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Toyonari Oine, Hiroshi Kugita, and Mikio Takeda : Studies on Benzoisogranatanine Derivatives. II.*1 Synthesis of 1-Phenethyl-2,4-propano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines.

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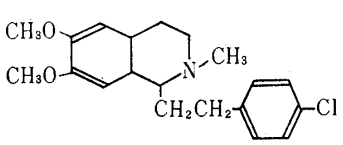
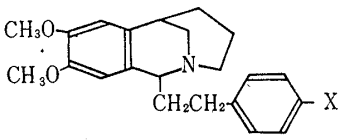
Brossi and co-workers recently reported synthesis of 1-substituted 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines for a new class of analgesics.[1] The 4-chlorophenethyl derivative (A) of this series has been applied to clinical cases with the analgesic activity almost equal to that of codeine.[2] Structural similarity of 2-methyl-1,2,3,4-tetrahydroisoquinoline to the benzoisogranatanine nucleus (2,4-propano-1,2,3,4-tetrahydroisoquinoline) led us to the synthesis of 1-phenethyl-2,4-propano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (B).



A



B

Bischler-Napieralski reaction of same derivatives of 3-(3,4-dimethoxyphenyl)piperidine[3] (II) proved unsuccessful probably due to the violation of the Bredt's rule[4] in the course of the reaction. An alternative approach was therefore undertaken.

5-(3,4-Dimethoxyphenyl)-2-piperidone (I) was hydrolized to the amino acid III in 85% yield. The Schotten-Baumann reaction of III with hydrocinnamoyl chlorides gave IV (X=H, Cl; R=H) which in turn were converted to the esters (IV) (R=Et). The Bischler-Napieralski reaction of IV (R=Et) with phosphorylchloride in toluene gave the 3,4-dihydroisoquinoline derivatives (V) in 70~80% yield. Sodium borohydride reduction of V in ethanol to the tetrahydroisoquinolines (VI), and lithium aluminum hydride reduction of VI gave the 4-hydroxypropyl derivatives (VII) (R=OH). Reaction of VII (R=OH) with thionyl bromide and dehydrobromination[5] of the bromides (VII) (R=Br) gave the 6,7-benzoisogranatanine derivatives (VIII).

The compounds (VIII) (X=H, Cl) showed no analgesic activity at 200 mg./kg. s.c. when tested by the hot plate method.

Experimental*3

5-(3,4-Dimethoxyphenyl)-2-piperidone (I)——Methyl 4-cyano-4-(3,4-dimethoxyphenyl)butylate[6] was

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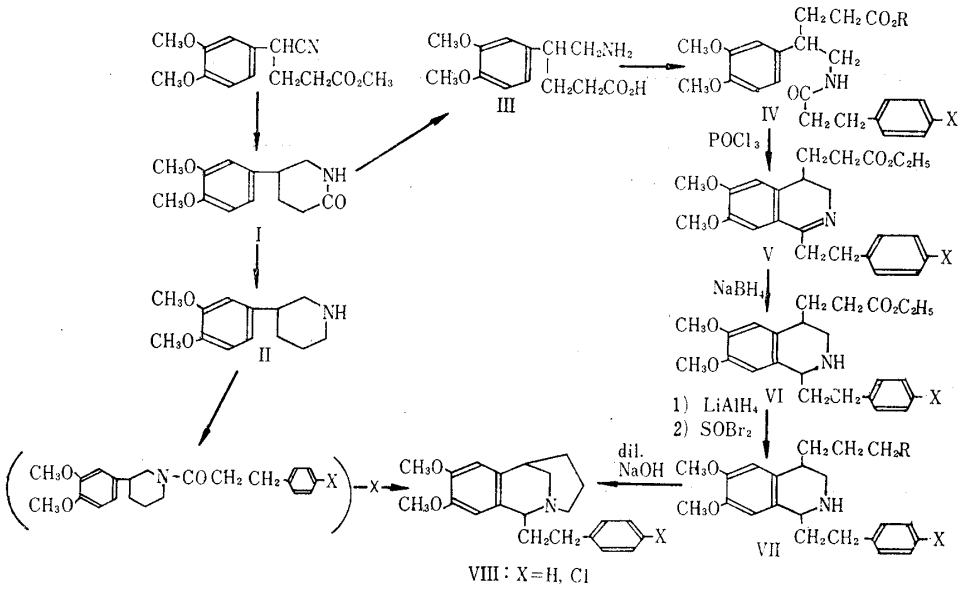
*3 All melting points were uncorrected.

1) A. Brossi, H. Besendorf, B. Pellmont, M. Walter, O. Schnider : Helv. Chim. Acta, **43**, 1459 (1960).
2) M. J. Schiffrin, S. M. Ali : The American Journal of the Medical Sciences, **241**, 103 (1961).
3) N. Sugimoto, H. Kugita : Yakugaku Zasshi, **75**, 183 (1955).
4) F. S. Fawcett : Chem. Revs., **47**, 219 (1950).
5) L. Ruzicka, G. Salomon, K. E. Meyer : Helv. Chim. Acta, **17**, 882 (1934).
6) The cyanoester was prepared from homoveratronitrile and methyl acrylate by the usual procedure. See part I, This Bulletin, **11**, 253 (1963)



hydrogenated with Raney-Ni in 10% NH_3-EtOH following the procedure employed in a preceding work.*1 Colorless plates (from EtOH), m.p. 164~165.5°; yield, 70~75 %. *Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found : C, 66.51; H, 7.04; N, 5.98.

3-(3,4-Dimethoxyphenyl)piperidine (II)——A mixture of the piperidone (I) (14.4 g.), $LiAlH_4$ (7 g.), abs. Et_2O (370 cc.) and dioxane (370 cc.) was refluxed (50~52°) for 11 hr. Working out as usual and distillation of the base yielded a colorless oil (8.5 g.), $b.p_8$ 180~185°.
Hydrochloride : Colorless needles (from EtOH-Me_2CO), m.p. 214~216°.[3]

Attempted Bischler-Napieralski Reaction of II——Acetyl derivative of II ($b.p_{0.2}$ 182~185°) (1g.) was heated with $POCl_3$ (5 cc.) in toluene (15 cc.) for 1.5 hr. Resine separated during the reaction. The solvents were distilled under reduced pressure, the residue was treated with dil. HCl, basified with K_2CO_3 and extracted with Et_2O. Evaporation of Et_2O gave a trace of basic material which was not identified.

Phenylacetyl and hydrocinnamoyl derivatives of II were also heated with $POCl_3$ in toluene or $POCl_3$ alone. No workable amount of basic product was obtained in each case.

4-(3,4-Dimethoxyphenyl)-5-aminopentanoic Acid (III)——I (16 g.) was refluxed with $Ba(OH)_2 \cdot 8H_2O$ (60 g.) in H_2O (600 cc.) for 4 hr., cooled and neutralized with dil. H_2SO_4. The filtered solution was concentrated, and crystalline residue was filtered, dissolved in MeOH (700 cc.), treated with charcoal and filtered. The solution was concentrated to ca. 200 cc., cooled and filtered to give III (14.2 g.), m.p. 156~158°. Recrystallization from MeOH gave colorless needles, m.p. 160~161°. *Anal.* Calcd. for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found : C, 61.67; H, 7.63; N, 5.59.

4-(3,4-Dimethoxyphenyl)-5-hydrocinnamoylaminopentanoic Acids (IV) (R=H), X=Cl——To a stirred solution of III (7.2 g.) and NaOH (5 g.) in H_2O (90 cc.) was added 4-chlorohydrocinnamoyl chloride (11.3 g.) at 0~3°. The reaction was continued for 2.5 hr. at 0~3° and then at room temperature for 1 hr. The mixture was acidified with dil. HCl and extracted with AcOEt. Evaporation of the solvent left crystalline residue which was filtered, washed with Et_2O and recrystallized from AcOEt. Colorless needles (9.1 g.), m.p. 140~141°. *Anal.* Calcd. for $C_{22}H_{26}O_5NCl$: C, 62.92; H, 6.24; N, 3.34. Found : C, 62.75; H, 6.11; N, 3.42.

X=H——The Schotten-Baumann reaction with hydrocinnamoyl chloride gave IV (R=H, X=H) in 80 % yield. Colorless prisms (from Me_2CO), m.p. 134~135°. *Anal.* Calcd. for $C_{22}H_{27}O_5N$: C, 68.55; H, 7.06; N, 3.63. Found : C, 68.58; H, 7.1; N, 3.67.

Ethyl 4-(3,4-Dimethoxyphenyl)-5-hydrocinnamoylaminopentanoates (IV) (R=Et), X=Cl——IV (R=H, X=Cl) (8.9 g.) in abs. EtOH (300 cc.) was saturated with dried HCl gas at 0~5° and left overnight at room temperature. EtOH was distilled, the residue was dissolved in AcOEt, washed with H_2O, dil. $NaHCO_3$ and dried. Evaporation of the solvent and recrystallization of the residue from Me_2CO-Et_2O gave colorless needles (7.8 g.), m.p. 105~106°. *Anal.* Calcd. for $C_{24}H_{30}O_5NCl$: C, 64.35; H, 6.75; N, 3.13. Found : C, 64.44; H, 6.7; N, 3.3.

X=H——Colorless prisms (from Me_2CO-Et_2O), m.p. 98~99°. *Anal.* Calcd. for $C_{24}H_{31}O_5N$: C, 69.71; H, 7.56; N, 3.39. Found : C, 69.95; H, 7.36; N, 3.46.

1-Phenethyl-4-(2-carbethoxyethyl)-6,7-dimethoxy-3,4-dihydroisoquinolines (V) X=Cl——A solution of IV (R=Et, X=Cl) (7.3 g.) and $POCl_3$ (35 cc.) in toluene (120 cc.) was refluxed for 3.5 hr. The solvents were distilled under a reduced pressure, the residue was dissolved in benzene and extracted with dil. HCl. The acid solution was basified with K_2CO_3, extracted with Et_2O, dried and evaporated to give an oil (6 g.), which was dissolved in abs. Et_2O and treated with HCl-MeOH. The hydrochloride was filtered and recrystallized from EtOH-Et_2O (1:3) to give colorless prisms (6.1 g.), m.p. 174~175° (decomp.). *Anal.* Calcd. for $C_{24}H_{29}O_4NCl_2$: C, 61.8; H, 6.27; N, 3.0. Found: C, 61.92; H, 6.27; N, 3.1.

X=H——The Bischler-Napieralski reaction of IV (R=Et, X=H) gave V (X=H)-HCl in 66 % yield. Colorless prisms (from Me_2CO), m.p. 155~156°. *Anal.* Calcd. for $C_{24}H_{30}O_4NCl$: C, 66.71; H, 7.0; N, N, 3.24. Found: C, 66.7; H, 7.2; N, 3.34.

1-Phenethyl-4-(2-ethoxycarbonylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (VI), X=Cl——To a solution of V (X=Cl)-HCl (5.8 g.) in EtOH (130 cc.) was added $NaBH_4$ (1.9 g.) and the mixture was left overnight at room temperature. Working out in a usual way gave an oil (5.4 g.) which was converted to hydrochloride and recrystallized from EtOH to give colorless prisms (3.9 g.), m.p. 169~171°. *Anal.* Calcd. for $C_{24}H_{31}O_4NCl_2$: C, 61.53; H, 6.67; N, 2.99. Found: C, 61.6; H, 6.66; N, 3.13.

X=H—— V (X=H) was reduced as above to give 88 % yield of hydrochloride, colorless needles (from Me_2CO-Et_2O), m.p. 145~147°. *Anal.* Calcd. for $C_{24}H_{32}O_4NCl$: C, 66.42; H, 7.43; N, 3.23. Found: C, 66.55; H, 7.6; N, 3.3.

1-Phenethyl-4-(3-hydroxypropyl)-6,7-dimethoxy-1,2,3,4-terahydroisoquinolines (VII) (R=OH), X=Cl——To a stirred solution of $LiAlH_4$ (1.0 g.) in abs. Et_2O (100 cc.) was added a solution of VI (X=Cl) (3.5 g.) in abs. Et_2O (50 cc.). The mixture was stirred under reflux for 10 hr., cooled, decomposed with water and filtered. The dried ethereal solution was evaporated, the residue was dissolved in abs. benzene and chromatograghed over Al_2O_3. A portion from Et_2O-MeOH (9:1) eluate was converted to hydrobromide and recrystallized from EtOH-Et_2O to give colorless prisms (2.2 g.), m.p. 162~163°. *Anal.* Calcd. for $C_{22}H_{29}O_3NBrCl\cdot H_2O$: C, 54.04; H, 6.39; N, 2.87. Found: C, 53.71; H, 6.37; N, 2.96. Picrate. Yellow needles (EtOH), m.p. 192~193° (decomp.). *Anal.* Calcd. for $C_{22}H_{28}O_3NCl\cdot C_6H_3O_7N_3$: C, 54.32; H, 5.05; N, 9.05. Found: C, 54.24; H, 5.09; N, 8.96.

X=H——$LiAlH_4$ reduction of VI (X=H) was carried out as above to give 50 % yield of VII (R=OH, X=H)-HBr. Colorless rectangles (from Me_2CO), m.p. 135~138°. *Anal.* Calcd. for $C_{22}H_{30}O_3NBr$: C, 60,55; H, 6.93; N, 3.21. Found: C, 60.36; H, 7.0; N, 3.28.

1-Phenethyl-4-(3-bromopropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (VII) (R=Br), X=Cl——VII (R=OH)-HBr (1.2 g.) was dissolved in $CHCl_3$ (60 cc.) and treated with $SOBr_2$ (0.69 g.). After standing overnight at room temperature the mixture was evaporated under reduced pressure, Et_2O was added to the residue, filtered and recrystallized from AcOEt to give colorless prisms (1.3 g.). m.p. 102~105°. *Anal.* Calcd. for $C_{22}H_2O_{28}NBrCl$: C, 49.5; H, 5.29; N, 2.62. Found: C, 50.68; H, 5.52; N, 2.63.

X=H——The bromination reaction of VII (R=OH, X=H) gave colorless prisms (from EtOH), m.p. 160~162°; yield, 91 %. *Anal.* Calcd. for $C_{22}H_{29}O_2NBr_2$: C, 52.9; H, 5.86; N, 2.81. Found: C, 52.9; H, 5.9; N, 2.77.

1-Phenethyl-2,4-propano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (VIII) X=Cl——VII (R = Br, X=Cl)-HBr (0.7 g.) was dissolved in H_2O (450 cc.) and heated to 50°. 1% NaOH (25 cc.) was added to the solution under a vigorous stirring. The mixture was stirred at 60~70° for 2 hr., cooled, extracted with Et_2O, dried and evaporated. The residue was heated with Ac_2O (3 cc.) and AcONa (0.1 g.) for 30 min., and concentrated under a reduced pressure. Treating of the residue with dil. HCl gave crystalline hydrochloride which was recrystallized from MeOH-Me_2CO to colorless needles (340 mg.), m.p. 198~200°. IR λ_{max}^{Nujol} μ: 2.96 (H_2O), 4.02 (broad). *Anal.* Calcd. for $C_{22}H_{27}O_2NCl_2\cdot H_2O$: C, 61.99; H, 6.86; N, 3.29. Found: C, 62.0; H, 6.92; N, 3.27.

X=H——The dehydrobromination reaction of VII (R=Br, X=H) and working up as the above gave VIII (X=H)-HCl, colorless needles (from Me_2CO), m.p. 187~189°; yield, 64 %. IR λ_{max}^{Nujol} μ: 2.96 (H_2O), 4.12 (broad). *Anal.* Calcd. for $C_{22}H_{28}O_2NCl\cdot\frac{1}{2}H_2O$: C, 69.0; H, 7.63; N, 3.69. Found: C, 68.88; H, 7.69; N, 3.84.

Summary

1-Phenethyl-2,4-propano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (B), a structure related to A has been synthesized by lithium aluminum hydride reduction of VI followed by the bromination to VIII (R=Br), and dehydrobromination with diluted alkaline solution.

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