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Studies on the Syntheses of Analgesics. V.[1] Synthesis of 1,2,3,4,5,6-Hexahydro-3-benzazocine Derivatives. (3)[2]

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Continuing our study on new types of non-narcotic analgesics, we synthesized 1,2,3,4,5,6-hexahydro-8-methoxy-6,6-dimethyl-3-benzazocine (XI) from 2-(2-cyano-1,1-dimethylethyl)-4-methoxybenzoic acid, through 3-(2-cyanomethyl-5-methoxyphenyl)-3-methylbutyronitrile (X). The reductive ring closure reaction of X was particularly investigated to obtain XI and the pathway of this reductive ring closure reaction was estimated from the reactivity of the by-products, 3-[2-(2-aminoethyl)-5-methoxyphenyl]-3-methylbutyronitrile and 3-[2-(2-aminoethyl)-5-methoxyphenyl]-3-methylbutylamine.

Interest in the unique analgesic action of galanthamine, Amaryllydaceae alkaloid, prompted us to synthesize 1,2,3,4-tetrahydro-5H-2-benzazepine derivatives[4] as simplified analogs of galanthamine. Furthermore, many 1,2,3,4,5,6-hexahydro-3-benzazocine derivatives[5,6] have been synthesized as simplified morphine analogs. These compounds were found to have analgesic action, and 1,2,3,4,5,6-hexahydro-8-hydroxy-3-benzazocine derivatives particularly showed strong activity. These benzazocines were synthesized by the Ullmann reaction of 3-benzyl-1,2,3,4,5,6-hexahydro-8,9-dimethoxy-6,6-dimethyl-3-benzazocine or by photo-reaction of N-chloroacetyl-3-(3-methoxyphenyl)-3-methylbutylamine.[6] The present paper describes their more useful synthetic method starting with 2-(2-cyano-1,1-dimethylethyl)-4-methoxybenzoic acid (I), which was reported on the previous paper.[1] Pecherer, *et al.*[7] synthesized 1,2,3,4,5,6-hexahydro-8-hydroxy-3-methyl-3-benzazocine, an analog of I, from 2-(2-cyanoethyl)-4-methoxybenzoic acid in thirteen steps, but the over-all yield was only 1.8%. So we investigated how to prepare 1,2,3,4,5,6-hexahydro-3-benzazocine derivatives more advantageously according to the scheme shown in Chart 1.

As stated in the previous paper,[1] we first tried to prepare 1,2,3,4,5,6-hexahydro-3-benzazocine derivatives from 3-(2-chloromethyl-5-methoxyphenyl)-3-methylbutylamine (II), but the over-all yield was poor. Especially cyanation of II gave a very poor yield. Then we tried the reductive ring closure reaction of 3-(2-cyanomethyl-5-methoxyphenyl)-3-methylbutyronitrile (X). I was converted to methyl 2-(2-cyano-1,1-dimethylethyl)-4-methoxybenzoate (V) with gaseous hydrogen chloride in methanol. Subsequent reduction of V did not proceed selectively, and always gave a mixture of 3-(2-hydroxymethyl-5-methoxyphenyl)-3-methylbutyronitrile (VII) and 3-(2-hydroxymethyl-5-methoxyphenyl)-3-methylbutylamine. I

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1) Part IV: Y. Sawa, T. Kato, T. Masuda, M. Hori, and H. Fujimura, *Chem. Pharm. Bull.* (Tokyo), 23, 1917 (1975).

2) Part of this paper was presented at the 3rd International Congress of Heterocyclic Chemistry, Sendai, Aug., 1971.

3) Location: *a) Juso-Hon-machi, Yodogawa-ku, Osaka; b) Mitahora-492-36, Gifu; c) Tsukasa-cho-40, Gifu.*

4) M. Hori, H. Fujimura, T. Masuda, and Y. Sawa, *Yakugaku Zasshi*, **95**, 131 (1975).

5) Y. Sawa, T. Kato, T. Masuda, M. Hori, and H. Fujimura, *Yakugaku Zasshi*, **95**, 251 (1975).

6) Y. Sawa, T. Kato, A. Morimoto, T. Masuda, M. Hori, and H. Fujimura, *Yakugaku Zasshi*, **95**, 261 (1975).

7) B. Pecherer, F. Humiec, and A. Brossi, *Helv. Chim. Acta*, **54**, 743 (1971).

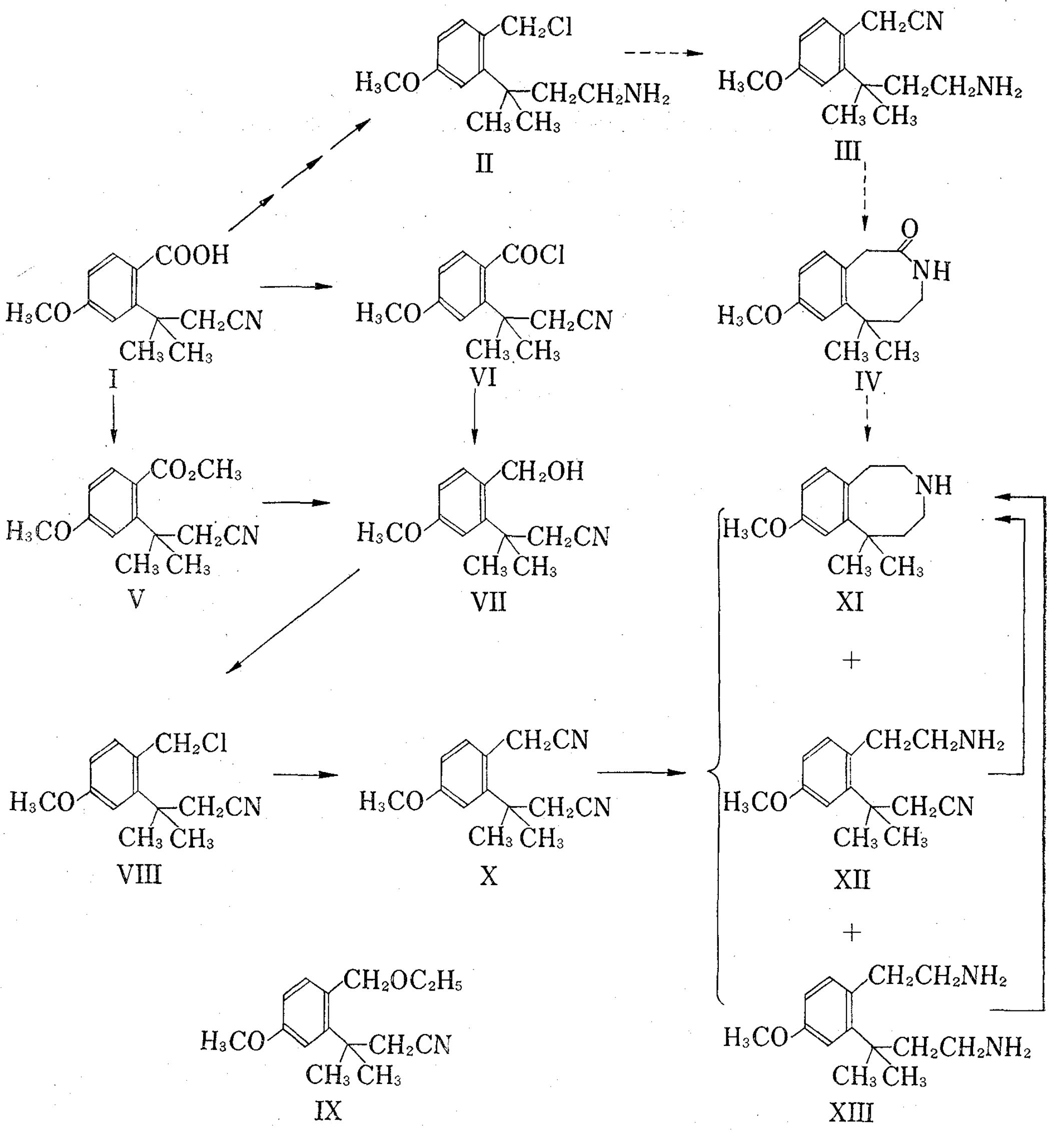

Chart 1

was converted with thionyl chloride to the acid chloride (VI), which was immediately reduced with sodium borohydride in ethanol to give VII in 81.9% yield. However, when this reduction was carried out in methanol, methanolysis occurred in preference to reduction, and only V was obtained. VII was readily chlorinated to 3-(2-chloromethyl-5-methoxyphenyl)-3-methylbutyronitrile (VIII) by known procedures, passing through gaseous hydrogen chloride in anhydrous benzene solution in the presence of calcium chloride or shaking with hydrochloric acid. For isolation of pure VIII, the crude product was subjected to silica gel column chromatography eluted with chloroform/acetone (19: 1), and two compounds (mp 58—59° and 81—82°) were obtained. The latter compound was identified as VII based on infrared (IR) and nuclear magnetic resonance (NMR) spectra and elemental analysis, and the former compound was presumed to be 3-(2-ethoxymethyl-5-methoxyphenyl)-3-methylbutyronitrile (IX), as indicated by the facts that the NMR spectrum was similar to that of VII except that it showed the NMR signal for the ethoxy function instead of the hydroxy function, the IR spectrum had no hydroxy absorption, and elemental analysis agreed with $C_{15}H_{21}O_2N$. Perhaps, IX was formed by solvolysis of VII with contaminated ethanol in chloroform or acetone during the column chromatography. Thus, isolation of VII was given up and the reaction mixture was immediately reacted with sodium cyanide to give X (mp 95—96°). The yield

Table I. Reductive Ring Closure Reaction of X

Catalyst (Raney)	Solvent (%)				Yield (%)			
	MeOH	H_2O	28% NH_4OH	AcOH	XI	XII	XIII	X
Co	100					10	10	40
Co	90	10			(trace)	25	25	10
Ni	100				20.8		36.6	
Ni	95	5			31.0		15.0	
Ni	90	10			31.3		19.3	
Ni	80	20			41.7		29.0	
Ni	70	30			26.0		36.2	
Ni	60	40			23.4		29.0	
Ni	50	50			20.8		24.2	
Ni	80	5	15		40.6a)		56.5a)	
Ni	80	15	5		37.3a)		44.4a)	
Ni	90		10		32.0		26.6	
Ni	80		20		43.8		24.2	
Ni	60		40		24.1		31.4	
Ni*	80	15		5	57.3		19.3	
Ni*	90			10	65.3		14.8	

H_2 pressure: 100 kg/cm^2 (*70 kg/cm^2); temperature: 100°
a) by gas chromatography

of this cyanation was markedly affected by the solvent: very poor (10.8%) in benzene and water system, 52% in dimethylformamide (DMF), 70.3% in dried acetone in presence of potassium iodide and quantitative in dimethyl sulfoxide (DMSO).

Intramolecular reductive ring closure reaction of dinitrile compounds has been reported for seven-membered ring compounds, 2,3,4,5-tetrahydro-1H-3-benzazepine derivatives, by Ruggli, *et al.*8a) and Pecherer, *et al.*,8b) but the reaction of eight-membered ring systems has not been reported yet. When we tried to obtain the eight-membered ring closure reaction product under seven-membered ring closure conditions, the yield was poor. Therefore, we investigated the ring closure conditions of X, particularly the effect of catalyst and solvent in this reaction (Table I). First, X was reduced in the presence of Raney cobalt catalyst, which is considered a mild catalyst. In this reaction, the formation of new two compounds were recognized by thin-layer chromatography (TLC). Next, water soluble substances were removed from the reaction mixture and the residue was chromatographed on a silica gel column eluted with chloroform/methanol (10: 1). X was eluted first and next an oily basic product (A, hydrochloride: mp 171—173°). The IR spectrum of A showed CN absorption at 2250 cm^{-1}. Elemental analysis of the hydrochloride of A agreed with $C_{14}H_{20}ON_2\cdot HCl$. The NMR spectrum showed the signal near 2.87 ppm for 4 protons of the $C\underline{H}_2C\underline{H}_2$ function of aminoethyl rest which was produced by the reduction of cyanomethyl rest in X. In the case, the signal of two adjacent methylene protons showed a singlet. Similar examples to this case have been observed in 3,4-dimethoxyphenethylamine and other compounds. If the CN function of butyronitrile rest of X was reduced to form 3-(2-cyanomethyl-5-methoxyphenyl)-3-methylbutylamine (XIV), the NMR spectrum would show a signal near 3.8 ppm corresponding to two methylene protons, and it seems unlikely that the signals resulting from newly generated methylene protons would be singlets. For example, in X the signals of 2.71 ppm, which are the other methylene protons, are slightly shifted to 2.76 ppm, existing in singlet. In addition, the mass spectrum of A showed a molecular ion peak at *m/e* 232 and prominent ion at *m/e* 203 (M^+-29), 202 ($M^+-CH_2NH_2$), 188 ($M^+-CH_2CH_2NH_2$), 163 (203—

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8) *a*) P. Ruggli, B.B. Bussemaker, W. Müller, and A. Staub, *Helv. Chim. Acta*, **18**, 1388 (1935); *b*) B. Pecherer, R.C. Sunbury, and A. Brossi, *J. Heterocyclic Chem.*, **9**, 617 (1972).

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CH_2CN) and 30 ($^+CH_2NH_2$, the base peak). The fragmentation pattern was resemble to that of 4-methoxyphenethylamine and differed from that of 3-(3-methoxyphenyl)-3-methylbutylamine. From these results, A is probably 3-[2-(2-aminoethyl)-5-methoxyphenyl]-3-methylbutyronitrile (XII). On the other hand, the water soluble compound was a massive crystal, which melted at 90—93° (hydrochloride: mp 273°). The IR spectrum of this crystal showed no CN-band, and the results of the NMR spectrum and elemental analysis agreed with 3-[2-(2-aminoethyl)-5-methoxyphenyl]-3-methylbutylamine (XIII).

When a small amount of water was added to the reaction solvent (methanol), the reduction proceeded smoothly increasing the formation of XII and XIII, and the objective compound XI was detected on TLC plate. When Raney nickel was used as a catalyst, the reduction proceeded more smoothly to give XI, XIII and a small amount of unknown compounds, and X and XII were not detected in the reaction products. In this case, addition of a small amount of water greatly influenced the yield of XI. Maximum yield of XI was 41.7% in 80% methanol. Addition of more water decreased the yield. Addition of ammonium hydroxide to the reaction solvent also caused the same result in the water-methanol system, and methanol containing 20% ammonium hydroxide gave the best yield of 43.8%. There was not a great difference compared with the case of the water-methanol system. It appears that there is no special meaning in the addition of ammonium hydroxide. The reaction pressure was examined in the range of 50 to 100 kg/cm^2, but the yields of XI, XIII and unknown compounds were not affected greatly. When Raney nickel was used below 50°, the reaction was very slow, and about 50% of the starting material (X) was recovered. The reaction proceeded completely at 90 to 100°, and a higher temperature had no positive effect.

In addition to these studies, we carried out the reaction in solvent containing acetic acid in order to depress the formation of the by-product under neutral or alkaline conditions and accelerate the reaction by capture of the yielded ammonia. Thus the formation of by-product, except for XIII, was not detected. The best yield of XI was about 65%, and separation of XI became easy, indicating this method was more profitable. XI agreed with an authentic sample which was prepared from N-chloroacetyl-3-(3-methoxyphenyl)-3-methylbutylamine by

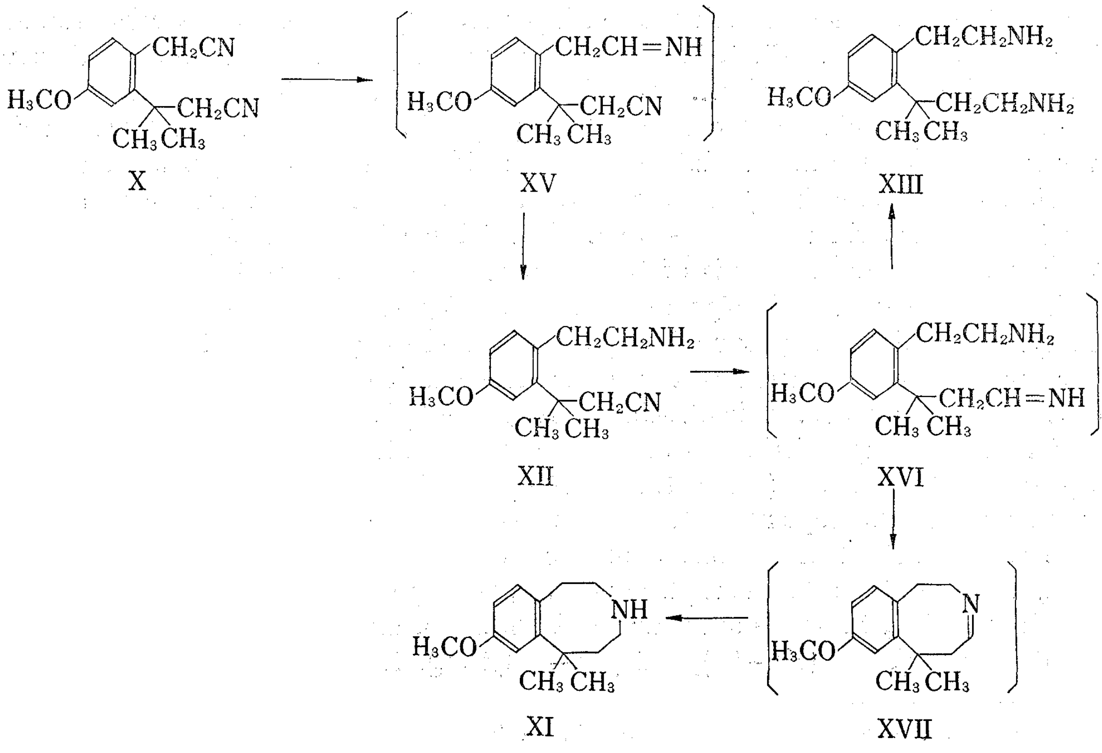


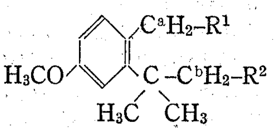
Chart 2

photo-ring closure reaction.

The reductive ring closure reaction of X is shown in Chart 2. This was understood from the fact that XII was isolated under mild conditions using Raney cobalt, and only XII was detected by gas chromatography. The existence of XII as a reaction intermediate is almost certain. Accordingly, it is reasonable that XIII, a by-product, is produced from XII *via* XVI under any conditions and the objective compound XI is produced from XVI *via* deammoniated ring closure compound (XVII). We can understand that the formation ratios of XI to XIII vary with the reaction conditions. The effect of acetic acid also can be explained considering that the reaction proceeded *via* XVI. When reduction of XII was carried out under these reductive ring closure conditions, XI and XIII were produced. The reaction producing XI from XIII, however, was unsuccessful in recovering XIII. These results indicate that XIII is not a intermediate in the reaction to XI from X.

Primary amines are known to yield secondary amines under reductive conditions. For example, Kindler[9] obtained a secondary amine from phenethylamine in 10% yield. We examined the method by which XI was synthesized from XIII under these ring closure conditions, and succeeded in obtaining XI in 60% yield by catalytic reduction using 5% Pd-on-charcoal or 2.5% Pd–$BaSO_4$ in xylene. That is, XI was obtained in 84% over-all yield from X by combining the reaction from X to XI and that from XIII to XI. But the ring closure reaction under pyrolysis or deammoniation conditions was unsuccessful.

Table II. NMR Data ($CDCl_3$) δ (ppm)



Compound	R^1	R^2	OCH_3 (3H, s)	Aromatic H (3H, m)	$C(CH_3)_2$ (6H, s)	C^aH_2 (2H, s)	C^bH_2 (2H, s)	R^1	R^2
VII	OH	CN	3.80	6.67—7.40	1.59	4.74	2.90		
VIII	Cl	CN	3.82	6.70—7.45	1.65	4.80	2.84		
IX	OC_2H_5	CN	3.78	6.63—7.39	1.58	4.55	2.87	3.45(2H, q, CH_2) 1.24(3H, t, CH_3)	
X	CN	CN	3.80	6.70—7.45	1.60	3.84	2.71		
XI	CH_2NHCH_2		3.72	6.45—6.95	1.36	2.80–3.10 (m)	2.14	2.80–3.10 (m, CH_2)	2.80–3.10 (m, CH_2)
XI·HCl[a]	CH_2NHCH_2		3.85	6.80—7.30	1.43	3.37	2.30–2.50 (t)	3.37 (s, CH_2)	3.37 (s, CH_2)
XII	CH_2NH_2	CN	3.72	6.50—7.12	1.56	2.87	2.76	2.87 (2H, s, CH_2)	
XII·HCl[a]	CH_2NH_2	CN	3.76	6.60—7.25	1.53	3.76	2.93	3.76 (2H, s, CH_2)	
XIII·HCl[a]	CH_2NH_2	CH_2NH_2	3.80	6.80—7.40	1.48	3.25	1.90–2.40 (m)	3.25 (2H, s, CH_2)	2.50–2.95 (2H, m, CH_2)

a) in D_2O

Experimental[10]

3-(2-Hydroxymethyl-5-methoxyphenyl)-3-methylbutyronitrile (VII)——A solution of 10 g of I[1] in 10 ml of purified $SOCl_2$ was refluxed gently on a water bath for 1 hr. Excess $SOCl_2$ was evaporated *in vacuo* to dryness

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9) K. Kindler, *Ann.*, **485**, 113 (1931).

10) All melting points were uncorrected. IR spectra were taken with a Hitachi EPI-S2 spectrophotometer and NMR spectra were taken with a Hitachi Perkin-Elmer R-20 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were taken with a Hitachi RMS-4 mass spectrometer. TLC were performed on silica gel G (Merck) plates and I_2 vapor or Dragendroff reagent was used as the coloring agent.

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to give the crude 2-(2-cyano-1,1-dimethylethyl)-4-methoxybenzoyl chloride (VI) as an oily product. To an ice-cold suspended solution of 5 g of $NaBH_4$ in 150 ml of EtOH was added dropwise a solution of VI in 40 ml of dried ether. The mixture was stirred at room temperature for 2 hr. After cooling, the reaction mixture was decomposed with cautious addition of H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated *in vacuo* to give 7.7 g (81.9%) of VII as colorless crystals which recrystallized from C_6H_6/ligroin, mp 81—83°. TLC: $Rf=0.63$ (C_6H_6/AcOEt (2: 1)) and 0.37 (C_6H_6/MeOH (6: 1)). *Anal.* Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.81; N, 6.38. Found: C, 71.08; H, 7.80; N, 6.51.

When VI was reduced with the suspended solution of $NaBH_4$ in MeOH, 7 g of methyl 2-(2-cyano-1,1-dimethylethyl)-4-methoxybenzoate (V) was obtained as slightly yellowish oily product, bp 175—185° (5 mmHg). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.88; H, 6.96; N, 5.53.

3-(2-Ethoxymethyl-5-methoxyphenyl)-3-methylbutyronitrile (IX)——Gaseous HCl was gently bubbled into a suspended solution of 440 mg of VII and 1 g of $CaCl_2$ in 18 ml of dried C_6H_6 and 5 ml of ligroin at $-10°$ for 4 hr. After removal of $CaCl_2$, the solution was concentrated *in vacuo* keeping the temperature below 30° to dryness. The resulting oily product was chromatographed on silica gel (10 g). The column was eluted with $CHCl_3$/acetone (19: 1). Each fractions were 5 ml and checked by TLC (solvent: $CHCl_3$/acetone (19: 1); detection: $Ce(SO_4)_2 \cdot nH_2O$ solution (violet)). The first compound was eluted with the 9th—11th fractions and recrystallized from C_6H_6/ligroin to give 170 mg of IX, mp 58—59°. TLC: $Rf=0.65$ ($CHCl_3$/acetone (19: 1)). *Anal.* Calcd. for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.61. Found: C, 72.85; H, 8.31; N, 5.61. The second compound was eluted with the 13th—21st fractions and recrystallized from C_6H_6/ligroin to give 100 mg of VII, mp 81—82°. TLC: $Rf=0.29$ ($CHCl_3$/acetone (19: 1)). *Anal.* Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.81; N, 6.38. Found: C, 71.00; H, 7.68; N, 6.31.

3-(2-Cyanomethyl-5-methoxyphenyl)-3-methylbutyronitrile (X)——An ice-cold mixture of 7.4 g of VII, 10.4 g of conc. HCl, and 30 ml of C_6H_6 was vigorously shaken for 10 minutes. The reaction mixture was extracted with C_6H_6. The extract was washed with successive, H_2O, diluted NH_4OH, and H_2O, dried and concentrated to give 7.1 g (88.5%) of VIII as colorless oily product. To suspended solution of 2 g of NaCN in 125 ml of DMSO was added dropwise a solution of 7.1 g of VIII in 40 ml of DMSO. The mixture was stirred at room temperature for 1.5 hr and poured into 300 ml of H_2O. The solution was extracted with C_6H_6. The extract was washed with H_2O, dried and concentrated to give 6.5 g (95.3%) of X as colorless crystals which were recrystallized from C_6H_6. mp 95—96°. *Anal.* Calcd. for $C_{14}H_{16}ON_2$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.62; H, 7.19; N, 12.08.

1,2,3,4,5,6-Hexahydro-8-methoxy-6,6-dimethyl-3-benzazocine (XI)——a) The suspended solution of 2 g of X and 0.5 g of Raney Co in 20 ml of H_2O and 180 ml of MeOH was placed into a high pressure autoclave (500 ml) arranged for agitation by shaking. The autoclave was filled with H_2 gas to 100 kg/cm^2 of initial pressure at 20° and shaked keeping the temperature at 100° (maximum pressure: 131 kg/cm^2) for 1 hr. The catalyst was removed by filtration. The solution was concentrated to give 2 g of brownish residue. The residue was dissolved in C_6H_6. The solution was washed with H_2O, dried and concentrated to give 1.6 g of oily product. The resulting oily product was subjected to chromatography on silica gel eluted with $CHCl_3$/MeOH (5: 1). The first elution was 0.2 g of X and the second elution was 0.5 g of oily 3-(2-aminoethyl-5-methoxyphenyl)-3-methylbutyronitrile (XII). XII·HCl: mp 171—173°. Mass Spectrum *m/e*: 232 (M^+), 203 (M^+-29), 202 ($M^+-CH_2NH_2$), 188 ($M^+-CH_2CH_2NH_2$), 163 ($203-CH_2CN$), 30 ($^+CH_2NH_2$). *Anal.* Calcd. for $C_{14}H_{20}ON_2 \cdot HCl$: C, 62.56; H, 7.88; N, 10.42. Found: C, 62.64; H, 7.71; N, 10.28. The third elution was a small amount of oily product containing XI which checked by TLC. The water washings were evaporated *in vacuo*, to give 0.5 g of 3-(2-aminoethyl-5-methoxyphenyl)-3-methylbutylamine (XIII) as colorless crystals, mp 90—93°. XIII·HCl: mp 273°. *Anal.* Calcd. for $C_{14}H_{24}ON_2 \cdot 2HCl$: C, 54.37; H, 8.47; N, 9.06. Found: C, 54.01; H, 8.55; N, 9.03.

b) The suspended solution of 2 g of X and 3 g of W-2 Raney Ni in 200 ml of MeOH was placed into a high pressure autoclave (500 ml). The apparatus and the reaction mixture were operated in a similar manner as above. The residue was purified by chromatography on silica gel eluted with $CHCl_3$/MeOH (6: 1) to give 0.4 g (20.8%) of yellowish oily XI. XI·HCl: mp 246—247° (from AcOEt/MeOH). *Anal.* Calcd. for $C_{14}H_{21}ON \cdot HCl$: C, 65.73; H, 8.67; N, 5.47. Found: C, 65.57; H, 8.44; N, 5.42. The water washings were evaporated *in vacuo* to give 0.8 g of XIII.

c) The suspended solution of 2 g of X and 3 g of W-2 Raney Ni in 180 ml of MeOH and 20 ml of AcOH was placed into a high pressure autoclave (500 ml). The autoclave was filled with H_2 gas to 70 kg/cm^2 of initial pressure at 20° and shaked keeping the temperature at 100° for 1 hr. The reaction mixture was operated in a similar manner as b). XI (1.16 g, 60.4%) and XIII (0.30 g, 14.5%) were obtained.

d) The suspended solution of 2 g of XII and 3 g of W-2 Raney Ni in 20 ml of H_2O and 180 ml of MeOH was placed into a high pressure autoclave (500 ml). The apparatus and the reaction mixture were operated in a similar manner as b). XI (0.79 g, 41.9%) and XIII (0.62 g, 30.5%) were obtained.

e) A solution of 1.5 g of XIII in 20 ml of xylene was treated with 1 g of 5% Pd–C (or 1.5 g of 2.5% Pd–$BaSO_4$) under H_2 atmosphere at 135—140° for 4 (or 8) hr. After cooling, the mixture was filterated and concentrated *in vacuo* to give a residue which contained XI (about 78%) and XIII (about 18%) (by gas chro-

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matography[11]). The residue was dissolved with C_6H_6 and the solution was washed with H_2O, dried and concentrated to give 0.94 g (65.3%) of XI as yellowish oil. The water washings were treated to give 0.23 g (14.8%) of XIII.

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11) Gas chromatography was carried out with Yanagimoto 550-FT gas chromatograph, using a glass column (1 m × 2.5 mm i.d.) with 3% Apiezon-L on chromosorb W-DMCS, column temperature 170°. Carrier gas: Helium, 25 ml/min. Retention time (min): XI = 1.0, XIII = 2.5, and unknown compound = 1.6.