

**Aztequine and Related Compounds. IV.<sup>1)</sup> A Synthesis of 2,2'-Dihydroxy-4,4'-bis(7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolylmethyl)diphenyl Ether (Studies on the Syntheses of Heterocyclic Compounds. CCXXX<sup>2)</sup>)**

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The alkaloids aztequine (I) was isolated by Pallares and Garza<sup>4)</sup> from the leaves of "Yoloxochitl," a plant belonging to the Mexican genus *Talauma* Juss of the family Magnoliaceae. Analysis indicated the formula  $C_{36}H_{40}O_7N_2$  and showed the presence of two methoxyl groups, four phenolic groups, and methylimino groups. Furthermore, they reported that the treatment of aztequine with hydriodic acid yielded two compounds,  $C_{18}H_{21}O_4N$  (Ia) and  $C_{18}H_{20}O_3NI$  (Ib). It is remarkable, if true, that hydriodic acid ruptures the diphenyl oxide linkage of I and leaves intact methoxyl groups. Pallares and Garza did not report the melting points of the above degradation products, and both specimens were identified only on the basis of their melting points, no mixed melting points with authentic samples being reported.

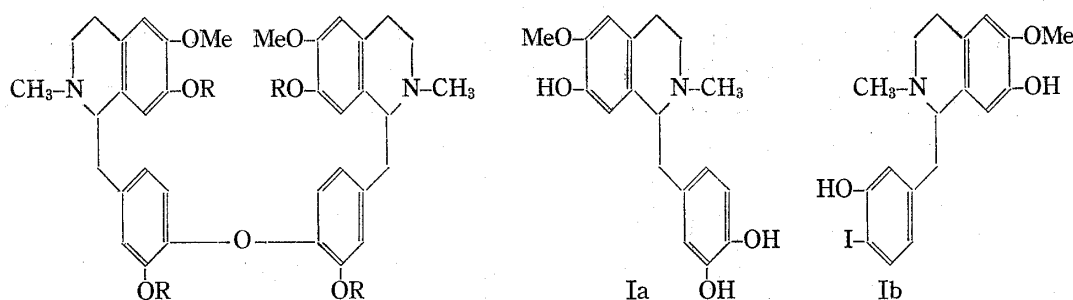


Chart 1

The purpose of the present investigation was to study the cyclization of the diamide (XIV) in order to obtain the corresponding dihydroisoquinoline derivative (XV) and its dimethiodide (XVI) as possible intermediates for the synthesis of stereoisomeric mixture of so-called aztequine, and to compare our synthetic sample with natural product from the point of physical characters. Furthermore, the cleavage reaction of biphenyl ether (V) with hydriodic acid according to Remick's procedure<sup>5)</sup> was carried out, in order to recognize whether the cleavage would occur as their report and to establish the structure of so-called aztequine.

At first, the treatment of 3,3'-dimethoxy-4,4'-oxybenzoic acid (V) with 57% and 30% hydriodic acid at atmospheric pressure or with the above hydriodic acid in a sealed tube yielded neither vanillic acid nor 4-iodo-3-methoxybenzoic acid, by the result of which the demethylated product (VI) was obtained in case of 57% hydriodic acid and a starting material

1) Part III: *Yakugaku Zasshi*, **87**, 753 (1967).

2) Part CCXXIX: *Chem. Pharm. Bull.* (Tokyo), **16**, 773 (1968).

3) Location: a) *Kita-4-bancho, Sendai*, b) *Kashiwagi-4-chome, Shinjuku-ku, Tokyo*.

4) E.S. Pallares and E.M. Garza, *Arch. Biochemistry*, **16**, 275 (1948).

5) A.E. Remick, *J. Org. Chem.*, **7**, 534 (1942).

was recovered in case of 30% hydriodic acid. Therefore, the formation of Ia and Ib as a result of the diphenyl ether cleavage could not be believed.

Secondly, an Ullmann reaction between methyl 4-bromo-3-methoxybenzoate and methyl vanillate gave the ether (IV), reduction of which with lithium aluminum hydride in tetrahydrofuran gave the alcohol (VII). This was converted by chlorination with thionyl chloride into the chloride (VIII), whose treatment with sodium cyanide and sodium iodide in methyl ethyl ketone afforded the dinitrile (IX). Hydrolysis of IX with 50% potassium hydroxide gave the homoacid (X), demethylation of which with a mixture of hydrobromic and hydriodic acid in glacial acetic acid gave the demethylated acid (XI). Esterification of XI, followed by benzylation, afforded bis(2-benzyloxy-4-methoxycarbonylphenyl) ether (XIII).

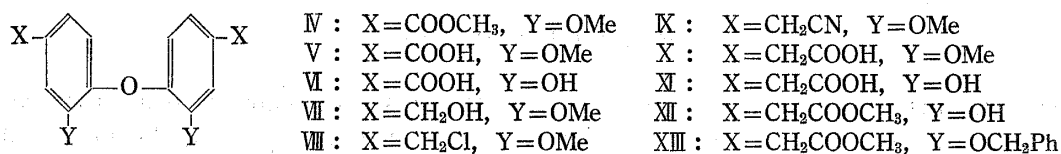


Chart 2

Condensation of XIII with 4-benzyloxy-3-methoxyphenethylamine by heating gave the diamide (XIV), whose cyclization with phosphoryl chloride as usual afforded the 3,4-dihydroisoquinoline derivative (XV). This was characterized as its dipicrate. IR spectrum of this compound (XV) showed no carbonyl absorption and was closely similar to that of the diamide obtained in case of the synthesis of so-called O-tetramethylaztequine (II)<sup>6</sup>. Reduction with sodium borohydride of the resultant dimethiodide (XVI), which was obtained by methylation of the base (XV), gave 1,2,3,4-tetrahydroisoquinoline derivative (III).

Finally, debenylation of III with ethanol-hydrochloric acid (1:1) afforded a stereoisomeric mixture of so-called aztequine (I) as its hydrochloride. An attempt to separate its free base under various conditions was examined, but was unsuccessful because of easy solubility in water and insolubility in almost all the organic solvents.

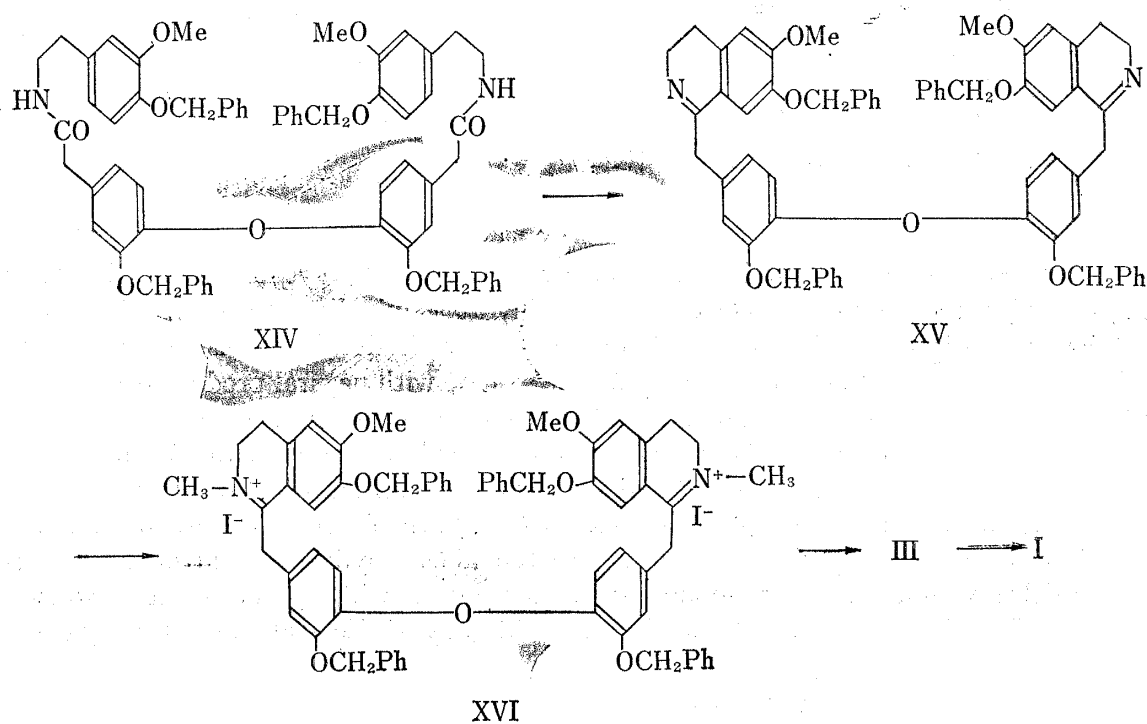


Chart 3

<sup>6</sup>) T. Kametani, M. Ro, and Y. Iwabuchi, *Yakugaku Zasshi*, **85**, 355 (1965).

The natural aztequine was not available for comparison, but the difference between natural and synthetic sample was so remarkable from the point of physical data that further work would be necessary in order to establish the structure of aztequine.

### Experimental<sup>7)</sup>

**Cleavage Reaction of Bis(4-carboxy-2-methoxyphenyl) Ether (V) with 57% HI aq. Solution [The Formation of Bis(4-carboxyphenyl-2-hydroxyphenyl) Ether (VI)]**—A suspension of 0.5 g of the ether<sup>6,8)</sup> (V) and 10 ml of 57% HI aq. solution was refluxed in a current of N<sub>2</sub> for 6 hr and evaporation of the reaction mixture gave 0.5 g of crude crystals, mp 255—260°. Recrystallization from ether gave 0.45 g of VI as colorless needles, mp 276—278°. *Anal.* Calcd. for C<sub>14</sub>H<sub>10</sub>O<sub>7</sub>: C, 57.94; H, 3.47. Found: C, 57.91; H, 3.62. IR cm<sup>-1</sup>:  $\nu_{\text{OH}}^{\text{KBr}}$  3395,  $\nu_{\text{C=O}}^{\text{KBr}}$  1708, 1695. Although this reaction was held in a sealed tube, almost the same results were given.

**Treatment of V with 30% HI aq. Solution**—A mixture of 0.5 g of V and 12 g of 30% HI aq. solution was refluxed in a current of N<sub>2</sub> for 6 hr. After the reaction an insoluble substance was collected by filtration, and recrystallization of the precipitate from dilute EtOH recovered 0.5 g of the starting material (V) as colorless needles, mp 254—255°. In this case, evaporation of the above filtrate gave no demethylated product (VI). Even if this reaction was also done in a sealed tube the same starting material as above was recovered.

**Bis(2-methoxy-4-methoxycarbonylphenyl) Ether (IV)**—A mixture of 36 g of methyl 4-bromo-3-methoxybenzoate, 45 g of methyl vanillate, 24 g of anhydrous K<sub>2</sub>CO<sub>3</sub>, 12 g of Cu powder, and 2 drops of pyridine was fused in an oil-bath at 90°, and the mixture was then heated at 180° for 3 hr with stirring. After the reaction mixture had been extracted with benzene while warm, the benzene layer was washed with 10% NaOH aq. solution and water, dried on Na<sub>2</sub>SO<sub>4</sub> and evaporated to give a brown syrup, which was distilled *in vacuo* to afford the starting bromo-compound as an oil, bp 105—106° (2 mmHg). In the case of distillation a considerable amount of a viscous syrup remained as the residue. Recrystallization of the resultant residue from MeOH afforded 14 g of IV as colorless needles, mp 112°. *Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>7</sub>: C, 62.42; H, 5.24. Found C, 62.56; H, 5.43.

**Bis(4-hydroxymethyl-2-methoxyphenyl) Ether (VII)**—To a solution of 28 g of the above diester (IV) in 100 ml of tetrahydrofuran was added dropwise a suspension of 5 g of LiAlH<sub>4</sub> in 50 ml of dry tetrahydrofuran under cooling, and the mixture was refluxed on a water-bath for 3 hr. After the reaction, the excess LiAlH<sub>4</sub> was decomposed carefully with water and filtered. The filtrate was dried on Na<sub>2</sub>SO<sub>4</sub> and distilled to give a dark-violet syrup, which was solidified on being triturated with EtOAc. Filtration and recrystallization from EtOAc afforded 10 g of VII as colorless prisms, mp 108—109°. *Anal.* Calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>5</sub>: C, 66.19; H, 6.24. Found: C, 65.81; H, 6.19.

**Bis(4-chloromethyl-2-methoxyphenyl) Ether (VIII)**—To 70 ml of SOCl<sub>2</sub> was added gradually 14 g of the dialcohol (VII) under cooling. After the mixture had been allowed to stand overnight, 10 ml of dry benzene was added, and evaporation of the excess SOCl<sub>2</sub> and solvent gave a reddish-brown syrup, which solidified on being triturated with *n*-hexane. Recrystallization from benzene-*n*-hexane yielded 12.5 g of VIII as colorless needles, mp 98°. *Anal.* Calcd. for C<sub>16</sub>H<sub>16</sub>O<sub>3</sub>Cl<sub>2</sub>: C, 58.72; H, 4.93. Found: C, 58.76; H, 4.99.

**Bis(4-cyanomethyl-2-methoxyphenyl) Ether (IX)**—To a solution of 25 g of the preceding dichloride (VIII) in 600 ml of MeCOEt was added a mixture of 49.8 g of NaCN and 39.8 g of NaI, and the mixture was stirred under reflux for 10 hr. After the reaction, removal of the solvent afforded a syrup, which was mixed with 100 ml of water and extracted with EtOAc. The extract was washed with 5% HCl, 5% NaOH aq. solution and then water, dried over Na<sub>2</sub>SO<sub>4</sub>, and distilled to give a pale brown syrup, which solidified on being triturated with *n*-hexane. Collection by filtration and recrystallization from benzene-*n*-hexane afforded 13 g of IX as colorless needles, mp 142°. *Anal.* Calcd. for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub>: C, 70.11; H, 5.23; N, 9.09. Found: C, 70.36; H, 5.56; N, 8.91. IR cm<sup>-1</sup>:  $\nu_{\text{CN}}^{\text{KBr}}$  2268.

**Bis(4-carboxymethyl-2-methoxyphenyl) Ether (X)**—A mixture of 13 g of the dinitrile (IX), 52 g of KOH, 130 ml of dioxane, 230 ml of MeOH, and 52 ml of water was heated under reflux on a water-bath for 20 hr. After removal of the solvent the residue was dissolved in 100 ml of water, the solution of which was washed with CHCl<sub>3</sub>. The resultant aqueous solution was acidified with 10% HCl aq. solution and extracted with EtOAc. The solvent was again extracted with 5% NaHCO<sub>3</sub> aq. solution, which was acidified with 10% HCl aq. solution and extracted with EtOAc. The extract was washed with water, dried on Na<sub>2</sub>SO<sub>4</sub>, and distilled to give 11 g of a dark brown syrup. After purification by silica gel chromatography using CHCl<sub>3</sub> as solvent, recrystallization of the resultant crystals from CHCl<sub>3</sub>-benzene afforded 8 g of X as colorless needles, mp 124—125° (decomp.). *Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>7</sub> · ½C<sub>6</sub>H<sub>6</sub><sup>9)</sup>: C, 63.48; H, 5.33. Found: C, 63.67; H, 5.49. IR cm<sup>-1</sup>:  $\nu_{\text{C=O}}^{\text{KBr}}$  1712.

7) All melting points were not corrected.

8) M. Tomita, *Yakugaku Zasshi*, **70**, 53 (1950).

9) IR spectrum of this solvate showed the presence of benzene of crystallization at 680 cm<sup>-1</sup> (KBr).

**Bis(4-carboxymethyl-2-hydroxyphenyl) Ether (XI)**—A mixture of 7 g of the acid (X), 200 ml of AcOH, 20 g of HBr aq. solution (s.p. 1.48), and 4 g of HI solution (s.p. 1.7) was refluxed in an oil-bath at 140° for 6 hr. After removal of the solvent the residue was extracted with EtOAc. The extract was washed with saturated NaCl aq. solution, dried on Na<sub>2</sub>SO<sub>4</sub>, and distilled to give a dark brown syrup, which was solidified on being triturated with a small amount of water. Recrystallization from water afforded 4 g of XI as colorless needles, mp 174° (decomp.). *Anal.* Calcd. for C<sub>16</sub>H<sub>14</sub>O<sub>7</sub>·½H<sub>2</sub>O: C, 58.72; H, 4.69. Found: C, 59.12; H, 4.64.

**Bis(2-hydroxy-4-methoxycarbonylmethylphenyl) Ether (XII)**—A solution of 4 g of the above acid (XI) in 50 ml of MeOH was saturated with HCl gas, and the mixture was refluxed on a water-bath for 7 hr. After the solvent had been distilled off, the residue was mixed with 50 ml of water and extracted with CHCl<sub>3</sub>. The extract was washed with 5% NaHCO<sub>3</sub> and saturated NaCl aq. solution, dried on Na<sub>2</sub>SO<sub>4</sub>, and distilled to give 3.5 g of a pale brown syrup, whose recrystallization from benzene-*n*-hexane afforded 3.0 g of XII as colorless needles, mp 104–105°. *Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>7</sub>: C, 62.42; H, 5.24. Found: C, 62.36; H, 5.71. IR cm<sup>-1</sup>:  $\nu_{\text{C=O}}^{\text{KBr}}$  1700, 1720.

**Bis(2-benzyloxy-4-methoxycarbonylmethylphenyl) Ether (XIII)**—A mixture of 4 g of the above ester (XII), 10 ml of dimethylformamide, 3 g of benzyl chloride, and 3.1 g of K<sub>2</sub>CO<sub>3</sub> was refluxed for 2 hr, which was poured into 200 ml of water and extracted with benzene. The extract was washed with 5% NaOH aq. solution and water, dried on Na<sub>2</sub>SO<sub>4</sub>, and distilled to give 4.0 g of XIII as a pale brown syrup, which could not be crystallized by purification using various chromatography. IR cm<sup>-1</sup>:  $\nu_{\text{C=O}}^{\text{CHCl}_3}$  1730, 1740 (ester).

**Bis(2-benzyloxy-4-[N-(4-benzyloxy-3-methoxyphenethyl)aminocarbonylmethyl]phenyl) Ether (XIV)**—A mixture of 1 g of the diester (XIII) and 1.5 g of 4-benzyloxy-3-methoxyphenethylamine was heated in an oil-bath at 180° in a current of N<sub>2</sub> for 2.5 hr, and the reaction mixture was extracted with CHCl<sub>3</sub>. The extract was washed with 5% HCl and 5% NaOH aq. solution, dried on Na<sub>2</sub>SO<sub>4</sub>, and distilled to give a dark brown powder, whose recrystallization from EtOAc afforded 0.6 g of XIV as a pale grayish powder, mp 151–152°. *Anal.* Calcd. for C<sub>62</sub>H<sub>60</sub>O<sub>9</sub>N<sub>2</sub>: C, 76.26; H, 6.18; N, 2.86. Found: C, 76.23; H, 6.23; N, 3.06. IR cm<sup>-1</sup>:  $\nu_{\text{NH}}^{\text{KBr}}$  3280;  $\nu_{\text{C=O}}^{\text{KBr}}$  1645.

**2,2'-Dibenzyloxy-4,4'-bis(7-benzyloxy-6-methoxy-3,4-dihydro-1-isoquinolylmethyl)diphenyl Ether (XV)**—A mixture of 1.3 g of the diamide (XIV), 50 ml of abs. toluene, and 50 ml of POCl<sub>3</sub> was refluxed for 3 hr in a current of N<sub>2</sub>, and, after an excess of *n*-hexane had been added to the reaction mixture, it was allowed to stand overnight. The upper layer was removed by decantation and the residue was washed with *n*-hexane to give 1 g of a brown syrup, which could not be crystallized and therefore characterized as its dipicrate. Recrystallization of the dipicrate from MeOH gave a yellow powder, mp 119–122° (decomp.). *Anal.* Calcd. for C<sub>62</sub>H<sub>56</sub>O<sub>7</sub>N<sub>2</sub>·2C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub>: C, 63.52; H, 4.46. Found: C, 64.02; H, 4.21.

**2,2'-Dibenzyloxy-4,4'-bis(7-benzyloxy-6-methoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolylmethyl)diphenyl Ether (III)**—A mixture of 0.4 g of XV, 40 ml of acetone and 5 ml of MeI was refluxed mildly for 3 hr in a current of N<sub>2</sub>, and removal of the reagents gave 0.4 g of a reddish-brown syrup, which was dissolved in a mixture of 15 ml of MeOH and 15 ml of CHCl<sub>3</sub>. To the above solution was added portionwise 0.5 g of NaBH<sub>4</sub> at room temperature with stirring, and the mixture was then stirred for 1.5 hr after the addition. After removal of the solvent, a solution of the resultant residue in 50 ml of water was extracted with benzene. The extract was washed with water, dried on K<sub>2</sub>CO<sub>3</sub>, and distilled to give 0.3 g of III as a brown syrup, which was characterized as its perchlorate. Recrystallization from MeOH-ether afforded a pale brown powder, mp 145–148° (decomp.). *Anal.* Calcd. for C<sub>62</sub>H<sub>64</sub>O<sub>7</sub>N<sub>2</sub>·2HClO<sub>4</sub>·H<sub>2</sub>O: C, 64.47; H, 5.58. Found: C, 64.11; H, 5.52. IR cm<sup>-1</sup>:  $\nu_{\text{N-CH}_3}^{\text{KBr}}$  2895;  $\nu_{\text{OH}}^{\text{KBr}}$  3540 (water of crystallization).

**2,2'-Dihydroxy-4,4'-bis(7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolylmethyl)diphenyl Ether (I)**—A mixture of 0.4 g of the preceding compound (III), 15 ml of EtOH, and 15 ml of conc. HCl aq. solution was refluxed in a current of N<sub>2</sub> for 2 hr. Removal of the reagents afforded a brown syrup, which was washed with ether. On being triturated with *n*-hexane, it was solidified and collected by filtration. Recrystallization from EtOH-ether afforded 20 mg of I as a pale brown hygroscopic powder, mp 199–202° (decomp.). *Anal.* Calcd. for C<sub>36</sub>H<sub>40</sub>O<sub>7</sub>N<sub>2</sub>·2HCl·2H<sub>2</sub>O: C, 59.92; H, 6.42; N, 3.88. Found: C, 60.21; H, 5.92; N, 3.88. IR cm<sup>-1</sup>:  $\nu_{\text{N-CH}_3}^{\text{KBr}}$  2840;  $\nu_{\text{OH}}^{\text{KBr}}$  3540 (water of crystallization).

An aqueous solution of the above HCl salt was treated with an excess of NH<sub>4</sub>OH aq. solution and extracted with various organic solvents, but our expected free base (I) could not be obtained.

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