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99. Junji Koizumi,*1 Shigeru Kobayashi,*2 and Shojiro Uyeo*3 : Galanthamine Chemistry. V.*4 Formation of Hydroxyapogalanthamine from Galanthaminone and the Synthesis of its Trimethyl Ether.

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Galanthamine and its congeners, *viz.* lycoramine (dihydrogalanthamine),[1~3] epigalanthamine,[4,5] narwedine (galanthaminone)[5,6] etc. are frequently encountered in the bulbs of the amaryllidaceae and their structures have been the subject of investigations since the early date in the history of chemistry of the amaryllidaceae alkaloids.

Several years ago we[7~10] reported that the structure of apogalanthamine, a product obtained by treatment of galanthamine with hydrobromic acid, was represented by the formula (I) and that the alkaloid must consequently be assigned the structure of either (II; OH and C=C unsettled) or (III; OH and C=C unsettled) depending on the possibility of an acid-catalyzed dienone-phenol rearrangement during the above treatment. Structure (III) was originally favored for galanthamine based on our findings that galanthamine resisted dehydrogenation and also that oxolycoramine (lycoramine lactam[8]) afforded on attempted dehydrogenation over a palladium-carbon catalyst oxolycoraminone (lycoraminone lactam[8]) and deoxyoxolycoramine (both of these were apparently the products of disproportionation of the starting material). It was decided to prepare an apo-compound which retained all oxygen atoms of the molecule of galanthamine in order to put all our conclusions on a definitively experimental basis. This paper gives detailed account of the work*5 carried out along the lines of this project which led to the elucidation of the structure of galanthamine*6 as III.

As a starting material for our degradative studies we used galanthaminone obtained by oxidation of galanthamine with active manganese dioxide.*7 First it was treated

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*4 The papers in refs. 7~10 are regarded as earlier parts of this series.
*5 A preliminary report of this work excluding the synthesis of hydroxyapogalanthamine trimethyl ether, has already been presented. S. Uyeo, Handbook XVIth IUPAC Congress, Paris 1957, p. 207.
*6 It may be added here that Barton and Cohen independently and concurrently suggested the same structure (III) for galanthamine as that proposed by us. (D. H. R. Barton, T. Cohen : "Festschrift Arthur Stoll." Birkhäuser, Basle, 1957, p. 117).
*7 Although this oxidation procedure has first been published by Wildman, *et al.* (See ref. 5), Kobayashi and Uyeo independently and simultaneously used the same method of oxidizing galanthamine to galanthaminone (See Kobayashi's Dissertation, 1956).

1) H. Kondo, K. Tomimura, S. Ishiwata : J. Pharm. Soc. Japan, **52**, 433 (1932).
2) H. Kondo, S. Ishiwata, S. Okayama : *Ibid.*, **58**, 1 (1938).
3) S. Ishiwata : *Ibid.*, **58**, 13 (1938).
4) H. Kondo, S. Ishiwata, S. Okayama : *Ibid.*, **53**, 807 (1933).
5) H. M. Fales, L. D. Giuffrida, W. C. Wildman : J. Am. Chem. Soc, **78**, 4145 (1956).
6) H. G. Boit, W. Döpke, A. Beitner : Chem. Ber., **90**, 2197 (1957).
7) S. Uyeo, S. Kobayashi : This Bulletin, **1**, 139 (1953).
8) S. Uyeo, J. Koizumi : *Ibid.*, **1**, 203 (1953).
9) S. Kobayashi, T. Shingu, S. Uyeo : Chem. & Ind. (London), **1956**, 177.
10) S. Kobayashi, S. Uyeo : J. Chem. Soc., **1957**, 638.

with concentrated hydrobromic acid to give a product which was, however, O-demethylgalanthaminone as shown by its conversion with diazomethane to the starting material, no aromatization of the cyclohexane ring in this ketone being observed. Finally galanthaminone was refluxed with constant-boiling hydriodic acid in the presence of red phosphorus to give hydroxyapogalanthamine hydriodide, $C_{16}H_{17}O_3N \cdot HI$, whose ultraviolet spectrum differed from that of galanthaminone, and resembled that of apogalanthamine hydrobromide (Fig. 1). Methylation of hydroxyapogalanthamine with diazomethane gave an oily base, $C_{19}H_{23}O_3N$, which was characterized as its perchlorate, m.p. 163~165°. Exhaustive methylation of this base afforded a methine which on oxidation with potassium permanganate yielded a dibasic acid, $C_{17}H_{16}O_7$, m.p. 208~210°, which was shown to be identical in all respects with 5,5′,6-trimethoxy-2,2′-biphenyldicarboxylic acid (Ⅳ). Synthetic samples of this acid were prepared either by hydrogen peroxide oxidation of 3,4,6-trimethoxy-9,10-phenanthraquinone (Ⅴ) or by the Ullmann condensation of methyl 2-bromoveratrate (Ⅵ) with methyl 2-iodoanisate (Ⅶ) and subsequent hydrolysis.

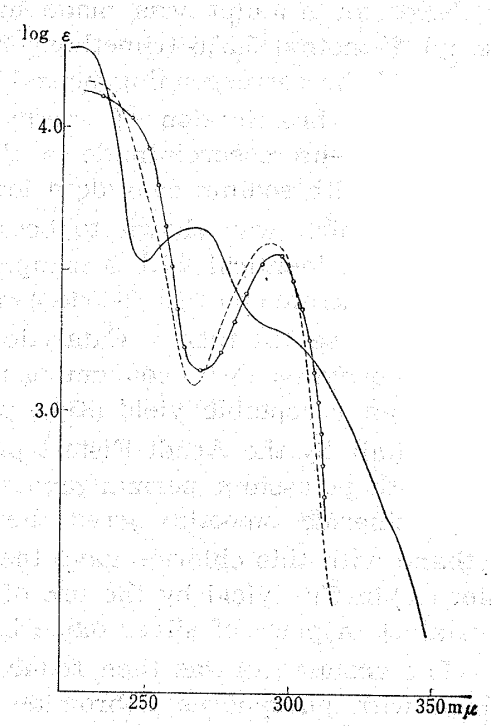


Fig. 1. Spectra of Hydroxyapogalanthamine·HI (-----), Apogalanthamine·HBr (-○-) and Galanthaminone (——) in 95% Ethanol

On the basis of these results, hydroxyapogalanthamine was formulated, in analogy with apogalanthamine (Ⅰ), as Ⅷ. Unambiguous confirmation of this structure has now been provided by the following synthesis of its trimethyl ether (Ⅸ).

The synthesis was accomplished using either the method which we had developed for the synthesis of apogalanthamine or the method involving the intermediate of a nitrostyrene. The key intermediate of the first route leading to the dibenzoazocine (Ⅸ) was dimethyl 5,5′,6′-trimethoxy-2,2′-biphenyldiacetate (Ⅹ). For the preparation of this compound (Ⅹ) a direct condensation of methyl 2-bromoveratrate (Ⅵ) and methyl-(2-iodo-4-methoxyphenyl)acetate (Ⅺ) by the Ullmann method was attempted without much success, the yield of the required product being very small. The low yield may have been due to the fact that the iodine atom is sterically hindered by the vicinal bulky group such as the acetate in methyl (2-iodo-4-methoxyphenyl)acetate (Ⅺ). Other unsuccessful experiments concerning the Ullmann condensation are to be found in the literature, *e.g.* attempted coupling of ethyl (2-iodophenyl)acetate with 2′-iodoacetophenone[11] or with ethyl 2′-iodo-2-biphenylcarboxylate.[12] An analogous instance was found in our previous experiment[13] where the condensation of 2′-iodo-4′-methoxyacetophenone (Ⅻ) and methyl 2-bromo- or 2-iodoveratrate in the presence of copper bronze proceeded in a very poor yield to give 2′-acetyl-5,5′,6-trimethoxy-2-biphenylcarboxylic acid (ⅩⅢ).

The difficulty of preparing ⅩⅢ in a sufficient amount precluded an application of Willgerodt reaction to this ketone for the preparation of the acetic acid (XIV).

11) W.S. Rapson, R.G. Schuttleworth: J. Chem. Soc., **1941**, 487.
12) R.G. Schuttleworth, W.S. Rapson, E.T. Stewart: *Ibid.*, **1944**, 71.
13) S. Kobayashi, C. Kuraishi: This Bulletin, **10**, 1137 (1962).

Next, an attempt was made unsuccessfully to convert the methyl side chain in methyl 2′-methyl-5,5′,6-trimethoxy-2-biphenylcarboxylate (XV) into an acetic acid (XIV) by way of the corresponding benzyl bromide and the benzyl cyanide. Thus the product obtained by bromination of methyl 2′-methyl-5,5′,6-trimethoxy-2-biphenylcarboxylate (XV) with N-bromosuccinimide in the presence of benzoyl peroxide gave on immediate treatment with sodium cyanide a low yield of an unexpected nitrogen-free compound, $C_{18}H_{18}O_6$, which was shown to be methyl 2′-formyl-5,5′,6-trimethoxy-2-biphenylcarboxylate (XVI), identical with a sample prepared by the Ullmann condensation of methyl 2-bromoveratrate (VI) with 2-iodo-4-methoxybenzaldehyde (XVII) in the presence of copper bronze in a sealed tube. Catalytic hydrogenation of the aldehyde (XVI) afforded the methyl derivative (XV), confirming the structure. Successful preparation of this aldehyde in an acceptable yield (35%) prompted us to lengthen the formyl chain by one carbon unit by the Arndt-Eistert procedure. For this purpose, the aldehyde was oxidized with potassium permanganate to an ester-acid (XVIII) which on treatment with oxalyl chloride smoothly gave the corresponding acid chloride. Reaction of diazomethane with this chloride gave the diazoketone which was transformed to the required ester (X) in 53% yield by the use of silver benzoate and triethylamine in methanol as a catalyst in place of silver oxide in methanol as employed usually.

The acetate (X) was then reduced with lithium aluminum hydride to the diol (XIX) which with phosphorus tribromide afforded the corresponding dibromide (XX). Cyclization of the dibromide to a nitrogen-containing eight-membered ring was accomplished by treatment with methylamine in a sealed tube, furnishing as the end product 6-methyl-1,2,11-trimethoxy-5,6,7,8-tetrahydrodibenz[*c*, *e*]azocine (IX). Identity of this synthetic product with O,O,O-trimethylhydroxyapogalanthamine was established by direct comparison of the respective styphnates and perchlorates.

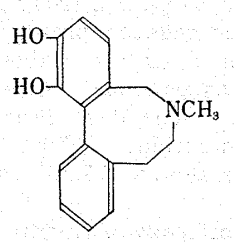
An alternative approach to the same compound (IX) has also been realized by the following sequence of reactions. The aldehyde-ester (XVI) was selected as a starting material also in this case and it was converted into the nitrostyrene (XXI) by treatment with nitromethane at 100° in the presence of ammonium acetate and acetic acid as condensing agents by the procedure used for the condensation of 2,4,6-trimethoxybenzaldehyde.[14]

A conventional condensing agent such as methanolic potassium hydroxide at low temparature was not useful with this aldehyde, since the starting material was recovered unchanged. When aniline[15] was substituted as the base a low yield of the required nitrostyrene (XXI) was obtained. The lithium aluminum hydride reduction of this nitrostyrene (XXI) in an ethereal solution gave an amino-alcohol (XXII), whose hydroxyl group was replaced by a bromine with phosphorus tribromide. Cyclization of the resulting amino-bromo-compound (XXIII) proceeded in methanolic potassium hydroxide, giving rise to the secondary amine (XXIV) which on methylation with formic acid and formaldehyde furnished the required tertiary amine (IX). Identity of this synthetic compound with the product obtained by an alternative route as mentioned above and hydroxyapogalanthamine trimethyl ether from natural sources was established by direct comparison of the corresponding salts. Thus the structure of hydroxyapogalanthamine has been conclusively clarified.

Since galanthaminone is an α,β-unsaturated ketone as pointed out by Fales, Giuffrida and Wildman[5] and still contains an active methylene adjacent to the ketonic function as shown by its positive Zimmermann test and the formation of a crystalline

14) J. Harley-Mason : J. Chem. Soc., **1953**, 200.
15) O. Schales, H. Graefe : J. Am. Chem. Soc., **74**, 4486 (1952).

piperonylidene derivative, there is no doubt that hydroxyapogalanthamine is the product of a dienone–phenol rearrangement and accordingly galanthamine is correctly represented by the formulation (Ⅲ). A structure such as Ⅱ which can be deduced straightforwardly from the structure of hydroxyapogalanthamine is to be rejected, since its equivalent ketone would contain no active methylene. Such a rearrangement as those of galanthamine and galanthaminone to apogalanthamine and hydroxyapogalanthamine, respectively, has a precedent in the rearrangement of Pummerer's ketone (XXV) to 2,5′–dihydroxy–2′,5–dimethylbiphenyl (XXVI) with acid.[16,17]



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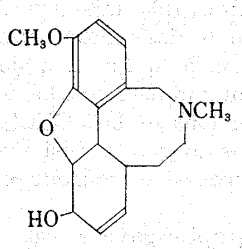

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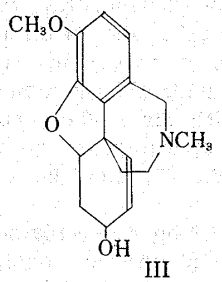

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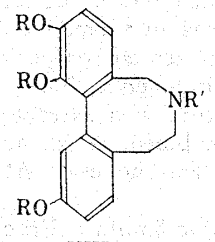
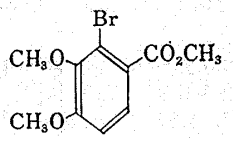
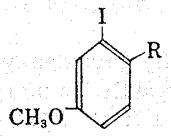


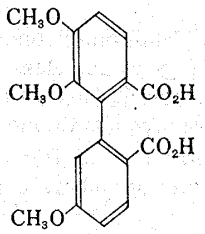
VIII : R=H; R′=CH_3
IX : R=CH_3; R′=CH_3
XXIV : R=CH_3; R′=H



VI



VII : R=CO_2CH_3
XI : R=$CH_2CO_2CH_3$
XII : R=$COCH_3$
XVII : R=CHO



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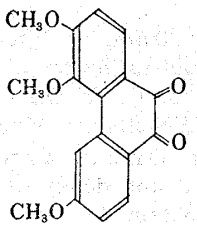
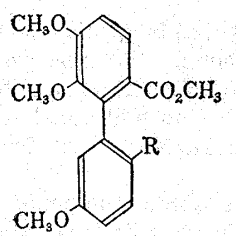
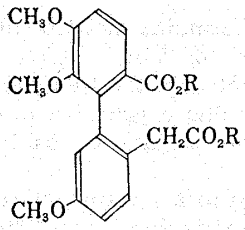
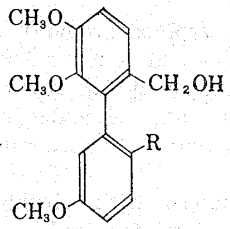
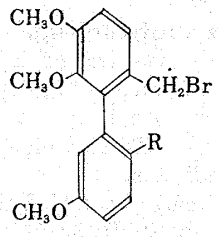


V







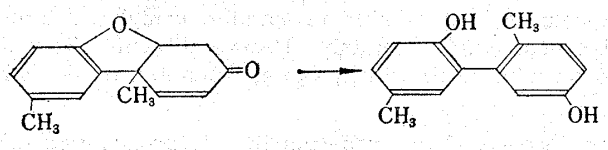


XIII : R=$COCH_3$
XV : R=CH_3
XVI : R=CHO
XVIII : R=CO_2H
XXI : R=CH=$CHNO_2$

X : R=CH_3
XIV : R=H

XIX : R=CH_2CH_2OH
XXII : R=$CH_2CH_2NH_2$

XX : R=CH_2CH_2Br
XXIII : R=$CH_2CH_2NH_2$



XXV XXVI

16) R. Pummerer, H. Puttfarcken, P. Schopflocher : Ber., **58**, 1808 (1925).
17) D. H. R. Barton, A. M. Deflorin, O. E. Edwards : J. Chem. Soc., **1956**, 530.

With the establishment of the structure of galanthamine, it has now become obvious that lycoramine is to be formulated as III (no olefinic double bond) since it is the hydrogenation product of galanthamine.*8 Epigalanthamine (base IX of Kondo)[4,5] is the epimer of galanthamine with respect to the configuration of the hydroxyl group.

Experimental

Dehydrogenation of Oxolycoramine——The following general procedure was employed for the dehydrogenation of oxolycoramine.

Oxolycoramine (lycoramine lactam[8]) (200 mg.) was thoroughly mixed with 30% Pd-C (200 mg.). The mixture was placed in a small Pyrex tube and dried in a desiccator under reduced pressure. The mixture was then heated for periods of time varying from 5 to 6 min. under a dry N_2 atmosphere in a metal-bath maintained at $300\pm5°$. During the reaction an amine-like odor was generated. After cooling, the reaction mixture was extracted with three 10 ml. portions of hot $CHCl_3$. The dark brown $CHCl_3$ extracts were combined, dried, and evaporated to dryness to give a resinous residue, which was chromatographed in benzene over Al_2O_3 (2.5 g.), and the successive benzene eluates of 15 ml. each were evaporated.

a) Reaction for 5 min. : Fraction (1) on rechromatography gave a trace of deoxyoxolycoramine, m.p. 135~140° (*vide infra.*). Fractions (2~5) afforded oxolycoraminone (lycoraminone lactam[8]) (95 mg.) as colorless prisms, m.p. 215~219°, after recrystallization from EtOH. The melting point was undepressed on admixture with a sample obtained by oxidation of oxolycoramine either by the Oppenauer method or with CrO_3-pyridine complex. Further elution with AcOEt (10 ml.) gave a small amount of additional oxolycoraminone.

b) Reaction for 20 min. : Fractions (3~5) on chromatography gave deoxyoxolycoramine (20 mg.), m.p. 135~148°. Recrystallization from EtOH gave colorless fine crystals, m.p. 148~150°. UV λ_{max}^{EtOH} mμ (log ε) : 260 (4.05), 297 (3.71). *Anal.* Calcd. for $C_{17}H_{21}O_3N$: C, 71.08; H, 7.31; N, 4.87. Found : C, 71.05; H, 7.07; N, 5.06. Fraction (8) yielded oxolycoraminone (50 mg.) m.p. 216~218°.

c) Reaction for 30 min. : Chromatography of the reaction product gave a small amount of Et_2O-soluble oily material and deoxyoxolycoramine (50 mg.), m.p. 148~150°. A negligible amount to oxolycoraminone was also obtained.

d) Reaction for 60 min. : The reaction product obtained from the $CHCl_3$ extracts was washed with Et_2O. Then this was chromatographed to yield deoxyoxolycoramine (15 mg.), m.p. 142~147°. Chromatography of the foregoing Et_2O washings over Al_2O_3 gave non-basic oily material, which distilled at 120~130° (0.02 mm.). Attempts to crystallize this material were unsuccessful, and this was not subjected to further investigation.

Demethyldeoxyoxolycoramine——Oxolycoramine (lycoramine lactam) (100 mg.) in glacial AcOH (3 ml.) saturated with HBr was heated in a sealed tube at 100° for 3 hr. After cooling, the tube was opened and the crystals, m.p. 234~235° (decomp.), which separated in the tube were collected on a filter. The filtrate was diluted with H_2O and concentrated under reduced pressure to give an additional crop of the crystalline product. Total yield, 100 mg. This compound gave a positive Beilstein test for halogen and a positive $FeCl_3$ test.

20% NaOH (7 ml.) was added dropwise with stirring to a mixture of this bromo-compound (100 mg.) and Zn dust (5 g.) in EtOH (30 ml.), and stirred under reflux for 1 hr. The excess Zn dust was filtered off and washed with hot EtOH. The filtrate and washings were combined and concentrated to about 10 ml., diluted with H_2O (10 ml.) and adjusted to pH 8.0 by passing CO_2 gas into the solution. Extraction of the aqueous solution with $CHCl_3$ and evaporation of the dried $CHCl_3$ extracts gave a white solid, m.p. 260~262°, which was recrystallized from EtOH to give demethyldeoxyoxolycoramine as colorless fine crystals, m.p. 265~266.5°. *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.32; H, 6.95; N, 5.12. Found : C, 70.23; H, 6.96; N, 5.08.

Deoxyoxolycoramine——To the foregoing demethyldeoxyoxolycoramine in MeOH was added an excess of Et_2O-CH_2N_2. The solution was allowed to stand overnight at room temperature and the solvents were evaporated to give deoxyoxolycoramine. Recrystallization from EtOH gave colorless crystals, m.p. 148~150°, undepressed on admixture with a sample obtained by dehydrogenation of oxolycoramine with

*8 In a previous paper (See ref. 7) we reported that hydrogenation of galanthamine over Pd-C gave, together with an overwhelming amount of lycoramine, a small yield of an oily isomer with somewhat higher optical rotation than those of lycoramine and galanthamine. Reinvestigation of this experiment has shown that this was due to a small amount of epigalanthamine in the sample of galanthamine which was used by us. Pure sample of galanthamine gives a quantitative yield of lycoramine upon catalytic hydrogenation.

Pd-C. This compound was also identical with a sample prepared by methylation of demethyldeoxyoxolycoramine with MeI and EtOH-KOH. *Anal.* Calcd. for $C_{17}H_{21}O_3N$: C, 71.08; H, 7.31; N, 4.87. Found : C, 71.08; H, 7.07; N, 5.06.

Manganese Dioxide Oxidation of Galanthamine——A mixture of galanthamine (0.2 g.) and MnO_2 (2 g.) prepared by the procedure described by Attenburrow, *et al.*[18] in $CHCl_3$ (10 ml.) was stirred at room temperature for 70 hr. After removing the MnO_2 by filtration and washing the dioxide with $CHCl_3$, the filtrate and washings were combined and concentrated to dryness. The oily residue (0.18 g.) was chromatographed in benzene on Al_2O_3. Elution with benzene gave galanthaminone (0.11 g.) as prisms, m.p. 187~188°, from MeOH. *Anal.* Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91. Found : C, 71.31; H, 6.72; N, 4.83.

Reaction of Galanthaminone with Hydrobromic Acid——Galanthaminone (100 mg.) in 46% HBr (3 ml.) was heated in a sealed tube at 100° for 5 hr. After cooling, H_2O (5 ml.) was added and the solution was concentrated to dryness under reduced pressure. The residue was taken up in H_2O (5 ml.) which was neutralized with 10% Na_2CO_3. The precipitate which formed was collected by filtration, washed with H_2O and then dried to give demethylgalanthaminone. Yield, 70 mg. This product gave a positive $FeCl_3$ test. UV : λ_{max}^{EtOH} 268 mμ (log ε 3.70).

This compound was dissolved in MeOH and treated with an excess of Et_2O-CH_2N_2. The solution was allowed to stand overnight at room temperature and the solvent was evaporated. Crystallization of the residue from EtOH gave galanthaminone as colorless prisms, m.p. and mixed m.p. 186~188°.

The methiodide of this compound, m.p. 210~213°, was shown to be identical with an authentic sample of galanthaminone methiodide by a mixed melting point determination.

Degradation of Galanthaminone with Hydriodic Acid——HI, b.p. 127° (15 ml.), was refluxed in the presence of red P (200 mg.) for 10 min. under CO_2 and a solution of galanthaminone (600 mg.) in glacial AcOH (5 ml.) was added. The mixture was refluxed under CO_2 in an oil bath for 40 min. and diluted with H_2O (40 ml.). The red P was filtered off and washed with small amounts of warm H_2O, and combined filtrate and washings were evaporated to dryness under reduced pressure at 60~65°. The resulting brown residue was dissolved in a small amount of abs. EtOH or Me_2CO and the solution was kept in a refrigerator. The precipitated pale yellow needles were collected by filtration and dried. Recrystallization from abs. EtOH containing a few drops of HI gave hydroxyapogalanthamine · HI (250 mg.) as colorless needles, m.p. 263~265° (decomp.). This compound gave a positive $FeCl_3$ test. UV : λ_{max}^{EtOH} 294 mμ (log ε 3.60). *Anal.* Calcd. for $C_{16}H_{17}O_3N \cdot HI$: C, 48.12; H, 4.51; N, 3.50. Found : C, 48.32; H, 4.80; N, 3.48.

Methylation of Hydroxyapogalanthamine——A solution of hydroxyapogalanthamine·HI (300 mg.) in H_2O (20 ml.) was adjusted to pH 7.8~8.0 by the addition of 10% Na_2CO_3. The light purple precipitate which formed was collected, washed with H_2O and dried over P_2O_5. A mixture of this compound, MeOH (20 ml.) and a large excess of Et_2O-CH_2N_2 was allowed to stand at room temperature for 2 days, during which period all the solid went into solution. The solvent was evaporated and the residue was taken into 5% HCl (20 ml.). After the insoluble material was removed, the filtrate was made alkaline with 10% NaOH and extracted with Et_2O, which was dried over K_2CO_3, and evaporated to dryness leaving oily material (200 mg.). This was dissolved in a small amount of MeOH, and acidified with 10% $HClO_4$, scratched and allowed to stand at room temperature. The precipitated perchlorate was recrystallized from abs. EtOH to give trimethylhydroxyapogalanthamine perchlorate as colorless needles, m.p. 163~165°. *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot HClO_4$: C, 55.13; H, 5.84; N, 3.38. Found : C, 54.98; H, 6.01; N, 3.29.

The perchlorate was treated with caustic alkali, and the resulting free base in MeOH was heated under reflux with an excess of MeI on a water bath for 1 hr. The mixture was evaporated and the residue crystallized from MeOH-Et_2O to give trimethylhydroxyapogalanthamine methiodide as pale yellow crystals, m.p. 232~235° (decomp.). *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot CH_3I$: C, 52.87; H, 5.76; N, 3.08; OCH_3, 20.47. Found : C, 52.99; H, 5.48; N, 3.26; OCH_3, 20.24.

Hofmann Degradation of Trimethylhydroxyapogalanthamine Methiodide and Potassium Permanganate Oxidation of the Product——A solution of the above methiodide (150 mg.) in H_2O (20 ml.) was stirred with Ag_2O (700 mg.) at room temperature for 1 hr. The inorganic material was filtered off and washed with several portions of H_2O. The combined filtrate and washing were evaporated to dryness under reduced pressure and heated at 100° for 3 hr. The resulting viscous oil was taken up in $CHCl_3$. The solution was filtered, dried, and evaporated to dryness to give a light brown viscous oil (90 mg.).

To a stirred mixture of this oil in benzene (15 ml.) and H_2O (25 ml.) was added in portions powdered $KMnO_4$ (300 mg.) and stirring was continued at 80° for 3 hr. and then at 95° for a further 2 hr., and finally the excess oxidant was destroyed by the addition of EtOH. After filtration of the mixture and

18) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, T. Walker : J. Chem. Soc., **1952**, 1094.

evaporation of the filtrate under reduced pressure, the residue was dissolved in H_2O (15 ml.). The solution was washed with Et_2O, acidified with 10% HCl and then extracted with several portions of Et_2O. Evaporation of the dried Et_2O extracts gave a pale yellow oil (40 mg.), which crystallized on trituration with AcOEt. The product melting at 200~204° was recrystallized 3 times from AcOEt to give the oxidation product as colorless prisms, m.p. 208~210°. *Anal.* Calcd. for $C_{17}H_{16}O_7$: C, 61.44; H, 4.85. Found: C, 61.28; H, 4.96. It was identical in all respects with synthetic 5,5',6-trimethoxy-2,2'-biphenyldicarboxylic acid.

5,5',6-Trimethoxy-2,2'-biphenyldicarboxylic Acid (IV)——1) The following method of preparation of the acid (IV) is similar to the procedure of Goto and Arai.[19]

A solution of 3,4,6-trimethoxy-9,10-phenanthraquinone (V) (100 mg.) in glacial AcOH (1.2 ml.) was heated with 30% H_2O_2 (25 mg.) on a water bath. After 30 min., the same quantities of 30% H_2O_2 and glacial AcOH as above were added and heating was continued for a further 15 min. After dilution with H_2O (5 ml.), the solvents were removed under reduced pressure, the red-brown oily residue was taken up in 5% Na_2CO_3 and the insoluble material was filtered off. The filtrate was washed with $CHCl_3$, acidified with HCl and extracted with $CHCl_3$. The extracts were dried and evaporated to give a pale yellow solid. Repeated recrystallization from AcOEt afforded 5,5',6-trimethoxy-2,2'-biphenyldicarboxylic acid (30 mg.), m.p. 210~212° (reported[19] m.p. 214°). *Anal.* Calcd. for $C_{17}H_{16}O_7$: C, 61.44; H, 4.85. Found: C, 61.25; H, 4.93.

2) A mixture of methyl 2-bromoveratrate (3 g.), methyl 2-iodoanisate (2.5 g.) and Cu powder (3 g.) was heated in a sealed tube in an oil bath at 220~230° for 3 hr. After cooling the reaction mixture was taken up in $CHCl_3$ and the solution was filtered, and evaporated to dryness to give a brown oil which crystallized on trituration with Et_2O. The white crystals, m.p. 138~140°, were collected by filtration and identified with dimethyl 5,5',6,6'-tetramethoxy-2,2'-biphenyldicarboxylate. The filtrate was concentrated and the residue distilled under reduced pressure. The first fraction boiling at 150~160° (bath-temp.) (0.02 mm.) was saponified to give 5,5'-dimethoxy-2,2'-biphenyldicarboxylic acid (0.4 g.), m.p. 176~178°, after recrystallization from AcOEt. Saponification of the second fraction boiling at 170~180° (bath-temp.) (0.02 mm.) yielded 5,5',6-trimethoxy-2,2'-biphenyldicarboxylic acid, m.p. 210~212°. Recrystallization from AcOEt gave an analytical sample, m.p. 212~213°. *Anal.* Calcd. for $C_{17}H_{16}O_7$: C, 61.44; H, 4.85. Found: C, 61.29; H, 4.95. This compound was identical in all respects with a sample prepared by H_2O_2 oxidation of V.

Piperonylidene Galanthaminone——To a solution of galanthaminone (100 mg.) and piperonal (125 mg.) in abs. EtOH (3.5 ml.) was added an ethanolic solution of EtONa (2.5 ml.) prepared from Na (80 mg.) and EtOH (2 ml.). The mixture was allowed to stand at room temperature overnight. The precipitate was collected, washed with a small amount af EtOH and H_2O and dried. Recrystallization from Me_2CO-MeOH gave piperonylidene derivative of galanthaminone as yellow fine crystals, m.p. 252~254° (decomp.). UV λ_{max}^{EtOH} mμ (log ε): 263 (3.89), 360 (3.64). *Anal.* Calcd. for $C_{25}H_{23}O_5N \cdot \frac{1}{2}H_2O$: C, 70.40; H, 5.62; N, 3.28. Found: C, 70.36; H, 5.66; N, 3.14.

2-Amino-4-methoxybenzoic Acid——2-Nitro-4-methoxybenzoic acid (5 g.) was catalytically hydrogenated in EtOH (100 ml.) in the presence of 6% Pd-C (2 g.) at room temperature. A work up in the usual way gave the amino acid (3.5 g.) which crystallized from EtOH as prisms, m.p. 173~175° (decomp.) (reported[20] m.p. 180~181°). *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.45; H, 5.22; N, 8.60,

2-Iodo-4-methoxybenzoic Acid——The foregoing amino acid (4 g.) in 9% H_2SO_4 (60 g.) was heated to 80° to effect dissolution, then rapidly cooled to 0°, and diazotized with stirring by adding $NaNO_2$ (1.7 g.) in H_2O (5 ml.). Stirring was continued for 30 min. and the diazonium salt was decomposed after addition of KI (6 g.) in H_2O (10 ml.) by gradual heating to 40° over a period of 4 hr. The mixture was extracted with Et_2O, and the ethereal solution was shaken with 5% NaOH. The aqueous layer was acidified with dil. HCl and extracted with Et_2O. Evaporation of the solvent left crystals (6 g.) which were recrystallized from benzene and from Et_2O to give 2-iodo-4-methoxybenzoic acid (4.1 g.) as white prisms, m.p. 181~183° (reported m.p. 184°[21] and 181~183°[22]). *Anal.* Calcd. for $C_8H_7O_3I$: C, 34.55; H, 2.54. Found: C, 34.39; H, 2.55.

When the neutral ethereal solution, from which 2-iodo-4-methoxybenzoic acid had been extracted with NaOH as mentioned above, was evaporated, and the residue distilled under vacuum, there was obtained a liquid, $b.p_{14}$ 114°, which was shown to be *m*-iodoanisole. *Anal.* Calcd. for C_7H_7OI: C, 35.92; H, 3.01. Found: C, 35.62; H, 2.98. The dibromo derivative, m.p. 113~115°, prepared by treatment of the oil with bromine in AcOH, was identical with a product of bromination of *m*-iodoanisole. *Anal.* Calcd. for $C_7H_5OBr_2I$: C, 21.46; H, 1.29. Found: C, 21.67; H, 1.36.

19) K. Goto, T. Arai: Bull. Chem. Soc. Japan, **18**, 248, (1943).
20) J. M. L. Stephen, I. M. Tonkin, J. Walker: J. Chem. Soc., **1947**, 1034.
21) H. Hodgson, T. A. Jenkinson: *Ibid.*, **1927**, 3041.
22) S. Kobayashi, S. Tagawa, S. Nakajima: This Bulletin, **11**, 123 (1963).

The formation of *m*-iodoanisole in this reaction is probably due to the ease with which 2-amino-4-methoxybenzoic acid is decarboxylated by heating in acids. It was confirmed that 2-amino-4-methoxybenzoic acid (0.1 g.) in 10% H_2SO_4 (0.5 ml.) was readily decarboxylated upon heating at 100° for 30 min. to give *m*-methoxyaniline, characterized as its picrate, m.p. and mixed m.p. 171~171.5° (from MeOH). *Anal.* Calcd. for $C_{13}H_{12}O_8N_4$: C, 44.32; H, 3.43; N, 15.91. Found : C, 44.57; H, 3.85; N, 15.72.

2-Iodo-4-methoxyphenylacetic Acid and its Methyl Ester (XI)——To a solution of 2-iodo-4-methoxybenzoic acid (2.9 g.) in dry Et_2O (150 ml.), were added $SOCl_2$ (12 ml.) and pyridine (0.8 ml.) and the whole was heated at 50° for 2 hr., and at 58° for an additional 10 min. Pyridine·HCl which precipitated was removed by filtration and the filtrate evaporated to dryness. Benzene (20 ml.) was added to the residue and again evaporated. The resulting acid chloride in Et_2O (120 ml.) was added to an ethereal solution of CH_2N_2 (prepared from nitrosomethylurea (15 g.)) with ice-cooling and the solution was kept at room temperature overnight. Evaporation of the Et_2O gave 2-iodo-4-methoxy-2′-diazoacetophenone as yellow needles (2 g.), m.p. 67~68.5° (decomp.), after two crystallizations from Et_2O. *Anal.* Calcd. for $C_9H_7O_2N_2I$: C, 35.74; H, 2.33; N, 9.27. Found : C, 36.21; H, 2.58; N, 9.06.

The diazo ketone (0.55 g.) in dry MeOH (120 ml.) was added dropwise to BzOAg (1 g.) in Et_3N (8 g.) at room temperature and the whole was stirred at that temperature for 2 hr., then heated to 80° for 30 min. and refluxed for 15 min. after the addition of charcoal (0.5 g.). The mixture was filtered, the filtrate concentrated to dryness and the residue taken up in Et_2O. The Et_2O was washed with 2% Na_2CO_3, dried and evaporated. The residue was dissolved in 15% EtOH-KOH (50 ml.), and heated under reflux for 2 hr. After the saponification had been completed, H_2O was added and the aqueous solution was washed with Et_2O, acidified with HCl, and extracted again with Et_2O. Evaporation of the latter extract and crystallization of the residue from benzene gave 2-iodo-4-methoxyphenylacetic acid (0.4 g.) as cubes, m.p. 112~114°. *Anal.* Calcd. for $C_9H_9O_3I$: C, 37.02; H, 3.11. Found : C, 36.89; H, 3.24.

The methyl ester (7.45 g.) was obtained by refluxing the acid (10 g.) in MeOH (800 ml.) and H_2SO_4 (40 ml.) for 6 hr. and had $b.p_{0.2}$ 130~132°.

Methyl 2′-Formyl-5,5′,6-trimethoxy-2-biphenylcarboxylate (XVI)——Methyl 2-bromoveratrate (VI) (9 g.), 2-iodo-4-methoxybenzaldehyde (XVII) (12 g.), and Cu bronze (15 g.) were heated in a sealed tube at 210° for 4.5 hr. The mixture was taken up in $CHCl_3$, which on concentration gave a residue. Extraction of this residue with Et_2O and evaporation of the solvent left an orange oil (13.3 g.), which on trituration with Et_2O solidified. This was fractionally crystallized from MeOH to give three crystalline fractions : First fraction which crystallized on concentration of the MeOH gave dimethyl 5,5′,6,6′-tetramethoxy-2,2′-biphenyldicarboxylate (0.7 g.), m.p. and mixed m.p. 140~143° (from MeOH). Further concentration of the mother-liquors yielded second fraction which on crystallization from MeOH formed prisms (3.1 g.) of methyl 2′-formyl-5,5′,6-trimethoxy-2-biphenylcarboxylate (XVI), m.p. 104~106°. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found : C, 65.20; H, 5.62. The third fraction was obtained on evaporation of the mother-liquors from the second fraction and it gave 5,5′-dimethoxy-2,2′-biphenyldicarboxaldehyde (0.7 g.), m.p. 100~102°, from MeOH. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found : C, 70.77; H, 5.05. The dialdehyde was identical with a product prepared by heating 2-iodo-4-methoxybenzaldehyde with Cu bronze at 200°. The ester (XVI) gave on hydrolysis in boiling 6% EtOH-$Ba(OH)_2$ for 1 hr. the corresponding acid which formed prisms, m.p. 149~151°, after chromatography on acid-washed Al_2O_3 and crystallization from Et_2O. *Anal.* Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found : C, 64.22; H, 4.84. Hydrogenation of the ester (XVI) (75 mg.) in AcOH (20 ml.) over 10% Pd-C (0.5 g.) gave methyl 2′-methyl-5,5′,6-trimethoxy-2-biphenylcarboxylate which on purification by passing through a column of Al_2O_3 in benzene and crystallization from Et_2O formed cubes, m.p. 97~99.5°. This ester was identical with a sample of the same compound obtained below.

Methyl 2′-Methyl-5,5′,6-trimethoxy-2-biphenylcarboxylate (XV)——Methyl 2-bromoveratrate (VI) (4 g.), 2-iodo-4-methoxytoluene (7.5 g.), and Cu bronze (6.3 g.) were heated in a sealed tube at 210° for 4 hr. The mixture was extracted with $CHCl_3$, the $CHCl_3$ solution evaporated, and the residue extracted with Et_2O. The ethereal solution was concentrated to give dimethyl 5,5′,6,6′-tetramethoxy-2,2′-biphenyldicarboxylate (0.46 g.) which was filtered off, and had m.p. and mixed m.p. 142~144°. The mother-liquors from the diester gave on concentration dimethyl-2′-methyl-5,5′,6-trimethoxy-2-biphenylcarboxylate (XV) (1.18 g.), m.p. 92~98°. The filtrate was distilled under vacuum and a fraction (0.74 g.), $b.p_{0.03}$ 29~140° was collected. On standing this fraction gave an additional crop (0.34 g). of the ester (XV), m.p. 93~99°. The combined ester (1.52 g.) was recrystallized from Et_2O to form rhombs, m.p. 100~101.5°. *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found : C, 68.27; H, 6.47.

The ester (XV) (0.1 g.) was hydrolyzed by refluxing in 15% EtOH-KOH (20 ml.) for 2 hr. and worked up in the usual way, yielding 70 mg. of the corresponding acid as prisms, m.p. 139~141° (from Et_2O). *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found : C, 67.05; H, 5.65.

A mixture of the ester (XV) (0.3 g.), N-bromosuccinimide (0.35 g.), and benzoyl peroxide (20 mg.) in CCl_4 (20 ml.) was refluxed for 30 min. After removal of the solvent and succinimide the resulting oily residue was heated with KCN (0.19 g.) in EtOH (20 ml.) for 3.5 hr. Working up the reaction mixture in the usual manner gave a yellow semi-solid (0.3 g.), which was crystallized from EtOH to yield methyl 2′-formyl-5,5′,6-trimethoxy-2-biphenylcarboxylate (XVI) as white plates (60 mg.), m.p. 103~105°. Found :

C, 65.59; H, 5.26. This aldehyde was identical with the sample prepared by the Ullmann condensation of Ⅵ with XVⅡ as described above.

2′-Methoxycarbonyl-5,5′,6′-trimethoxy-2-biphenylcarboxylic Acid (XVIII)——The formyl ester (XVI) (2.7 g.) obtained above was oxidized in Me_2CO (100 ml.) by adding powdered $KMnO_4$ (3.9 g.) in portions at 55～60°. The acid (XVⅢ) was crystallized from MeOH and formed cubes (2.1 g.), m.p. 163～165°. *Anal.* Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found : C, 62.63; H, 5.30.

Hydrolysis of the ester (XVⅢ) (30 mg.) with 15% EtOH-KOH (15 ml.) gave after crystallization from Me_2CO 5,5′,6-trimethoxy-2,2′-biphenyldicarboxylic acid (Ⅳ) as prisms, m.p. and mixed m.p. 211～213°. *Anal.* Calcd. for $C_{17}H_{16}O_7$: C, 61.44; H, 5.10. Found : C, 61.00; H, 4.78.

2′-Carboxy-5,5′,6′-trimethoxy-2-biphenylylacetic Acid (XIV) and its Methyl Ester (X)——i) The ester (Ⅺ) (2.7 g.) obtained above, methyl 2-bromoveratrate (Ⅵ) (2 g.), and Cu bronze (4.2 g.) were heated in a sealed tube at 220° for 4.5 hr. The mixture was extracted with $CHCl_3$, the organic phase was evaporated, and the residue extracted with Et_2O. After concentration, trituration of the residue (4 g.) with Et_2O gave methyl 5,5′,6,6′-tetramethoxy-2,2′-biphenylcarboxylate (0.3 g.), m.p. and mixed m.p. 138～142°. The mother-liquors from this diester were evaporated and fractionally distilled under a vacuum to give fractions : (a) $b.p_{0.15}$ 90～120° (0.93 g.) : (b) $b.p_{0.06}$ 123～128° (0.4 g.) : (c) $b.p_{0.15}$ 130～170° (0.08 g.) : (d) $b.p_{0.18}$ 203～210° (0.8 g.). Fractions (a), (b), and (c) were oils and not further investigated. Fraction (d) gave on trituration with Et_2O an additional crop of the above symmetrical dicarboxylate (0.2 g.). The mother-liquors from this ester were concentrated to dryness and the residue (0.6 g.) was hydrolyzed by boiling in 10% EtOH-KOH (80 ml.) for 1 hr. The mixture was worked up in the usual way and the residue (0.4 g.) was triturated with Et_2O to give crystals which were partly soluble in MeOH-Me_2CO. The soluble portion gave cubes of 2′-carboxy-5,5′,6′-trimethoxy-2-biphenylacetic acid (XIV) (30 mg.), m.p. 235～237°, after crystallization from MeCOEt. *Anal.* Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found : C, 62.44; H, 5.38.

The acid (15 mg.) in MeOH (15 ml.) was added to an ethereal solution of diazomethane and was kept overnight. After working up, there was obtained methyl 2′-methoxycarbonyl-5,5′,6′-trimethoxy-2-biphenylacetate (X) as plates, m.p. 87～89° (from MeOH). *Anal.* Calcd. for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found : C, 64.02; H, 5.71.

ii) A mixture of the foregoing acid ester (XVⅢ) (2 g.) and $COCl_2$ (21 g.) was kept at room temperature for 2.5 hr., and at 35° for a further 20 min. The mixture was evaporated under reduced pressure to give an oily acid chloride. This was dissolved in Et_2O, added to an Et_2O-CH_2N_2 solution (prepared from nitrosomethylurea (32 g.)) with ice cooling and then kept overnight. After removal of the Et_2O, the residue was dissolved in MeOH (200 ml.) and BzOAg (9 g.) in Et_3N (60 ml.) was added with stirring in small portions, the temperature being raised gradually to 70° over a period of 2.5 hr. After the mixture had been refluxed for a further 1.5 hr., it was filtered and concentrated under reduced pressure. The residue was extracted with Et_2O, the extracts were washed with saturated aq. $NaHCO_3$, 5% HCl, and H_2O, dried, and concentrated. The residue (2.65 g.) crystallized on trituration with MeOH to give the dimethyl ester (X) (1.2 g.), m.p. 85～89°, which formed after chromatographic purification on Al_2O_3 and recrystallization from MeOH-petr. ether (b.p. 40～60°), plates, m.p. 88～89°. Found : C, 64.31; H, 5.29. The mother-liquor from the above crystals was again chromatographed to yield an additional crop (0.31 g.) of the desired ester (X).

The dimethyl ester (X) (50 mg.) was hydrolyzed with 10% EtOH-KOH (20 ml.) to give after crystallization from EtOH the dicarboxylic acid (XIV) as cubes, m.p. 235～237°. Found : C, 62.50; H, 5.19.

The acid (XIV) and its ester (X) obtained by the method (i) were identical with the respective samples prepared by the procedure (ii).

6′-Hydroxymethyl-2′,3′,5-trimethoxy-2-biphenylethanol (XIX)——To a suspension of $LiAlH_4$ (2 g.) in dry Et_2O (110 ml.), methyl 2′-methoxycarbonyl-5,5′,6-trimethoxy-2-biphenylacetate (X) (0.65 g.) in dry Et_2O (110 ml.) was added dropwise with stirring. Stirring was continued at room temperature for 2 hr. and under reflux for a further 15 min. After the addition of Et_2O saturated with H_2O and of saturated aq. Na_2SO_4 the Et_2O layer was separated, dried, and evaporated to give an oil (0.69 g.) which crystallized on trituration with Et_2O-petr. ether to give the diol (XIX) as plates, m.p. 90～92° (from Et_2O-petr. ether). *Anal.* Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.67. Found : C, 67.90; H, 6.92.

Methyl 2′-(2-Nitrovinyl-5,5′,6-trimethoxy-2-biphenylcarboxylate (XXI)——i) To a mixture of the formyl ester (XVI) (30 mg.) in MeOH (3 ml.) and CH_3NO_2 (0.02 ml.), 5% MeOH-KOH (1 ml.) was added with stirring at −4°. Stirring was continued at the same temperature for 15 min. and at 10～11° for a further 2.5 hr. A work up of the mixture gave the unchanged starting material (25 mg.), m.p. and mixed m.p. 96～100°.

ii) The ester (XVI) (0.9 g.), CH_3NO_2 (0.9 g.), and aniline (1.5 ml.) were heated in a sealed tube at 100° for 11 hr. The reaction mixture was poured into an ice-cooled HCl solution and the precipitate which formed was collected and crystallized from EtOH to give cubes, m.p. 152～154° (These were not the desired nitrostyrene (XXI) and this point is still under investigation). The aqueous filtrate from the precipitate was extracted with Et_2O. The Et_2O solution and the mother-liquors from the crystals were combined and chromatographed in benzene on Al_2O_3. Elution with benzene gave nitrostyrene (XXI) (30 mg.) as

yellow needles, m.p. 124~126° (decomp.), after crystallization from EtOH. *Anal.* Calcd. for $C_{19}H_{19}O_7N$: C, 61.12; H, 5.13; N, 3.75. Found: C, 61.35; H, 5.03; N, 3.83.

iii) The ester (XVI) (0.55 g.), CH_3NO_2 (1.5 g.), and $AcONH_4$ (0.7 g.), in AcOH (18 ml.) were heated in a sealed tube at 100° for 9 hr. After removal of the solvent and addition of H_2O, the mixture was extracted with benzene, the extracts were washed with 2% NH_4OH and H_2O, dried and evaporated. The residue gave after crystallization from Et_2O the nitrostyrene (XXI) as yellow needles (320 mg.), m.p. 124~126°. Found: C, 61.35; H, 5.03; N, 3.83. The mother-liquors from this product gave on standing a small amount of plates, m.p. 145~146°, which was not further examined.

The nitrostyrene obtained by the method (ii) was identical with the sample prepared by the procedure (iii).

1,2,11-Trimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (XXIV)——To a suspension of $LiAlH_4$ (3.2 g.) in dry Et_2O (80 ml.), was added dropwise a solution of the foregoing nitrostyrene (XXI) (0.35 g.) in dry Et_2O (110 ml.). The mixture was stirred at room temperature for 1 hr., then under reflux for a further 6 hr. After addition of Et_2O saturated with H_2O and of saturated aq. Na_2SO_4, the Et_2O layer was separated and the aqueous layer extracted with Et_2O. The combined Et_2O extracts were shaken with 8% HCl which was washed with Et_2O, basified with powdered Na_2CO_3, and extracted with benzene. Evaporation of the benzene left the amine (XXII) as an oil (0.28 g.) which was directly used for the next reaction. A mixture of the amine (XXII) (0.32 g.) and PBr_3 (2 ml.) in benzene (13 ml.) was kept at room temperature for 2 hr., warmed at 45° for 2 hr. and then at 60° for a further 2 hr. The solvent was then removed under reduced pressure, and the residue was poured into ice-cooled 10% NaOH (50 ml.), and extracted with $CHCl_3$. Removal of the solvent gave a bromide (XXIII) as an oil (0.32 g.) which was heated under reflux with KOH (2 g.) in MeOH (35 ml.) for 2 hr. The solvent was evaporated under reduced pressure, and the residue extracted with 8% HCl which was basified with Na_2CO_3 and extracted with $CHCl_3$. After removal of the solvent, the residue was passed through a column of Al_2O_3 in benzene and the eluate converted into its styphnate which crystallized from EtOH as yellow needles. 1,2,11-Trimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (XXIV) styphnate (120 mg.) thus obtained had m.p. 212~215° (decomp.). *Anal.* Calcd. for $C_{18}H_{21}O_3N \cdot C_6H_3O_8N_3$: C, 52.94; H, 4.44; N, 10.29. Found: C, 53.09; H, 4.56; N, 10.58.

6-Methyl-1,2,11-trimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (O,O,O-Trimethylhydroxyapogalanthamine) (IX)——i) From the diol (XIX): The diol (XIX) (0.4 g.) and PBr_3 (9 g.) were kept at room temperature for 45 min., then PBr_3 (3 g.) and benzene (4 ml.) were added, and the whole was kept at 50~55° for 1 hr. Excess PBr_3 and the solvent were removed under reduced pressure, $CHCl_3$ was added to the residue, and the solution was washed with ice-cold H_2O, dried, and evaporated to give the dibromide (XX) as an orange oil. This was treated in a sealed tube with $MeNH_2$ (8 g.) in MeOH (15 ml.) at 130° for 3 hr. After working up in the usual manner, the resulting base (X) was converted into its styphnate in EtOH. Recrystallization of the styphnate gave yellow prisms (40 mg.), m.p. 178~181°. *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot C_6H_3O_8N_3$: C, 53.76; H, 4.69; N, 10.01. Found: C, 53.98; H, 4.75; N, 9.97. The melting point of this styphnate was undepressed on admixture with an authentic specimen of O,O,O-trimethylhydroxyapogalanthamine styphnate from natural sources. The IR spectrum of the synthetic styphnate was also identical with that of the same compound derived from galanthaminone. The free base regenerated from the styphnate was converted to its perchlorate which had m.p. 167~170° (decomp.) (from Et_2O-EtOH), alone or admixed with an authentic sample.

ii) From the cyclic amine (XXIV): The cyclic amine (XXIV) (40 mg.), HCO_2H (0.15 g.), and formalin (0.15 g.) were heated at 100° for 15 hr. After concentration to dryness, 8% HCl was added to the residue, the acidic solution washed with Et_2O, then basified with Na_2CO_3, and extraced with $CHCl_3$. The base (X) thus obtained gave a styphnate (20 mg.), which had m.p. and mixed m.p. 176~179°. Found: C, 54.01; H, 4.74; N, 10.20.

The perchlorate, m.p. and mixed m.p. 165~168°, was obtained by the same procedure as described above. *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot HClO_4$: C, 55.14; H, 5.85; N, 3.38. Found: C, 54.95; H, 5.80; N, 3.68.

Summary

Treatment of galanthaminone with hydriodic acid gave hydroxyapogalanthamine, the structure of which has been elucidated by degradation to the known diphenic acid (IV). The trimethyl ether of hydroxyapogalanthamine has been synthesized by two methods, confirming the structure of this important transformation product of galanthaminone. Based on this and other chemical evidence it has been concluded that galanthamine is represented by formula (III).

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