75. **Tatsuhiko Nakano**: Studies on the Alkaloids of Magnoliaceous Plants. XIV.[1] Alkaloids of *Magnolia grandiflora* L. (3). Structure of Magnoflorine.*

*(Pharmaceutical Institute, Medical Faculty, University of Kyoto**)*

In the previous paper[1] of this series, the isolation of a new quaternary base, termed magnoflorine, from the bark of *Magnolia grandiflora* L., was described. The present paper deals with the chemical structure of this new alkaloid.

As described in the experimental section, magnoflorine styphnate,[1] m.p. 218.5~219° (decomp.), was decomposed with hydrochloric acid to obtain the chloride, but attempts to crystallize it failed. Magnoflorine, however, gave a well-crystallizing iodide forming colorless pillars, m.p. 248~249°(decomp.), from methanol-acetone. By analysis it was found to possess the empirical formula, $C_{20}H_{24}O_4NI$, $[\alpha]_D^{35}$: +220.1° (methanol). It showed two methoxyl groups and one $N(CH_3)_2$ group (Vieböck-Brecher). The picrate was difficult to crystallize, showing a great tendency to separate as an oil, but crystallization was induced by following the technique described in the experimental section. It forms slightly brownish yellow slender pillars, m.p. 205~206°(decomp.), from ethanol-acetone. Analyses gave values corresponding to a formula $C_{20}H_{24}O_4N \cdot C_6H_2O_7N_3$ and revealed the presence of two methoxyl groups (Vieböck-Brecher).

Magnoflorine iodide gave a blue color with the Gibbs reagent, and in an aqueous solution, a dark yellowish brown color with ferric chloride.

It gave a negative test for a methylenedioxy group with the Gaebel reagent. With concentrated sulfuric acid it produced a weak violet color, changing to blood-red on the addition of potassium nitrate. The infrared spectrum showed the presence of a phenolic hydroxyl function (Nujol mull).

From these data, it seems highly probable that of the four oxygen atoms in magnoflorine iodide, two are present in the methoxyl groups, and the remaining two, as phenolic hydroxyl groups. The formula may therefore be extended as follows : $C_{20}H_{24}O_4NI = C_{16}H_{10} \cdot (OCH_3)_2(OH)_2{>}N(CH_3)_2 \cdot I$

As is shown in Fig. 1, the ultraviolet absorption spectrum of magnoflorine iodide exhibits a marked characteristics of those of the aporphine alkaloids.[2]

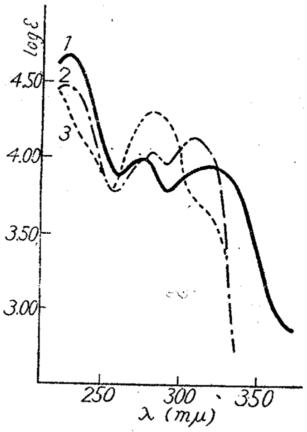

Fig. 1.

Ultraviolet Absorption Spectra

1. Magnoflorine iodide (in water)
2. Laurifoline chloride (in methanol)
3. Crebanine (in methanol)

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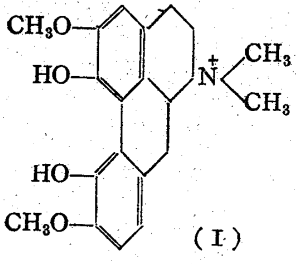
* Masao Tomita : Studies on the Alkaloids of Magnoliaceous Plants. XIV.

** Yoshida-konoe-cho, Sakyo-ku, Kyoto (中野立彥).

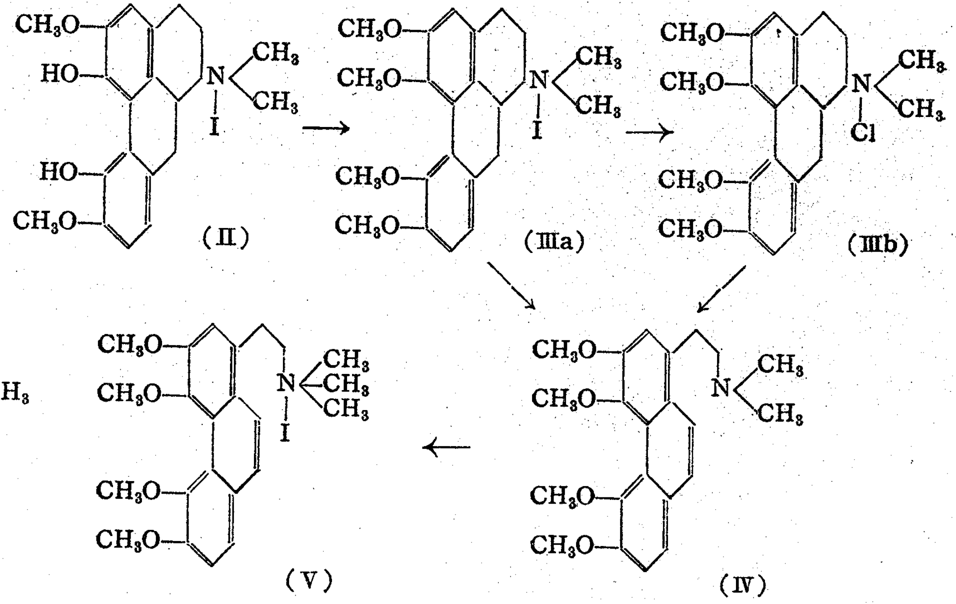
1) Part XIII. T. Nakano : This Bulletin, 2, 326(1954).

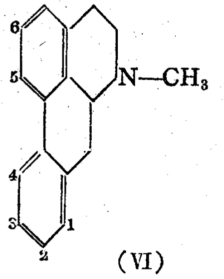
2) A. Girardet : J. Chem. Soc., **1931**, 2630; G. Barger, L. J. Sargent : *Ibid.*, **1939**, 993; T. R. Govindachari, B. R. Pai : J. Org. Chem., **18**, 1352(1953).

The O-methylation of magnoflorine iodide (II) encountered with difficulty, not smoothly going to completion. However, it was successfully accomplished by employing procedures described in the experimental section. O,O-Dimethylmagnoflorine iodide (IIIa) thus obtained crystallizes from methanol-acetone in the form of colorless needles, m.p. 242.5~243° (decomp.), and gave analytical values corresponding to a composition, $C_{22}H_{28}O_4NI$. In the methoxyl determination (Vieböck-Brecher), four methoxyl groups were confirmed. The infrared spectrum showed the complete absence of free hydroxyl absorption (Nujol mull). (IIIa), on treatment with silver chloride, yieled O,O-dimethylmagnoflorine chloride (IIIb), $C_{22}H_{28}O_4NCl$, colorless prisms, m.p. 236~237°(decomp.).



(I)





(VI)

When (IIIa) was submitted to the first stage of Hofmann degradation, the methine base (IV) was obtained as an oil, which by treatment with methyl iodide, was isolated as the methiodide (V). It forms colorless silky needles, m.p. 270~271°(decomp.), from methanol-acetone, is optically inactive, and has a formula $C_{23}H_{30}O_4NI$. The ultraviolet absorption spectrum of the methine methiodide (V) is shown in Fig. 2, together with that of O,O-dimethyllaurifoline-methine methiodide[3]. The close similarity between them is presumably due to the common phenanthrene system.

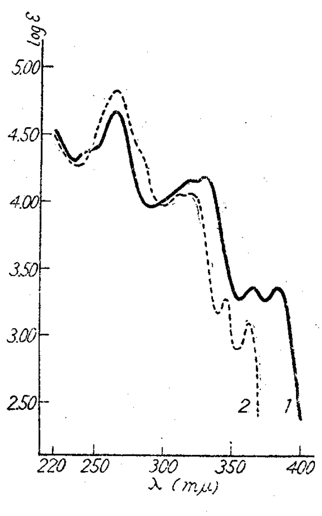


Fig. 2

Ultraviolet Absorption Spectra (in methanol)

1. O,O-Dimethylmagnoflorine-methine methiodide
2. O,O-Dimethyllaurifoline-methine methiodide

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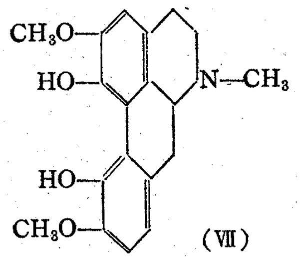
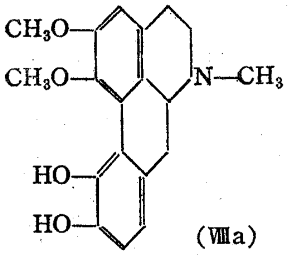
[3] M. Tomita, F. Kusuda: This Bulletin, **1**, 1, 5(1953); F. Kusuda: *Ibid.*, **1**, 55(1953).

On the basis of the foregoing experimental evidences, there is no doubt that magnoflorine has an aporphine nucleus, and since O,O-dimethylmagnoflorine iodide (IIIa) is not identical with O,O-dimethyllaurifoline iodide[3] (O,O-dimethylboldine methiodide, glaucine methiodide), it follows that the four methoxyl groups must be situated not at 2, 3, 5, and 6 positions in the aporphine (VI) nucleus, but at 3, 4, 5, and 6 or 1, 2, 5, and 6 positions. On comparison of the ultraviolet absorption spectra of the 3,4,5,6- or 2,3,5,6-substituted aporphine derivatives with those of the aporphine alkaloids bearing substituents at the positions of 1, 2, 5, and 6 or 1, 5, and 6, for example, crebanine[4] or stephanine[5], a detectable difference is observed between them. In the latter alkaloids, as is apparent from Fig. 1, the third maximum of absorption corresponding to that in the former disappears, being inclined to form a shoulder centered at ca. 320 mμ. From these facts, it seems reasonable to assume that the four substituents in magnoflorine are present at the position of 3, 4, 5, and 6. Furthermore, magnoflorine iodide gives a positive Gibbs reaction[6], which indicates the lack of a substituent in the *para*-position of the phenolic hydroxyl.

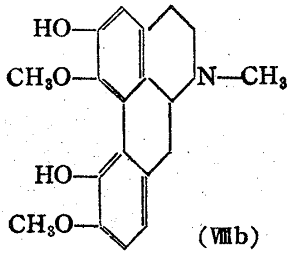
Of the aporphine alkaloids so far recorded in the literature, possessing two methoxyl and two phenolic hydroxyl groups at the positions of 3, 4, 5, and 6, corytuberine (VII)[7] and suaveoline[8] (VIIIa or VIIIb) are in keeping with the assumption stated above.



(VII)



(VIIIa)



(VIIIb)

The melting points of magnoflorine iodide and its degradation products, along with those of certain of the corresponding derivatives of corytuberine, are compared in Table I.

TABLE I.

Magnoflorine (I)		Corytuberine (VII) m.p. 242°(decomp.), $[\alpha]_D^{20}$: +282.6°(EtOH)	
Iodide (I')	m.p. 248~249°(decomp.) $[\alpha]_D^{35}$: +220.1°(MeOH)	Methiodide (II)	m.p. >250°[7]
Dimethyl ether iodide (IIIa)	m.p. 242.5~243°(decomp.)	Dimethyl ether methiodide (IIIa)	
Dimethyl ether chloride (IIIb)	m.p. 236~237°(decomp.)	Dimethyl ether methochloride (IIIb)	m.p. 236~237°(decomp.)[7] or m.p. 243°(decomp.)[9]
Methine base (IV)	oil	Methine base (IV)	oil[7]
Methine methiodide (V)	m.p. 270~271°(decomp.)	Methine methiodide (V)	m.p. >260°[7]

In view of the resemblance between the two series, it was decided to prepare from corytuberine some of the corresponding derivatives for direct comparison. Through the kindness of Dr. R. H. F. Manske a sample of corytuberine[10] was provided. As recorded in

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[4] M. Tomita, H. Shirai: J. Pharm. Soc. Japan, **62**, 381 (1942); **63**, 233 (1943); H. Shirai: *Ibid.*, **63**, 517, 532 (1943).
[5] M. Tomita, H. Shirai: *Ibid.*, **62**, 381 (1942); H. Shirai: *Ibid.*, **64B**, 208 (1944).
[6] M. Tomita, S. Uyeo: *Ibid.*, **61**, 449 (1941); M. Satomi: *Ibid.*, **72**, 834 (1952); F. Kusuda: This Bulletin, **1**, 191 (1953).
[7] J. Gadamer: Arch. Pharm., **240**, 94 (1902); **249**, 503, 641, 669 (1911); E. Späth, F. Berger: Ber., **64**, 2038 (1931).
[8] G. Barger, L. J. Surgent: J. Chem. Soc., **1939**, 991; E. Schlittler, H. U. Huber: Helv. Chim. Acta, **35**, 111 (1953).
[9] J. M. Gulland, R. D. Haworth: J. Chem. Soc., **1928**, 1834.
[10] R. H. F. Manske: C. A., **28**, 4537 (1934); Can. J. Research, **10**, 521 (1934); C. A., **35**, 128(1941); Can. J. Research, **18**, B, 288 (1940).

the literature[7], a sample of corytuberine available is unstable and is liable to darken in air. Treatment with methyl iodide gave the methiodide (II) crystallizing from methanol-acetone in the form of colorless pillars, m.p. 248°(decomp.). Unlike the original corytuberine, this substance is very stable and does not color when allowed to stand in air for many days, which is in accord with the fact that magnoflorine iodide suffers no change after exposure to air. The identity was established by admixture with magnoflorine iodide, m.p. 248~249°(decomp.). A portion of the methiodide was treated with sodium styphnate, yielding N-methylcorytuberine styphnate from acetone-ethanol as yellow prisms, m.p. 219~220°(decomp.), undepressed on admixture with magnoflorine styphnate, m.p. 218.5~219°(decomp.). In a similar way, from another portion of the methiodide, N-methylcorytuberine picrate was prepared, which crystallized from ethanol-acetone to slightly brownish yellow slender pillars, m.p. 205~206°(decomp.), either alone or on admixture with magnoflorine picrate, m.p. 205~206°(decomp.). In the O-methylation of corytuberine, Gadamer[7] has already noted the same difficulty as that encountered in the O-methylation of magnoflorine. The method employed for the O-methylation of magnoflorine was followed and O,O-dimethylcorytuberine methiodide (IIIa) was obtained as colorless needles, m.p. 242°(decomp.), undepressed by admixture with O,O-dimethylmagnoflorine iodide, m.p. 242.5~243°(decomp.). These results are summarized in Table II.

Furthermore, the properties of magnoflorine iodide agree closely with those of corytuberine methiodide, and the two substances also gave identical infrared spectra (Nujol mull) and Rf values in paper chromatography. It follows, therefore, that magnoflorine iodide is quite identical with corytuberine methiodide and in consequence, has structure (II) of the aporphine type. For the representation of magnoflorine, formula (I) may be considered as appropriate.

TABLE II.

Magnoflorine iodide (II)	m.p. 248~249°(decomp.)	Mixed m.p. 248°(decomp.)
Corytuberine methiodide (II)	m.p. 248°(decomp.)	
O,O-Dimethylmagnoflorine iodide (IIIa)	m.p. 242.5~243°(decomp.)	Mixed m.p. 243°(decomp.)
O,O-Dimethylcorytuberine methiodide (IIIa)	m.p. 243°(decomp.)	
Magnoflorine styphnate	m.p. 218.5~219°(decomp.)	Mixed m.p. 219°(decomp.)
N-Methylcorytuberine styphnate	m.p. 219~220°(decomp.)	
Magnoflorine picrate	m.p. 205~206°(decomp.)	Mixed m.p. 205~206° (decomp.)
N-Methylcorytuberine picrate	m.p. 205~206°(decomp.)	

Although a considerable number of the aporphine alkaloids is so far known to occur in plants, the discovery of a quaternary alkaloid of this type is the second instance following that of laurifoline chloride[3] from *Cocculus laurifolius* DC. (Menispermaceae). This is the first instance of the occurrence of a quaternary base of this type from the Magnoliacea family.

The author acknowledges his indebtedness to Prof. Dr. M. Tomita for his interest in this work and to Dr. R. H. F. Manske for his generous gift of a sample of corytuberine. The author's thanks are also offered to Mr. Y. Matsui of the Research Laboratory, Shionogi & Co., Ltd., for the measurement of the infrared spectra. The cost of this investigation was partly met by a Grant in Aid for Scientific Research from the Ministry of Education and is hereby gratefully acknowledged.

Experimental[11]

Magnoflorine Iodide (II)—2.3 g. of magnoflorine styphnate was decomposed by dissolving it in a small volume of acetone and adding a volume of 1% aq. HCl equivalent to the calculated amount of magnoflorine present. The aq. phase was shaken repeatedly with ether until all of the styphnic acid was removed. The aq. solution was evaporated *in vacuo* at 45°, whereby the chloride was obtained

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[11] Melting points are all uncorrected. Ultraviolet absorption spectra were determined with the Beckman Model DU V spectrophotometer. Infrared spectra were measured with the Perkin-Elmer Model 12 C Recording Spectrometer. The author is indebted to Mr. K. Hozumi and his associates for the microanalyses.

as a syrup which did not readily crystallize. This was then dissolved in the minimum amount of water and treated with an aq. KI solution. The precipitate which formed was washed successively with ether and a little water, and after drying weighed 1.7 g. After recrystallization from a mixture of MeOH and a small volume of acetone it crystallized in colorless pillars, m.p. 248~249°(decomp.). It is very sparingly soluble in water and acetone, and relatively sparingly soluble in MeOH; it is very stable and is not colored when allowed to stand in air for many days. The analytical sample was dried *in vacuo* at 90° over P_2O_5. $[\alpha]_D^{35}$: +220.1° (c=0.099, MeOH, $l=0.5$ dm.). *Anal.* Calcd. for $C_{20}H_{24}O_4NI$: C, 51.18; H, 5.15; N, 2.98; OCH_3, 13.22; NCH_3, 6.41. Found: C, 51.28, 51.38; H, 5.23, 5.27; N, 3.19; OCH_3, 12.43, 12.63; NCH_3, 5.99. Ultraviolet absorption spectra (Fig.1): Magnoflorine iodide: $\lambda_{max}^{H_2O}$ 227 mμ (log ε=4.68); 275 (3.99); 315 (3.96). Laurifoline chloride: λ_{max}^{MeOH} 227 mμ (log ε=4.48), 281 (4.04); 307 (4.14). Crebanine: λ_{max}^{MeOH} 279 mμ (log ε=4.31). This substance gave a blue color with the Gibbs reagent, and in an aq. solution, a dark yellowish brown color with $FeCl_3$. It gave a negative test for a methylenedioxy group with the Gaebel reagent. With concd. H_2SO_4 it produced a feeble violet color, changing to blood-red on addition of KNO_3. The infrared spectrum showed the presence of a phenolic hydroxyl (Nujol mull).

Magnoflorine Picrate—A portion of the iodide was treated with an aq. sodium picrate solution, which caused an immediate yellow precipitate. This resisted efforts at crystallization, showing a great tendency to separate as an oil from acetone, water, MeOH, EtOH, and AcOEt, or any solvent mixture tried. Crystallization, however, was induced by dissolving it in a mixture of acetone and EtOH, concentrating the solution until nearly all of the solvents were removed, and standing after addition of a few drops of acetone. After many hrs., slightly brownish yellow slender pillars, m.p. 208~209° (decomp.), deposited out slowly. They are readily soluble in acetone, and sparingly soluble in MeOH and EtOH. A sample was dried *in vacuo* at 95° over P_2O_5 and had m.p. 205~206°(decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_4N \cdot C_6H_2O_7N_3$: C, 54.73; H, 4.59; OCH_3, 10.88. Found: C, 54.78, 55.01; H, 4.54, 4.46; OCH_3, 10.68.

O,O-Dimethylmagnoflorine Iodide (IIIa)—To a solution of 0.5 g. of magnoflorine iodide in MeOH, a methanolic solution of 0.5 g. of KOH and an excess of MeI were added. After this mixture had been heated under reflux during 6 hrs., a further similar amounts of methanolic KOH and MeI were added, and heating was continued for a further 6 hrs. This process was repeated until in all four such additions of methanolic KOH had been made. Subsequently, a methanolic solution of 1 g. of KOH and an excess of MeI were added, and the mixture was refluxed for a further 6 hrs. After two such repetitions of similar process, the solution was evaporated *in vacuo*, and the residue which contained a voluminous inorganic material was extracted with a large amount of $CHCl_3$. $CHCl_3$ solution was dried over anhyd. K_2CO_3 and evaporated, depositing crystals. Recrystallization from MeOH-acetone furnished 0.4 g. of colorless needles, m.p. 242.5~243° (decomp.). They are soluble in MeOH and $CHCl_3$, and sparingly soluble in acetone and water. The analytical sample was dried *in vacuo* at 80° over P_2O_5 before analysis. *Anal.* Calcd. for $C_{22}H_{28}O_4NI$: C, 53.12; H, 5.48; OCH_3, 24.96. Found: C, 53.81, 54.09; H, 5.71, 5.93; OCH_3, 24.89, 24.57. The infrared spectrum showed the complete absence of free hydroxyl absorption (Nujol mull).

O,O-Dimethylmagnoflorine Chloride (IIIb)—0.2 g. of O,O-dimethylmagnoflorine iodide was dissolved in a mixture of MeOH and a little water, and shaken with freshly prepared AgCl (from 0.3 g. of $AgNO_3$). After 1 hr. the solution, which was free from iodide ions, was filtered and evaporated to dryness under reduced pressure, whereupon the entire readily crystallized out. Recrystallization from EtOH-acetone yielded colorless prisms, m.p. 236~237° (decomp.), which were dried *in vacuo* at 70° over P_2O_5 for analysis. *Anal.* Calcd. for $C_{22}H_{28}O_4NCl$: C, 65.09; H, 6.95. Found: C, 64.95; H, 7.09.

Hofmann Degradation of O,O-Dimethylmagnoflorine Iodide (IIIa): O,O-Dimethylmagnoflorine Methine Methiodide (V)—0.6 g. of O,O-dimethylmagnoflorine iodide was dissolved in 40 cc. of water and treated with 20 cc. of 50% aq. KOH. The mixture was boiled for 2 hrs., during which time a yellowish resin slowly separated. The cooled mixture was extracted with ether. The aq. solution was again heated for an additional 2 hrs., and after cooling extracted with ether. After one more repetition of this process, the ether extracts were combined, dried over anhyd. K_2CO_3, and the ether removed, leaving a yellowish oil. This was chromatographed in benzene on Brockmann's alumina, and the chromatogram developed with the same solvent. The eluate was fractionated into 11 portions of ca. 15 cc. Each fraction, on removal of the solvent, exhibited fluorescence under the ultraviolet rays, each distinguishable as follows: Nos. 1~3—yellowish green fluorescence; Nos. 4~7, a mixture of a yellowish green and a violet; and Nos. 8~11, a violet. From the alumina in the column, the last fraction was obtained by extracting with MeOH, which had a violet fluorescence. Attempts to crystallize all these fractions failed. Nos. 4~11 and the last fractions were combined and refluxed in MeOH with MeI for 30 mins. Upon removal of the solvent the methine methiodide readily crystallized. It is readily soluble in MeOH and sparingly soluble in acetone. Recrystallization from MeOH-acetone afforded 0.3 g. of colorless silky needles, which were dried *in vacuo* at 80° over P_2O_5 and showed m.p. 270~271° (decomp.). This substance is optically inactive. *Anal.* Calcd. for $C_{23}H_{30}$-

O_4NI : C, 54.01; H, 5.91; N, 2.58. Found : C, 53.31, 53.66; H, 6.22, 6.21; N, 2.30, 2.58. Ultraviolet absorption spectra (MeOH solution) (Fig. 2) : O,O-Dimethyllaurifoline methine methiodide : λ_{max} 264 mμ (log=4.83); 309 (4.07); 321 (4.07); 345 (3.28); 362 (3.10). O,O-Dimethylmagnoflorine methine methiodide : λ_{max} 265 mμ (log ε=4.68); 319 (4.16); 330 (4.19); 365 (3.37); 383 (3.37).

Nos. 1~3 fractions were refluxed in MeOH with an excess of MeI for 2 hrs., after which MeOH was evaporated, depositing crystals. Recrystallization from EtOH-acetone gave 50 mg. of colorless prisms. After drying *in vacuo* at room temp. over P_2O_5, they had m.p. 235~237°(decomp.) and an amine-like odor. $[\alpha]_D^{28}$: +21.2° (c=0.849, MeOH, l=0.5 dm.). Found : C, 20.83, 20.97; H, 5.72, 6.02.

Corytuberine Methiodide (II)—0.2 g. of corytuberine was refluxed in MeOH with an excess of MeI for 2 hrs. During concentration of the solution to a small bulk, crystals appeared. Recrystallization from MeOH-acetone yielded colorless pillars, m.p. 248° (decomp.). The analytical sample was obtained after further recrystallization from the same solvent mixture and drying *in vacuo* at 80° over P_2O_5. *Anal.* Calcd. for $C_{20}H_{24}O_4NI$: C, 51.18; H, 5.15. Found : C, 51.35; H, 5.44. This substance is far more stable than the original corytuberine, and when exposed to air for many days, it is not colored at all. Admixture with magnoflorine iodide, m.p. 248~249°(decomp.), gave no depression in m.p.

N-Methylcorytuberine Styphnate—A portion of corytuberine methiodide was treated with an aq. solution containing a 1:1 mixture of styphnic acid and NaOH, and the resulting precipitate was recrystallized from acetone and EtOH to yellow prisms. After drying *in vacuo* at 80° over P_2O_5, they melted at 219~220° with decomposition. This decomposition point, as well as that of magnoflorine styphnate depended somewhat upon the rate of heating. *Anal.* Calcd. for $C_{20}H_{24}O_4N \cdot C_6H_2O_8N_3$: C, 53.34; H, 4.47. Found : C, 53.51; H, 4.69. A mixed m.p. with magnoflorine styphnate, m.p. 218.5~219°(decomp.), showed no depression.

N-Methylcorytuberine Picrate—The picrate also showed a great tendency to separate as an oil, but crystallization was induced by following a procedure similar to that described for the preparation of magnoflorine picrate. It formed slightly brownish yellow slender pillars and showed m.p. 205~206°(decomp.) after drying *in vacuo* at 80° over P_2O_5. *Anal.* Calcd. for $C_{20}H_{24}O_4N \cdot C_6H_2O_7N_3$: C, 54.73; H, 4.59. Found : C, 54.56; H, 4.37. The substance gave no depression in m.p. when mixed with magnoflorine picrate, m.p. 205~206° (decomp.).

O,O-Dimethylcorytuberine Methiodide (III a)—The dimethyl ether of corytuberine methiodide was prepared in the same manner as for O,O-dimethylmagnoflorine iodide. It formed from MeOH-acetone colorless needles and after drying *in vacuo* at 80° over P_2O_5, had m.p. 242° (decomp.), undepressed on admixture with O,O-dimethylmagnoflorine iodide, m.p. 242.5~243° (decomp.). *Anal.* Calcd. for $C_{22}H_{28}O_4NI$: C, 53.12; H, 5.48. Found : C, 53.28; H, 5.61.

Paper Chromatography—The procedure was quite the same as described in the previous paper[1], and for the detection of alkaloidal spots, the Dragendorff reagent[1] and fluorescence by the ultraviolet ray were used.

	Rf in BuOH-AcOH-H_2O	
	63-10-27	50-10-40
Magnoflorine iodide	0.50	0.49
Corytuberine methiodide	0.50	0.49

Summary

In an earlier paper[1] of this series, the isolation of a new quaternary alkaloid, termed magnoflorine, from the bark of *Magnolia grandiflora* L. was described. In the present paper, magnoflorine iodide was shown to be identical with corytuberine methiodide (II). Thus, the structure of magnoflorine has been established as having formula (I). This is the first instance of the occurrence of the aporphine alkaloid of the quaternary type from the Magnoliaceae family.

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