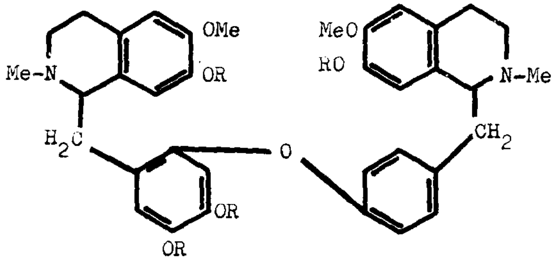
Tetrahedron Letters No.15, pp. 953-958, 1965. Pergamon Press Ltd.
Printed in Great Britain.

A TOTAL SYNTHESIS OF THE STEREOISOMERIC MIXTURE OF MAGNOLAMINE

T. Kametani and H. Yagi
Pharmaceutical Institute, Tohoku University School of Medicine
No. 85. Kitayobancho, Sendai, Japan

(Received 19 February 1965)

Magnolamine, $C_{36}H_{40}N_2O_7$, m.p. 119°, one of the alkaloids of Magnoliaceae plants, was isolated from the leaves of *Magnolia fuscata* belonging to the order of Caucasian Magnoliaceae by Proskurnina and Orekhoff (1) in 1939. The structure of magnolamine was assigned as (I) by chemical methods (2, 3, 4). However, a total synthesis of magnolamine has not yet been achieved.



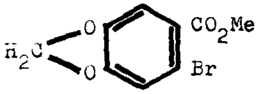
I : R=H
II : R=CH_2Ph

The purpose of the present investigation was to study the cyclization of the diamide (IX) in order to obtain the corresponding dihydroisoquinoline derivative (X) and its dimethiodide (XI) as possible intermediates for the synthesis of magnolamine (I). A study of the reduction of (XI), followed by hydrolysis of O-tetrabenzylmagnolamine (II), eventually led to a synthesis of racemic magnolamine that supports the structure (I).

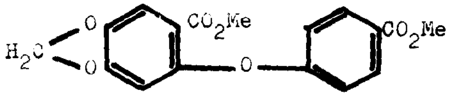
Ullmann reaction of methyl 2-bromo-4,5-methylenedioxybenzoate (III) (5) with methyl 4-hydroxybenzoate gave 4,5-methylenedioxy-2,4'-dimethoxycarbonylbiphenyl ether (IV), which was recrystallized from methanol to give colourless prisms, m.p. 96 - 97° (Found: C, 61.93; H, 3.90. $C_{17}H_{14}O_7$ requires C, 61.82; H, 4.27%). Cleavage of the methylenedioxy radical of the biphenyl ether (IV) by the action of phosphorus pentachloride followed by hydrolysis (6) was carried out to give the corresponding 4,5-dihydroxy-derivative (V), whose recrystallization from methanol afforded colourless needles, m.p. 148 - 149° (Found: C, 60.36; H, 4.43. $C_{16}H_{14}O_7$ requires, C, 60.38; H, 4.43%). Methylation of (V) with diazomethane afforded methyl magnolamate (Va) (7), m.p. 132.5 - 133°.

Benzylation of the above compound (V) in the presence of sodium hydroxide in methanol afforded 4,5-bisbenzyloxy-2,4'-dimethoxycarbonylbiphenyl ether (VI) as colourless needles, m.p. 95 - 96° (MeOH) (Found: C, 72.38; H, 5.10. $C_{30}H_{26}O_7$ requires C, 72.28; H, 5.26%), which was converted into the corresponding dicarboxylic acid (VII) by hydrolysis. Recrystallization of this acid from dimethyl sulphoxide-water yielded 4,5-bisbenzyloxy-2,4'-dicarboxylbiphenyl ether (VII) as colourless feathers, m.p. 256 - 257° (Found: C, 71.33; H, 4.73. $C_{28}H_{22}O_7$ requires C, 71.48; H, 4.71%), which was converted into the acid chloride (VIII) by chlorination with thionyl chloride.

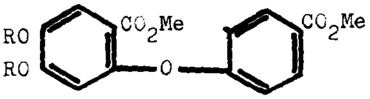
Arndt-Eistert reaction (8) of 3-methoxy-4-benzyloxyphenethylamine with the diazoketone, which was obtained from the acid



III

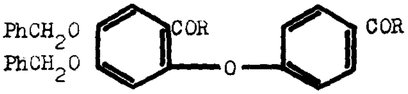


IV



V : R=H

Va : R=Me



VI : R=OMe

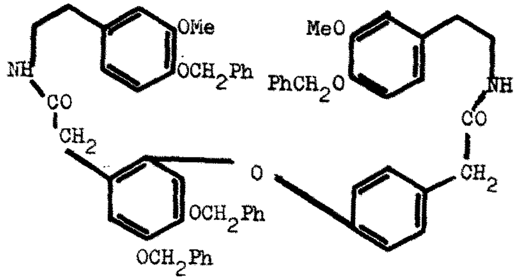
VII : R=OH

VIII : R=Cl

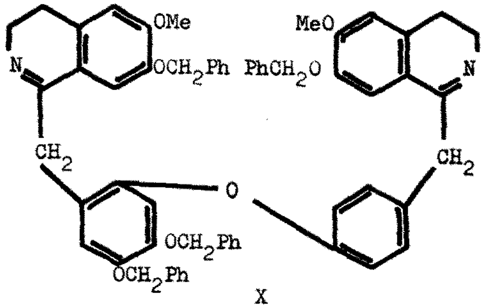
chloride (VIII) and diazomethane in ether gave the diamide (IX) as a colourless powder, m.p. 167 - 168° (benzene) (Found: C, 76.03; H, 5.96; N, 3.15. $C_{62}H_{60}N_2O_9$ requires C, 76.21; H, 6.19; N, 2.87%).

Bischler-Napieralski cyclization of the above diamide (IX) with phosphoryl chloride in benzene afforded the dihydroisoquinoline derivative (X) as a yellowish-brown glass, whose dipicrate was recrystallized from chloroform-ether to give a yellowish orange powder, m.p. 103 - 105° (decomp.) (Found: N, 7.54. $C_{62}H_{56}N_2O_7$ $2C_6H_3N_3O_7$ requires N, 8.00%).

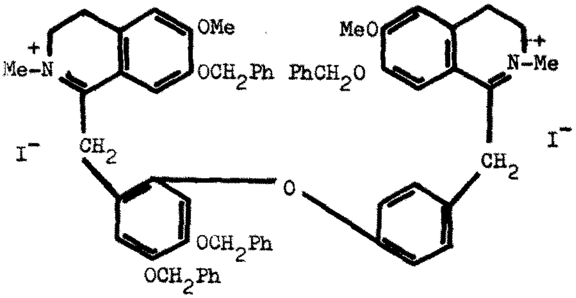
Reduction of the amorphous dimethiodide (XI), which could


OMe
NH
CO
CH2
OCH2Ph
MeO
PhCH2O
NH
CO
CH2
O
OCH2Ph
OCH2Ph

IX


OMe
N
OCH2Ph
MeO
PhCH2O
N
CH2
CH2
O
OCH2Ph
OCH2Ph

X


OMe
+
Me-N
OCH2Ph
MeO
PhCH2O
+
N-Me
I⁻
CH2
CH2
I⁻
O
OCH2Ph
OCH2Ph

XI

not be purified by recrystallization, with sodium borohydride in methanol or chloroform-methanol afforded O-tetrabenzylmagnolamine (II), whose diperchlorate was recrystallized from chloroform-ether to give a colourless powder, m.p. 115 - 118° (Found: C, 65.69; H, 5.77; N, 2.44. $C_{64}H_{64}N_2O_7,2HClO_4$ requires C, 65.47; H, 5.67; N, 2.39%). In this case the attempts to separate one of the two diastereoisomers in a crystalline state under a variety of procedures resulted in failure.

Hydrolysis of the above O-tetrabenzylmagnolamine (II) with ethanolic concentrated hydrochloric acid gave a stereoisomeric mixture of magnolamine (I) as a yellow syrup, which formed a pale yellowish-brown powder on being triturated with hexane. Recrystallization from chloroform-petroleum ether gave synthetic magnolamine as a pale brown powder, m.p. 112 - 116° (Found: C, 70.64; H, 6.67. $C_{36}H_{40}N_2O_7$ requires C, 70.57; H, 6.58%).

The synthetic magnolamine and natural one behaved similarly on paper-chromatography. The infrared (in chloroform) and ultraviolet (in ethanol) spectra were superimposable on those of natural magnolamine donated by Prof. M. Tomita, but attempted purification in a crystalline state at this stage failed. Therefore, it is not obvious whether our synthetic magnolamine would be the mixture of (±)-magnolamine and its diastereoisomer or not, but it was proved that our synthetic sample had the same planar structure (I) as the natural magnolamine. These facts reveal that the total synthesis of the stereoisomeric mixture of magnolamine has been accomplished.

We express our deep gratitude to Prof. M. Tomita of Kyoto University for the gift of natural magnolamine.

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