Trituration of the product with acetone yielded XXI (91 mg.). Further recrystallization with acetone gave the analytical sample, m.p. 205~207°, $[\alpha]_D^{29}$ −94° (c=0.67), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2790, 2732 (w), 2704 (w), 2664, 1728. ORD (c=0.061): $[\alpha]_{290}$ +734, $[\alpha]_{302}$ 0, $[\alpha]_{328}$ −1615, $[\alpha]_{337}$ −1615, [A]=−117. *Anal.* Calcd. for $C_{33}H_{52}O_3$: C, 79.78; H, 10.55. Found: C, 79.75; H, 10.51.

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Summary

A sapogenin, for which the name saikogenin A is proposed, has been obtained from saponins of *Bupleurum falcatum* L (Mishimasaiko). The present study has given the structural formula (I) for saikogenin A,

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142. Shojiro Uyeo,*1 Hideaki Shirai,*2 Akira Koshiro,*1 Tamotsu Yashiro,*2 and Kengo Kagei*1 : Galanthamine Chemistry. VII.*3 Synthesis of Analogues of Galanthamine.

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Galanthamine, an alkaloid isolable from some species of the Amaryllidaceae, due to its anticholinesterase activity,[1] has become popular in the clinical treatment of poliomyelitis. Furthermore this alkaloid bears some resemblance to morphine in the ring system and has been shown to have analgesic action, the duration of effect approaching that of morphine and codeine.[2] The purpose of our present investigation was to synthesize compounds structurally related to galanthamine (I), in particular II, and to test their biological effects, especially their anticholinesterase activities. The compound (II) differed from galanthamine only in the absence of the oxide ring and the double bond in the cyclohexane ring. Compound (III), an isostere of II, was a by-product obtained in the course of synthesis.

Michael reaction of *m*-methoxybenzyl cyanide (IV)[3] with methyl acrylate in the presence of Triton B yielded methyl γ-cyano-γ-(*m*-methoxyphenyl)pimelate (V) which gave the keto-ester (VI) after a Dieckmann cyclization. Saponification of VI followed by decarboxylation resulted in the formation of the keto-nitrile (VII).

Ketalization of the keto-nitrile (VII) and hydrolysis of the nitrile group in VII afforded the ketal-acid (IX) which on treatment with lithium aluminum hydride gave the ketal-alcohol (X). Chromic acid oxidation of the alcohol (X) gave the aldehyde (XI) which was

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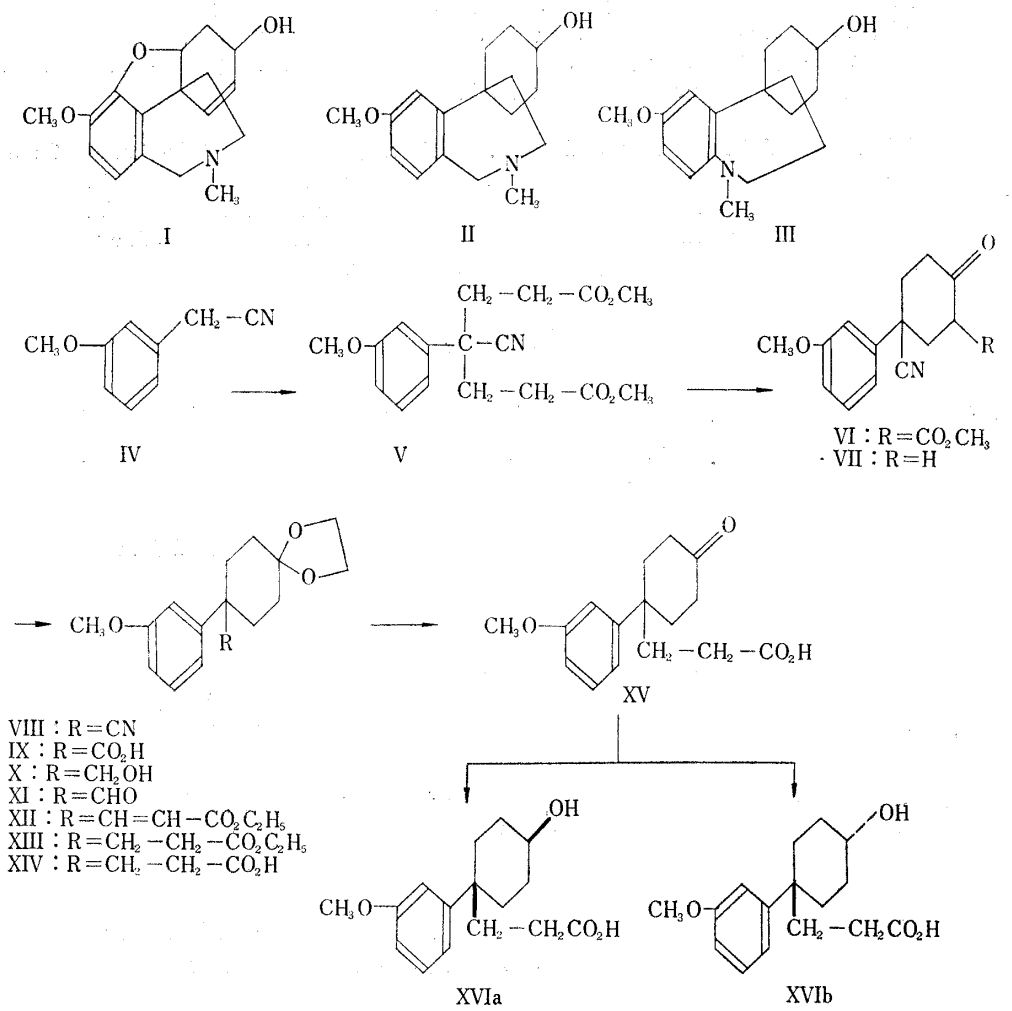

Chart 1.

converted into the ketal-propionate (XIII) by the Wittig reaction with ethyl (diethylphosphono)acetate[4] in the presence of sodium hydride followed by hydrogenation of the resulting ketal-acrylate (XII) over Adams catalyst.

Hydrolysis of the ester group in XIII in an alkaline solution and the ketal grouping in the resulting XIV in an acid solution furnished the keto-acid (XV) which with sodium borohydride gave a mixture of two hydroxy-acids (XVIa and XVIb) in nearly equal amounts. The epimeric nature of the hydroxyl groups was confirmed by reoxidation with chromic acid to the starting keto-acid (XV).

Since oxidation of the alcohol (X) to the aldehyde (XI) underwent in low yield (44%), and the formation of two diastereoisomers (XVIa and XVIb) was undesired, we turned to an alternative approach which turned out to be superior.

Lithium aluminum hydride reduction of the keto-nitrile (VII) gave the hydroxy-aldehyde (XVII) which was not heterogeneous according to thin-layer chromatography. This aldehyde formed the hemiacetal (XIX) on long standing at room temperature, indicating that the hydroxyl and the aldehyde groups are *cis* oriented. Since the benzene ring attached to C-4 in XVII must be equatorial due to its bulkiness and hence the geminal aldehyde axial, the hydroxyl group at C-1 takes the equatorial conformation, as expected. The hemiacetal (XIX) gave the acetate (XX) which was also obtained by treatment of the hydroxy-aldehyde (XVII) with acetic anhydride and *p*-toluenesulfonic

4) W.S. Wadsworth, W.D. Emmons: J. Am. Chem. Soc., 83, 1733 (1961).

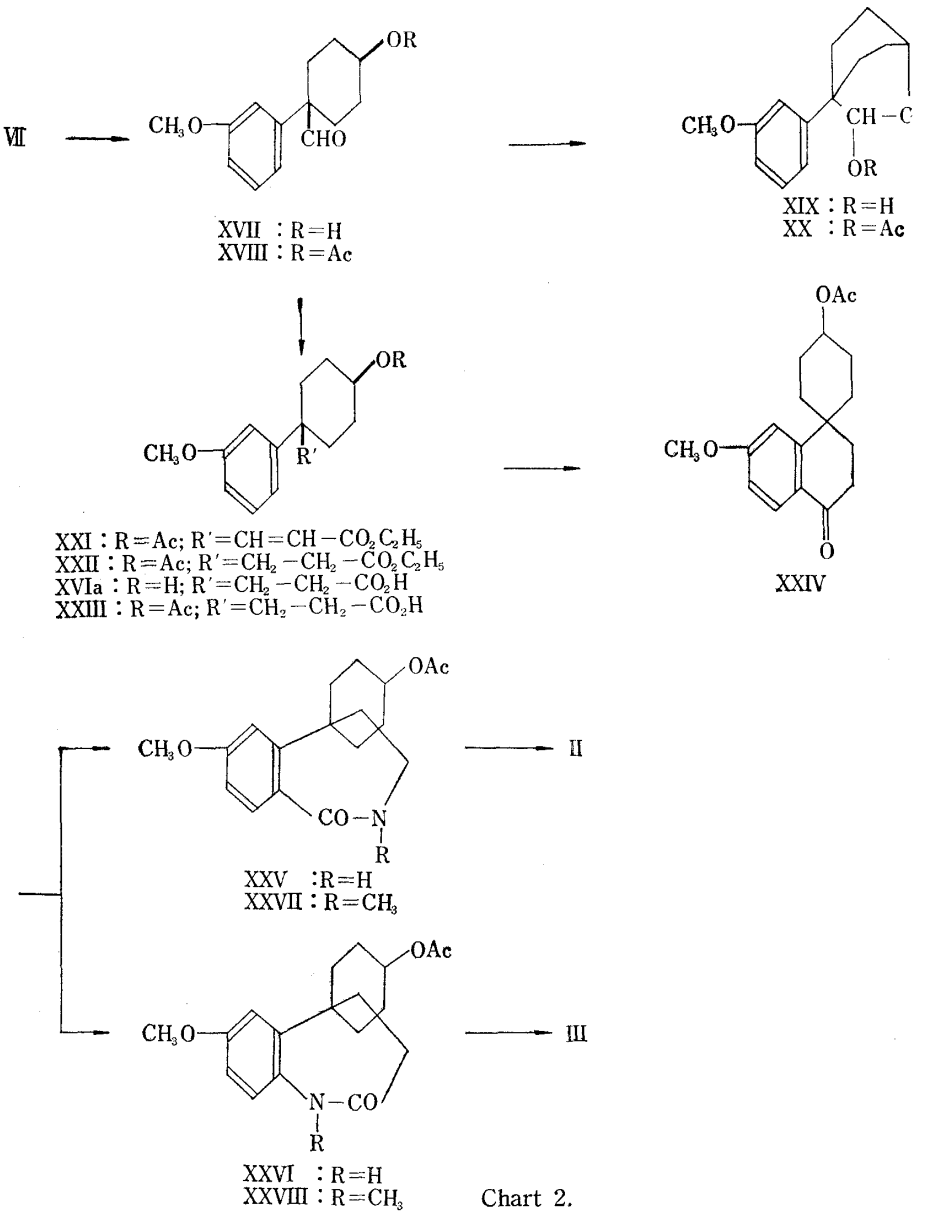

Chart 2.

acid in boiling benzene. It should be noted that acetylation of the hydroxy-aldehyde (XVII) with acetic anhydride in pyridine at room temperature affords only the acetoxy-aldehyde (XVIII).

The Wittig reaction on XVIII with ethyl (diethylphosphono)acetate and sodium hydride underwent smoothly, giving the acetoxy-acrylate (XXI) in 92% yield. Hydrogenation of XXI followed by hydrolysis of the ester group in XXII gave a hydroxy-propionic acid, identical with the compound (XVIa) obtained above. Reacetylation of the hydroxy-acid (XVIa) gave the acetoxypropionic acid (XXIII) which was treated first with phosphorus pentachloride to give the acid chloride and then with stannic chloride to effect cyclization to furnish the spiro-ketone (XXIV). The Schmidt reaction with this ketone by the use of sodium azide in trichloroacetic acid gave isomeric acetoxy-lactams (XXV and XXVI in a ratio of 6:4) and a small amount of a tetrazole, which were separated by chromatography on silica gel.

N-methylation of XXV with methyl iodide in the presence of sodium hydride and subsequent reduction of the lactam grouping with lithium aluminum hydride gave the compound (II) whose ultraviolet absorption spectra in ethanol and acidic ethanol were

almost identical, proving its structure. On the other hand, the lactam (XXVI), after similar N-methylation and reduction, gave the compound (Ⅲ) which exhibited a hypsochromic shift in the ultraviolet spectrum in acidic solution with a smaller extinction coefficient than that measured in ethanol. This result supports structure (Ⅲ).

The anticholinesterase activity of compounds (Ⅱ) and (Ⅲ) was investigated at the Research Laboratory, Dainippon Pharmaceutical Co. in Osaka with the following results. They were shown to have far less activity against cholinesterase, each having ED_{50}'s more than $10^{-4}M$ while that of galanthamine, physostigmine, and neostigmine was $3.5\times10^{-6}M$, $6.0\times10^{-7}M$ and $3.5\times10^{-7}M$, respectively. Other biological effects are still under investigation.

Experimental

Methyl γ-Cyano-γ-(*m*-methoxyphenyl)pimelate (V)——A solution of 30% methanolic Triton B (2 g.) in *t*-BuOH (4 ml.) was added with stirring to a solution of *m*-methoxybenzyl cyanide (Ⅳ) (5.8 g.) and methyl acrylate (7 g.) in *t*-BuOH (20 ml.) at 65~70° over a period of 30 min. After further heating under reflux for 2 hr., the reaction mixture was concentrated to dryness under reduced pressure to yield an oil which was taken up in $CHCl_3$. The $CHCl_3$ solution was washed successively with dil. HCl, 5% aqueous Na_2CO_3 and H_2O, and dried over $MgSO_4$. Evaporation of the $CHCl_3$ left a tan oil which crystallized on standing for several hours at room temperature. Crystallization from ether gave the methyl cyano-pimelate (V) (8.5 g.) as needles, m.p. 64~65°. *Anal.* Calcd. for $C_{17}H_{21}O_5N$: C, 63.93; H, 6.63; N, 4.39. Found: C, 64.04; H, 6.65; N, 4.42. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), 1745 (CO).

Methyl 2-Oxo-5-cyano-5-(*m*-methoxyphenyl)cyclohexanecarboxylate (VI)——A mixture of NaH (2 g.) (50% in mineral oil), the methyl cyano-pimelate (V) (5 g.), toluene (130 ml.) and a few drops of MeOH was heated under reflux in nitrogen for 7 hr. After cooling, a small amount of AcOH was added and the mixture was washed with 5% Na_2CO_3 and H_2O, dried over $MgSO_4$, and evaporated to dryness to give a residue. Crystallization of the residue from EtOH gave the β-keto-ester (Ⅵ) (4.2 g.) as needles, m.p. 95~96°. *Anal.* Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.73; H, 5.89; N, 4.67. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250(CN), 1665 (CO).

1-(*m*-Methoxyphenyl)-4-oxocyclohexanecarbonitrile (VII)——A solution of the β-keto-ester (Ⅵ) (14.4 g.), conc. HCl (152 ml.) and conc. H_2SO_4 (16 ml.) in EtOH (304 ml.), was heated on a water bath for 10 hr., concentrated under reduced pressure to 160 ml., and diluted with H_2O (300 ml.) which was extracted with ether. The ether extract was washed with 5% aqueous Na_2CO_3 and H_2O, and dried over $MgSO_4$. Evaporation of the ether gave a residue which was crystallized from petroleum ether to give the cyano-ketone (Ⅶ) (9.7 g.) as prisms, m.p. 75.5~76°. *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.28; H, 6.61; N, 6.16. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2242 (CN), 1728 (CO).

1-(*m*-Methoxyphenyl)-4-oxocyclohexanecarbonitrile Ethylene Ketal (VIII)——A mixture of the cyano-ketone (Ⅶ) (4.5 g.), ethylene glycol (100 ml.), BF_3-ether (3 ml.), and dry dioxane (50 ml.) was allowed to stand at room temperature overnight. The mixture was poured into 10% aqueous Na_2CO_3 and extracted with ether. The extract was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent gave the cyano-ketone ethylene ketal (Ⅷ) (4.5 g.) which was recrystallized from *n*-hexane as prisms, m.p. 72~73°. *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.28; H, 7.25; N, 5.15. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2220 (CN).

1-(*m*-Methoxyphenyl)-4-oxocyclohexanecarboxylic Acid Ethylene Ketal (IX)——A mixture of the cyano-ketone ethylene ketal (Ⅷ) (300 mg.), diethylene glycol (16 ml.) and 5% aqueous KOH (10 ml.) was heated under reflux for 4 hr. After being diluted with H_2O (140 ml.), the mixture was acidified with conc. HCl, and extracted with ether, which was washed with H_2O and dried over Na_2SO_4. Evaporation of the ether gave a residue which was crystallized from petroleum ether to give the ketal-carboxylic acid (Ⅸ) (300 mg.) as needles, m.p. 134~135°. *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.78; H, 6.87. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480~2500 (COOH), 1700 (CO).

4-Hydroxymethyl-4-(*m*-methoxyphenyl)cyclohexanone Ethylene Ketal (X)——A mixture of the ketal-carboxylic acid (Ⅸ) (4 g.), $LiAlH_4$ (1.04 g.) and ether (90 ml.) was heated under reflux for 20 hr. After the excess $LiAlH_4$ had been destroyed by the careful addition of H_2O, the mixture was filtered, and the filtrate was concentrated to dryness to give a residue which was taken up in ether. The ether solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give the ketal-alcohol (X) (3.2 g.) as needles, m.p. 50~52° (from petroleum ether). *Anal.* Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.00; H, 8.01. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH).

1-(*m*-Methoxyphenyl)-4-oxocyclohexanecarboxyaldehyde Ethylene Ketal (XI)——To a mixture of CrO_3 (0.2 g.) and dry pyridine (5 ml.) was added with stirring a solution of the ketal-alcohol (X) (0.2 g.) in dry pyridine (4 ml.). The mixture was allowed to stand at room temperature for 2 days, poured into H_2O (20 ml.) and extracted with ether. The ether extract was washed successively with dil. HCl, 5% aqueous Na_2CO_3

and H_2O, and dried over Na_2SO_4. Evaporation of the ether gave a yellow oil which was chromatographed in benzene on Al_2O_3. The benzene eluate gave the ketal-aldehyde (XI) (87 mg.) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2750 (CHO), 1728 (CO). On further elution with $CHCl_3$ the ketal-alcohol (X) (20 mg.), m.p. and mixed m.p. 50~52° was recovered unchanged.

Ethyl 1-(*m*-Methoxyphenyl)-4-oxocyclohexaneacrylate Ethylene Ketal (XII)——Ethyl (diethylphosphono)-acetate (350 mg.) was added dropwise with stirring to a suspended solution of NaH (85 mg.) (50% in mineral oil) in dry benzene (5 ml.) under cooling in an ice-water bath. Stirring was continued at room temperature until hydrogen evolution ceased. A solution of the ketal-aldehyde (XI) (536 mg.) in dry benzene (5 ml.) was then added dropwise to the above solution with ice cooling. The mixture was stirred at room temperature for 45 min. and then at an elevated temperature for a further 30 min. After cooling, the reaction mixture was poured into ice-water and extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness to give an oil, which was chromatographed in $CHCl_3$ on SiO_2 gel. The $CHCl_3$ eluate gave the ketal-acrylate (XII) (640 mg.) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO), 1643 (C=C).

Ethyl 1-(*m*-Methoxyphenyl)-4-oxocyclohexanepropionate Ethylene Ketal (XIII)——The ketal-acrylate (XII) (200 mg.) was hydrogenated in EtOH (50 ml.) over Adams catalyst. After the theoretical amount of hydrogen had been taken up, the solution was filtered, and the filtrate was concentrated under reduced pressure to give a residue which was chromatographed in $CHCl_3$ on SiO_2 gel. The $CHCl_3$ eluate gave the ketal-propionate (XIII) (200 mg.) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1723 (CO).

1-(*m*-Methoxyphenyl)-4-oxocyclohexanepropionic Acid Ethylene Ketal (XIV)——A solution of the ketal-propionate (XIII) (300 mg.) in 5%-ethanolic NaOH (55 ml.) was heated on a water bath for 2 hr. The acidic product which was isolated by working up the solution in the usual manner was chromatographed in $CHCl_3$ on SiO_2 gel. The $CHCl_3$ eluate gave the ketal-propionic acid (XIV) (225 mg.) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500~2500 (COOH), 1723 (CO).

1-(*m*-Methoxyphenyl)-4-oxocyclohexanepropionic Acid (XV)——A solution of the ketal-propionic acid (XIV) (300 mg.) in AcOH (15 ml.) was heated on a water bath for 4 hr. Working up in the usual way gave the keto-propionic acid (XV) (255 mg.) as prisms, m.p. 142~143°(from ether). *Anal.* Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.61; H, 7.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500~2500 (COOH), 1715 (CO).

1-(*m*-Methoxyphenyl)-4-hydroxycyclohexanepropionic Acid (XVIa and XVIb)——The keto-acid (XV) (200 mg.) was treated with efficient stirring with $NaBH_4$ (100 mg.) in THF (10 ml.) and H_2O (2 ml.) at room temperature for 4 hr. The mixture was concentrated to dryness, taken up in dil. HCl and extracted with ether which was washed with H_2O and dried over Na_2SO_4. Removal of the ether gave an oil which was chromatographed in $CHCl_3$ on SiO_2 gel. The first $CHCl_3$ eluate gave the *trans*-hydroxy-propionic acid (XVIb) (92 mg.) as prisms, m.p. 102~104°(from ether). *Anal.* Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.21; H, 7.86. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 3400~2600 (COOH), 1710 (CO).

Further elution with $CHCl_3$-EtOH (10:1) afforded the *cis*-hydroxypropionic acid (XVIa) (96 mg.) as needles, m.p. 106~107°(from ether). *Anal.* Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.17; H, 7.82. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 3400~2600 (COOH), 1710 (CO). Both of the hydroxy-acids (XVIa and XVIb) were oxidized with CrO_3-pyridine complex to give the same keto-acid (XV).

4-Formyl-4-(*m*-methoxyphenyl)cyclohexanol (XVII)——The cyano-ketone (VII) (500 mg.) was refluxed with $LiAlH_4$ (100 mg.) in dry THF (100 ml.) for 6 hr. After the excess $LiAlH_4$ was decomposed by the careful addition of H_2O, the mixture was filtered and the filtrate was concentrated to dryness to give a residue which was taken up in ether. The ether solution was extracted with dil. HCl. The aqueous layer was basified with 5% aqueous NH_3 and extracted with ether which was washed with H_2O and dried over K_2CO_3. Evaporation of the ether gave an oil which was heated in AcOH (10 ml.), and 2% H_2SO_4 (20 ml.) on a water bath for 1 hr. After cooling, the mixture was diluted with H_2O (100 ml.) and extracted with ether. The ether extract was washed with 5% aqueous Na_2CO_3 and H_2O, dried over Na_2SO_4 and evaporated to give a residue, which was chromatographed in benzene on Al_2O_3 to yield the hydroxy-aldehyde (XVII) (358 mg.) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 2700 (CHO), 1730 (CO). The hydroxy-aldehyde was kept for several days at room temperature, when crystals separated which was recrystallized from ether-EtOH to give the hemiacetal (XIX) as prisms, m.p. 157°. *Anal.* Calcd. for $C_{14}H_{18}O_3 \cdot H_2O$: C, 66.64; H, 7.99. Found: C, 66.66; H, 7.99. IR ν_{max}^{KBr} cm^{-1}: 3430 (OH). The hemiacetal (XIX) gave the oily acetate (XX) on treatment with Ac_2O and pyridine.

The Hemiacetal Acetate (XX)——A mixture of the *cis*-hydroxy-aldehyde (XVII) (60 mg.), Ac_2O (0.5 ml.) and *p*-toluenesulfonic acid (6 mg.), and dry benzene (10 ml.) was refluxed for 5 hr. After cooling, the mixture was diluted with ether, washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent-mixture gave an oil which was chromatographed in benzene on Al_2O_3. Elution with benzene gave the hemiacetal acetate (XX) (55 mg.) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732 (CO). This acetate was identical with the sample obtained by acetylation of the hemiacetal with Ac_2O and pyridine.

Acetylation of the Hydroxy-aldehyde (XVII) with Acetic Anhydride and Pyridine——A mixture of the *cis*-hydroxy-aldehyde (XVII) (200 mg.), dry pyridine (2 ml.) and Ac_2O (1 ml.) was allowed to stand at room temperature overnight. Working up in the usual way gave an oil which was purified by chromatography in benzene on SiO_2 gel. The $CHCl_3$ eluate gave the *cis*-acetoxy-aldehyde (XVIII) (212 mg.) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (CO).

Wittig Reaction of the Acetoxy-aldehyde (XVIII)——The *cis*-acetoxy-aldehyde (XVIII) (200 mg.) was treated with Wittig reagent prepared from ethyl (diethylphosphono)acetate and NaH in the same manner as described above. After working up in the same way, the resulting neutral oil was chromatographed in $CHCl_3$ on SiO_2 gel. The $CHCl_3$ eluate gave the acetoxy-acrylate (XXI) (240 mg.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (CO), 1645 (C=C).

Ethyl 1-(*m*-methoxyphenyl)-4-acetoxycyclohexanepropionate (XXII)——The acetoxy-acrylate (XXI) (100 mg.) was hydrogenated over Adams PtO_2 (24 mg.) in EtOH (20 ml.) at room temperature. After the theoretical volume of H_2 had been absorbed, the mixture was filtered, and the filtrate concentrated to dryness under reduced pressure to give a residue which was taken up in ether, and dried over Na_2SO_4. Evaporation of the ether gave the acetoxy-propionate (XXII) (100 mg.) which was crystallized from petroleum ether as prisms, m.p. 62~63°. *Anal.* Calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.01; H, 8.08. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1739 (CO).

1-(*m*-Methoxyphenyl)-4-hydroxycyclohexanepropionic Acid (XVIa)——A solution of the acetoxy-propionate (XXII) (150 mg.) in 5% ethanolic NaOH (50 ml.) was heated on a water bath for 2 hr. Evaporation of the EtOH under reduced pressure gave a residue which was taken up in ice-water. The aqueous solution was acidified with 20% HCl and extracted with ether which was washed with H_2O, dried over Na_2SO_4 and evaporated to give the hydroxy-propionic acid (XVIa) (105 mg.). It was crystallized from ether as needles, m.p. and mixed m.p. 106~107°. Acetylation of the hydroxy-acid (XVIa) with Ac_2O and pyridine gave the oily acetate (XXIII) in good yield, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500~2600 (COOH), 1735, 1715 (CO).

4-Acetoxy-7'-methoxyspiro[cyclohexane-1,1'(2'*H*)-naphthalen]-4'(3'*H*)-one (XXIV)——To a solution of the acetoxy-acid (XXIII) (200 mg.) in dry benzene (10 ml.) was added PCl_5 (200 mg.) under cooling in an ice bath, and the mixture was stirred for 45 min. Then $SnCl_4$ (500 mg.) was added to the mixture in one portion and stirring was continued at 0° for 45 min. and at room temperature for an additional 10 min. The mixture was diluted with ice cold conc. HCl and extracted with ether. The ether extract was washed with 5% aqueous Na_2CO_3 and H_2O, dried over Na_2SO_4, and evaporated to dryness to give the spiro-ketone (XXIV) (149 mg.) which was crystallized from ether as prisms, m.p. 132~133°. *Anal.* Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.52; H, 7.46. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1672 (CO). UV λ_{max}^{EtOH} mμ (log ε): 227 (4.12); 279 (4.13).

Schmidt Reaction with the Acetoxy-tetralone (XXIV)——NaN_3 (129 mg.) was added with stirring to a mixture of the spiro-keton (XXIV) (300 mg.) and $CCl_3 \cdot COOH$ (5.1 g.) at 60°. Stirring was continued at 60~63° for 4 hr. The mixture was poured into 30% aqueous NH_3 with cooling, extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with H_2O, and dried over Na_2SO_4. Evaporation of the $CHCl_3$ gave an oil which was chromatographed in $CHCl_3$ on SiO_2 gel. The first elution with $CHCl_3$ gave a crystalline mass (20 mg.) which was recrystallized from EtOH to give a tetrazole derivative as prisms, m.p. 136~138°. *Anal.* Calcd. for $C_{18}H_{22}O_3N_4$: C, 63.14; H, 6.48; N, 16.36. Found: C, 63.18; H, 6.50; N, 16.42. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (CO).

The second elution with $CHCl_3$ gave the acetoxy-1-benzazepin-2-one (XXVI) (100 mg.) which was crystallized from EtOH as prisms, m.p. 202~203°. *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.21; H, 7.28; N, 4.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3200 (NH), 1730, 1670 (CO). UV λ_{max}^{EtOH} mμ (log ε): 249~251 (4.14); 290 (shoulder 3.42).

Finally elution with $CHCl_3$-EtOH (10:2) gave the acetoxy-2-benzazepin-1-one (XXV) (150 mg.) as prisms, m.p. 204~206° (from ether-EtOH). *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.24; H, 7.30; N, 4.56. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3200 (NH), 1730, 1650 (CO). UV λ_{max}^{EtOH} mμ (log ε): 251 (3.98).

2-Methyl-4'-acetoxy-7-methoxy-3,4-dihydrospiro[5*H*-2-benzazepin-5,1'-cyclohexan]-1(2*H*)-one (XXVII)——A mixture of the acetoxy-2-benzazepin-1-one (XXV) (90 mg.), NaH (50% in mineral oil, 90 mg.), and toluene (40 ml.) was heated under reflux for 12 hr. After cooling, CH_3I (0.4 ml.) was added to the mixture and the whole was stirred at room temperature for 1 hr. and at an elevated temperature for an additional 2 hr. After decomposition of the excess NaH with AcOH, the mixture was diluted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give a crystalline mass. Recrystallization of the residue from petroleum ether gave the N-methyl-acetoxy-2-benzazepin-1-one (XXVII) (83 mg.) as prisms, m.p. 108~109°. *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.73; H, 7.59; N, 4.36. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1630 (CO). UV λ_{max}^{EtOH} mμ (log ε): 252 (4.14).

2-Methyl-4'-hydroxy-7-methoxy-1,2,3,4-tetrahydrospiro[5*H*-2-benzazepine-5,1'-cyclohexane] (II)——A mixture of the N-methyl-acetoxy-2-benzazepin-1-one (XXVII) (60 mg.), $LiAlH_4$ (65 mg.) and THF (30 ml.) was heated under reflux for 10 hr. A small amount of H_2O was added to the mixture and the precipitate formed was removed by filtration. The filtrate was evaporated to dryness to give a residue which was taken up in $CHCl_3$. The $CHCl_3$ solution was extracted with dil. HCl, and the acidic extract was basified with 5% aqueous NH_3 and extracted with ether. The ether extract was washed with H_2O, dried over K_2CO_3 and concentrated to give an oil which was chromatographed in $CHCl_3$ on Al_2O_3. The $CHCl_3$ eluate gave the hydroxy-2-benzazepine (II) (44 mg.) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3686 (OH). UV λ_{max}^{EtOH} mμ (log ε): 230 (3.91), 280 (shoulder 3.29). UV $\lambda_{max}^{EtOH\text{-}HCl}$ mμ (log ε): 232 (3.99), 280 (shoulder 3.21). The base (II) gave the crystalline

hydrochloride as prisms, m.p. 144～145°(from MeOH–ether). *Anal.* Calcd. for $C_{17}H_{25}O_2N \cdot HCl$: C, 65.47; H, 8.40; N, 4.49; Cl, 11.37. Found: C, 65.56; H, 8.44; N, 4.53; Cl, 11.51. IR ν_{max}^{KBr} cm^{-1}: 3375 (OH), 2650 (N^+H).

N-Methylation of the Acetoxy-1-benzazepin-2-one (XXVI)——The acetoxy-1-benzazepin-2-one (XXVI) (90 mg.) was methylated with NaH and CH_3I by the same method as described for the N-methylation of the benzazepin-1-one (XXV). The resulting N-methylbenzazepinone (XXVIII) (86 mg.) was crystallized from petroleum ether as prisms, m.p. 115°. *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.72; H, 7.71; N, 4.35. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1738, 1650 (CO). UV λ_{max}^{EtOH} mμ (log ε): 247 (4.44), 290 (shoulder 3.65).

Reduction of the N-Methyl-1-benzazepin-2-one (XXVIII) with Lithium Aluminum Hydride——The N-methyl-1-benzazepin-2-one (XXVIII) (90 mg.) in THF (50 ml.) was heated under reflux with $LiAlH_4$ (114 mg.) for 4 hr. Working up in the usual manner gave a basic oil which was chromatographed in $CHCl_3$ on Al_2O_3. The $CHCl_3$ eluate gave the hydroxy-1-benzazepine (III) (64 mg.) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3686 (OH). UV λ_{max}^{EtOH} mμ (log ε): 254 (3.83), 299 (3.38). $\lambda_{max}^{EtOH-HCl}$ mμ (log ε): 225 (4.02), 280 (3.19).

The oily amine (III) gave the crystalline hydrochloride, m.p. 134～136°(from MeOH–ether). *Anal.* Calcd. for $C_{17}H_{25}O_2N \cdot HCl$: C, 65.47; H, 8.40; N, 4.49; Cl, 11.37. Found: C, 65.41; H, 8.38; N, 4.41; Cl, 11.43. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650 (OH), 2480 (N^+H).

Summary

4-Acetoxy-7′-methoxyspiro[cyclohexane-1,1′(2′*H*)-naphthalen]-4′(3′*H*)-one (XXIV) has been synthesized and subjected to the Schmidt reaction to give the isomeric benzazepinones (XXV and XXVI). N-methylation followed by reduction with lithium aluminum hydride of these compounds (XXV and XXVI) afforded the 1- and 2-benzazepine (II and III), respectively. In contrast to the inhibitory effect of galanthamine (I) on acetylcholinesterase, neither of these two synthetics showed appreciable anticholinesterase activity.

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143. Hiroaki Nomura and Keiichi Sugimoto: Synthesis of L-Ascorbic Acid Acyl Derivatives stabilized against Oxidation.*1

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Benzoylations of the enediol system in L-ascorbic acid have been studied with the aim of obtaining L-ascorbic acid derivatives which are antiscorbutically active and stabilized against oxidation.

This paper deals with the relationship between the reaction conditions and the structures of the products which were inter alia identified as 2-O-benzoyl-L-ascorbic acid, 3-O-benzoyl-5,6-isopropylidene-L-ascorbic acid, 2,6-di-O-benzoyl-L-ascorbic acid, 3,6-di-O-benzoyl-L-ascorbic acid, and 3,5,6-tri-O-benzoyl-L-ascorbic acid as shown in Chart 1.

Only a few reports relate to the syntheses of the acyl derivatives of L-ascorbic acid in which the enediol system has been acylated; these include 3-acetyl-5,6-isopropylidene-L-ascorbic acid,[1] tribenzoylated-L-ascorbic acid[2] and 3-palmitoyl-L-ascorbic acid.[3]

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