30. Masao Tomita and Takehiko Kugo: Studies on the Alkaloids of
Magnoliaceae Plants. XI.¹⁾
Structure of Magnolamine. (3).²⁾

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Proskournina³⁾ assigned an empirical formula $C_{36}H_{40}O_7N_2 = C_{32}H_{24}O(OH)_4(OCH_3)_2(NCH_3)_2$ for magnolamine, an alkaloid of Caucasian *Magnolia fuscata*, and by oxidation of its tetramethyl ether, he obtained 1-keto-6,7-dimethoxy-N-methyltetrahydroisoquinoline and magnolamic acid, $C_{16}H_{14}O_7$, m.p. 280~281° (dimethyl ester, m.p. 131~132°). Not only from these experimental results but also from the facts that magnolamic acid furnished 4-hydroxybenzoic acid by alkali fusion and from the color reaction with ferric chloride, magnolamine was considered to possess the phenolic hydroxyl groups in the vicinal form. The same investigator assumed magnolamic acid to be identical with dimethoxydiphenyl ether-dicarboxylic acid, and proposed formula (I) or (II) for the representation of magnolamine.

If formula (I) or (II), proposed for magnolamine by Proskournina, be correct, then magnolamic acid should be 2,3-dimethoxydiphenyl ether-5,4'-dicarboxylic acid (Ia; R=H) or 2,6-dimethoxydiphenyl ether-4,4'-dicarboxylic acid (IIa; R=H). However, Tomita and Fujita⁴⁾ synthesized these corresponding acids (Ia; R=H) and (IIa; R=H), and their dimethyl esters (Ia; R=CH₃ and IIa; R=CH₃), as a result of which it was proved that they differ entirely from magnolamic acid and its methyl ester in melting points. Subsequently, Tomita, Fujita, and Nakamura⁵⁾, from the considerations of biogenesis of the biscoclaurine type of alkaloids, synthesized 3,4-dimethoxydiphenyl ether-6,4'-dicarboxylic acid (IIIa; R=H), m.p. 285°, and its dimethyl ester (IIIa; R=CH₃), m.p. 132.5~133°, and clarified that they are in good agreement⁵⁾ with magnolamic acid, m.p. 280~281°, and its dimethyl ester, m.p. 131~132°, in melting points. Consequently, a modified formula (III) was put forward for magnolamine.

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1) Part X: M. Tomita, H. Yamaguchi: J. Pharm. Soc. Japan, 73, 495(1953).

2) Part (2): M. Tomita, E. Fujita, T. Nakamura: J. Pharm. Soc. Japan, 71, 1075(1951) (C.A., 46, 5060(1952)).

3) N.F. Proskournina: J. Gen. Chem. (USSR), 16, 129(1946) (C.A., 41, 460(1947)).

4) M. Tomita, E. Fujita: J. Pharm. Soc. Japan, 70, 411(1950) (C.A., 45, 2492(1951)).

5) It is impossible to confirm them by direct comparison, because no communication with Proskournina is at present available.

Yet, from the results so far obtained in the investigation of magnolamine, formula (IV) must still be taken into consideration. If magnolamine be (IV), magnolamic acid should be 2,3-dimethoxydiphenyl ether-6,4'-dicarboxylic acid (IVa; R=H). In the present series of experiments, attempts to synthesize (IVa; R=H) and (IVa; R=CH₃) have been made, so that the final confirmation may be attained.

The starting material for the substance (IVa) was methyl 2-bromo-3,4-dimethoxybenzoate (IX), which was prepared in the following sequence: 2-Nitro-3,4-dimethoxybenzoic acid (VI) was first prepared through the process vanillin (V)→acetovanillin→2-nitroacetovanillin→2-nitrovanillin, following the method employed by Butenandt, *et al.*⁶⁾ Subsequently, according to the literature recorded by Pschorr, *et al.*⁷⁾, (VI) was reduced with ferrous sulfate and ammonia to 2-amino-3,4-dimethoxybenzoic acid (VIIIa), the amino group of which was diazotized by the method of Zincke *et al.*⁸⁾, and then replaced with bromine by the Sandmeyer reaction. The esterification of the latter substance led to the objective (IX).

6) A. Butenandt, H.G. Schlossberger: Chem. Ber., 85, 565 (1952).

7) R. Pschorr, C. Sumuleanu: Ber., 32, 3407 (1899).

8) T. Zincke, B. Francke: Ann., 293, 187 (1896).

However, the authors found that in the case of synthesizing the substance (IX), it was far more better in yield and more simple in operation to choose the process through (VI)→(VII)→(VIII)→(IX), which has not been described in the literature, than the hitherto known process. Methyl 2-bromo-3,4-dimethoxybenzoate (IX) prepared by both of the above procedures, was obtained as colorless needles, m.p. 44~46°.

Finally, methyl 2-bromo-3,4-dimethoxybenzoate (IX) was condensed with the potassium salt of methyl 4-hydroxybenzoate by the Ullmann method to yield 2,3-dimethoxydiphenyl ether-6,4'-dicarboxylic acid (IVa; R=H) and its dimethyl ester (IVa; R=CH₃). The acid (IVa; R=H) thus obtained crystallized in the form of colorless microscopic prisms, m.p. 255~257°, from acetone, and as a result of analyses corresponds to the composition of C₁₆H₁₄O₇. The dimethyl ester formed colorless pillars, m.p. 65~67°. On comparison of the acid (IVa; R=H) and its ester (IVa; R=CH₃) with magnolamic acid and its dimethyl ester, both gave different data in melting points. It follows, therefore, that formula (IV) for the structure of magnolamine is inconceivable.

The foregoing experimental results lead to a decisive conclusion that, as suggested in an earlier paper²⁾ of this series, magnolamic acid should be identical with 3,4-dimethoxydiphenyl ether-6,4'-dicarboxylic acid (IIIa; R=H) and in consequence, the structure of magnolamine should be represented by formula (III).

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Experimental⁹⁾

(1) **Methyl 2-Amino-3,4-dimethoxybenzoate (VIII)**—10 g. of 2-Nitroveratric acid (VI), prepared from vanillin by a procedure similar to that employed by Butenandt⁹⁾, was heated with 90 cc. of absolute methanol and 10 cc. of concentrated sulfuric acid on a water bath for 5 hrs. The ester (VII) so obtained formed colorless needles, m.p. 127~128°; yield, 9.6 g. (90%). 5 g. of methyl 2-nitro-3,4-dimethoxybenzoate (VII) was then dissolved in 100 cc. of ethyl acetate and reduced by means of Raney-Ni catalyst (prepared from 7 g. of Raney alloy). After 1680 cc. of hydrogen had been absorbed at 20° (the theoretical amount, 1498 cc.), the catalyst was filtered off and the solvent removed. The residue was treated with dilute hydrochloric acid, and after alkalization, extracted with ether. The ether extract was dried over anhydrous potassium carbonate and the solvent removed, yielding 3.4 g. of colorless prisms, m.p. 69~70°. The identity of this substance (VIII), which according to Rodinov, *et al.*¹⁰⁾, was obtained from hemipinimide and recorded as m.p. 69~70°, was confirmed by direct comparison with methyl 2-amino-3,4-dimethoxybenzoate obtained by methylation of 2-amino-3,4-dimethoxybenzoic acid (VIIIa) (m.p. 180~183°) with methanol and concentrated sulfuric acid. (VIIIa) was prepared directly by reduction of the nitro compound (VI) with ammonia water and ferrous sulfate according to the Pschorr method.⁷⁾ *Anal.* Calcd. for C₁₀H₁₃O₄N: C, 56.86; H, 6.20. Found: C, 56.64; H, 6.12.

(2) **Methyl 2-Bromo-3,4-dimethoxybenzoate (IX)**—To a solution of 2 g. of methyl 2-amino-3,4-dimethoxybenzoate (VIII) in 15 g. of 10% sulfuric acid was added with stirring and cooling 2 cc. of concentrated sulfuric acid, when microscopic crystals (the sulfate) deposited. The diazotization was carried out by adding aqueous sodium nitrite solution dropwise to the content kept at 5°. The solution gradually changed to a yellow color and the white precipitate of the sulfate disappeared. After ensuring the completeness of the reaction by iodine-starch paper, aqueous cuprous bromide was added until the solution gave no coloration with alkaline naphthol solution, and the solution became yellowish green, and orange precipitate resulted. During this period, the temperature was maintained between 5° and 20°. After standing overnight, the reaction mixture was extracted with chloroform, and the solvent removed. Recrystallization of the residue from petroleum benzine yielded 1.8 g. of colorless needles (IX), m.p. 44~46°; yield, 72%. The identity of this compound was confirmed as follows: 2-Amino-3,4-dimethoxybenzoic acid (VIIIa), prepared by the Pschorr

9) All melting points are uncorrected. The authors wish to express their thanks to Messrs. Hozumi, Imaeda, and Kinoshita in this Laboratory for carrying out the microanalyses herein reported.

10) V.M. Rodinov, A.M. Fedrova: Bull. soc. chim. France, [V], 6, 478(1939).

method⁷⁾, was diazotized according to the literature reported by Zincke⁸⁾, and then decomposed with cuprous bromide to 2-bromo-3,4-dimethoxybenzoic acid (IXa) (m.p. 202~204°), which was methylated with methanol and concentrated sulfuric acid to yield methyl 2-bromo-3,4-dimethoxybenzoate (m.p. 44~46°); admixture with (IX) gave no depression in the melting point. Zincke⁸⁾ reported m.p. 46° for (IX). *Anal.* Calcd. for $C_{10}H_{11}O_4Br$: C, 43.65; H, 4.03. Found: C, 44.12; H, 4.40.

(3) **2-Bromo-3,4-dimethoxybenzoic Acid (IXa)**—The methyl ester (IX) obtained above was heated with alcoholic potash on a water bath for 2 hrs., after which the solvent was removed under a reduced pressure, and water added to the residue. An aqueous solution thus obtained was made acid with hydrochloric acid and deposited crystals, which were recrystallized from alcohol to colorless needles, m.p. 203° (Zincke recorded m.p. 201~202°). *Anal.* Calcd. for $C_9H_9O_4Br$: C, 41.40; H, 3.47. Found: C, 41.66; H, 3.83.

(4) **2,3-Dimethoxydiphenyl Ether-6,4'-dicarboxylic Acid (IVa; R=H)**—To a solution of 0.3 g. of metallic potassium in 8 cc. of absolute methanol was added 1.1 g. of methyl 4-hydroxybenzoate, and the mixture was evaporated *in vacuo* to dryness under reduced pressure to remove the solvent. The residue was mixed well with 2 g. of methyl 2-bromo-3,4-dimethoxybenzoate (IX), 0.1 g. of copper powder, and 0.1 g. of anhydrous copper sulfate, and the mixture heated in an oil bath at 190~200° for 5 hrs. After the completion of the reaction, the content was extracted several times with ether on a water bath, and the ether extracts were combined and washed with 3% aqueous potassium hydroxide solution. After drying with anhydrous sodium sulfate, the ether was distilled off. The residue was distilled at a reduced pressure of 0.45 mm. Hg, and the fraction with the boiling points lower than 120° was discarded. The remainder left after distillation was heated with *N* alcoholic potash on a water bath for 2 hrs., after which the solvent was removed *in vacuo*, and the residue was dissolved in water and filtered. The filtrate was made acid with hydrochloric acid and the depositing slightly yellowish crystals were collected. The crystals were washed with a small amount of ether to remove ether-soluble material, and then recrystallized from acetone. They crystallized in the form of colorless microscopic prisms, m.p. 255~257°; yield, 0.7 g. (31%). *Anal.* Calcd. for $C_{18}H_{14}O_7$: C, 60.38; H, 4.43. Found: C, 60.36; H, 4.57.

(5) **Methyl 2,3-Dimethoxydiphenyl Ether-6,4'-dicarboxylate (IVa; R=CH₃)**—30 mg. of the acid (IVa; R=H) was methylated in methanol with ethereal diazomethane. After removal of the solvent, the product was taken up in ether and washed with 3% potassium carbonate solution. The ether layer was dried with anhydrous sodium sulfate and the ether removed. The residue, after being kept in an ice chest, solidified to a crystalline mass. It was recrystallized from alcohol-benzene and formed colorless pillars, m.p. 65~67°. *Anal.* Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.42. Found: C, 62.18; H, 5.47.

Summary

2,3-Dimethoxydiphenyl ether-6,4'-dicarboxylic acid (IVa; R=H) and its methyl ester (IVa; R=CH₃) were synthesized. It was found that these compounds gave entirely different data from those of magnolamic acid, obtained by the oxidation of magnolamine tetramethyl ether, and its methyl ester. Thus it was confirmed that, as suggested by Tomita, Fujita, and Nakamura in an earlier paper²⁾ of this series, magnolamic acid should be identical with 3,4-dimethoxydiphenyl ether-6,4'-dicarboxylic acid (IIIa; R=H), and accordingly the structure of magnolamine should be represented by formula (III).

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