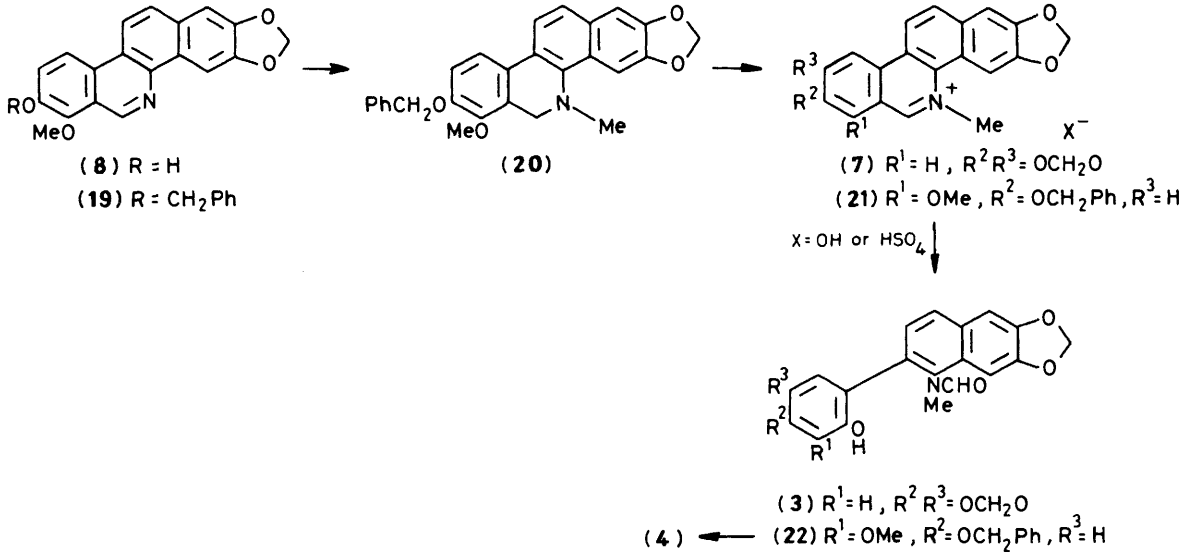
Subsequently, the ^{1}H n.m.r. spectrum of integriamide (**3**) was similar to that of isoarnottianamide (**2**) except for the appearance of two methylenedioxy signals instead of one methylenedioxy and two methoxy signals in isoarnottianamide (**2**). This fact suggested strongly that avicine (**7**) could be the biogenetic precursor of integriamide (**3**). Treatment of avicine (**7**) hydroxide† with *m*CPBA and trifluoroacetic acid in HMPA gave integriamide (**3**) in 79.0% yield.

The ^{1}H n.m.r. spectrum of iwamide (**4**), the fourth amide alkaloid, was similar to that of arnottianamide (**1**) except for lack of a signal due to one methoxy group. This observation led us to imagine that iwamide (**4**) might be one of two possible de-*O*-methylarnottianamide derivatives. On the other hand, since decarine[2a,2c,8] (**8**), which corresponds to de-*O*-methylnorchelerythrine, is relatively widely distributed in plants belonging to the *Xanthoxylum* genus, we assumed that iwamide (**4**) would be derived from decarine (**8**) in the plant body by quaternization of decarine (**8**) followed by Baeyer–Villiger-type oxidation. According to our assumption, we undertook a synthesis of iwamide (**4**) from decarine (**8**).

Treatment of decarine (**8**) with benzyl chloride and potassium carbonate in dimethylformamide (DMF) gave *O*-benzyldecarine (**19**) in 84.9% yield.

Since quaternization of the benzo[*c*]phenanthridine nucleus by a reported method,[9] which consisted in treatment with an alkylating agent in a mixed solution of nitrobenzene and xylene, gave an inseparable mixture of salts of the starting tertiary base and of the resulting quaternary base as described in the preceding paper[10] and other papers,[11] we applied our newly developed method[10] to *O*-benzyldecarine (**19**). Treatment of *O*-benzyldecarine (**19**) with sodium borohydride and dimethyl sulphate in HMPA gave *O*-benzyl-*N*-methyl-5,6-dihydrodecarine (**20**) in 98.9% yield. Dehydrogenation of the dihydro-base (**20**) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in benzene followed by treatment with sulphuric acid provided the desired *O*-benzyl-*N*-methyldecarinium (**21**) sulphate in 50.4% yield. Baeyer–Villiger-type oxidation of the quaternary base (**21**) sulphate with *m*CPBA in HMPA gave *O*-benzyliwamide (**22**) in 77.9% yield. Catalytic hydrogenation of benzyliwamide (**22**) over 5% palladium–charcoal produced iwamide (**4**) (Scheme 2).

The success of Baeyer–Villiger-type oxidation of an immonium group of a benzo[*c*]phenanthridinium skeleton *in vitro* and the natural occurrence of some of the corresponding products would suggest that this type of reaction would be a real biogenetical pathway to these compounds.



Scheme 2.

Experimental

All m.p.s were measured on a micro melting-point hot stage (Yanagimoto) and are uncorrected. I.r. spectra were recorded for Nujol mulls on a Hitachi EPI-G3 spectrophotometer. U.v. spectra were recorded on a Hitachi EPS-3T instrument for solutions in 95% ethanol. ^{1}H N.m.r. spectra were recorded on a JEOL JNM-4H-100 spectrometer in deuteriochloroform unless otherwise stated, with tetramethylsilane as internal reference. All NH and OH signals were confirmed by disappearance of their signals after addition of deuterium oxide. Mass spectra were measured with a Hitachi RMU-6E spectrometer using a direct-inlet system. For chromatography, silicic acid (100 mesh; Mallinckrodt Chemical Works), silica gel 60 (70—230 mesh ASTM; Merck), and aluminium oxide (neutral, grade I; Woelm) were used, while for t.l.c. and preparative t.l.c., silica gel GF_{254}

* We also oxidized these quaternary bases (**5**) and (**6**) sulphates with performic acid, but the desired amide alkaloids were obtained in only 25.6% yield in the case of chelerythrine (**5**) and in 32.1% yield in the case of nitidine (**6**).

† Treatment of avicine (**7**) sulphate with *m*CPBA in HMPA resulted in recovery of the starting material because of insolubility of the sulphate in HMPA. Moreover, although oxidation of the sulphate with performic acid gave the desired integriamide (**3**) in 60.4% yield, the yield of the reaction under these conditions varied over a wide range.

(Merck) was used. Products were identified by i.r., mixed m.p., and t.l.c. The spectroscopic abbreviations used are as follows: s, singlet; d, doublet; m, multiplet; br, broad; dif, diffused; sh, shoulder. *m*-Chloroperbenzoic acid (85%) (*m*CPBA) was purchased from Nakarai Chemicals, Ltd., Kyoto, Japan.

Arnottianamide (**1**).—As reported previously, arnottianamide (**1**) was isolated in 0.179, 0.036, and 0.002% yield from the root bark of *X. arnottianum* Maxim.,[2c] from the xylem bark of the same plant,[2c] and from the root bark of *X. cuspidatum* Champ. (*F. cuspidata* Engl.),[2a] respectively. Recrystallization of the crude material from chloroform–methanol gave prisms, m.p. 267—269 °C (Found: C, 65.8; H, 4.9; N, 3.6. Calc. for $C_{21}H_{19}NO_6$: C, 66.15; H, 5.0; N, 3.65%); $\nu_{max.}$ 3 200—3 450 and 1 663 cm^{-1}; $\lambda_{max.}$ 236, 280sh, 321sh, 324, and 332 nm (log ε 4.73, 4.01, 3.63, 3.65, and 3.81); *m/z* 381 (M^+, 100%).

Isoarnottianamide (**2**).—Isoarnottianamide (**2**) was isolated in 0.0009% yield from the bark of *X. cuspidatum* Champ. (*F. cuspidata* Engl.).[2a] Recrystallization of the crude material from chloroform–methanol or chloroform–benzene gave prisms, m.p. 254—257 °C (decomp.) (Found: C, 65.65; H, 5.05; N, 3.65. Calc. for $C_{21}H_{19}NO_6$: C, 66.15; H, 5.0; N, 3.65%); $\nu_{max.}$ 1 670 cm^{-1}; $\lambda_{max.}$ 237.5, 290, and 332 nm (log ε 4.73, 4.00, and 3.86); *m/z* 381 (M^+, 100%).

Integriamide (**3**).—Integriamide (**3**) was isolated in 0.000 24% yield from the root wood of *X. integrifoliolum* (Merr.) Merr. (*F. integrifoliola* Merr.).[2b] Recrystallization of the crude material from chloroform–methanol gave prisms, m.p. 302—304 °C (Found: C, 65.05; H, 4.05; N, 3.7. Calc. for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.15; N, 3.85%); $\nu_{max.}$(KBr) 1 657 cm^{-1}; δ($CDCl_3$ + CD_3OD) 3.01 (3 H, s, NMe), 5.91 (2 H, s, OCH_2O), 6.07 (2 H, s, OCH_2O), 6.48 (1 H, s, 3′-H), 6.53 (1 H, s, 6′-H), 7.02 (1 H, s, 5-H), 7.20 (1 H, s, 8-H), 7.28 (1 H, d, *J* 8.5 Hz, 4-H), 7.74 (1 H, d, *J* 8.5 Hz, 3-H), and 8.10 (1 H, s, CHO).

Iwamide (**4**).—Iwamide (**4**) was isolated in 0.0008 and 0.0009% yield from the root bark and the xylem bark, respectively, of *X. arnottianum* Maxim.[2c] Recrystallization of the crude material from chloroform–methanol gave prisms, m.p. 271—273 °C (Found: C, 65.1; H, 4.65; N, 3.65. Calc. for $C_{20}H_{17}NO_6$: C, 65.4; H, 4.65; N, 3.8%); $\nu_{max.}$(KBr) 3 480 and 1 646 cm^{-1}; δ($CDCl_3$ + CD_3OD) 2.97 (3 H, s, NMe), 3.82 (3 H, s, OMe), 6.05 (2 H, s, OCH_2O), 6.43 (1 H, d, *J* 9.0 Hz, 5′-H), 6.66 (1 H, d, *J* 9.0 Hz, 6′-H), 7.00 (1 H, s, 5-H), 7.18 (1 H, s, 8-H), 7.27 (1 H, d, *J* 9.0 Hz, 4-H), 7.71 (1 H, d, *J* 9.0 Hz, 3-H), and 8.07 (1 H, s, CHO).

Deoxoarnottianamide (**13**).—To a stirred solution of arnottianamide (**1**) (35.0 mg) in dry tetrahydrofuran (THF) (10 ml) was gradually added lithium aluminium hydride (70 mg) and the mixture was refluxed for 1.5 h. After the excess of the reagent had been decomposed by addition of wet diethyl ether, the mixture was evaporated to dryness. The residue was dissolved in water and extracted with chloroform. The extract was dried over potassium carbonate and evaporated to dryness under reduced pressure. Recrystallization of the residue from benzene–methanol gave *prisms* (19.2 mg), m.p. 200—202 °C (Found: C, 68.7; H, 5.8; N, 3.8. $C_{21}H_{21}NO_5$ requires C, 68.65; H, 5.75; N, 3.8%); $\nu_{max.}$ 3 390 cm^{-1}; $\lambda_{max.}$ 229, 263sh, 315sh, and 331 nm (log ε 4.76, 4.40, 3.79, and 3.75); δ 2.72 (6 H, s, NMe_2), 3.91 (3 H, s, OMe), 3.95 (3 H, s, OMe), 5.99 (2 H, s, OCH_2O), 6.51 (1 H, d, *J* 8.5 Hz, 5′-H), 6.77 (1 H, s, OH), 6.81 (1 H, d, *J* 8.5 Hz, 6′-H), 7.09 (1 H, s, 5-H), 7.18 (1 H, d, *J* 8.5 Hz, 4-H), 7.43 (1 H, d, *J* 8.5 Hz, 3-H), and 7.52 (1 H, s, 8-H); δ(CF_3CO_2H) 3.71 (6 H, br s, NMe_2), 4.03 (3 H, s, OMe), 4.15 (3 H, s, OMe), 6.15 (2 H, s, OCH_2O), 6.87 (1 H, d, *J* 8.5 Hz, 5′-H), 7.16 (1 H, d, *J* 8.5 Hz, 6′-H), 7.30 (1 H, d, *J* 8.5 Hz, 4-H), 7.35 (1 H, s, 5-H), 7.43 (1 H, s, 8-H), 7.92 (1 H, d, *J* 8.5 Hz, 3-H), and 8.40 (1 H, br s, OH).

Deoxo-O-methylarnottianamide (**14**).—A solution of deoxoarnottianamide (**13**) (39.0 mg) in anhydrous toluene (3 ml) was treated with a methanolic solution of trimethylanilinium methoxide (Rodionow's reagent) prepared from trimethylanilinium tosylate (461 mg) according to a reported procedure.[7] After confirmation of completion of the reaction by t.l.c. monitoring, a large amount of water was added to the reaction mixture and toluene and dimethylaniline in the reaction mixture were removed as an azeotropic mixture by distillation. The aqueous solution which remained was extracted with chloroform. The extract was dried over potassium carbonate and evaporated to dryness under reduced pressure. Preparative t.l.c. of the residue {R_F 0.45 [chloroform–benzene (2:1 v/v)]} followed by recrystallization from benzene–n-hexane gave *prisms* (22.0 mg), m.p. 166.5—168.5 °C (Found: C, 69.55; H, 6.1; N, 3.55. $C_{22}H_{23}NO_5$ requires C, 69.25; H, 6.1; N, 3.65%); δ 2.63 (6 H, s, NMe_2), 3.85 (3 H, s, OMe), 3.90 (6 H, s, OMe × 2), 5.98 (2 H, s, OCH_2O), 6.67 (1 H, d, *J* 8.5 Hz, 5′-H), 6.83 (1 H, d, *J* 8.5 Hz, 6′-H), 7.06 (1 H, d, *J* 8.5 Hz, 4-H), 7.08 (1 H, s, 5-H), 7.37 (1 H, d, *J* 8.5 Hz, 3-H), and 7.55 (1 H, s, 8-H).

O-*Methylarnottianamide* (**15**).—To a solution of arnottianamide (**1**) (33.6 mg) in HMPA (5 ml) was added a solution of diazomethane in diethyl ether prepared from *N*-methyl-*N*-nitrosourea (1 g), and then the mixture was kept at room temperature for 6 d. The solvent was distilled off under reduced pressure [65—66 °C (1 mmHg)]. After addition of water, the mixture was extracted with ethyl acetate. The extract was repeatedly washed with water, dried over potassium carbonate, and evaporated to dryness. Preparative t.l.c. of the residue {R_F 0.65—0.84 [chloroform–ethyl acetate (10:1 v/v)]} followed by recrystallization from chloroform–methanol or benzene–n-hexane afforded *prisms** (22.6 mg, 64.9%), m.p. 202—204.5 °C (Found: C, 66.95; H, 5.35; N, 3.5. $C_{22}H_{21}NO_6$ requires C, 66.8; H, 5.35; N, 3.55%); $\nu_{max.}$(KBr) 1 676 cm^{-1}; δ 2.95 (3 H, s, NMe), 3.62 (3 H, s, OMe), 3.89 (6 H, s, OMe × 2), 6.04 (2 H, s, OCH_2O), 6.67 (1 H, d, *J* 8.5 Hz, 5′-H), 6.81 (1 H, d, *J* 8.5 Hz, 6′-H), 7.06 (1 H, s, 5-H), 7.18 (1 H, s, 8-H), 7.28 (1 H, d, *J* 8.5 Hz, 4-H), 7.70 (1 H, d, *J* 8.5 Hz, 3-H), and 8.08 (1 H, s, CHO).

Arnottianamide (**1**) *from Chelerythrine* (**5**) *Sulphate*.— A suspension of chelerythrine (**5**) sulphate (89.0 mg) and *m*CPBA (243 mg) in HMPA (10 ml) was stirred at 40 °C for 5 h. After addition of a solution of sodium sulphite (151 mg) in water (3 ml), the mixture was stirred at room temperature for 2 h and evaporated to dryness under reduced pressure. The residue was dissolved in a large amount of ethyl acetate, washed in turn with 10% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulphate, and evaporated to dryness under reduced pressure. Recrystallization of the residue from chloroform–methanol gave prisms (53.9 mg), m.p. 267—269 °C. This material was identical with a sample of arnottianamide (**1**) obtained from the natural source.

Oxidation of Nitidine (**6**) *Chloride with* m*CPBA*.—(i) *Chloroisoarnottianamide* (**16**). A suspension of nitidine (**6**) chloride (192 mg) and *m*CPBA (402 mg) in HMPA (10 ml) was stirred at room temperature for 4 h. After addition of a solution of sodium sulphite (189 mg) in water (3 ml), the mixture was stirred at room temperature for 0.5 h, poured into a large amount of water, and extracted with diethyl ether. The extract

* This material was also prepared by treatment of arnottianamide (**1**) with Rodionow's reagent by the usual manner in 41.7% yield.

was washed in turn with 5% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulphate, and evaporated to dryness. Recrystallization of the residue from chloroform–methanol or acetone gave *prisms* (70 mg), m.p. 256—260 °C (Found: C, 60.75; H, 4.3; N, 3.3%; M^+, 415.0834. $C_{21}H_{18}ClNO_6$ requires C, 60.65; H, 4.35; N, 3.35%; *M*, 415.0823); $\nu_{max.}$ 3 100—3 400 and 1 673 cm^{-1}; δ 2.99 (3 H, s, NMe), 3.77 (3 H, s, OMe), 3.91 (3 H, s, OMe), 5.40 (1 H, s, OH), 6.02 (2 H, s, OCH_2O), 6.57 (1 H, s, ArH), 7.03 (1 H, s, 5-H), 7.15 (1 H, s, 8-H), 7.23 (1 H, d, *J* 8.5 Hz, 4-H), 7.70 (1 H, d, *J* 8.5 Hz, 3-H), and 8.10 (1 H, s, CHO).

(ii) *Isoarnottianamide* (**2**). Preparative t.l.c. {R_F 0.28 [chloroform–ethyl acetate (10:1 v/v) double development]} of the material obtained from the mother liquor of recrystallization of chloroisoarnottianamide (**16**) gave prisms (7.2 mg), m.p. 252—256 °C, which were recrystallized from methanol. This material was identical with a sample of isoarnottianamide (**2**) obtained from the natural source.

Chlorodeoxoisoarnottianamide (**17**).—A mixture of chloroisoarnottianamide (**16**) (45 mg) and lithium aluminium hydride (90 mg) in dry THF (10 ml) was refluxed for 0.5 h. After decomposition of the excess of the reagent with wet diethyl ether, the mixture was extracted with diethyl ether. The extract was dried over magnesium sulphate and evaporated to dryness under reduced pressure. Preparative t.l.c. {R_F 0.85 [diethyl ether–n-hexane (4:1 v/v)]} of the residue followed by recrystallization from methanol gave *prisms* (28.0 mg), m.p. 151—153 °C (Found: C, 62.7; H, 4.95; N, 3.4. $C_{21}H_{20}ClNO_5$ requires C, 62.75; H, 5.0; N, 3.5%); $\nu_{max.}$ 3 450 cm^{-1}; δ 2.81 (6 H, s, NMe_2), 3.82 (3 H, s, OMe), 3.94 (3 H, s, OMe), 6.02 (2 H, s, OCH_2O), 6.66 (1 H, s, ArH), 7.11 (1 H, s, 5-H), 7.13 (1 H, d, *J* 8.5 Hz, 4-H), 7.46 (1 H, s, 8-H), and 7.47 (1 H, d, *J* 8.5 Hz, 3-H).

Chlorodeoxo-O-methylisoarnottianamide (**18**).—The Rodionows reagent prepared from trimethylanilinium tosylate (461 mg) in anhydrous methanol (0.68 ml) and a solution of sodium metal (34 mg) in anhydrous methanol (0.9 ml) was added to a solution of the above chlorodeoxoisoarnottianamide (**17**) (21 mg) in anhydrous toluene (3.5 ml). After methanol was removed from the reaction mixture by distillation at 70—80 °C, the resulting solution was refluxed for 2 h. After addition of water, the reaction mixture was evaporated to dryness under reduced pressure. A large amount of water was added to the residue and the mixture was extracted with diethyl ether. The extract was dried over potassium carbonate and evaporated to dryness under reduced pressure. Purification of the residue by preparative t.l.c. {R_F 0.76 [benzene–chloroform (4:1 v/v)]} followed by recrystallization from methanol gave *prisms* (15 mg), m.p. 158.5—159.5 °C (Found: C, 63.35; H, 5.25; N, 3.3. $C_{21}H_{22}ClNO_5$ requires C, 63.55; H, 5.35; N, 3.4%); δ 2.69 (6 H, s, NMe_2), 3.51 (3 H, s, OMe), 3.83 (3 H, s, OMe), 3.94 (3 H, s, OMe), 6.01 (2 H, s, OCH_2O), 6.65 (1 H, s, ArH), 7.10 (1 H, s, 5-H), 7.11 (1 H, d, *J* 8.5 Hz, 4-H), 7.40 (1 H, d, *J* 8.5 Hz, 3-H), and 7.53 (1 H, s, 8-H).

Dechlorination of Chloroisoarnottianamide (**16**) [*Isoarnottianamide* (**2**)].—A solution of chloroisoarnottianamide (**16**) (32.0 mg) in methanol (10 ml) and 1M potassium hydroxide–methanol (10 ml) was hydrogenated over Raney nickel[12] prepared from the aluminium–nickel alloy (2 g) at room temperature and atmospheric pressure for 4 h. After removal of the catalyst by filtration, the filtrate was evaporated to dryness under reduced pressure. Preparative t.l.c. of the residue {R_F 0.14 [chloroform–ethyl acetate (4:1 v/v)]} gave prisms (8.0 mg), m.p. 252—255 °C, which were recrystallized from diethyl ether–n-hexane. This material was identical with a sample of isoarnottianamide (**2**).

Isoarnottianamide (**2**) *from Nitidine* (**6**) *Sulphate*.—A suspension of nitidine (**6**) sulphate (130 mg) and *m*CPBA (342 mg) in HMPA (10 ml) was stirred at 70—80 °C for 0.5 h. After addition of a solution of sodium sulphite (212 mg) in water (5 ml), the mixture was stirred at room temperature for 2 h and evaporated to dryness under reduced pressure. The residue was dissolved in a large amount of water and extracted with ethyl acetate. The extract was washed in turn with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulphate, and evaporated to dryness. The residue was purified by preparative t.l.c. (double development) with a mixed solvent [chloroform–ethyl acetate (5:1 v/v)]. Recrystallization of the fraction with R_F 0.31 from chloroform–methanol gave prisms (62.1 mg), m.p. 252—256 °C. This material was identical with a sample of isoarnottianamide (**2**) obtained from the natural source.

Oxidation of Avicine (**7**) *Hydroxide with Trifluoroperacetic Acid* [*Synthetic Integriamide* (**3**)].—To a stirred solution of avicine (**7**) hydroxide (972 mg) in HMPA (30 ml) containing trifluoroacetic acid (0.18 ml) was added *m*CPBA (951 mg) at room temperature. The mixture was stirred at room temperature for 1 h. After addition of sodium sulphite (595 mg), the mixture was kept at room temperature overnight and evaporated to dryness under reduced pressure. When the residue was treated with a small amount of water, the crude material solidified. The solid (A) was collected by filtration and washed with a small amount of methanol. The filtrate and washings were combined, diluted with water, and extracted with ethyl acetate. The extract was washed in turn with water, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride, dried over magnesium sulphate, and evaporated to dryness. Column chromatography of the residue over silica gel with a mixed (gradient) solvent [benzene–ethyl acetate (10:1 → 1:1 v/v)] gave a slightly brown solid. The solid was combined with the solid which was obtained by filtration (solid A). Recrystallization of the combined solid from chloroform–methanol gave prisms (673 mg), m.p. 294—296.5 °C. This compound was identical with a sample of integriamide (**3**) obtained from the natural source.

O-*Benzyldecarine* (**19**).—A mixture of decarine (**8**) (433 mg), benzyl chloride (0.17 ml), and potassium carbonate (376 mg) in DMF (14 ml) was heated at 50 °C for 4 h. The mixture was poured into water. The resulting precipitate was collected by filtration and repeatedly washed with water. Recrystallization of the solid mass from benzene–methanol afforded *needles* (471 mg), m.p. 218—220 °C (Found: C, 76.3; H, 4.65; N, 3.35. $C_{26}H_{19}NO_4$ requires C, 76.25; H, 4.7; N, 3.4%); δ 4.12 (3 H, s, OMe), 5.24 (2 H, s, OCH_2Ph), 6.04 (2 H, s, OCH_2O), 7.20 (1 H, s, 1-H), 7.30—7.60 (6 H, m, ArH), 7.75 (1 H, d, *J* 9.0 Hz, 12-H), 8.21 (1 H, d, *J* 9.0 Hz, 11- or 10-H), 8.24 (1 H, d, *J* 9.0 Hz, 10- or 11-H), 8.66 (1 H, s, 4-H), and 9.68 (1 H, s, 6-H).

O-*Benzyl*-N-*methyl*-5,6-*dihydrodecarine* (**20**).—A solution of *O*-benzyldecarine (**19**) (250 mg) in HMPA (8 ml) was heated at 50 °C. Dimethyl sulphate (2 ml) and sodium borohydride (233 mg) in limited amounts were alternately added to the heated solution during 2 h. After decomposition of the excess of dimethyl sulphate by addition of 5% aqueous sodium hydroxide (20 ml), the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride, dried over potassium carbonate, and evaporated to dryness. Column chromatography of the residue over aluminium oxide with chloroform as eluant gave fine *needles* (257 mg), m.p. 183.5—185.5 °C, which were recrystallized from benzene–methanol (Found: C, 76.1; H, 5.45; N, 3.1. $C_{27}H_{23}NO_4$ requires C, 76.2; H, 5.45; N, 3.3%); δ 2.58 (3 H, s, NMe), 3.91 (3 H, s,

OMe), 4.29 (2 H, s, ArCH_2N), 5.15 (2 H, s, OCH_2Ph), 6.00 (2 H, s, OCH_2O), 6.95 (1 H, d, *J* 9.0 Hz, 9-H), 7.08 (1 H, s, 1-H), 7.30—7.55 (7 H, m, ArH), 7.65 (1 H, s, 4-H), and 7.67 (1 H, d, *J* 9.0 Hz, 11-H).

O-Benzyl-N-methyldecarinium (**21**) *Sulphate*.—A solution of DDQ (512 mg) in benzene (14 ml) was added to a two-phase solution of *O*-benzyl-*N*-methyl-5,6-dihydrodecarine (**20**) (354 mg) in benzene (20 ml) and 5% aqueous sodium hydroxide (10 ml). The mixture was vigorously stirred at room temperature for 3 h. After removal of benzene in the mixture by distillation, the residual aqueous solution was extracted with ethyl acetate. The extract was dried over potassium carbonate and evaporated to dryness under reduced pressure. The residue was treated with a small amount of ethyl acetate and 10% sulphuric acid under ice-cooling to give orange needles * (219 mg), m.p. 260—265 °C, which were recrystallized from methanol, δ(CF_3CO_2H) 4.28 (3 H, s, OMe), 4.93 (3 H, dif. s, N^+Me), 5.29 (2 H, s, OCH_2Ph), 6.06 (2 H, s, OCH_2O), 7.18—7.36 (6 H, m, ArH), 7.84 (1 H, s, 4-H), 7.96 (2 H, d, *J* 8.0 Hz, 9- and 12-H), 8.33 (2 H, d, *J* 8.0 Hz, 10- and 11-H), and 9.51 (1 H, s, 6 H).

O-Benzyliwamide (**22**).—A suspension of the above quaternary base (**21**) sulphate (52 mg) and *m*CPBA (102 mg) in HMPA (5 ml) was stirred at 40 °C for 1 h. After addition of a solution of sodium sulphite (72 mg) in water (3 ml), the mixture was stirred at room temperature for 3 h and then extracted with ethyl acetate. The extract was washed in turn with 10% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulphate, and evaporated to dryness under reduced pressure. Recrystallization of the residue from chloroform–methanol gave *prisms* (36 mg), m.p. 249—252 °C (Found: C, 70.55; H, 5.0; N, 3.05. $C_{27}H_{23}NO_6$ requires C, 70.9; H, 5.05; N, 3.05%); $\nu_{max.}$(KBr) 1 675 cm^{-1}; δ 2.99 (3 H, s, NMe), 3.97 (3 H, s, OMe), 5.12 (2 H, s, OCH_2Ph), 5.99 (1 H, s, OH), 6.05 (2 H, s, OCH_2O), 6.58 (1 H, d, *J* 8.5 Hz, 5′-H), 6.78 (1 H, d, *J* 8.5 Hz, 6′-H), 7.08 (1 H, s, 5-H), 7.19 (1 H, s, 8-H), 7.36—7.53 (6 H, m, ArH), 7.73 (1 H, d, *J* 8.5 Hz, 3-H), and 8.17 (1 H, s, CHO).

Synthetic Iwamide (**4**).—A solution of *O*-benzyliwamide (**22**) (26 mg) in anhydrous ethanol (30 ml) was hydrogenated over 5% palladium–charcoal (30 mg) at room temperature under atmospheric pressure until absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was evaporated to dryness under reduced pressure. Recrystallization of the residue from chloroform–methanol gave prisms (20 mg), m.p. 267—268.5 °C. This material was identical with a sample of iwamide (**4**) isolated from the natural source.

* Elemental analyses of this material does not give a definite result because some samples had variable amounts of water of crystallization.

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