129. *The Constitution of* apo*Galanthamine.*

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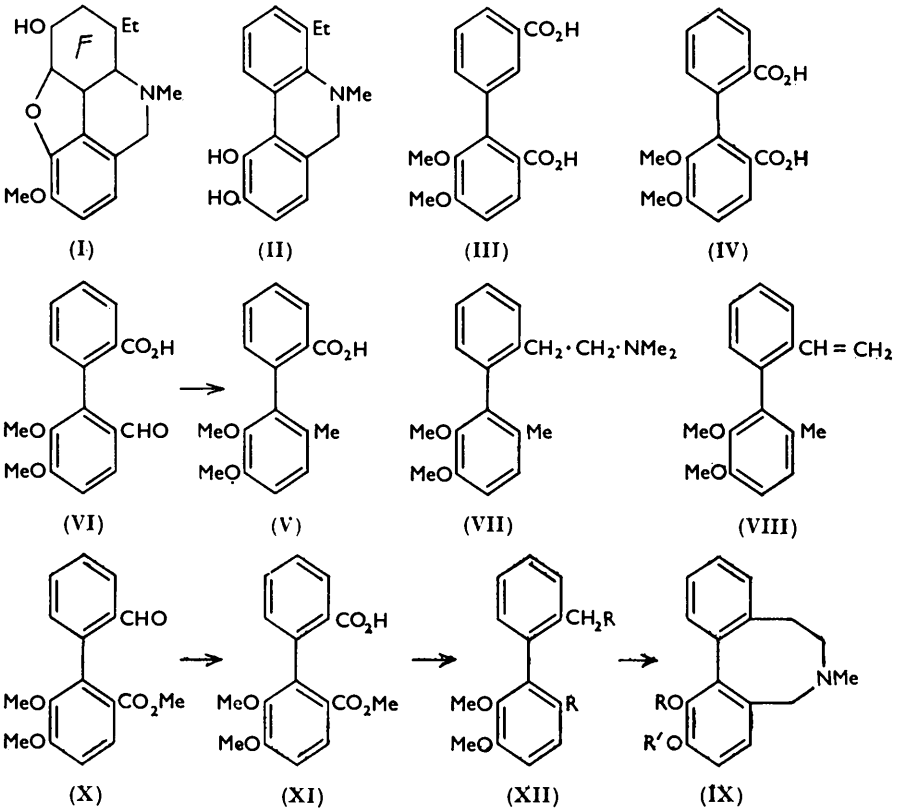
The constitution (IX; R = R′ = H) of *apo*galanthamine, formed from galanthamine by hydrobromic acid, has been deduced by degradations and confirmed by synthesis of its methylation product.

PROSKURNINA and YAKOVLEVA [1] recently reported a transformation of galanthamine (lycoremine),[2,3,4] $C_{17}H_{21}O_3N$, an alkaloid of the Amaryllidaceae, into a dihydric phenolic base, $C_{16}H_{17}O_2N$, now named *apo*galanthamine, by treatment with hydrobromic acid which causes demethylation and cleavage of the oxide ring, accompanied by aromatisation of a *cyclo*hexane ring with concomitant loss of an alcoholic hydroxyl group. This finding was of interest in view of our previous study [5] of lycoramine (dihydrogalanthamine), which in contrast to galanthamine, did not suffer cleavage of the oxide ring when heated with concentrated hydrobromic acid or even with hydriodic acid, the only isolable product being an *O*-demethylhalogenodeoxy-compound. Apparently the ethylenic linkage in the *cyclo*hexane ring of galanthamine is necessary for ready aromatisation and fission of the oxide bridge. On further degradation of *OO*-dimethyl*apo*galanthamine by the Emde method and subsequent oxidation of the resulting base with potassium permanganate in acetone, Proskurnina and her collaborator isolated a nitrogen-free dibasic acid, galanthamic acid, $C_{16}H_{14}O_6$, m. p. 202—203°. Although they formulated *apo*galanthamine and galanthamic acid as (II) and (III), respectively, and advanced for galanthamine the structure (I) based on this sequence of reactions and biogenetic considerations, no proof has been adduced in support of their formulations and it seemed to us rather difficult to correlate satisfactorily the series of reactions made by Proskurnina *et al.* in terms of the formulæ (II) and (III); and moreover the postulated structure (I) of galanthamine appeared inconsistent with the results obtained by us with galanthamine and lycoramine during recent years. We have, therefore, re-examined the Russian work and have made a

[1] Proskurnina and Yakovleva, *Zhur. obshchei Khim.*, 1955, **25**, 1035.
[2] Uyeo and Kobayashi, *Pharm. Bull.* (*Japan*), 1953, **1**, 139.
[3] Boit, Paul, and Stender, *Chem. Ber.*, 1955, **88**, 133.
[4] Kobayashi, Shingu, and Uyeo, *Chem. and Ind.*, 1956, 177.
[5] Uyeo and Koizumi, *Pharm. Bull.* (*Japan*), 1953, **1**, 202.

brief report concerning the structure of *apo*galanthamine.[4] A complete account of this work is presented here along with the final proof of the structure of *apo*galanthamine by synthesis of its *OO*-dimethyl derivative.

We have confirmed the ready cleavage of the oxide ring of galanthamine by hydrobromic acid, to give *apo*galanthamine, m. p. 202° (IX; R = R′ = H), in good yield and found further that treatment with hydrochloric acid converted the alkaloid smoothly into *O*-methyl*apo*galanthamine, m. p. 204—206° (IX; R = H, R′ = Me). On methylation of *apo*galanthamine with diazomethane, Proskurnina *et al.* isolated, in addition to *OO*-dimethyl*apo*galanthamine (substance A), a small amount of a second product (substance B), m. p. 205—206°, which is now considered to be the above mentioned *O*-methyl-*apo*galanthamine. Complete methylation of *apo*galanthamine, as well as of *O*-methyl-*apo*galanthamine, in alkali afforded an *OO*-dimethyl*apo*galanthamine metho-salt, identical with the quaternisation product of *OO*-dimethyl*apo*galanthamine. Emde degradation of the quaternary salt gave a satisfactory yield of a base, the crystalline hydrobromide of which showed the same melting point as that given by Proskurnina *et al.*, though the melting point given for the starting material, *OO*-dimethyl*apo*galanthamine methiodide



was far lower than that of our material. Oxidation of the Emde base with potassium permanganate gave a mixture of two acids readily separable by chromatography over acid-washed alumina: one, m. p. 205—207°, had the formula, $C_{16}H_{14}O_6$, and was no doubt identical with galanthamic acid of Proskurnina *et al.*[1] The second acid, m. p. 124—126°, $C_{16}H_{16}O_4$, was hitherto unknown, but is considered to be a monobasic acid in which a methyl group takes the place of one of the carboxyl groups of galanthamic acid. Clearly both acids have been formed with loss of one carbon atom, together with the dimethylamino-group, of the Emde base, $C_{17}H_{19}O_2{\cdot}NMe_2$. Although Proskurnina *et al.* postulated

structure (III) for galanthamic acid, an alternative formula (IV) was thought to be more plausible; however we undertook the preparation of both compounds. Ullmann condensation of methyl 2-bromoveratrate and methyl *m*-iodobenzoate in the presence of copper bronze, followed by fractionation and hydrolysis, afforded, along with two symmetrical diphenyldicarboxylic acids, the desired unsymmetrical acid, 5 : 6-dimethoxydiphenyl-2 : 3′-dicarboxylic acid (III), m. p. 223°, clearly different from galanthamic acid. On the other hand, 5 : 6-dimethoxydiphenyl-2 : 2′-dicarboxylic acid (IV), m. p. 205—207°, isolated from the condensation products of methyl 2-bromoveratrate and methyl *o*-iodobenzoate, was identical with galanthamic acid. It followed that the second acid, $C_{16}H_{16}O_4$,

FIG. 1. FIG. 2.

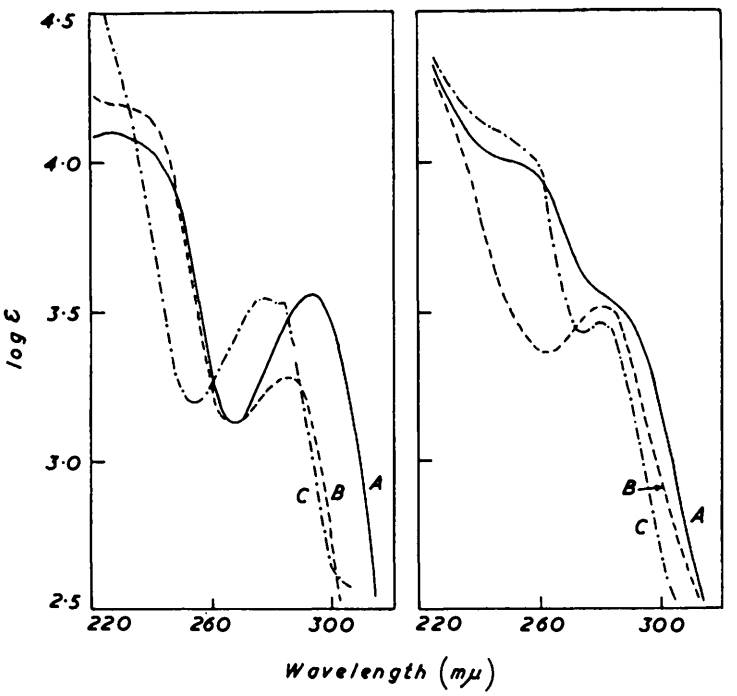


FIG. 1. *Absorption spectra of* (*A*) apo*galanthamine* (IX; R = R′ = H) *hydrobromide*, (*B*) OO-*dimethyl*-apo*galanthamine* (IX; R = R′ = Me), *and* (*C*) *the Emde base* (VII) *methiodide, all in* 95% *ethanol.*

FIG. 2. *Absorption spectra of* (*A*) *galanthamic acid* (IV), (*B*) 2′ : 3′-*dimethoxy*-6′-*methyldiphenyl*-2-*carboxylic acid* (V), *and* (*C*) *the Hofmann degradation product* (VIII), *all in* 95% *ethanol.*

should be 2′ : 3′-dimethoxy-6′-methyldiphenyl-2-carboxylic acid (V), it being considered that the Emde degradation took place, in analogy with known cases, on the benzyl side of the quaternary nitrogen atom. This inference was proved to be correct when we synthesised the acid (V) by hydrogenation of the aldehyde (VI) which was in turn prepared by condensation of 2-bromoveratraldehyde and methyl *o*-iodobenzoate.

With the structure of the two acids derived from the Emde base of *apo*galanthamine established, coupled with the fact that *apo*galanthamine contained no *C*-methyl group, we could now formulate the Emde base as (VII). In agreement with this, the Hofmann degradation product (VIII) of the Emde base showed bands at 995 and 910 cm.$^{-1}$, characteristic of a vinyl group and gave formaldehyde on ozonolysis. On the basis of these results *apo*galanthamine must be (IX; R = R′ = H) which has been placed beyond doubt by the following synthesis of its *OO*-dimethyl derivative (IX; R = R′ = Me).

Condensation of methyl 2-bromoveratrate and *o*-iodobenzaldehyde by the Ullmann method afforded methyl 5 : 6-dimethoxy-2′-formyldiphenyl-2-carboxylate (X) which on oxidation gave the acid (XI). The Arndt–Eistert reaction then led to 2′ : 3′-dimethoxy-6′-carboxy-2-diphenylylacetic acid (XII; R = CO_2H). Later we found that a preferred route to the same acid was direct condensation of methyl 2-bromoveratrate and methyl *o*-iodophenylacetate. The acid (XII; R = CO_2H) was converted into its dimethyl ester (XII; R = CO_2Me), reduced by lithium aluminium hydride to the diol (XII; R = CH_2·OH), and then treated with phosphorus tribromide to give the dibromide (XII; R = CH_2Br). Cyclisation to an eight-membered heterocyclic ring was accomplished by heating the dibromide with methylamine in a sealed tube. The synthetic amine (IX; R = R′ = Me) thus obtained was compared as its crystalline styphnate and methiodide with an authentic sample of *OO*-dimethyl*apo*galanthamine and shown to be identical with it.

The ultraviolet spectra of *apo*galanthamine and its degradation products are recorded in Figs. 1 and 2. The eight-membered bridging ring and a further substitution at the second *ortho*-position of one benzene ring in *apo*galanthamine and *OO*-dimethyl*apo*galanthamine lead to twisting of the two benzene rings about the common axis and consequently considerable reduction in conjugation of the aromatic rings, as indicated by their ultraviolet spectra. This effect is also observed in the spectra of the Emde base and its oxidation product as well as its Hofmann degradation product, which are all tri-*o*-substituted diphenyl derivatives.

In regard to the structure of galanthamine and lycoramine, it is hoped that final evidence will be presented in a forthcoming paper.

Experimental

apo*Galanthamine*.—Galanthamine (0·5 g.) was heated with 48% hydrobromic acid (7 c.c.) [or with acetic acid (7 c.c.) saturated at 0° with hydrobromic acid] in a sealed tube for 5 hr. at 100°. Concentration under reduced pressure then gave *apo*galanthamine hydrobromide (0·51 g.), which crystallised from dilute hydrobromic acid in scales, m. p. 234° (decomp.) (Proskurnina *et al.* give m. p. 228—230°), $[\alpha]_D$ ±0° (*c* 0·2 in EtOH) (Found : C, 54·2; H, 5·6; N, 4·0. Calc. for $C_{16}H_{17}O_2N,HBr,H_2O$: C, 54·2; H, 5·7; N, 4·0%).

The hydrobromide was dissolved in water and aqueous ammonia added to the solution to precipitate the free base which was collected and crystallised from methanol as cubic crystals, m. p. 202° (decomp.) (Proskurnina *et al.* give m. p. 202—203°). The base was sparingly soluble in ether, benzene, chloroform, or ethyl acetate, discolored in air, and gave a green colour with ferric chloride. A sample dried at room temperature contained water of crystallisation (Found : C, 69·9; H, 7·0; N, 4·6. Calc. for $C_{16}H_{17}O_2N,H_2O$: C, 70·3; H, 7·0; N, 5·1%).

O-*Methyl*apo*galanthamine*.—Galanthamine (0·3 g.) was treated in a sealed tube for 6 hr. at 100° with acetic acid (4 c.c.) saturated with dry hydrogen chloride at 0°. After concentration, water was added and the solution basified with aqueous ammonia. The precipitate thus formed was filtered off, dried, and crystallised from benzene and then as needles from ethanol, to give O-*methyl*apo*galanthamine* (0·17 g.), m. p. 204—206° (Found : C, 76·1; H, 7·0; N, 5·0; OMe, 11·3. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2; OMe, 11·5%). The *hydrobromide* crystallised from ethanol as prisms, m. p. 234° (Found : C, 54·8; H, 5·8; N, 3·7. $C_{17}H_{19}O_2N,HBr,H_2O$ requires C, 55·4; H, 6·0; N, 3·8%).

OO-*Dimethyl*apo*galanthamine*.—*apo*Galanthamine (0·44 g.) in ethanol (15 c.c.) was treated with an excess of ethereal diazomethane for 2 days. After evaporation of the solvent, the residual oil was taken up in 10% hydrochloric acid, and the solution washed with ether, basified with aqueous sodium hydroxide, and extracted with chloroform. The dried extracts, on evaporation to dryness, yielded *OO*-dimethyl*apo*galanthamine as an oil which was converted into its *styphnate*, m. p. 214—216° after crystallisation from acetone–ethanol (Found : C, 54·8; H, 4·6; H, 10·6; OMe, 11·2. $C_{18}H_{21}O_2N,C_6H_3O_8N_3$ requires C, 54·5; H, 4·6; N, 10·6; OMe, 11·8%).

*Dimethyl*apo*galanthamine Methiodide*.—(*a*) Dimethyl*apo*galanthamine regenerated from the styphnate was treated with methyl iodide in methanol, yielding the methiodide which crystallised from acetone in cubes, m. p. 225—227° (decomp.) (Proskurnina *et al.* give 144—150°) (Found : C, 53·8; H, 5·8; N, 3·4; OMe, 14·2; *C*-Me, 0. Calc. for $C_{18}H_{21}O_2N,CH_3I$: C, 53·7; H, 5·7; N, 3·3; OMe, 14·6%).

(*b*) *apo*Galanthamine hydrobromide (0·36 g.) was dissolved in 5% aqueous sodium hydroxide (60 c.c.), and dimethyl sulphate (6 c.c.) was added dropwise during 12 hr. with stirring. After neutralisation with hydriodic acid and addition of potassium iodide (1 g.), the mixture was evaporated to dryness under reduced pressure and the residue extracted with ethanol. The extracts were concentrated to dryness and again extracted with chloroform. The chloroform extracts were evaporated, and the residue crystallised from acetone giving *OO*-dimethyl*apo*galanthamine methiodide (0·35 g.), m. p. and mixed m. p. 224° (decomp.) [with the sample obtained as above].

(*c*) *O*-Methyl*apo*galanthamine (30 mg.) in methanol (6 c.c.) was treated with methyl iodide in the presence of potassium hydroxide. This gave a methiodide (from acetone), m. p. and mixed m. p. 224—226°.

Emde Degradation of OO-*Dimethyl*apo*galanthamine Methiodide.*—The foregoing methiodide (0·32 g.) in water (15 c.c.) was converted into its methochloride by shaking with silver chloride, and then the filtered solution was heated on a water-bath with 4% sodium amalgam (30 g.) for 8 hr. The oil which separated was taken up in ether, and the ethereal extracts were washed with water, dried, and evaporated, to give an oil (0·24 g.) which was converted into the hydrobromide (0·28 g.), m. p. 172—174° (Proskurnina *et al.* give 173—175°) after crystallisation from acetone (Found : C, 60·1; H, 6·9; N, 3·7. Calc. for $C_{19}H_{25}O_2N$,HBr : C, 60·0; H, 6·9; N, 3·7%).

Oxidation of the Emde Base.—The foregoing base (0·21 g.) regenerated from its hydrobromide was dissolved in acetone (15 c.c.), and powdered potassium permanganate (0·66 g.) added in portions with stirring at 55° during 5 hr. After addition of water and removal of acetone, sulphur dioxide was passed into the oxidation mixture to dissolve the manganese dioxide, and then hydrochloric acid was added to the solution. A gum which separated was taken up in benzene and extracted with aqueous sodium hydroxide; the alkaline extracts were made acidic with hydrochloric acid and extracted with ether. Evaporation of the ether left an almost colourless gum (60 mg.) which was chromatographed in benzene on acid-washed alumina. Elution with benzene gave white needles (12 mg.), m. p. 124—126° after recrystallisation from ether–light petroleum (b. p. 60—80°) (Found : C, 70·7, 70·9; H, 5·9, 5·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). This acid was identified as 2′ : 3′-dimethoxy-6′-methyldiphenyl-2-carboxylic acid, m. p. 124—126°, prepared synthetically as described below, by a mixed m. p. and the infrared spectrum. Further elution with ether–benzene (1 : 1) afforded galanthamic acid as white leaflets, m. p. 205—207° (Proskurnina *et al.* give 200—203°) (Found : C, 62·9; H, 4·5. Calc. for $C_{16}H_{14}O_6$: C, 63·6; H, 4·7%), undepressed on admixture with 5 : 6-dimethoxydiphenyl-2 : 2′-dicarboxylic acid obtained as described below, but depressed by 5 : 6-dimethoxydiphenyl-2 : 3′-dicarboxylic acid, m. p. 223°, prepared synthetically as shown below. Final elution with methanol gave a further crop of somewhat impure galanthamic acid, m. p. 196—200°.

2′ : 3′-*Dimethoxy*-6′-*formyldiphenyl*-2-*carboxylic Acid.*—2-Bromoveratraldehyde [6] (4·5 g.), methyl *o*-iodobenzoate (7 g.), and copper bronze (12 g.) were heated in a sealed tube for 5 hr. at 220—230°. The mixture was diluted with ether and filtered from inorganic material. On concentration of the filtrate and washings, 2 : 2′ : 3 : 3′-*tetramethoxy*-6 : 6′-*diformyldiphenyl* (0·7 g.) separated which was collected and crystallised from acetone as prisms, m. p. 130—132° (Found : C, 65·5; H, 5·4; OMe, 37·6. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5; OMe, 37·6%). The mother-liquors from this crystallisation were evaporated to dryness and fractionally distilled in a vacuum, to give fractions : (*a*) b. p. 64—67°/3 mm. (0·45 g.); (*b*) b. p. up to 185° (bath-temp.)/0·08 mm. (0·77 g.); (*c*) b. p. 185—200° (bath-temp.)/0·08 mm. (0·77 g.). Fractions (*a*) and (*b*) were oils and not further examined. Fraction (*c*) solidified (m. p. 60—65°) and was identified as crude methyl diphenate. The dark brown distillation residue (3 g.) was dissolved in benzene, chromatographed on alumina, and eluted with benzene. The first fraction (20 c.c.) gave a product which after one crystallisation from methanol had m. p. 67—70°, undepressed on admixture with methyl diphenate, m. p. 74—75°. The second fraction (10 c.c.) left on evaporation a product, m. p. 40—80°, which on crystallisation from methanol gave 2 : 2′ : 3 : 3′-tetramethoxy-6 : 6′-diformyldiphenyl, m. p. 128—130°. The same compound was isolated from the third and the fourth fraction (10 c.c. each). Further eluates (100 c.c.) gave only oils. The mother-liquors and the oily fractions were combined and treated with 5% methanolic barium hydroxide (33 c.c.) under reflux for 1 hr. After addition of water and evaporation of methanol, the alkaline solution was washed with ether, then made acidic with hydrochloric acid,

[6] Henry and Sharp, *J.*, 1930, 2279.

and extracted with ether. The ethereal extracts were dried and evaporated to give a mixture (1 g.), from which diphenic acid (0·17 g.), m. p. 225—228°, was isolated on trituration with benzene. The filtrate from this acid was diluted with benzene and filtered through a column of acid-washed alumina (10 g.). The benzene eluate yielded a product (0·3 g.), m. p. 173—180°, which was recrystallised from methanol–ether, to give 2′ : 3′-*dimethoxy*-6′-*formyldiphenyl*-2-*carboxylic acid* as prisms, m. p. 182—185° (Found : C, 66·9; H, 5·0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). Further elution with ether gave diphenic acid (20 mg.).

2′ : 3′-*Dimethoxy*-6′-*methyldiphenyl*-2-*carboxylic Acid.*—The foregoing aldehydic acid (0·22 g.) in acetic acid (15 c.c.) was hydrogenated over 35% palladium–carbon (0·3 g.) until a little more than 2 mols. of hydrogen had been absorbed during 40 min. The filtered solution was diluted with water and extracted with ether, and the ethereal extracts were dried and evaporated, to yield a residue (0·15 g.) which was chromatographed in benzene on acid-washed alumina. The eluate gave on crystallisation from benzene–light petroleum (b. p. 60—80°) 2′ : 3′-*dimethoxy*-6′-*methyldiphenyl*-2-*carboxylic acid* as long prisms, m. p. 125—127° (Found : C, 70·5; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

5 : 6-*Dimethoxydiphenyl*-2 : 2′-*dicarboxylic Acid.*—Methyl 2-bromoveratrate [6] (3·7 g.), methyl *o*-iodobenzoate (5 g.), and copper bronze (10 g.) were heated in a sealed tube for 5 hr. at 230—235°. The mixture was extracted with chloroform, the solution evaporated, and the residue extracted with ether. After concentration of the ether, the residual oil was fractionally distilled, giving materials (*a*—*e*). Fraction (*a*), b. p. 44—74°/0·5 mm. (0·8 g.), was discarded. Fraction (*b*), b. p. 112—122°/0·5 mm. (1·2 g.), hydrolysed with 10% ethanolic potassium hydroxide followed by working up in the usual way, yielded a solid mixture from which veratric acid (0·5 g.), m. p. 178—180° after crystallisation from methanol, and diphenic acid (60 mg.), m. p. 226—228° after crystallisation from methanol, were isolated. Fraction (*c*), b. p. 129—134°/0·3 mm. (0·6 g.), when hydrolysed as above, yielded veratric acid (0·17 g.). Fraction (*d*), b. p. 167—174°/0·3 mm. (1·6 g.), on trituration with ether, gave *methyl* 5 : 6 : 5′ : 6′-*tetramethoxydiphenyl*-2 : 2′-*dicarboxylate* (0·2 g.), m. p. 146—147° (from acetone–methanol) (Found : C, 61·6; H, 5·8. $C_{20}H_{20}O_8$ requires C, 61·5; H, 5·7%). The mother-liquor from this ether was saponified by 10% ethanolic potassium hydroxide (30 c.c.) under reflux for 2 hr., water was then added, and the whole acidified with hydrochloric acid and extracted with ether. The ethereal extracts were dried and concentrated and the product, m. p. 194—201° (0·38 g.), which separated, was filtered off and recrystallised from methanol to give 5 : 6-dimethoxydiphenyl-2 : 2′-dicarboxylic acid, m. p. 205—207° (Found : C, 63·3; H, 4·6. Calc. for $C_{16}H_{14}O_6$: C, 63·6; H, 4·7%). Fraction (*e*), b. p. 180—190°/0·3 mm. (0·6 g.), crystallised on trituration with ether, to give methyl 5 : 6 : 5′ : 6′-tetramethoxydiphenyl-2 : 2′-dicarboxylate (0·17 g.).

5 : 6-*Dimethoxydiphenyl*-2 : 3′-*dicarboxylic Acid.*—Methyl 2-bromoveratrate (2 g.), methyl *m*-iodobenzoate (3 g.), and copper bronze (5 g.) were heated in a sealed tube for 5 hr. at 230—235°. The mixture was worked up as above and distilled to give two fractions : (*a*) b. p. up to 100°/0·2 mm. (1·5 g.) and (*b*) b. p. 163—186°/0·2 mm. (1·5 g.). Trituration of the latter with ether afforded methyl 5 : 6 : 5′ : 6′-tetramethoxydiphenyl-2 : 2′-dicarboxylate (0·19 g.), m. p. 146—147°, plates from acetone. Hydrolysis of this ester and recrystallisation from ethyl methyl ketone gave the free *acid* as needles, m. p. 219° (Found : C, 59·7; H, 5·0. $C_{18}H_{18}O_8$ requires C, 59·7; H, 5·0%). The mother-liquors from the symmetrical ester were hydrolysed by 10% methanolic potassium hydroxide. After evaporation of the methanol and addition of water, the solution was made acid with hydrochloric acid and extracted with chloroform. A small amount of crystals which were insoluble in chloroform was filtered off and crystallised from methanol, to give diphenyl-3 : 3′-dicarboxylic acid (25 mg.), m. p. >330° (Found : C, 69·5; H, 4·1. Calc. for $C_{14}H_{10}O_4$: C, 69·4; H, 4·2%). The chloroform extracts were dried and evaporated, and the residue triturated with acetone. The product (0·5 g.) which separated was filtered off and recrystallised thrice from acetone, to yield 5 : 6-*dimethoxydiphenyl*-2 : 3′-*dicarboxylic acid* as prisms, m. p. 223° (Found : C, 63·6; H, 4·6. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·7%).

Hofmann Degradation of the Emde Base Methiodide.—The Emde base (0·36 g.) derived from dimethyl*apo*galanthamine, methyl iodide (2 c.c.), and methanol (2 c.c.) were heated on a water-bath for 2 hr. to yield the *methiodide* (0·48 g.), m. p. 221—223°, needles from acetone (Found : C, 54·7; H, 6·5; N, 3·1. $C_{19}H_{25}O_3N,CH_3I$ requires C, 54·4; H, 6·4; N, 3·2%). The methiodide (0·45 g.) was converted into its hydroxide by treatment with silver oxide in water, the filtered solution evaporated to dryness under reduced pressure, and the residue heated in a vacuum for

1 hr. at 100°. The product was taken up in ether, and the ethereal solution washed with 5% hydrochloric acid, then with water, dried, evaporated, and distilled under reduced pressure, to give 2 : 3-*dimethoxy*-6-*methyl*-2'-*vinyldiphenyl* (0·14 g.), b. p. 140° (bath-temp.)/0·05 mm. (Found : C, 80·2; H, 7·1. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). The volatile amine which had been eliminated during the reaction was absorbed by dilute hydrochloric acid and identified as trimethylamine by its aurichloride, m. p. 245° (decomp.) (Found : C, 9·2; H, 2·6; Au, 49·7. Calc. for $C_3H_9N,HAuCl_4$: C, 9·0; H, 2·5; Au, 49·4%). After ozonisation of the foregoing nitrogen-free substance (80 mg.) in chloroform at 0° for 1 hr. and decomposition of the resulting ozonide by hot water, the mixture was steam-distilled and the distillate treated with dimedone in ethanol, yielding the formaldehyde–dimedone compound (13 mg.), m. p. and mixed m. p. 184—186°.

Methyl 5 : 6-*Dimethoxy*-2'-*formyldiphenyl*-2-*carboxylate*.—*o*-Iodobenzaldehyde [7] (5 g.), methyl 2-bromoveratrate (3 g.), and copper bronze (6 g.) were heated in a sealed tube for 5 hr. at 210°. Working up gave a reddish-brown oil which on trituration with ether partly crystallised, to give methyl 5 : 6 : 5' : 6'-tetramethoxydiphenyl-2 : 2'-dicarboxylate (0·5 g.). The mother-liquors were concentrated and fractionally distilled to remove the portion (0·53 g.) boiling up to 130°/0·02 mm., which was discarded. The distillation residue (2·5 g.) was hydrolysed by refluxing in 6% ethanolic barium hydroxide (70 c.c.) for 1·5 hr., then water was added to the mixture, methanol removed, and the alkaline aqueous solution washed with ether, acidified with hydrochloric acid, and extracted with ether. Evaporation of the ether yielded an oil (2 g.) which afforded crystals (0·7 g.), m. p. 120—138°, when kept. These were digested in hot benzene and filtered off while hot. The insoluble residue yielded 5 : 6 : 5' : 6'-tetramethoxydiphenyl-2 : 2'-dicarboxylic acid (70 mg.), m. p. and mixed m. p. 217—219°, while the benzene solution afforded 5 : 6-dimethoxy-2'-formyldiphenyl-2-carboxylic acid (0·35 g.), m. p. 171—173° after crystallisation from methanol (Found : C, 67·1; H, 4·9. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). The latter was treated in methanol (40 c.c.) with sulphuric acid (1 c.c.) under reflux for 3·5 hr. and worked up in the usual way, yielding *methyl* 5 : 6-*dimethoxy*-2'-*formyldiphenyl*-2-*carboxylate* as prisms (0·25 g.), m. p. 88—90° (from methanol) (Found : C, 68·0; H, 5·0. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). In the second run, the distillation residue obtained similarly as above was chromatographed on alumina and eluted with benzene. The first (10 c.c.) and the second fraction (15 c.c.) yielded the desired ester and the third fraction (10 c.c.) the symmetrical ester.

Methyl 5 : 6-*Dimethoxy*-2'-*carboxydiphenyl*-2-*carboxylate*.—Methyl 5 : 6-dimethoxy-2'-formyldiphenyl-2-carboxylate (0·18 g.) was oxidised in acetone (30 c.c.) by adding powdered potassium permanganate (0·2 g.) in portions at 50—60°. After removal of the acetone by distillation, water was added, sulphur dioxide passed in until the manganese dioxide dissolved, and the whole was acidified with hydrochloric acid and extracted with ether. The ethereal solution was extracted with 10% sodium carbonate solution, and the aqueous layer again acidified and extracted with ether. On evaporation of the ether, *methyl* 5 : 6-*dimethoxy*-2'-*carboxydiphenyl*-2-*carboxylate* (0·12 g.) crystallised and formed after crystallisation from methanol prisms, m. p. 173—174° (Found : C, 64·2; H, 4·8. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%).

2' : 3'-*Dimethoxy*-6'-*carboxy*-2-*diphenylylacetic Acid*.—(*a*) Methyl 5 : 6-dimethoxy-2'-carboxydiphenyl-2-carboxylate (0·2 g.) was heated with an excess of thionyl chloride at 30—40° for 2 hr. The thionyl chloride was then removed under reduced pressure, dry benzene added to the residue, and the whole evaporated in a vacuum. The acid chloride thus obtained was treated with ethereal diazomethane at room temperature overnight. After evaporation of the ether, the remaining syrupy diazo-ketone was taken up in dioxan (10 c.c.) and added to a mixture of silver oxide [prepared from silver nitrate (0·5 g.) and sodium hydroxide] and sodium thiosulphate (1 g.) in water (10 c.c.). After 4 hr. at 20—25° and then a further hr. at 50°, during which brisk evolution of nitrogen was observed, the mixture was filtered, acidified with dilute nitric acid, and extracted with ether. The ester-acid thus obtained was hydrolysed with 10% sodium hydroxide solution under reflux for 0·5 hr., acidified with hydrochloric acid, and extracted with ether. Removal of the ether afforded an oil (0·2 g.) which solidified, giving 2' : 3'-*dimethoxy*-6'-*carboxy*-2-*diphenylylacetic acid* (30 mg.), m. p. 214—216° (from methanol–ether) (Found : C, 64·2; H, 5·0. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%).

(*b*) *o*-Iodobenzoic acid (31 g.) was converted with thionyl chloride into the acid chloride which was treated with diazomethane in ether, yielding ω-*diazo*-o-*iodoacetophenone* in yellow prisms, m. p. 57—59° (from methanol and then from ether) (Found : C, 35·8; H, 2·1; N, 10·6.

[7] Rapson and Shuttleworth, *J.*, 1941, 487.

$C_8H_5ON_2I$ requires C, 35·8; H, 1·8; N, 10·3%). To a solution of the diazo-ketone (24 g.) in methanol (370 c.c.) was added in portions silver oxide [prepared from silver nitrate (25 g.) and sodium hydroxide and washed well with methanol], and the mixture was heated at 40—45° for 1 hr. and then under reflux for a further 3 hr. The mixture was filtered, the filtrate evaporated under reduced pressure, and the residue distilled, to give methyl *o*-iodophenylacetate as an oil (17·8 g.), b. p. 105—106°/2 mm. A small amount of the ester was hydrolysed, giving an acid, m. p. 103—107°, identical with authentic *o*-iodophenylacetic acid.[7] Methyl *o*-iodophenylacetate (5 g.), methyl 2-bromoveratrate (3·5 g.), and copper bronze (6 g.) were heated in a sealed tube for 5 hr. at 215—220°. The mixture was taken up in ether, the ethereal solution concentrated, and methyl 5 : 6 : 5′ : 6′-tetramethoxydiphenyl-2 : 2′-dicarboxylate (0·82 g.) which separated was filtered off and had m. p. and mixed m. p. 145—147°. The mother-liquors were distilled : the first fraction (1·9 g.), b. p. 60—107°/2 mm., was not further examined. The second fraction (0·55 g.), b. p. 95—96°/0·01 mm., gave methyl veratrate, m. p. and mixed m. p. 56—58° (from methanol) (Found : C, 61·6; H, 6·0. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·2%). The third fraction (0·55 g.), b. p. 140—150°/0·01 mm., was a yellow oil which was hydrolysed by boiling 15% ethanolic potassium hydroxide (20 c.c.) for 1 hr. After working up in the usual way, the resulting acid was extracted with ether, and the extract dried and concentrated, yielding 2′ : 3′-dimethoxy-6′-carboxy-2-diphenylylacetic acid (0·2 g.) as needles, m. p. and mixed m. p. 214—217° after crystallisation from methanol–ether (Found : C, 64·3; H, 5·4%).

2 : 3-*Dimethoxy*-2′-*hydroxyethyl*-6-*hydroxymethyldiphenyl*.—The foregoing acid (0·69 g.) was treated with an excess of ethereal diazomethane, to give the dimethyl ester as an oil (0·7 g.). To a suspension of lithium aluminium hydride (1 g.) in dry ether (80 c.c.) was added dropwise a solution of the dimethyl ester (0·7 g.) in dry ether (90 c.c.) with stirring, which was continued for 2 hr. at room temperature and then for a further hr. under reflux. After addition of water (10 c.c.) and acidification with 10% sulphuric acid (40 c.c.), the ethereal layer was separated, dried, and evaporated to give the product (0·52 g.), m. p. 110—113°. On chromatography in benzene on alumina and subsequent crystallisation from methanol–ether, 2 : 3-*dimethoxy*-2′-*hydroxyethyl*-6-*hydroxymethyldiphenyl* formed plates, m. p. 114—116° (Found : C, 71·0; H, 6·8. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%).

Synthesis of OO-*Dimethyl*apo*galanthamine*.—The foregoing diol (0·45 g.) and phosphorus tribromide (6·5 g.) were kept for 1 hr. at 0°, for a further half hr. at 15°, and finally for 1 hr. at 45°. Next morning, excess of phosphorus tribromide was removed under reduced pressure, chloroform (50 c.c.) added to the residue, the chloroform solution washed several times with ice-cold water, dried and evaporated to give the dibromide as an orange oil. This was treated in a sealed tube with a methanolic solution (30 c.c.) of methylamine (10 g.) at 130° for 3 hr. The mixture was concentrated under reduced pressure, the residue taken up in benzene (100 c.c.), and the benzene layer extracted with hydrochloric acid. The acid solution was made alkaline with sodium carbonate and extracted with chloroform, and the extracts were dried and evaporated, to yield the product (0·1 g.) which was dissolved in chloroform and filtered through a column of alumina. The eluate was converted into its styphnate (90 mg.) and crystallised from acetone–ethanol, yielding 3′ : 4′-*dimethoxy*-1-*methyl*-1-*aza*-3 : 4-5 : 6-*dibenzo*cycloocta-3 : 5-*diene styphnate*, m. p. 213—215°, undepressed on admixture with an authentic sample of dimethyl*apo*galanthamine styphnate from the natural source. The infrared spectrum of the synthetic styphnate was also identical with that of the same compound derived from galanthamine (Found : C, 54·8, 54·9; H, 4·9, 4·3; N, 10·5, 10·6. $C_{18}H_{21}O_2N,C_6H_3O_8N_3$ requires C, 54·5; H, 4·6; N, 10·6%).

The free base regenerated from the foregoing styphnate (20 mg.) was boiled with methyl iodide in methanol for 3 hr. The resulting methiodide, recrystallised from methanol–acetone, had m. p. 222—224° (decomp.) alone or mixed with an authentic sample.

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