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THE STRUCTURE OF MAGNOLAMINE

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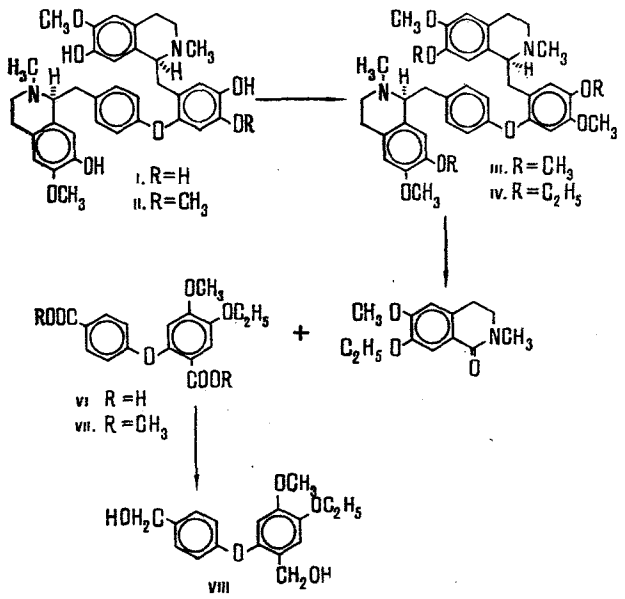
The bisbenzylisoquinoline alkaloid magnolamine was first isolated from the leaves of Michelia fuscata Blume (synonym Magnolia fuscata Andr.) in 1938, and the structure (I) was proposed for it [1-4].

Continuing the study of magnolamine, we have found that its spectral characteristics contradict formula (I).

The NMR spectrum of magnolamine (Fig. 1) contains, in addition to the protons of the bisbenzylisoquinoline skeleton, two singlets of N-methyl groups at 2.34 and 2.43 ppm and the sharp singlets of three aryl methoxy groups at 3.74, 3.76, and 3.78 ppm. At the same time, according to (I) there should be the signals of only two methoxy groups. A quantitative determination of methoxyls by the method of Vieböck and Brecher confirmed the presence of three methoxy groups in the magnolamine molecule. It must also be noted that magnolamine does not show the color reaction with ferric chloride that is characteristic for an orthodiphenyl group.



The methylation of magnolamine with diazomethane led to a hexamethoxy derivative (III), identical with that described previously [2]. The NMR spectrum of this compound has the singlets of six methoxy groups at 3.57 (3H), 3.60 (3H), 3.74 (6H), and 3.80 (6H) ppm.

The ethylation of magnolamine with diazomethane gave a substance (IV) with mp 101-102°C (from ethanol) which, according to its NMR spectrum, had three methoxy groups [3.83 (3H), 3.88 (6H), ppm] and three ethoxy groups [1.46 (9H), 3.70-4.18 (6H) ppm].

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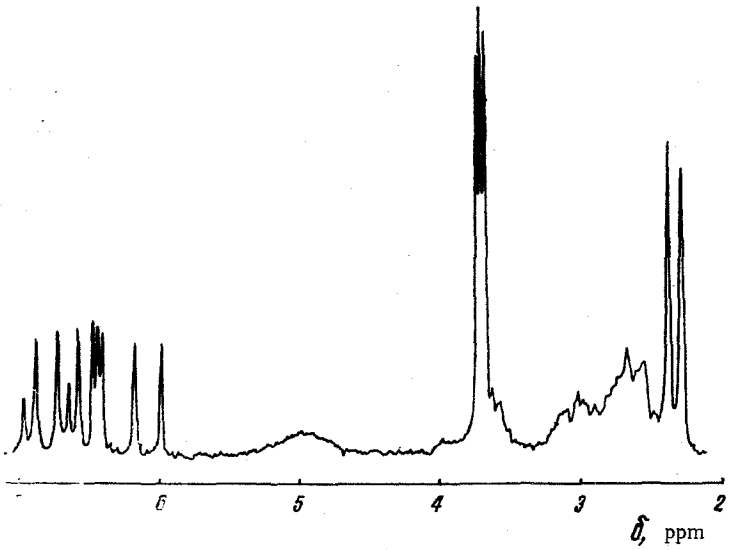

Fig. 1. NMR spectrum of magnolamine.

The absence of a color reaction for a catechol grouping and also the presence in the mass spectrum of magnolamine of an intense (100%) signal of a dihydroisoquinolinium ion with m/e 192 shows that two methoxy groups are present in the isoquinoline nuclei of this alkaloid and the third in the diphenyl ether part of the molecule.

The oxidation of compound (IV) with potassium permanganate confirmed this assumption. As the oxidation product we isolated the 7-ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-one (V) described previously [2], and also a diacid (VI) containing, according to its NMR spectrum, one methoxy group (3.89 ppm) and one ethoxy group (1.52 ppm, t, 7 Hz, 3H, and 4.33 ppm, q, 7 Hz, 2H) in the aromatic nucleus. The weak-field singlet of an aromatic proton (7.76 ppm) is assigned to the proton at C_3 (electron-accepting influence of a carboxy group in the ortho position) and a singlet in the strong field (6.70 ppm) to the proton at C_6 (meta position with respect to the carboxyl screening the influence of the second phenyl nucleus).

The position of the methoxy group in the dimethyl ester (VII) was determined by measuring the intramolecular nuclear Overhauser effect (NOE). In the presence of an additional field corresponding to the resonance of the protons of the methoxy group, the integral intensity of the signal from the C_6–H increased by 25%. Thus, the methoxy group is present in position 5 and the ethoxy group in position 4 of the dimethyl ester (VII) and, consequently, of the acid (VI). For comparison we obtain the diol (VIII) by reduction of the ester (VII) with lithium aluminum hydride.

An Overhauser effect was also used to confirm the structure of the isoquinoline derivative (V): irradiation at the frequency of the protons of the methoxy group increased the integral intensity of the signal from the C_5–H (6.97 ppm) by 19%.

Japanese authors who have studied the structure of magnolamine [5] have described an independent synthesis of the acid obtained by the potassium permanganate oxidation of the ethylation product of magnolamine. On the basis of the assertion that this alkaloid has the structure (I) and the oxidation product ("acid") is 4,5-diethoxydiphenyl ether 2,4'-dicarboxylic ester,* the authors synthesized this compound. The substance synthesized has mp 245-247°C, which is 30°C different from the melting point of the acid obtained from the natural product [2]. Nevertheless, no direct comparison of these compounds was made [5].

Our results indicate that the 4,5-diethoxydiphenyl ether 2,4'-dicarboxylic ester synthesized by M. Tomita and T. Kugo [5] and the acid obtained by the oxidation of the ethylation product of magnolamine – 4-ethoxy-5-methoxydiphenyl ether 2,4'-dicarboxylic ester – are different compounds.

In 1966, T. Kametani and H. Yagi [6] reported the synthesis of magnolamine of formula (I). The compound obtained showed a similar pattern of paper chromatograms and similar UV and IR spectra to those of natural magnolamine. However, attempts to obtain a crystalline sample of the synthetic compound proved unsuccessful. Recrystallization from a mixture of chloroform and petroleum ether gave a brownish powder with mp 112-116°C, while natural magnolamine readily crystallizes from benzene or chloroform with the formation of colorless

*In the relevant paper [5], this compound is called 3,4-diethoxydiphenyl ether 4',6-dicarboxylic ester.

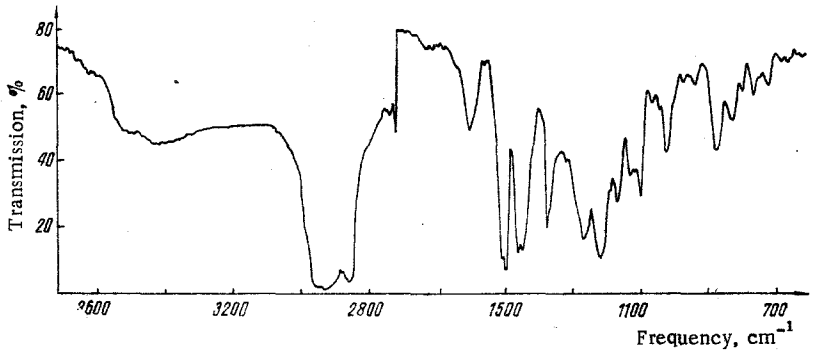

Fig. 2. IR spectrum of magnolamine.

crystals having, after drying, mp 117-118°C. The authors assumed that the difference in the properties of the synthetic compound and of natural magnolamine is due to the presence of a mixture of diastereoisomeric forms in the synthetic sample.

The absence of the results of a direct comparison of the product synthesized and the natural alkaloid, and also of information on NMR spectroscopy did not permit these compounds to be identified sufficiently convincingly.

Thus, the investigations that we have performed show that the substance synthesized by T. Kametani and H. Yagi and natural magnolamine are different compounds.

The proposed structure of magnolamine (II) agrees well with a scheme for the biogenetic formation of this alkaloid from d-N-methylcoclaurine and d-reticuline, according to which the diphenyl ether bond must be formed in the ortho or para position to a hydroxy group.

EXPERIMENTAL

The NMR spectra were obtained on an NA-100 instrument (100 MHz) at 20°C with tetramethylsilane as internal standard. In the measurement of the NOE in (VII) we used a degassed solution of the substance in $CDCl_3$. The IR spectra were taken on a UR-10 spectrophotometer.

The analyses of all the compounds corresponded to the calculated figures.

Isolation of Magnolamine. The combined alkaloids from the leaves of Michelia fuscata Blume were obtained by the usual dichloroethane method and the magnoline and magnolamine was separated by their basicities [2]. The magnolamine was purified by crystallization from benzene or chloroform. The substance forms crystalline solvates with benzene and chloroform having the composition $C_{37}H_{42}N_2O_7 \cdot C_6H_6$ and $C_{37}H_{42}N_2O_7 \cdot CHCl_3$. After drying in vacuum at 100°C, the substance loses the solvents and has the composition $C_{37}H_{42}N_2O_7$ with mp 117-118°C, $[\alpha]_D^{22}$ +180° (c 0.95; ethanol) [2].

The magnolamine isolated was completely identical, according to a direct comparison, with the sample described previously [1, 2] in its chromatographic mobility on alumina and silica gel, melting point, angle of rotation, and NMR and IR spectra (Figs. 1 and 2), and also in the properties of its O-methyl and O-ethyl derivatives and its degradation products.

NMR spectrum, $CDCl_3$, δ, ppm: 2.34, c, 3H; 2.43, c, 3H ($2N-CH_3$); 3.74, c, 3H; 3.76, c, 3H; 3.78, c, 3H ($3Ar-OCH_3$); 6.02, c 1H; 6.21, c, 1H (C_8-H, $C_8'-H$); 6.73, d, 8 Hz, 2H; 6.98 d, 8 Hz, 2H ($C_{10}-H$, $C_{11'}-H$, $C_{13'}-H$, $C_{14'}-H$); 6.46, c, 1H; 6.49, c, 1H; 6.53, c 1H; 6.64, c, 1H(C_5-H, $C_5'-H$, $C_{11}-H$, $C_{14}-H$). IR spectrum, $CHCl_3$, cm^{-1}: 3545 (OH).

Tri-O-methylmagnolamine (III). A solution of 1 g of magnolamine in methanol was treated with an ethereal solution of diazomethane, and the mixture was allowed to stand for two days. After the ether had been distilled off, a colorless crystalline precipitate was obtained, which, after recrystallization from ethanol, had the composition $C_{40}H_{28}N_2O_7$ and mp 150-151°C.

NMR spectrum, $CDCl_3$, δ, ppm: 2.41, c, 3H; 2.49, c, 3H ($2N-CH_3$); 3.57, c 3H; 3.60, c, 3H; 3.74, c 6H; 3.80, c, 6H ($6\,Ar-OCH_3$); 6.12, c, 2H (C_8-H, $C_8'-H$); 6.75, d, 8 Hz, 2H; 7.00, d 8 Hz, 2H ($C_{10'}-H$, $C_{11'}-H$, $C_{13'}-H$; $C_{14'}-H$); 6.50, c 1H; 6.52, c 2H; 6.57, c, 1H (C_5-H, $C_5'-H$, $C_{11}-H$, $C_{14}-H$).

Tri-O-ethylmagnolamine (IV). Similarly, 3.5 g of magnolamine and diazoethane in anhydrous ethanol (2 days) yielded 2.7 g of substance (IV), $C_{43}H_{54}N_2O_7$, mp 101-102°C (from ethanol).

NMR spectrum, $CDCl_3$, δ, ppm: 1.46, m, 9H ($3O-CH_2CH_3$); 2.49, c, 3H; 2.58, c, 3H ($2N-CH_3$); 3.83, c, 3H; 3.88, c, 6H ($3\,Ar-OCH_3$); 3.70-4.18, m, 6H ($3O-CH_2CH_3$); 6.25, c, 1H; 6.29, c, 1H (C_3-H, $C_8'-H$); 6.82, d, 8 Hz, 2H; 7.08, d, 8 Hz, 2H($C_{10}'-H$, $C_{11}'-H$, $C_{13}'-H$, $C_{14}'-H$); 6.58, c, 1H; 6.60, c, 2H; 6.66, c, 1H (C_5-H, $C_5'-H$, $C_{11}-H$, $C_{14}-H$).

Oxidation of Tri-O-ethylmagnolamine with Potassium Permanganate. A solution of 2 g of (IV) in 100 ml of acetone was treated with 6 g of powdered potassium permanganate and the mixture was left to stand for 2 days. The manganese dioxide was separated off and washed on the filter first with acetone until the reaction for alkaloids had disappeared and then with hot water until the wash waters gave no turbidity on acidification. After concentration by evaporation, the acetone solution yielded crystalline 7-ethoxy-6-methoxy-2-methyl-1,2,-3,4-tetrahydro-isoquinoline-1-one (V), 0.9 g, $C_{13}H_{17}NO_3$, mp 120-121°C (from ethanol).

NMR spectrum, CF_3COOH, δ, ppm: 1.50, t, 7 Hz, 3H ($OCH_2\underline{CH_3}$); 3.17 t, 7 Hz, 2H ($Ar-CH_2-$); 3.90, t, 7 Hz, 2H ($N-CH_2-$); 3.50, c, 3H ($N-CH_3$); 4.04, c 3H ($Ar-OCH_3$); 4.27, q, 7 Hz, 2H (OCH_2CH_3); 6.97, c, 1H (C_5-H); 7.59, c, 1 H (C_8-H). IR spectrum, paraffin oil, cm^{-1}; 1645 (CO).

The aqueous solutions after the washing of the manganese dioxide were acidified with dilute hydrochloric acid and the substance was extracted with ether. The ethereal extract yielded 0.78 g of 4-ethoxy-5-methoxy-diphenyl ether 2,4'-dicarboxylic acid (VI), mp 275-276°C (from acetic acid; composition $C_{17}H_{16}O_7$.

NMR spectrum, CF_3COOH δ, ppm: 1.52, t, 7 Hz, 3H ($O-CH_2\underline{CH_3}$); 3.89, c, 3H ($Ar-OCH_3$); 4.33, q, 7 Hz, 2H ($O-CH_2\underline{CH_3}$); 6.70, c, 1H (C_6-H); 7.76, c, 1H (C_3-H); 7.09, d, 8 Hz, 2H; 8.14, d, 8 Hz, 2H ($C_2'-H$, $C_3'-H$, $C_5'-H$, $C_6'-H$).

IR spectrum, paraffin oil, cm^{-1}: 1680 (CO).

4-Ethoxy-5-methoxy-2,4'-dimethoxycarbonyldiphenyl Ether (VII). The methylation with diazomethane of 0.6 g of 4-ethoxy-5-methoxydiphenyl ether 2,4'-dicarboxylic acid (VI) yielded 0.42 g of 4-ethoxy-5-methoxy-2,4'-dimethoxy-carbonyldiphenyl ether (VII) with the composition $C_{19}H_{20}O_7$, mp 110-111°C (from ethanol).

NMR spectrum, $CDCl_3$, δ, ppm: 1.60, t, 7 Hz, 3H ($OCH_2\underline{CH_3}$); 3.84 c, 3H; 4.02, c, 3H ($2OCH_3$); 4.00, c, 3H ($Ar-OCH_3$); 6.76, c, 1H(C_6-H); 7.64, c, 1H (C_3-H); 7.00, d, 8 Hz, 2H; 8.12, d, 8 Hz, 2H($C_2'-H$, $C_3'-H$, $C_5'-H$, $C_6'-H$).

Reduction of 4-Ethoxy-5-methoxy-2,4'-dimethoxycarbonyldiphenyl Ether (VII) with Lithium Tetrahydro-aluminate. A solution of 0.3 g of substance (VII) in 100 ml of anhydrous ether was added to a suspension of 0.3 g of lithium tetrahydroaluminate in ether. The mixture was boiled for 6 h. After the usual working up, 0.15 g of substance with mp 80-81°C consisting of 4-ethoxy-2,4'-di(hydroxymethyl)-5-methoxydiphenyl ether (VII), composition $C_{17}H_{20}O_5$, was obtained.

NMR spectrum, $CDCl_3$, δ, ppm: 1.46, t, 7 Hz, 3H ($OCH_2\underline{CH_3}$); 2.23, c, 2H (OH); 3.72, c, 3H (OCH_3); 4.09, q, 7 Hz, 2H ($\underline{OCH_2}CH_3$); 4.52, c, 2H ($-CH_2-$); 4.56, c, 2H ($-CH_2-$); 6.47, c, 1H (C_6-H); 6.81, d, 8 Hz, 2H; 7.21, d, 8 Hz, 2H ($C_2'-H$, $C_3'-H$, $C_5'-H$, $C_6'-H$); 6.95, c, 1H (C_3-H).

SUMMARY

It has been shown that the bisbenzylisoquinoline alkaloid magnolamine has the structure (II) and not the (I) proposed previously. The structure was determined on the basis of a study by the methods of NMR spectroscopy and mass spectrometry with the alkaloid and its transformation products.

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