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Synthesis of Spiro[1,2,3,4-tetrahydro-7-methoxy-2-methyl-5*H*-2-benzazepine-5,1′-4′-hydroxycycloheptane]

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For the purpose of testing the biological activity, spiro[1,2,3,4-tetrahydro-7-methoxy-2-methyl-5*H*-2-benzazepine-5,1′-4′-hydroxycycloheptane] (IV) and its isomer (V) were synthesized by a sequence of reactions including ring enlargement of the acetoxy-1-tetralone (XXV) to a seven-membered nitrogenous ring compound (XXVI and XXVII) by the use of Schmidt reaction.

In earlier publications the authors have reported the synthesis of spiro[1,2,3,4-tetrahydro-7-methoxy-2-methyl-5*H*-2-benzazepine-5,1′-4′-hydroxycyclohexane] (II)[2] and spiro[4-hydroxycyclohexane-1,4′-2′,3′-dihydro-6′-methoxy-2′-methyl-1′*H*-isoquinoline] (III)[3] which are structurally related to galanthamine (I), an Amaryllidaceae alkaloid. We now wish to report the synthesis of spiro[1,2,3,4-tetrahydro-7-methoxy-2-methyl-5*H*-2-benzazepine-5,1′-4′-hydroxycycloheptane] (IV) which has a seven–membered ring in place of the cyclohexane ring in the compound (II). The isomeric compound (V), was also obtained as a by–product in the course of the synthesis.

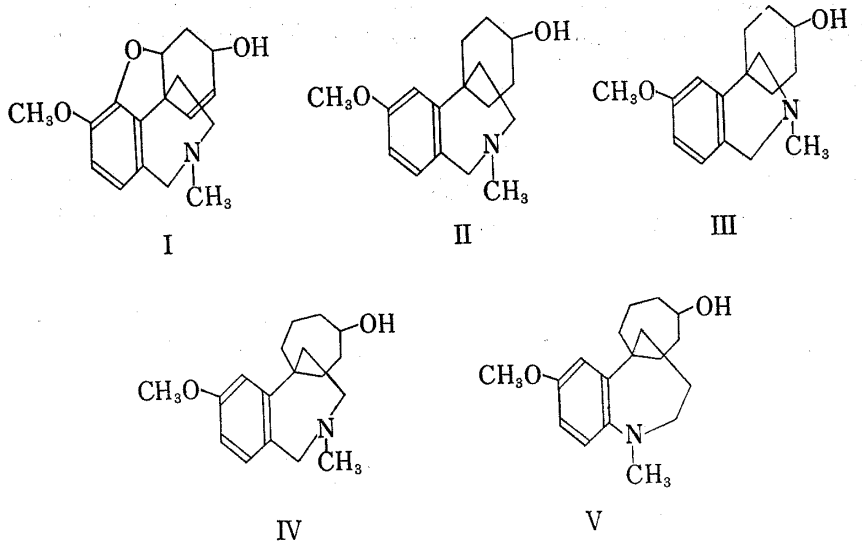

Chart 1

1-(*m*-Methoxyphenyl)-4-oxocyclohexanecarbonitrile (VI)[2] was served as starting material for our present synthesis. Treatment of the compound (VI) with nitrosomethylurethane and sodium carbonate in methanol afforded 1-(*m*-methoxyphenyl)-4-oxocycloheptanecarbonitrile (VII) in 71% and the epoxide (VIII) in 18% yield.

Reduction of the hepthanone–nitrile (VII) with sodium borohydride at room temperature gave the hydroxy–nitrile (XI). Lithium aluminum hydride reduction of the heptanone–nitrile (VII) or the hydroxy–nitrile (XI) gave an aldimine which was readily hydrolyzed with

1) Location: *3–1, Tanabe–dori, Mizuho–ku, Nagoya.*
2) S. Uyeo, H. Shirai, A. Koshiro, T. Yashiro, and K. Kagei, *Chem. Pharm. Bull.* (Tokyo), **14**, 1033 (1966).
3) H. Shirai, T. Yashiro, and T. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1564 (1969).

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acid to give the hydroxy–aldehyde (IX). The hydroxy–amine (X) was obtained as a by-product. The *cis*-configuration of the hydroxyl and the nitrile or the aldehyde group in XI or IX was proved by the fact that the corresponding hydroxy–carboxylic acid (XII) formed a lactone (XIII).

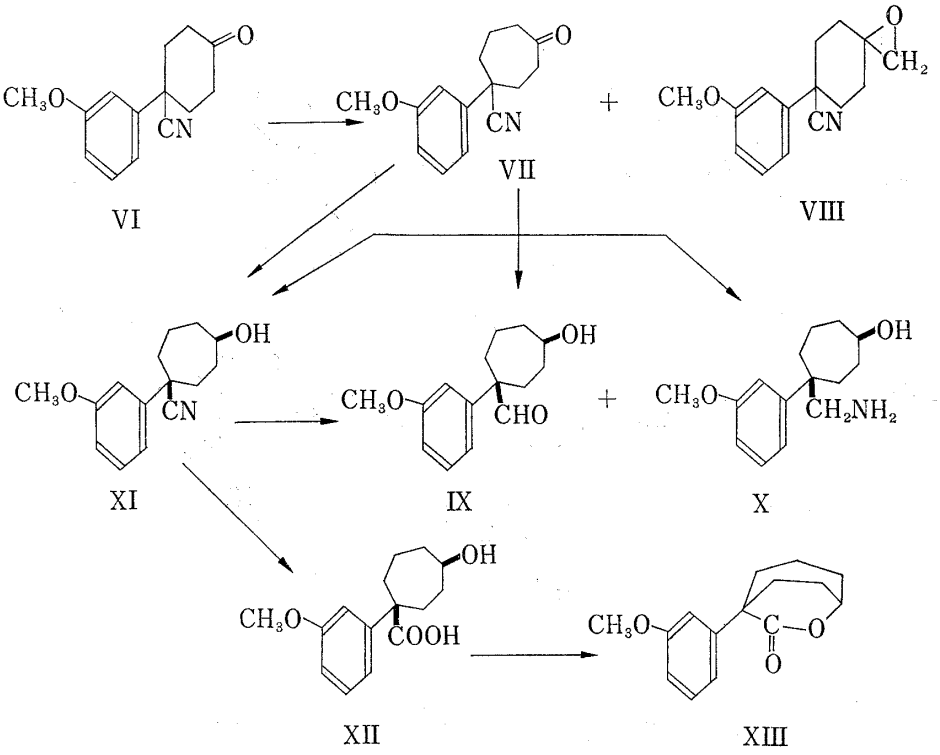

Chart 2

Acetylation of the hydroxy–aldehyde (IX) with acetic anhydride in pyridine afforded the acetoxy- aldehyde (XIV). The Wittig reaction[4] on XIV with ethyl(diethylphosphono)-acetate and sodium hydride underwent smoothly, giving the acetoxy–acrylate (XV) in an excellent yield.

Hydrogenation of XV in the presence of Adams' catalyst afforded the acethoxy–propionic ester (XVI), which on hydrolyses with ethanolic alkali afforded the hydroxy- propionic acid (XVII). This compound (XVII) was alternatively prepared from 1-(*m*-methoxyphenyl)-4-oxocyclohexanepropionic acid (XVIII) as follows.[2] The keto–propionic acid (XVIII) was treated with nitrosomethylurethane and sodium carbonate in methanol and the resulting keto–ester (XIX) and epoxy–ester (XXI) were hydrolysed with alkali to give XX and XXII, respectively.

Reduction of the keto–acid (XX) with sodium borohydride at room temperature gave a mixture of epimeric hydroxy–acids (XVII and XXIII) in a ratio of 3:1, one of which was identical with the compound (XVII) obtained above. The epimeric hydroxy–acid (XVIII) was reverted to the starting keto–acid (XX) on reoxidation with chromic acid–pyridine.

Reacetylation of the hydroxy–propionic acid (XVII) gave the acetoxy–propionic acid (XXIV) which was treated with phosphorus pentachloride and then cyclized by the Friedel–Crafts reaction using stannic chloride as a catalyst furnishing the acetoxy-tetralone (XXV). The infrared spectrum of XXV showed a conjugated carbonyl band at 1675 cm^{-1}, and absorptions due to out-of-plane CH deformation vibration at 862 and 817 cm^{-1}, indicating that this compound was a 1:2:4-tri-substituted benzene derivative. The ultraviolet absorption and

4) G. Wittig and V. Schöllkopf, *Ber.*, **87**, 1318 (1954); W.S. Wadsworth and W.D. Emmons, *J. Am. Chem. Soc.*, **83**, 1773 (1961).

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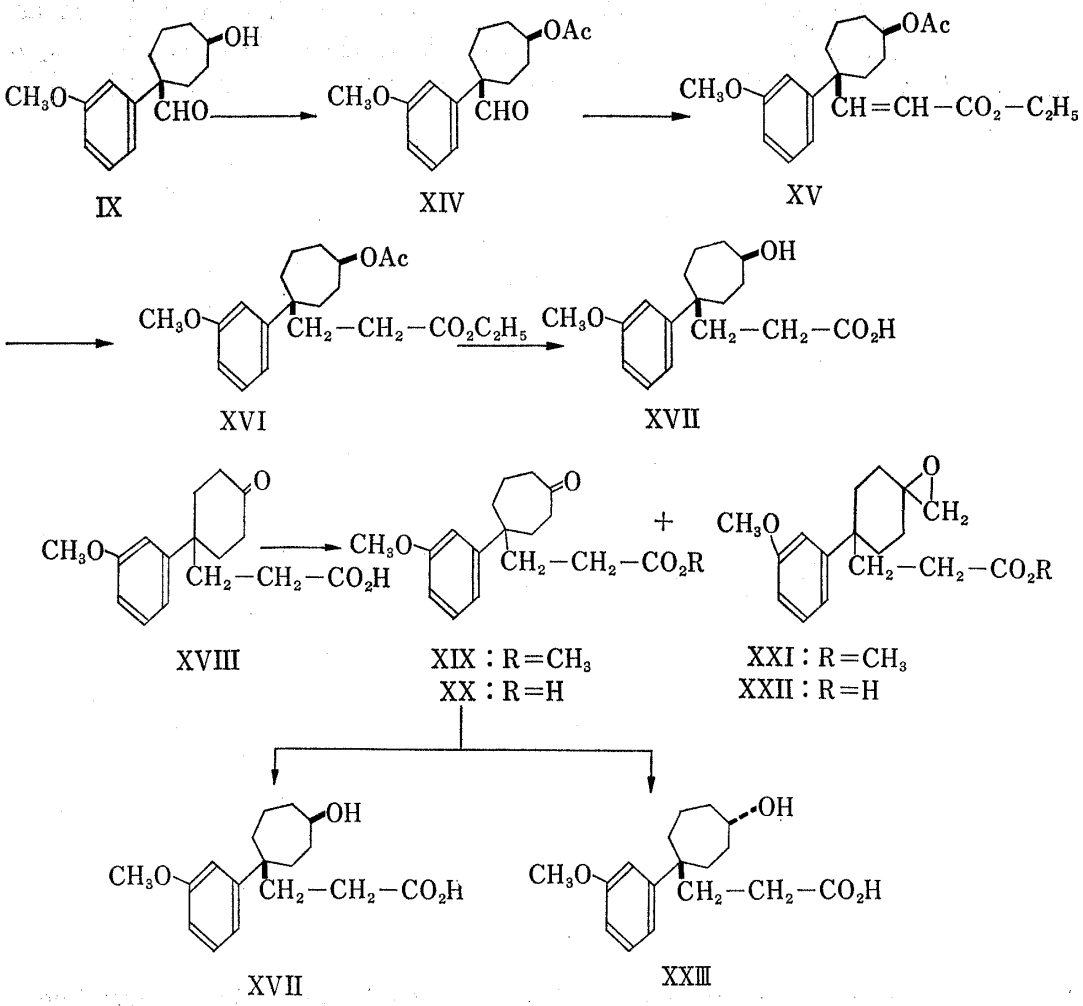

Chart 3

nuclear magnetic resonance spectra gave data which were in agreement with the assigned structure (XXV).

The Schmidt[5] reaction on the acetoxy-tetralone (XXV) by the use of sodium azide in trichloroacetic acid gave two seven-membered ring lactams (XXVI and XXVII) in a ratio of 4:6, which were separated by column chromatography on silica gel using chloroform as an eluent. The distinction between the structures of the isomeric lactams (XXVI and XXVII) was made by comparing their spectral properties. The infrared absorption spectra of XXVI showed carbonyl band which was at a lower frequency by 18 cm^{-1} than that of XXVII. The nuclear magnetic resonance spectrum of XXVII showed a multiplet (2H) due to $-NH-CO-\underline{CH_2}-CH_2-$ at 7.60—7.90 τ which was almost unchanged on replacement of the hydrogen attached to nitrogen by deuterium. In contrast, the nuclear magnetic resonance spectrum of XXVI indicated a significant difference in the region (6.90 τ) of the methylene adjacent to nitrogen from that resulted from the deuterium exchange reaction. The nuclear magnetic resonance spectrum of XXVI displayed a 9-position aromatic proton at 2.30 τ (doublet) in a lower field than XXVII because of the anisotropy effect of the carbonyl group.

N-Methylation of XXVI with methyl iodide in the presence of sodium hydride and subsequent reduction of the lactam grouping with lithium aluminum hydride gave the compound (IV) whose ultraviolet absorption spectra in neutral ethanol and acidic ethanol were almost identical. On the other hand, the lactam XXVII, after N-methylation and reduction in a

5) K.F. Schmidt, *Ber.*, **57**, 704 (1924); H.J. Schmidt, A. Hunger, and K. Hoffmann, *Helv. Chim. Acta*, **39**, 607 (1956); D.E. Evans and I.M. Lockhart, *J. Chem. Soc.*, **1965**, 4801.

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similar manner gave the compound (V) which exhibited a hypsochromic shift in the ultraviolet spectrum in acidic solution with a smaller extinction coefficient than that measured in ethanol. These results support the assigned structures for IV and V. Infrared, mass, and nuclear magnetic resonance spectra gave also data in agreement with those structures (IV andV).

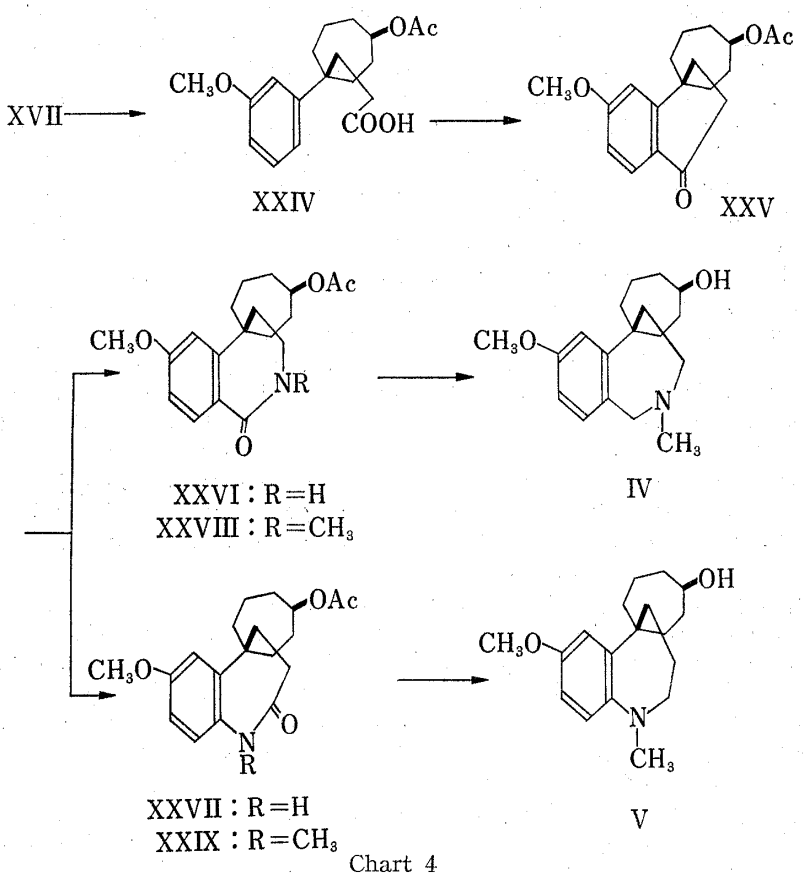

Chart 4

The anticholinesterase activity of compounds (IV) and (V) 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} more than 10^{-4}M while that of galanthamine and neostigmine was 3.5×10^{-6}M and 3.0×10^{-7}M, respectively. Other biological effects are still under investigation.

Experimental[6]

1-(*m*-Methoxyphenyl)-4-oxocycloheptanecarbonitrile (VII)——To a mixture of the hexanone-nitrile (VI)[2] (5 g), methanol (100 ml) and finely powdered sodium carbonate (200 mg) was added a solution of nitrosomethylurethane (6 ml) dropwise with stirring at 20—25° over a period of 20 min. Stirring was continued at room temperature for 1 hr and inorganic salts were removed by filtration. The filtrate was concentrated to dryness to give a residue which was taken up in ether. The ethereal extract was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness to give an oil, which was chromatographed in $CHCl_3$ on silica gel. Elution with chloroform gave 6-cyano-6-(*m*-methoxyphenyl)-1-oxaspiro-[2,5]octane (VIII) (970 mg), which crystallized from *n*-hexane as prisms, mp 70—71°. *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.03; H, 7.26; N, 6.01. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN). NMR (in $CDCl_3$) τ: 2.52—3.20 (3H, multiplet, aromatic protons), 6.18 (3H, singlet, $-OCH_3$), 7.24 (2H, singlet, $-CH_2-O-$), 7.33—7.93 (8H, multiplet, $-CH_2-CH_2-$). Further elution with the same solvent gave

6) All melting points were measured on a Yanagimoto micromelting point determination apparatus, and all melting and boiling points were uncorrected. Nuclear magnetic resonance spectra were taken on a Varian associate A-60 spectrometer for deuteriochloroform solutions with tetramethylsilane as internal standard.

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the heptanone-nitrile (VII) (3.76 g) as an oil, bp 150—155° (1 mmHg) (bath temp.). *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.12; H, 7.23; N, 5.81. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), 1703 (C=O). Elution with $CHCl_3$–EtOH (100:1) recovered the starting material (VI) (140 mg), mp and mixed mp 77.5—76° unchanged.

Treatment of the Heptanone-nitrile (VII) with Lithium Aluminum Hydride——The heptanone-nitrile (VII) (500 mg) in dry tetrahydrofuran (100 ml) was heated under reflux with $LiAlH_4$ (130 mg) for 5 hr. The excess reagent was decomposed with H_2O and the resultant precipitate was filtered off. The filtrate was evaporated to dryness to give a residue which was taken up in ether. The ether solution was washed with dilute ice-cold HCl, dried and evaporated to dryness to give a solid which on chromatography in $CHCl_3$ on silica gel and elution with $CHCl_3$ gave the hydroxy-nitrile (XI) (120 mg) as an oil, bp 155—160° (0.15 mmHg) (bath temp.). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.62; H, 7.69; N, 5.66. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 2230 (CN). Further elution with the same solvent gave the hydroxy-aldehyde (IX) (40 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 2700 (CHO), 1723 (C=O). The aqueous layer separated from the ether solution was basified with 5% aqueous NH_3 and extracted with ether. The ethereal extract was washed with H_2O, dried, and evaporated to dryness to give an oil, which was heated in AcOH (10 ml) and 20% 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 $CHCl_3$. The $CHCl_3$ extract was washed with 5% aqueous Na_2CO_3 and H_2O, dried over anhydrous Na_2SO_4 and evaporated to give a residue, which was chromatographed in benzene on Al_2O_3 to yield the hydroxy-aldehyde (IX) (110 mg) as an oil. The aqueous layer separated from the $CHCl_3$ solution was basified with 5% aqueous NH_3 and extracted with ether, and the ethereal solution was washed with H_2O and dried over anhydrous K_2CO_3. Evaporation of the ether gave an oil which was chromatographed in $CHCl_3$ on Al_2O_3. The $CHCl_3$ eluate gave the hydroxyamine (X) (165 mg) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3400 (NH_2 broad). The hydrochloride of the amine (X) formed prisms, mp 107—109° (from MeOH-ether). *Anal.* Calcd. for $C_{15}H_{23}O_2N \cdot HCl$: C, 62.99; H, 8.46; N, 4.90; Cl, 12.40. Found: C, 63.14; H, 8.65; N, 4.75; Cl, 12.62.

1-(*m*-Methoxyphenyl)-4-hydroxycycloheptanecarbonitrile (XI)——To the heptanone-nitrile (VII) (1.2 g) in tetrahydrofuran (50 ml) was added $NaBH_4$ (600 mg) in H_2O (5 ml). The mixture was stirred at room temperature for 4 hr and evaporated to dryness. The residue was taken up in H_2O (40 ml), acidified with dilute HCl, and extracted with ether and the ethereal solution was washed with H_2O and dried over anhydrous Na_2SO_4. Removal of the ether gave an oil which was chromatographed in $CHCl_3$ on silica gel. The $CHCl_3$ eluate gave the *cis*-hydroxy-nitrile (XI) (920 mg) as an oil, bp 155—160° (0.15 mmHg) (bath temp.), identical in all respects with the sample described above.

1-(*m*-Methoxyphenyl)-4-hydroxycycloheptanecarboxylic Acid (XII)——A mixture of the *cis*-hydroxy-nitrile (XI) (200 mg), diethylene glycol (10 ml) and 40% aqueous NaOH (15 ml) was heated under reflux for 10 hr. The solution was diluted with H_2O (100 ml) and washed with ether. The aqueous layer was acidified with concentrated HCl and extracted with AcOEt. The AcOEt extract was washed H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness to give an oil, which was chromatographed in $CHCl_3$ on silica gel. The $CHCl_3$ eluate gave the *cis*-hydroxycarboxylic acid (XII) (170 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3500—2400 (COOH). and 1720 (C=O).

1-(*m*-Methoxyphenyl)-4-hydroxycycloheptanecarboxylic Lactone (XIII)——A mixture of *cis*-hydroxy-carboxylic acid (XII) (80 mg) and Ac_2O (5 ml) was heated on a water bath for 5 hr. Removal of the excess solvent by evaporation under reduced pressure gave a residue which was distillated to give the lactone (XIII) (69 mg) as an oil, bp 123—125° (1 mmHg) (bath temp.). *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.88; H, 7.51. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1739(C=O).

Treatment of the *cis*-Hydroxy-nitrile (XI) with Lithium Aluminum Hydride——The *cis*-hydroxy-nitrile (XI) (180 mg) and $LiAlH_4$ (40 mg) in tetrahydrofuran (20 ml) was heated under reflux for 5 hr. The excess reagent was decomposed with H_2O and the resultant precipitate was filtered off. The filtrate was concentrated to dryness to give a residue which was taken up in ether and extracted with dilute HCl. The ether layer gave, on washing with H_2O, drying and evaporation, the unreacted starting material (68 mg). The dilute HCl layer was basified with 5% aqueous NH_3, and extracted with ether. The ethereal extract was washed with H_2O, dried over anhydrous K_2CO_3 and concentrated to give an oil which was taken up in AcOH (10 ml). The solution was diluted with H_2O (5 ml) containing 3 drops of concentrated H_2SO_4 and heated on a water bath for 1 hr. The mixture was diluted with H_2O, extracted with $CHCl_3$, and the extract was washed with 5% aqueous Na_2CO_3 and H_2O, dried and concentrated to dryness to give the *cis*-hydroxy-aldehyde (IX) (34 mg) as an oil. The infrared spectrum of this oil was identical with the sample described above. The aqueous layer separated from the $CHCl_3$ solution was basified with aqueous NH_3 and extracted with ether. The ethereal extract was washed with H_2O, dried and evaporated to give the *cis*-hydroxy-amine (X) (49 mg) as an oil. The amine (X) gave the hydrochloride as prisms, mp and mixed mp 107—108°.

1-(*m*-Methoxyphenyl)-4-acetoxycycloheptanecarboxyaldehyde (XIV)——A mixture of the *cis*-hydroxy-aldehyde (IX) (300 mg), dry pyridine (3 ml) and Ac_2O (1.5 ml) was allowed to stand at room temperature overnight. After the addition of ice–water, the mixture was acidified with concentrated HCl and extracted with ether. The ethereal extract was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to

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dryness. Purification of the residue by chromatography in $CHCl_3$ on silica gel gave the *cis*-acetoxy-aldehyde (XIV) (300 mg) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726 (C=O).

Ethyl 1-(*m*-Methoxyphenyl)-4-acetoxycycloheptaneacrylate (XV)——Ethyl (diethylphosphono) acetate (160 mg) was added dropwise with stirring to a slurry of NaH (38.5 mg) (50% in mineral oil) in dry benzene (5 ml) at 15—20°. The mixture was stirred at room temperature until hydrogen evolution had ceased. The *cis*-acetoxy-aldehyde (XIV) (130 mg) in dry benzene (5 ml) was added dropwise to the above solution with ice cooling. Stirring was continued at room temperature for a further 2.5 hr, during which time a brown gummy precipitate appeared. After cooling, the reaction mixture was poured into ice–water and extracted with ether. The ethereal extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to dryness to give an oil, which was chromatographed in $CHCl_3$ on silica gel. The $CHCl_3$ eluate gave the *cis*-acetoxy-acrylate (XV) (110 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1718 (C=O), 1644 (C=C).

Ethyl 1-(*m*-Methoxyphenyl)-4-acetoxycycloheptanepropionate (XVI)——The *cis*-acetoxy-acrylate (XV) (120 mg) was hydrogenated over Adams' PtO_2 (30 mg) in EtOH (30 ml) at room temperature until the calculated amount of hydrogen had been absorbed. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue which was chromatographed in $CHCl_3$ on silica gel. The $CHCl_3$ eluate gave the *cis*-acetoxy-propionate (XVI) (110 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1737 (C=O).

1-(*m*-Methoxyphenyl)-4-hydroxycycloheptanepropionic Acid (XVII)——The *cis*-acetoxy-propionate (XVI) (200 mg) was heated in 5% ethanolic NaOH (50 ml) on a water bath for 1 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. The ethereal extract was washed with H_2O, dried and evaporated to give the *cis*-hydroxy-propionic acid (XVII) (130 mg) which crystallized from ether as prisms, mp 122—123°. *Anal.* Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.78; H, 8.41. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3500—2600 (COOH), 1720 (C=O).

Ring Enlargement of the Hexanone-propionic Acid (XVIII)——The hexanone-propionic acid (XVIII)[2] (230 mg) was added with stirring to finely powdered sodium carbonate (16 mg) in MeOH (10 ml). To the mixture was added dropwise with stirring a solution of nitrosomethylurethane (0.32 ml) over a period of 5 min maintaining the temperature below 25°. The mixture was stirred at room temperature for 1 hr, filtered, and the filtrate was evaporated to dryness to leave a residue which was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness to give an oil (165 mg), which was chromatographed in $CHCl_3$ on silica gel. The initial $CHCl_3$ eluate gave ethyl 6-(*m*-methoxyphenyl)-1-oxaspiro [2,5] octanepropionate (XXI) as an oil (59 mg) which exhibited in the IR spectrum an ester band at 1738 cm^{-1}. Hydrolysis of the oil in EtOH (20 ml) and 5% aqueous KOH (10 ml) by heating to reflux for 1 hr, and work-up in the usual manner gave 6-(*m*-methoxyphenyl)-1-oxaspiro [2,5] octanepropionic acid (XXII) (32 mg) as plates, mp 140—141° (from *n*-hexane–EtOH). *Anal.* Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.30; H, 7.51. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500—2500 (COOH), 1715 (C=O). Further elution with $CHCl_3$–EtOH (20:1) gave the heptanone-propionate (XIX) (108 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1738 (ester), 1705 (C=O). Hydrolysis of this compound in ethanolic NaOH gave the heptanone-propionic acid (XX) as prisms, mp 155—156° (from ether). *Anal.* Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.20; H, 7.81. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500—2500 (COOH), 1718 (shoulder), 1705 (C=O).

1-(*m*-Methoxyphenyl)-4-hydroxycycloheptanepropionic Acid (XVII and XXIII)——Sodium borohydride (100 mg) in H_2O (2 ml) was added to heptanone-propionic acid (XX) (200 mg) in tetrahydrofuran (20 ml). The mixture was stirred at room temperature for 4 hr, concentrated to dryness, acidified with dilute HCl and extracted with ether which was washed with H_2O and dried over anhydrous Na_2SO_4. Removal of the ether gave an oil (165 mg) which was chromatographed in $CHCl_3$ on silica gel. The initial eluate gave the *trans*-hydroxy-propionic acid (XXIII) (45 mg) as prisms, mp 119—120° (from ether). *Anal.* Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.80; H, 8.32. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3500—2600 (COOH), 1720 (C=O). Further elution with $CHCl_3$–EtOH (100:3) afforded the *cis*-hydroxy-propionic acid (XVII) (104 mg) as prisms, mp and mixed mp 122—123° (from ether).

Respective hydroxy-propionic acids (XVII and XXIII) were oxidized with CrO_3-pyridine complex to give the same keto-propionic acid (XX).

1-(*m*-Methoxyphenyl)-4-acetoxycycloheptanepropionic Acid (XXIV)——A mixture of the *cis*-hydroxy-propionic acid (XVII) (200 mg), dry pyridine (2 ml) and Ac_2O (1 ml) was allowed to stand at room temperature overnight. The mixture was evaporated to dryness to leave a residue which was chromatographed in $CHCl_3$ on silica gel to give the *cis*-acetoxy-propionic acid (XXIV) (210 mg) as plates, mp 152—153° (from ether). *Anal.* Calcd. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.35; H, 7.68. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1738 (shoulder), 1715 (C=O).

Friedel-Crafts Cyclization of the *cis*-Acetoxy-propionic Acid (XXIV)——Finely powdered phosphorus pentachloride (278 mg) was added to the *cis*-acetoxy-propionic acid (XXIV) (270 mg) in dry benzene (150 ml) with cooling in an ice bath and the mixture was stirred for 45 min. Stannic chloride (680 mg) was added to the mixture in one portion and stirring was cotinued at 0° for a further 45 min and then at room temperature for an additional 10 min. The mixture was poured into ice containing concentrated HCl, and extracted with ether. The ethereal extract was washed with 5% aqueous Na_2CO_3 and H_2O, dried

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over anhydrous Na_2SO_4 and evaporated to dryness to give the acetoxy-1-tetralone (XXV) (217 mg) which was crystallized from ether as prisms, mp 126—127°. *Anal.* Calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.19; H, 7.84. IR ν_{max}^{KBr} cm^{-1}: 1734 (AcO), 1673 (conjugated C=O), 860, 810 (1,2,4-trisubstituted benzene). UV λ_{max}^{EtOH} $m\mu$ (log ε): 226 (4.17), 279 (4.16). NMR (in $CDCl_3$) τ: 1.98 (1H, doublet, $J=9.0$ cps, aromatic proton), 2.98—3.29 (2H, multiplet, aromatic protons), 4.80—5.0 (1H, multiplet, >CH–OAc), 6.12 (3H, singlet, $-OCH_3$), 7.25—7.50 (4H, multiplet, $-CO-CH_2-CH_2-$), 7.93 (3H, singlet, –OAc), 7.72—8.53 (10H, multiplet, $-CH_2-CH_2-$).

Schmidt Reaction with the Acetoxy-1-tetralone (XXV)——Sodium azide (180 mg) was added with stirring to a mixture of the acetoxy-1-tetralone (XXV) (400 mg) and trichloroacetic acid (6.8 g) at 60—63°. Stirring was continued at the same temperature for 4 hr. The mixture was diluted with ice-water, made alkaline with 30% aqueous NH_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness to leave an oil which was chromatographed in $CHCl_3$ over silica gel. The initial $CHCl_3$ eluate recovered the starting acetoxy-1-tetralone (XXV) (25 mg), mp 126—127° unchan ged, and subsequent $CHCl_3$ eluate gave the acetoxy-1-benzazepinone (XXVII) (197 mg) which was crystallized from ether–EtOH as prisms, mp 168—169°. *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.85; H, 7.51; N, 4.15. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1733 (acetyl C=O), 1668 (amide C=O). UV λ_{max}^{EtOH} $m\mu$ (log ε): 255 (3.86). NMR (in $CDCl_3$) τ: 2.35 (1H, singlet, NH), 2.84—3.24 (3H, multiplet, aromatic protons), 6.10 (3H, singlet, $-OCH_3$), 5.0—5.55 (1H, multiplet, >CH–OAc), 7.95 (3H, singlet, –OAc), 7.60—7.90 (2H, multiplet, $-NH-CO-C\underline{H}_2-CH_2-$), 7.62—8.44 (10H, multiplet, $-CH_2-CH_2-$).

Final elution with $CHCl_3$–EtOH (50:1) gave the acetoxy-2-benzazepinone (XXVI) (125 mg) as prisms, mp 175—177° (from ether–EtOH). *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.81; H, 7.56; N, 4.11. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 3200 (NH), 1730 (acetyl C=O), 1650 (amide C=O). UV λ_{max}^{EtOH} $m\mu$ (log ε): 244 (3.79). NMR (in $CDCl_3$) τ: 2.30 (1H, doublet, $J=9.0$ cps, aromatic proton), 3.05—3.30 (2H, multiplet, aromatic protons), 3.32 (1H, broad, NH), 5.02—5.40 (1H, multiplet, >CH–OAc), 6.17 (3H, singlet, $-OCH_3$), 6.90 (2H, quartet, $J=7.0$, 7.0 cps, $-NH-CH_2-CH_2-$), 7.97 (3H, singlet, –OAc), 8.02—8.47 (10H, multiplet, $-CH_2-CH_2-$).

Spiro [3,4-dihydro-7-methoxy-2-methyl-5*H*-2-benzazepine-5,1′-4′-acetoxycycloheptane-1(2*H*)-one] (XXVIII)——A mixture of the acetoxy-2-benzazepinone (XXVII) (120 mg) and NaH (90 mg) (50% in mineral oil) in dry toluene (50 ml) was heated under reflux for 12 hr. After cooling, CH_3I (1 ml) was added to the mixture and the whole was stirred at room temperature for 1 hr and with heating under reflux for a further 2 hr. After decomposition of the excess NaH with AcOH, the mixture was diluted with benzene, washed with H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness. The resultant neutral oil was chromatographed in $CHCl_3$ on silica gel. The $CHCl_3$ eluate gave the N-methyl-2-benzazepinone (XXVIII) (103 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (acetyl C=O), 1630 (amide C=O).

Spiro [1,2,3,4-tetrahydro-7-methoxy-2-methyl-5*H*-2-benzazepine-5,1′-4′-hydroxycycloheptane] (IV)——A mixture of the N-methyl-2-benzazepinone (XXVIII) (107 mg), $LiAlH_4$ (142 mg) and tetrahydrofuran (55 ml) was heated under reflux for 14 hr. A small amount of water was added to the mixture and the precipitate which 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 dilute HCl, the acidic aqueous layer was basified with 5% aqueous NH_3 and extracted with ether. The ethereal extract was washed with H_2O, dried over K_2CO_3, and evaporated to dryness to give the hydroxy-2-benzazepine (IV) (67 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH). UV λ_{max}^{EtOH} $m\mu$ (log ε): 231 (4.86), 260 (shoulder 4.23). $\lambda_{max}^{EtOH-HCl}$ $m\mu$ (log ε): 230 (4.80), 260 (shoulder 4.23). NMR (in $CDCl_3$) τ: 2.90—3.45 (3H, multiplet, aromatic protons), 6.10 (2H, singlet, $-CH_2-N<$), 6.20 (3H, singlet, $-OCH_3$), 7.60 (1H, singlet, –OH), 7.69 (3H, singlet, >N–CH_3), 7.99—8.44 (10H, multiplet, $-CH_2-CH_2-$). Mass Spectrum *m/e*: 289 (M^+).

The base (IV) gave the hydrochloride as prisms, mp 156—158° (from MeOH–ether). *Anal.* Calcd. for $C_{18}H_{27}O_2N\cdot HCl$: C, 66.31; H, 8.66; N, 4.30; Cl, 10.88. Found: C, 66.51; H, 8.52; N, 4.35; Cl, 10.96. IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 2650 (N^+–H).

N-Methylation of the Acetoxy-1-benzazepinone (XXVII)——The acetoxy-1-benzazepinone (XXVII) (200 mg) was methylated with NaH and CH_3I by the same method as described for the N-methylation of the acetoxy-2-benzazepinone (XXVI). The resultant neutral oil was chromatographed in $CHCl_3$ on silica gel. The $CHCl_3$ eluate gave the N-methyl-1-benzazepinone (XXIX) (160 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1734 (acetyl C=O), 1643 (amide C=O).

Reduction of the N-Methyl-1-benzazepinone (XXIX) with Lithium Aluminum Hydride——The N-methyl-1-benzazepinone (XXIX) (133 mg) in tetrahydrofuran (50 ml) was heated under reflux with $LiAlH_4$ (173 mg) for 5 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 (V) (75 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH). UV λ_{max}^{EtOH} $m\mu$ (log ε): 254 (4.72), $\lambda_{max}^{EtOH-HCl}$ $m\mu$ (log ε): 229 (4.64). NMR (in $CDCl_3$): 3.0—3.41 (3H, multiplet, aromatic protons), 6.22 (3H, singlet, $-OCH_3$), 7.21 (3H, singlet, >N–CH_3), 7.90 (1H, singlet, –OH), 8.0—8.75 (10H, multiplet, $-CH_2-CH_2-$). Mass Spectrum *m/e*: 289 (M^+). The oily amine (V) gave the hydrochloride

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as prisms, mp 177—179° (from EtOH). *Anal.* Calcd. for $C_{18}H_{27}O_2N \cdot HCl$: C, 66.31; H, 8.66; N, 4.30; Cl, 10.88. Found: C, 66.18; H, 8.59; N, 4.42; Cl, 10.69. IR ν_{max}^{KBr} cm^{-1}: 3650 (OH), 2550 (N^+–H).

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