Notes

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Hiroshi Kugita and Toyonari Oine : Benzoisogranatanine Derivatives. I.
 Synthesis of 2'-Hydroxy-5-alkyl-6,7-benzoisogranatanines.

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A series of morphinan isomers, in which the nitrogen atom occupies other positions (e.g., 9, 14, 6, 7 and 8) than the original position, 13, in the morphinan skeleton has been reported by Sugimoto and co-workers.¹⁾ Among the compounds synthesized so far, 2,3,4,4a-tetrahydro-1*H*,6*H*-5,10b-propanophenanthridin-9-ol (3-hydroxy-9-aza-des-N-morphinan) exhibited about the same activity as morphine in the animal test.²⁾ Clinical trials revealed also that this compound is effective in relieving both post-partum and post-operative pain.³⁾

Researches in the field of benzomorphan derivatives carried out by May and co-workers⁴⁾ disclosed that strong analgesic activity resides as well in this class of compounds which are devoid of the C-ring of the morphinan structure. Our present work was motivated by the expectation that a similar relationship would exist between the parent morphinan isomer, 2,3,4,4a-tetrahydro-1*H*,6*H*-5,10b-propanophenanthridine (9-aza-des-N-morphinan) (A) and the title compounds (B).

The synthesis of a B-structure compound, 2',3'-dimethoxy-6,7-benzoisogranatanine by the Pictet-Spengler cyclization of 3-(3,4-dimethoxyphenyl)piperidine has been reported.⁵⁾ Synthesis of the key intermediate of the present study, 3-arylpiperidines (VI), first followed the reaction sequence employed in the previous synthesis of 3-(3,4-dimethoxyphenyl)piperidine. Catalytic hydrogenation of 2-(*m*-methoxyphenyl)-2-methylglutaronitrile (V), however, resulted in an unsatisfactory yield of the 3-arylpiperidine (VI, R=CH₃).

A more feasible approach to VI appeared to be the sequence II→III→IV→VI as shown in the chart. Addition of methyl acrylate to 2-(*m*-methoxyphenyl)propionitrile (II, R=CH₃) and butyronitrile (II, R=C₂H₅) with the catalytic amount of Triton-B in dioxane yielded the cyano esters (III, R=CH₃) and (III, R=C₂H₅) respectively. Reductive cycliza-

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1) N. Sugimoto, H. Kugita : This Bulletin, **3**, 11 (1955); N. Sugimoto, S. Ohshiro : *Ibid.*, **4**, 353, 357 (1956); N. Sugimoto, S. Ohshiro, H. Kugita, S. Saito : *ibid.*, **5**, 63, 317 (1957); N. Sugimoto, H. Kugita : *ibid.*, **5**, 67 (1957), **6**, 430 (1958); N. Sugimoto, S. Ohshiro : *Tetrahedron*, **8**, 296 (1960); S. Ohshiro : *ibid.*, **10**, 175 (1960).

2) N. Sugimoto, H. Kugita : This Bulletin, **3**, 11 (1955).

3) Results of the clinical trials will be published elsewhere.

4) Everette L. May, National Institutes of Health, U.S.A. : A series of papers, "Structures related to Morphine" has been reported. Latest papers of series; *J. Org. Chem.*, **26**, 188, 1621, 1954 (1961).

5) N. Sugimoto, H. Kugita : *J. Pharm. Soc. Japan*, **75**, 183 (1955).

tion⁶⁾ of the cyano esters with Raney-Ni afforded the 2-piperidones (IV, R=CH₃ and C₂H₅). Compound IV was reduced with lithium aluminum hydride in dioxane to give the 3-arylpiperidines (VI, R=CH₃ and C₂H₅).

A Pictet-Spengler type reaction of VI (R=CH₃) with formaldehyde and formic acid²⁾ yielded conclusively the N-methylated derivative IX (R=CH₃) which was in accordance with the product derived from XI (R=CH₃) by the reaction with formaldehyde followed by catalytic hydrogenation. Reaction of VI (R=CH₃ and C₂H₅) with formaldehyde and hydrochloric acid gave the cyclization products VII (R=CH₃ and C₂H₅) which were hydrolyzed to the hydroxy compounds VIII (R=CH₃ and C₂H₅).

6) R. K. Hill, C. E. Glassick : J. Am. Chem. Soc., 81, 737 (1959); E. Tagmann, E. Sury, K. Hoffmann : Helv., 35, 1235 (1952).

In the course of the present study an attempt was made to synthesize 2-acetyl-2-(*m*-methoxyphenyl)propionitrile (XII) and butyronitrile (XIII').

2-Acetyl-2-(*m*-methoxyphenyl)acetonitrile (XI) was methylated with methyl iodide in ethanol containing an equimolar amount of sodium ethoxide. The reaction product (75% yielded) was identified by the spectral evidence as 2-(*m*-methoxyphenyl)propionitrile (II, R=CH₃) rather than the expected product XII.⁷⁾ Similar reaction of XI with ethyl bromide, on the other hand, resulted in the formation (in a 4:1 ratio) of the deacetylated starting material I and a crystalline product to which was assigned the structure XIII' by spectral and analytical data. Although the scission of the -COCH₃ group of XI in sodium ethoxide-ethanol is not without precedent,⁸⁾ the difference in the reaction paths between methyl iodide and ethyl bromide seems noteworthy.

Compounds VII, VIII, IX and X were tested for analgesic activity by the pharmacological section of this laboratory. Compounds VII (R=CH₃ and C₂H₅) and VIII (R=CH₃, C₂H₅) showed high toxicity, and no appreciable activity was detected in these compounds; IX and X were generally less toxic than the cyclized compounds. Compound X (R=CH₃) had one-fourth the activity of meperidine.

Experimental*2

2-(*m*-Methoxyphenyl)propionitrile (II, R=Me)—To NaNH₂ (prepared from Na, 3.7 g.) in anhyd. Et₂O (300 cc.) was added over 1 hr. (*m*-methoxyphenyl)acetonitrile (I) (24 g.) at 10°, and the mixture was refluxed for 3.5 hr. To the cooled mixture (5°) was added dropwise MeI (31 g.) in Et₂O (30 cc.) during 3 hr., stirred at 5~10° for 2 hr. and additional 3 hr. at the reflux temperature, then cooled, washed twice with H₂O and dried over CaCl₂. The filtered solution was treated with benzaldehyde (7 g.) and ethanolic EtONa (Na, 0.7 g. in abs. EtOH, 10 cc.). After standing for 24 hr. at room temperature the solution was filtered from the separated crystals, dried and concentrated. Distillation of the residual oil yielded II (R=Me) (12 g.), b.p._{1.5} 109~112°.

2-(*m*-Methoxyphenyl)butyronitrile (II, R=Et)—Ethylation of I was carried out similarly with replacement of benzene for Et₂O as solvent. From I (22.5 g.), freshly prepared NaNH₂ (from Na, 3.9 g.) and EtBr (25 g.) was obtained II (R=Et) (13 g.), b.p.₅ 140~145°. *Anal.* Calcd. for C₁₀H₁₃ON: C, 75.4; H, 7.48; N, 7.99. Found: C, 75.58; H, 7.41; N, 7.5.

Methyl 4-cyano-4-(*m*-methoxyphenyl)pentanoate (III, R=Me)—To a stirred solution of II, (R=Me) (12 g.) and Triton B (1.2 cc.) in dioxane (40 cc.) was added methyl acrylate (8.6 g.) during 1 hr. at 75~80°. The solution was stirred for 5 hr. at that temperature, then concentrated *in vacuo* to give viscous residue which was dissolved in Et₂O, washed with H₂O, dried and evaporated. Distillation of the residue yielded 11.7 g. of III (R=Me) as a colorless oil, b.p._{0.35} 145~153°. *Anal.* Calcd. for C₁₄H₁₇O₃N: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.01; H, 6.93; N, 5.89.

Methyl 4-Cyano-4-(*m*-methoxyphenyl)hexanoate III, (R=Et)—The Michael reaction of II, (R=Et) with methyl acrylate was carried out similarly, 34% yield of III (R=Et) being obtained as a colorless oil, b.p._{0.5} 153~155°. *Anal.* Calcd. for C₁₅H₁₉O₃N: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.77; H, 7.02; N, 5.55. Fifty percent of the starting material was recovered.

5-Alkyl-5-(*m*-methoxyphenyl)-2-piperidones (IV). R=Me—III (R=Me) (8.7 g.) was hydrogenated in EtOH (50 cc.) containing NH₃ (ca. 10%) over Raney-Ni with an initial pressure of 63 atm. Theoretical volume of H₂ was absorbed at 50~70°. The filtered solution was concentrated under reduced pressure giving a viscous residue which crystallized upon treating with H₂O. Recrystallization from MeOH-H₂O (4:1) gave colorless plates of hydrated piperidone (IV, R=Me), m.p. 58~60°; yield, 5.6 g. (67%). *Anal.* Calcd. for C₁₃H₁₇O₂N·H₂O: C, 65.75; H, 8.07; N, 5.9. Found: C, 65.4; H, 7.97; N, 6.27.

R=Et—III (R=Et) (8.8 g.) in 10% NH₃-EtOH (50 cc.) was hydrogenated as above. The product was recrystallized from MeOH-H₂O (1:1) as colorless needles, m.p. 71~73°; yield, 6.0 g. (70.5%). *Anal.* Calcd. for C₁₄H₁₉O₂N·H₂O: C, 66.9; H, 8.42; N, 5.57. Found: C, 66.97; H, 8.03; N, 5.7.

2-(*m*-Methoxyphenyl)-2-methylglutaronitrile (V)—To a stirred solution of II (R=Me) (13 g.) and

*2 Melting points are uncorrected.

7) T. H. Gohsh and S. Dutta reported similar reaction of α -aceto- α -phenylacetonitrile with methyl iodide to give α -aceto- α -phenylpropionitrile: J. Ind. Chem. Soc., **31**, 316 (1954).

8) W. H. Kutz, H. Adkins: J. Am. Chem. Soc., **52**, 4391 (1930); R. G. Pearson, A. C. Sandy: *Ibid.*, **73**, 931 (1951).

Triton B (1 cc.) in dioxane (40 cc.), was added acrylonitrile (5 g.) in dioxane (20 cc.) during 1.5 hr. at 15~20°. The mixture was stirred at 40~50° for 2 hr. and concentrated under reduced pressure. The viscous residue was dissolved in Et₂O, washed with H₂O and dried. Evaporation of the solvent and distillation of the residue gave colorless viscous oil V, b.p._{0.6} 170~175°; yield, 10.3 g. (57.8%). *Anal.* Calcd. for C₁₃H₁₄N₂O: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.09; H, 6.64; N, 12.87.

3-Alkyl-3-(*m*-methoxyphenyl)piperidines (VI) R=Me—a) V (12 g.) in NH₃-saturated EtOH (80 cc.) was hydrogenated with Raney-Ni at elevated temperature under starting pressure of 70 atm. The reaction took place at 80~90°, and at that temperature the vessel was shaken for 2 hr. The catalyst was removed by filtration and the solvent was distilled. The residue was dissolved in 10% HCl, extracted once with Et₂O, then basified with 10% NaOH and extracted with AcOEt. The dried extract was concentrated and the residual oil was distilled giving a fraction boiling at 155~165° (0.8 mm.) which was converted to oxalate. Fractional recrystallization of the oxalate from MeOH gave colorless needles of IV (R=Me)-oxalate (0.9 g.), m.p. 166~168°. *Anal.* Calcd. for C₁₃H₁₅ON·C₂H₂O₄: C, 61.0; H, 7.17; N, 4.74. Found: C, 60.97; H, 7.06; N, 5.03. The free base showed the *sec*-amine reaction by the Hinsburg and Liebermann tests.

Another oxalate obtained in major quantity from the mixture was a *prim*-amine oxalate (Hinsburg test), and no further study was made of it.

b) To a stirred boiling solution of LiAlH₄ (2.2 g.) in Et₂O (100 cc.) was added dropwise a solution of IV (R=Me) (5 g.) in dioxane (80 cc.) and the reaction was continued at the boiling temperature (70~75°) for 10 hr. The mixture was treated with H₂O (5 cc.), filtered and concentrated in a reduced pressure, the residue was dissolved in 5% HCl, extracted once with Et₂O, basified with K₂CO₃ and extracted with Et₂O. The dried ethereal solution was evaporated and the residue was distilled to give colorless liquid, b.p._{1.6} 140~143°; yield, 2.1 g. (45.1%). Oxalate: Colorless needles, m.p. 165~167°. Admixture with the sample obtained by a) did not depress its melting point.

R=Et—IV (R=Et) (5.7 g.) was similarly reduced with LiAlH₄ (2.8 g.), yield, 4.3 g. (80.5%), b.p._{0.4} 120~124°. Hydrobromide: Colorless needles (from EtOH-E₂O), m.p. 170~171°. *Anal.* Calcd. for C₁₄H₂₁ON·HBr: C, 56.0; H, 7.39; N, 4.67. Found: C, 56.24; H, 7.32; N, 4.74.

2'-Methoxy-5-alkyl-6,7-benzoisogranatanines (VII). R=Me—VI (R=Me) (1.1 g.) 37% HCHO (0.53 cc.) and H₂O (3 cc.) were heated in a H₂O bath for 30 min. The solution was decanted from the precipitate and the gummy residue was washed with H₂O three times. The gum was dissolved in conc. HCl (5 cc.) and heated in a H₂O bath for 1 hr., then concentrated under reduced pressure, the residue was dissolved in H₂O, basified with K₂CO₃ and extracted with AcOEt. The dried extract was evaporated and distilled at 125~128° (0.8 mm.) to give a colorless oil (0.8 g.) which was dissolved in Et₂O and treated with HCl-EtOH. Recrystallization of the crude hydrochloride from MeOH-Et₂O formed colorless needles, m.p. 258~260°; yield, 0.45 g. (35%). *Anal.* Calcd. for C₁₄H₁₉ON·HCl: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.5; H, 7.74; N, 5.64.

R=Et—Cyclization of VI (R=Et) (1.0 g.) was carried out by the procedure mentioned above to give VII (R=Et)-HBr, colorless needles, m.p. 206~208° (from EtOH-Et₂O); yield, 0.4 g. *Anal.* Calcd. for C₁₅H₂₁ON·HBr: C, 57.69; H, 7.1; N, 4.49. Found: C, 57.46; H, 6.9; N, 4.66.

2'-Hydroxy-5-alkyl-6,7-benzoisogranatanines (VIII). R=Me—VII (R=Me)-HCl (0.5 g.) and 47% HBr (5 cc.) were heated under reflux for 1.5 hr., and cooled. The separated crystalline hydrobromide was filtered and recrystallized from 47% HBr to give colorless rectangles, m.p. 299~301° (decomp.); yield, 0.5 g. (89%). *Anal.* Calcd. for C₁₃H₁₇ON·HBr: C, 54.93; H, 6.38; N, 4.93. Found: C, 55.0; H, 5.97; N, 5.13.

R=Et—VII (R=Et)-HBr (0.5 g.) in 47% HBr (5 cc.) was refluxed for 1.5 hr., cooled and filtered. The crude hydrobromide was recrystallized from EtOH-Et₂O in colorless prisms, m.p. 234~236°; yield, 0.28 g. (59%). *Anal.* Calcd. for C₁₄H₁₉ON·HBr: C, 56.38; H, 6.76; N, 4.7. Found: C, 56.27; H, 6.42; N, 4.71.

1-Methyl-3-alkyl-3-(*m*-methoxyphenyl)piperidines (IX). R=Me—a) A mixture (VI, R=Me) (1.9 g.), 37% HCHO (1.5 g.), 96% HCOOH (4 cc.) and H₂O (5 cc.) was heated in a sealed tube at 130~140° for 7 hr.²⁾ The solution was concentrated under reduced pressure, H₂O was added to the residue, and the clear aqueous solution was basified with K₂CO₃, extracted with Et₂O and dried. Evaporation of the solvent and distillation of the residue gave a colorless liquid, 1.7 g. which was dissolved in Et₂O and treated with HBr-EtOH. Recrystallization of the crude hydrobromide from AcOEt-EtOH gave colorless needles, m.p. 160~163°; yield, 1.7 g. *Anal.* Calcd. for C₁₄H₂₁ON·NBr: C, 56.02; H, 7.39; N, 4.67. Found: C, 56.15; H, 7.34; N, 4.63.

b) VI (R=Me) (0.5 g.) in EtOH (15 cc.) was treated with 37% HCHO (0.24 cc.) and warmed at 40~50° for 30 min. The mixture was hydrogenated under atmospheric pressure with 10% Pd-C (0.2 g.), theoretical volume of H₂ being absorbed in 1 hr. at room temperature. The catalyst was removed, the solvent was distilled, then the residue was dissolved in Et₂O and treated with HBr-EtOH. The crude hydrobromide was recrystallized from AcOEt-EtOH; yield, 0.5 g., m.p. 161~162°. Mixed m.p. with the product of a), 160~162°.

R=Et—N-Methylation of VI (R=Et) (1 g.) was carried out by method b) yielding XI (R=Et)

(0.8 g.), b.p.₂ 145~147°. Hydrobromide: Colorless needles, m.p. 153~155° (from EtOH-Et₂O). *Anal.* Calcd. for C₁₅H₂₃ON·HBr: C, 57.32; H, 7.7; N, 4.46. Found: C, 57.19; H, 7.51; N, 4.61.

1-Methyl-3-alkyl-3-(*m*-hydroxyphenyl)piperidines (X)—Demethylation of IX, (R=Me, Et) was carried out by heating with 47% HBr for 1.5 hr. R=Me. Hydrobromide: Colorless needles, m.p. 209~211° (from MeOH-Et₂O). *Anal.* Calcd. for C₁₃H₁₉ON·HBr: C, 54.55; H, 7.04; N, 4.89. Found: C, 54.49; H, 7.18; N, 4.98.

R=Et. Hydrochloride: Colorless prisms, m.p. 217~219° (from EtOH-Et₂O). *Anal.* Calcd. for C₁₄-H₂₁ON·HCl: C, 65.73; H, 8.67; N, 5.47. Found: C, 65.55; H, 8.54; N, 5.57.

2-(*m*-Methoxyphenyl)acetoacetonitrile (XI)—To a stirred, heated (70~80°) solution of EtONa (21.4 g.) in abs. EtOH (100 cc.) was added a mixture of AcOEt⁹⁾ (34 g.) and I (37 g.) during 1.5 hr. The reaction mixture was refluxed for 3 hr., then concentrated and diluted with Et₂O. The Na salt of XI was filtered, dissolved in H₂O, treated with dil. AcOH and filtered. Colorless rectangles of XI was obtained from dil. MeOH, m.p. 81~82.5°; yield, 31.5 g. (66%). *Anal.* Calcd. for C₁₁H₁₁O₂N: C, 69.82; H, 5.86; N, 7.4. Found: C, 69.71; H, 5.83; N, 7.37.

Attempted Alkylation of XI. Reaction of XI with CH₃I—XI (18.2 g.) was added to a solution of EtONa (6.8 g.) in abs. EtOH. To this clear solution was added under stirring CH₃I (20.6 g.) during 1 hr. Temperature was maintained at 25° during the addition and stirring was continued for additional 1 hr. at that temperature. The mixture was refluxed for 3 hr., then concentrated, diluted with H₂O and extracted with Et₂O. The ethereal extract was washed with 5% NaOH and H₂O, and dried. Evaporation of Et₂O and distillation of the residue gave a colorless liquid, b.p.₃ 129~132°, yield, 12.0 g. (79%). IR spectra of the product and II (R=Me) were superimposable.

Reaction of XI with EtBr—Reaction procedure was the same as the above. Reaction of XI (14.7 g.), EtONa (6 g.) and EtBr (21 g.) in EtOH (110 cc.) gave two products; a) b.p.₃ 129~132°, 7.8 g. b) b.p.₂ 180~185°, 1.9 g. The product (a) was identified as I from its IR spectrum which was the same as that of I. The product (b) crystallized upon standing. Recrystallization from Et₂O-ligroin gave colorless plates, m.p. 63~65°. IR $\lambda_{\text{max}}^{\text{MeOH}}$ μ : 4.5, 6.23. Microanalysis supported the structure XII' for (b). *Anal.* Calcd. for C₁₃H₁₅O₂N: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.09; H, 6.9; N, 6.8.

Summary

Cyclization of 3-(*m*-methoxyphenyl)-3-methyl(or ethyl)piperidine followed by hydrolysis gave 2'-hydroxy-5-methyl-6,7-benzoisogranatanine and 5-ethyl analog. The two and intermediate compounds were tested for analgesic activity.

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9) AcOEt was distilled over P₂O₅ before the reaction. *Org. Syntheses*, **18**, 66 (1938).