Notes

UDC 547.837.6.07

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

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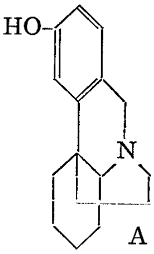
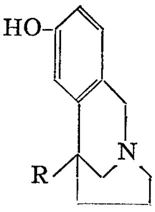
A series of morphinan isomers, in which the nitrogen atom occupies other positions (e.g., 9, 14, 6, 7 and 8) than the original position, 13, in the morphinan skeleton has been reported by Sugimoto and co-workers.[1] Among the compounds synthesized so far, 2,3,4,4a-tetrahydro-1*H*,6*H*-5,10b-propanophenanthridin-9-ol (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-workers[4] 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).



A



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, $R=CH_3$).

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, $R=CH_3$) and butyronitrile (II, $R=C_2H_5$) with the catalytic amount of Triton-B in dioxane yielded the cyano esters (III, $R=CH_5$) and (III, $R=C_2H_5$) 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).

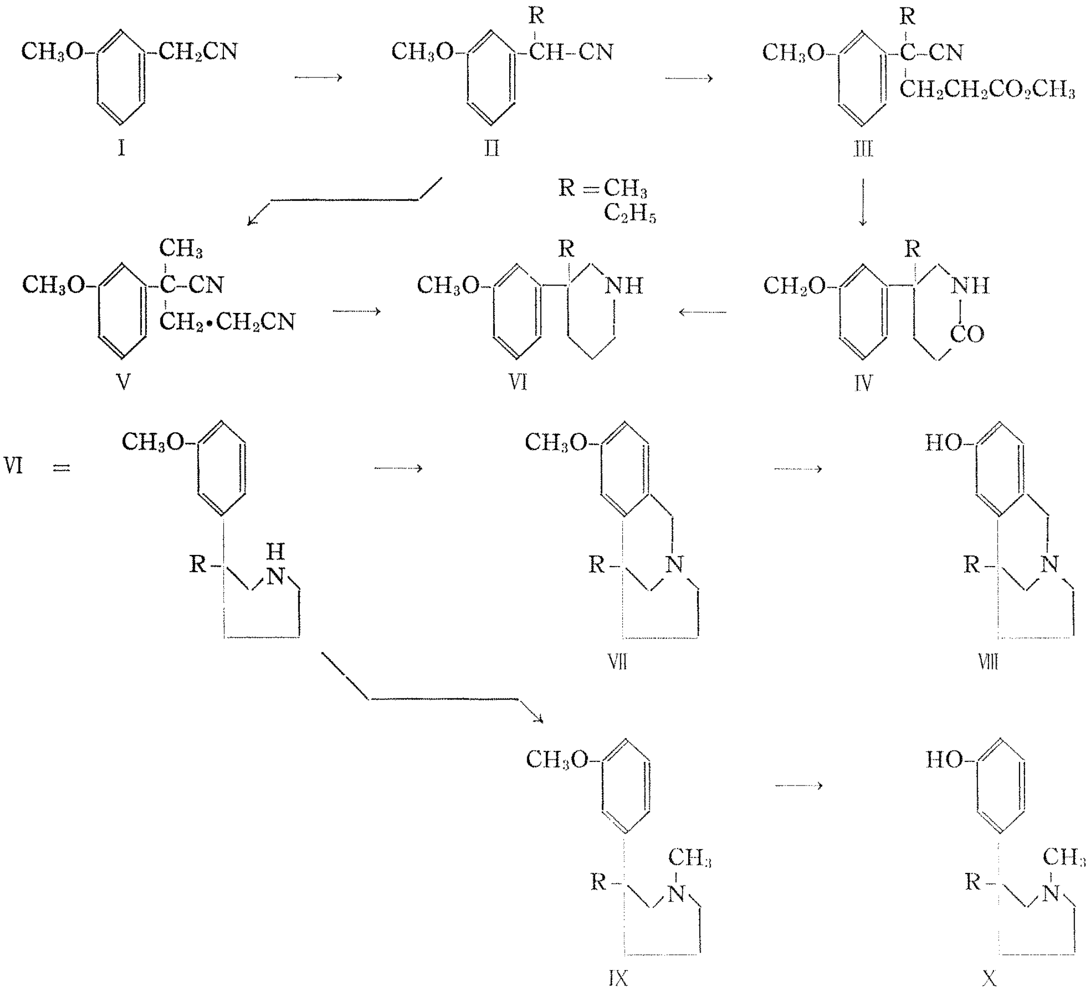
[2] N. Sugimoto, H. Kugita : This Bulletin, **3**, 11 (1955).

[3] Results of the clinical trials will be published elswhere.

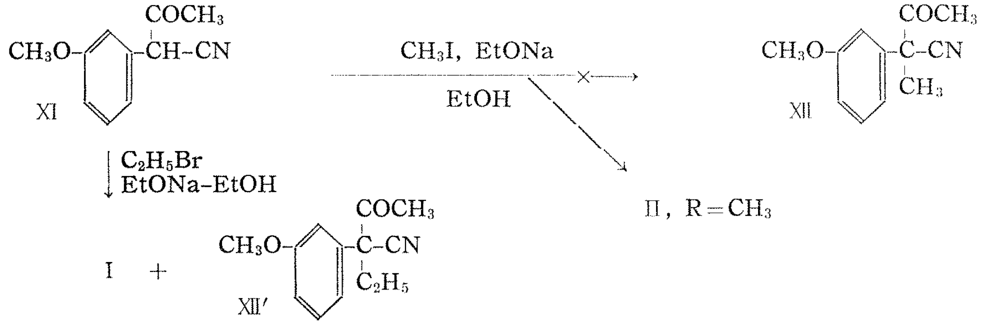
[4] Everette L. May, National Institutes of Health, U.S.A. : A series of papers, "Structures related to Morphine" has been reported. Latest papers of series; J. Org. Chem., **26**, 188, 1621, 1954 (1961).

[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, $R=CH_3$ and C_2H_5). Compound IV was reduced with lithium aluminum hydride in dioxane to give the 3-arylpiperidines (VI, $R=CH_3$ and C_2H_5).



A Pictet-Spengler type reaction of VI ($R=CH_3$) with formaldehyde and formic acid²⁾ yielded conclusively the N-methylated derivative IX ($R=CH_3$) which was in accordance with the product derived from XI ($R=CH_3$) by the reaction with formaldehyde followed by catalytic hydrogenation. Reaction of VI ($R=CH_3$ and C_2H_5) with formaldehyde and hydrochloric acid gave the cyclization products VII ($R=CH_3$ and C_2H_5) which were hydrolyzed to the hydroxy compounds VIII ($R=CH_3$ and C_2H_5).



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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 (XII′).

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% yieled) was identified by the spectral evidence as 2-(*m*-methoxyphenyl)propionitrile (II, R=CH_3) 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 XII′ by spectral and analytical data. Although the scission of the -$COCH_3$ 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=CH_3 and C_2H_5) and VIII (R=CH_3,C_2H_5) 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=CH_3) had one-fourth the activity of meperidine.

Experimental[*2]

2-(*m*-Methxoyphenyl)propionitrile (II, R=Me)——To $NaNH_2$ (prepared from Na, 3.7 g.) in anhyd. Et_2O (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 Et_2O (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 H_2O and dried over $CaCl_2$. 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 Et_2O as solvent. From I (22.5 g.), freshly prepared $NaNH_2$ (from Na, 3.9 g.) and EtBr (25 g.) was obtained II (R=Et) (13 g.), b.p$_5$ 140~145°. *Anal.* Calcd. for $C_{10}H_{13}ON$: 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 Et_2O, washed with H_2O, 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 $C_{14}H_{17}O_3N$: 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 $C_{15}H_{19}O_3N$: 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 NH_3 (ca. 10%) over Raney-Ni with an initial pressure of 63 atm. Theoretical volume of H_2 was absorbed at 50~70°. The filtered solution was concentrated under reduced pressure giving a viscous residue which crystallized upon treating with H_2O. Recrystallization from MeOH-H_2O (4 : 1) gave colorless plates of hydrated piperidone (IV, R=Me), m.p. 58~60°; yield, 5.6 g. (67%). *Anal.* Calcd. for $C_{13}H_{17}O_2N \cdot H_2O$: 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% NH_3-EtOH (50 cc.) was hydrogenated as above. The product was recrystallized from MeOH-H_2O (1 : 1) as colorless needles, m.p. 71~73°; yield, 6.0 g. (70.5%). *Anal.* Calcd. for $C_{14}H_{19}O_2N \cdot H_2O$: 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

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[*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 Et$_2$O, washed with H$_2$O 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 $C_{13}H_{14}N_2O$: 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 NH$_3$-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 Et$_2$O, 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 $C_{13}H_{19}ON\cdot C_2H_2O_4$: 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 LiAlH$_4$ (2.2 g.) in Et$_2$O (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 H$_2$O (5 cc.), filtered and concentrated in a reduced pressure, the residue was dissolved in 5% HCl, extracted once with Et$_2$O, basified with K$_2$CO$_3$ and extracted with Et$_2$O. The dried ethereal solution was evaporated and the residue was distilled to give colorless liquid, b.p$_{1.5}$ 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 LiAlH$_4$ (2.8 g.), yield, 4.3 g. (80.5%), b.p$_{0.4}$ 120~124°. Hydrobromide : Colorless needles (from EtOH-E$_2$O), m.p. 170~171°. *Anal.* Calcd. for $C_{14}H_{21}ON\cdot HBr$: 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 H$_2$O (3 cc.) were heated in a H$_2$O bath for 30 min. The solution was decanted from the precipitate and the gummy residue was washed with H$_2$O three times. The gum was dissolved in conc. HCl (5 cc.) and heated in a H$_2$O bath for 1 hr., then concentrated under reduced pressure, the residue was dissolved in H$_2$O, basified with K$_2$CO$_3$ 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 Et$_2$O and treated with HCl-EtOH. Recrystallization of the crude hydrochloride from MeOH-Et$_2$O formed colorless needles, m.p. 258~260°; yield, 0.45 g. (35%). *Anal.* Calcd. for $C_{14}H_{19}ON\cdot HCl$: 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-Et$_2$O); yield, 0.4 g. *Anal.* Calcd. for $C_{15}H_{21}ON\cdot HBr$: 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 $C_{13}H_{17}ON\cdot HBr$: 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-Et$_2$O in colorless prisms, m.p. 234~236°; yield, 0.28 g. (59%). *Anal.* Calcd. for $C_{14}H_{19}ON\cdot HBr$: 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 H$_2$O (5 cc.) was heated in a sealed tube at 130~140° for 7 hr.[2] The solution was concentrated under reduced pressure, H$_2$O was added to the residue, and the clear aqueous solution was basified with K$_2$CO$_3$, extracted with Et$_2$O and dried. Evaporation of the solvent and distillation of the residue gave a colorless liquid, 1.7 g. which was dissolved in Et$_2$O 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 $C_{14}H_{21}ON\cdot NBr$: 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 atomospheric pressure with 10% Pd-C (0.2 g.), theoretical volume of H$_2$ being absorbed in 1 hr. at room temperature. The catalyst was removed, the solvent was distilled, then the residue was dissolved in Et$_2$O 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-Et_2O). *Anal.* Calcd. for $C_{15}H_{23}ON \cdot HBr$: 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-Et_2O). *Anal.* Calcd. for $C_{13}H_{19}ON \cdot HBr$: 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-Et_2O). *Anal.* Calcd. for $C_{14}H_{21}ON \cdot HCl$: 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 AcOEt[9] (34 g.) and I (37 g.) during 1.5 hr. The reaction mixture was refluxed for 3 hr., then concentrated and diluted with Et_2O. The Na salt of XI was filtered, dissolved in H_2O, 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 $C_{11}H_{11}O_2N$: 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 CH_3I——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 CH_3I (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 H_2O and extracted with Et_2O. The ethereal extract was washed with 5% NaOH and H_2O, and dried. Evaporation of Et_2O 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 Et_2O-ligroin gave colorless plates, m.p. 63～65°. IR $\lambda_{\max}^{\mathrm{MeOH}}$ μ : 4.5, 6.23. Microanalysis supported the structure XII′ for (b). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: 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 P_2O_5 before the reaction. Org. Syntheses, **18**, 66 (1938).