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Studies on the Syntheses of Analgesics. VI.¹⁾ Synthesis of 1,2,3,4,5,6-Hexahydro-1,5-methano-3-benzazocine Derivatives

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Continuing our study of new types of non-narcotic analgesics, we synthesized several 1,2,3,4,5,6-hexahydro-6,6-dimethyl-1,5-methano-3-benzazocine derivatives from ethyl 4-methoxyphenylacetate *via* the ring closure reaction of 5-(1-hydroxy-1-methylethyl)-3-(4-methoxyphenyl)-2-piperidinone (V). The by-product which was produced by the ring closure reaction of V, was presumed to be 1,2,3,4,5,6-hexahydro-8-methoxy-6,6-dimethyl-9-sulfo-1,5-methano-3-benzazocine (VII). The synthesized compounds were tested for analgesic activity in mice.

In the previous paper³⁾ we reported the synthesis of a number of derivatives of 1,2,3,4,5,6-hexahydro-3-benzazocine (A), having stronger analgesic activity than pentazocine. Although 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (B) derivatives such as pentazocine were energetically investigated by many groups represented by May and his co-workers,⁴⁾ 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine (C) derivatives have little been investigated. Thus, we were interested in the biological activity, particularly the analgesic activity, of C derivatives in connection with the activity of derivatives of A and B.

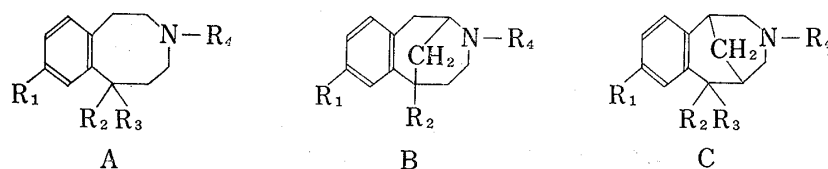


Chart 1

In 1959, Hill, *et al.*⁵⁾ reported the initial synthesis of 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine-2,6-dione associated with compound C. Since 1967, a few investigators^{5,6)} have reported their results and Mitsuhashi, *et al.*^{6a)} and Chang, *et al.*^{6b)} have also studied the biological activity of synthesized compounds, however, detailed results of the former were not made clear and the latter did not find the active compound.

- 1) Part V: Y. Sawa, Y. Kawakami, T. Hattori, T. Masuda, M. Hori, and H. Fujimura, *Chem. Pharm. Bull.* (Tokyo), **23**, No. 10 (1975).
- 2) Location: a) Juso-Hon-machi, Yodogawa-ku, Osaka; b) Mitahora-492-36, Gifu; c) Tsukasa-machi-40, Gifu.
- 3) Y. Sawa, T. Kato, T. Masuda, M. Hori, and H. Fujimura, *Yakugaku Zasshi*, **95**, 251 (1975).
- 4) E.L. May and L.J. Sargent, "Analgetics," Chapter IV, ed. by deStevens; Academic Press Inc., New York, N. Y., 1966.
- 5) R.K. Hill, C.E. Glassick, and L.J. Fliedner, *J. Am. Chem. Soc.*, **81**, 737 (1959); G.N. Walker and D. Alkalay, *J. Org. Chem.*, **32**, 2213 (1967); A. Kitahonoki, K. Matsuura, and K. Kotera, *Tetrahedron Letters*, **1968**, 1651; K. Kitahonoki, Y. Takano, A. Matsuura, and K. Kotera, *Tetrahedron*, **25**, 335 (1969); M.P. Geargiadis, M.A. Davis, and K. Wiesner, U.S. Patent 3535322 (1971) [*C.A.*, **75**, 63647h (1971)].
- 6) a) S.K. Mitsuhashi, S. Shiotani, R. Oh-uchi, and K. Shiraki, *Chem. Pharm. Bull.* (Tokyo), **17**, 434 (1969); b) W.K. Chang, L.A. Walter, and R.I. Taber, *J. Med. Chem.*, **14**, 1011 (1971).

On the other hand, Braenden, *et al.*⁷⁾ concluded that potent analgesic compounds require four structural features: (1) a tertiary nitrogen atom; (2) a quaternary carbon atom; (3) a phenyl group, or an isosteric with phenyl, connected to the quaternary carbon; and (4) a 2-carbon chain separating the tertiary nitrogen and the quaternary carbon. However, no one has synthesized derivatives of compound C with these four features. In this paper, we describe the synthesis and analgesic activity of 1,2,3,4,5,6-hexahydro-6,6-dimethyl-1,5-methano-3-benzazocine derivatives having the most simplified quaternary carbon at the 6-position.

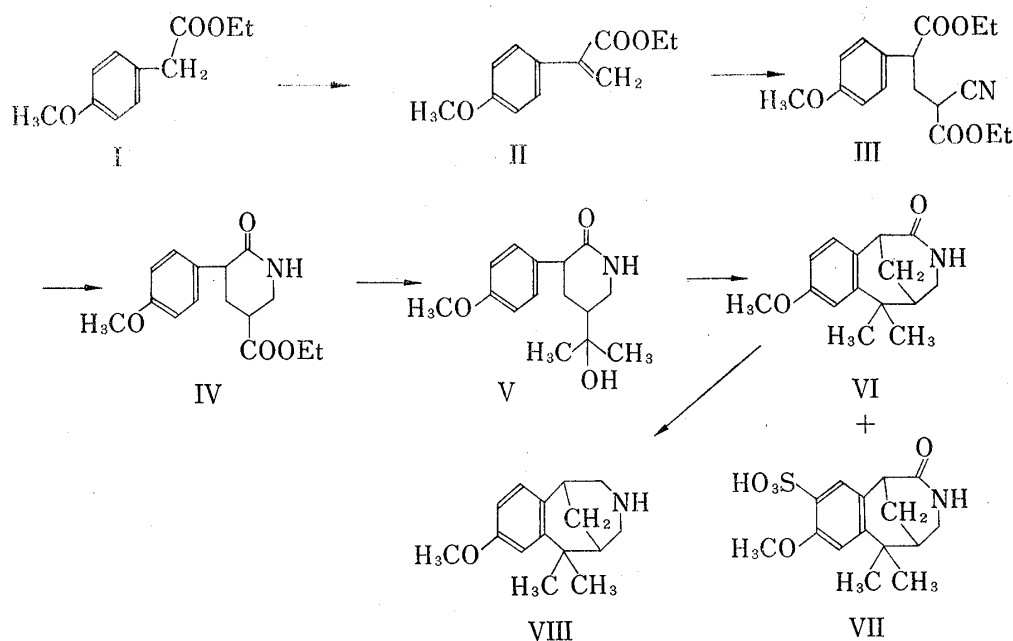


Chart 2

First, we synthesized 1,2,3,4,5,6-hexahydro-8-methoxy-6,6-dimethyl-1,5-methano-3-benzazocine (VIII) as a key compound by the procedure shown in Chart 2. Ethyl 2-(4-methoxyphenyl)-2-propenoate (II) was prepared from ethyl 4-methoxyphenylacetate (I) by a modification of the procedure of Ames, *et al.*⁸⁾ I was treated with ethyl oxalate in the presence of sodium ethoxide to give the oxalo ester, which was further treated with formaldehyde to give II. Condensation of II with ethyl cyanoacetate in the presence of sodium ethoxide gave the crude diethyl 2-cyano-4-(4-methoxyphenyl)pentanedioate (III) in 66.5% yield. Catalytic hydrogenation of the crude III over Raney nickel under high pressure at 80–90° gave only a 27% yield of ethyl 3-(4-methoxyphenyl)-2-oxo-5-piperidinecarboxylate (IV). But when III purified by distillation was used, IV was obtained in 56% yield. The Grignard reaction of IV in benzene with methylmagnesium iodide easily gave 5-(1-hydroxy-1-methylethyl)-3-(4-methoxyphenyl)-2-piperidinone (V), but this reaction produced little in ether and the complete progress of this reaction required at least a 4 molar equivalent weight of methylmagnesium iodide based on IV.

V was treated with 80% sulfuric acid according to our previous procedure³⁾ to afford 1,2,3,4,5,6-hexahydro-8-methoxy-6,6-dimethyl-1,5-methano-3-benzazocin-2-one (VI) in 60.5% yield. The elemental analysis of VI was compatible with $C_{15}H_{19}O_2N$ and the NMR spectrum (in trifluoroacetic acid) exhibited roughly an ABX-type signal at 6.8–7.5 ppm due to the 1,2,4-trisubstituted aromatic protons and a pair of singlets at 1.48 and 1.58 ppm due to two methyl groups connected to the quaternary carbon. These data supported the structure

7) J. Braenden, N.B. Eddy, and Halbach, *Bull. World Health Organ.*, **13**, 937 (1955).

8) G.R. Ames and W. Davey, *J. Chem. Soc.*, **1958**, 1794.

of VI. Moreover, the phenomenon in which a signal at 1.07 ppm due to the protons of two methyl groups of the open-ring compound (V) shifted to a pair of singlets at 1.48 and 1.58 ppm in the closed-ring compound (VI), is compatible with the information obtained from a synthetic study of 1,2,3,4,5,6-hexahydro-3-benzazocines.³⁾ In this ring closure reaction, the crystalline by-product (VII), which is insoluble in general organic solvents and soluble in alkali and melts at over 260°, was obtained. The NMR spectrum (in NaOD) of VII was similar to that of VI, except for a signal pattern for the two aromatic protons which are singlets at 7.19 and 7.52 ppm. Thus, VI was considered to be sulfonated at the C-9 position. Further, the elemental analysis and measurement of the water content by Karl-Fischer's method of the sodium salt of VII were compatible with $C_{15}H_{18}O_5NSNa \cdot 3H_2O$. According to these data, VII was presumed to be 1,2,3,4,5,6-hexahydro-8-methoxy-6,6-dimethyl-9-sulfo-1,5-methano-3-benzazocin-2-one. V was treated with polyphosphoric acid instead of 80% sulfuric acid, to avoid formation of VII, to afford VI in a good yield. Reduction of VI with lithium aluminum hydride in dioxane afforded VIII in 75% yield.

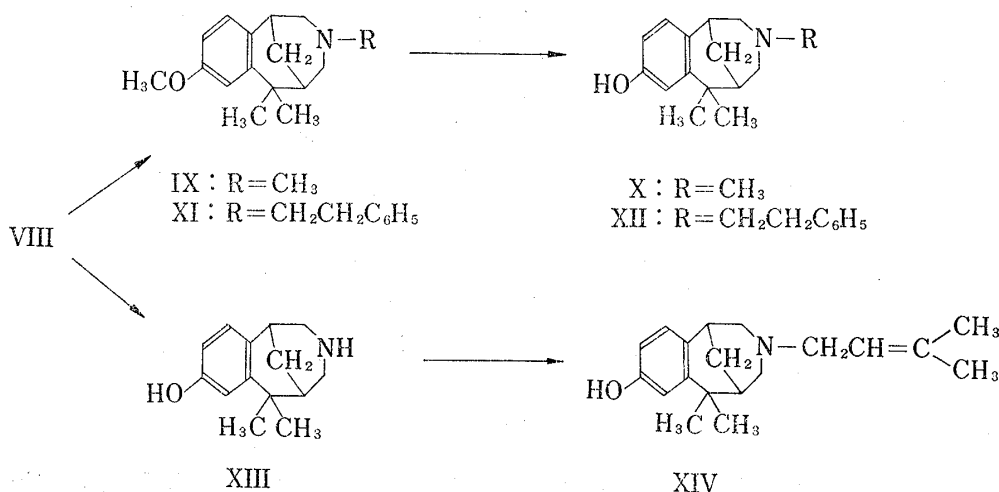


TABLE I. Analgesic Activity of 1,2,3,4,5,6-Hexahydro-6,6-dimethyl-1,5-methano-3-benzazocine Derivatives


Compound	AcOH-stretching method ED ₅₀ mg/kg s.c.
X	3.7 (3.20 — 4.30)
XI	12.6 (8.44 — 17.70)
XII	13.7 (10.46 — 17.95)
XIV	11.8 (9.90 — 14.00)
Pentazocine	2.3 (2.05 — 2.58)
Codeine	6.4 (4.35 — 7.32)

The Eschweiler-Clarke modification of the Leukart reaction of VIII gave the 3-methyl derivative (IX). VIII was treated with phenethyl bromide in the presence of sodium bicarbonate to afford the 3-phenethyl compound (XI). VIII, IX, and XI were converted with 47% aqueous hydrobromic acid into the phenols, 1,2,3,4,5,6-hexahydro-8-hydroxy-6,6-dimethyl-1,5-methano-3-benzazocine (XIII) and its 3-substituted derivatives (X) and (XII), respectively. Treatment of XIII with 1-bromo-3-methyl-2-butene afforded 1,2,3,4,5,6-hexahydro-8-hydroxy-6,6-dimethyl-3-(3-methyl-2-butenyl)-1,5-methano-3-benzazocine (XIV). When XIV hydrochloride was recrystallized from alcohol or alcohol-containing solvents, it gave crystals including alcohol of crystallization, the removal of which was very difficult.

The analgesic activity of the compounds synthesized in this study was estimated by the acetic acid stretching-inhibiting method using a group consisting of 10 mice; results are shown in Table I. The most active compound was X, but its activity was only about 2 times that of codeine and about 0.6 times that of pentazocine, against our expectations. Also, the activity of XIV was only about 0.25 times that of pentazocine.

Experimental⁹⁾

Ethyl 2-(4-Methoxyphenyl)-2-propenoate (II)—The method of Ames, *et al.*⁸⁾ was modified in the following manner. Ethyl oxalate (146 g) and 194 g of ethyl 4-methoxyphenylacetate were successively added to EtONa foam (from 23 g of Na) in 400 ml of C_6H_6 , and the mixture was left overnight at room temperature. Precipitates (Na salts of intermediate) were collected by filtration and washed with $(C_2H_5)_2O$. The yield of the Na salt was 213 g (67.4%). The $(C_2H_5)_2O$ washings were washed with H_2O and concentrated to recover 65 g (33%) of ethyl 4-methoxyphenylacetate. The cold solution of 213 g of the Na salt in 300 ml of H_2O was acidified with HCl, and added dropwise to the solution of 90 ml of 37% HCHO and 150 ml of H_2O over a 0.5 hr period. The mixture was added dropwise to the solution of 81 g of K_2CO_3 in 150 ml of H_2O at 16–18° over a 0.5 hr period, and vigorously stirred at room temperature for 2 hr. The separated oily product was extracted with $(C_2H_5)_2O$. The extract was washed with H_2O , dried, and evaporated to give 130 g (93.6%) of II. NMR (CCl_4) δ : 1.23 (3H, t, $J=7.0$ Hz, C- CH_3), 3.71 (3H, s, OCH₃), 4.18 (2H, q, $J=7.5$ Hz, -CH₂-Me), 5.91 (2H, q, $J=1.5$ Hz, $>C=CH_2$), 6.9–7.4 (4H, m, aromatic protons). If the Na salt of intermediate was thoroughly washed with $(C_2H_5)_2O$, II was able to use as a starting material for the next reaction without further purification.

Diethyl 2-Cyano-4-(4-methoxyphenyl)pentanedioate (III)—To the solution of 16.1 g of Na in 700 ml of absolute EtOH was added with cooling 308 g of ethyl cyanoacetate and the solution of 130 g of II in 150 ml of absolute EtOH. After the mixture was left at room temperature for 40 hr, the EtOH was removed and the residual oil taken up in $(C_2H_5)_2O$, washed with H_2O , dried, and concentrated to give 232 g of the residue. When ethyl cyanoacetate was removed from the residue, the yield of crude III was 144 g. This crude oil was distilled *in vacuo* to give 95.6 g (44%) of III as colorless oil, bp 175–185° (0.4 mmHg). IR ν_{max}^{liq} cm^{-1} : 2250, 2200 (CN), 1745 (shoulder), 1735 (CO₂Et). NMR (CCl_4) δ : 1.19 (3H, t, $J=7.5$ Hz, C- CH_3), 1.30 (3H, t, $J=7.5$ Hz, C- CH_3), 1.9–2.9 (2H, m, C-CH₂-C), 3.41 (1H, t, $J=7.0$ Hz, $>CH-CN$), 3.74 (4H, s, $>CH-$  and OCH₃), 4.13 (4H, q, $J=7.0$ Hz, -CH₂-Me $\times 2$), 6.6–7.3 (4H, m, aromatic protons).

Ethyl 3-(4-Methoxyphenyl)-2-oxo-5-piperidinecarboxylate (IV)—The suspended solution of 175 g of crude III in 500 ml of EtOH was placed into the high pressure autoclave. The autoclave was filled with placed into the high pressure autoclave. The autoclave was filled with H_2 gas to 100 kg/cm² of initial pressure at 20° and shaken keeping the temperature at 81–89° for 2.5–3.5 hr. The catalyst and solvent were removed. The residual oil was refluxed in 500 ml of C_6H_6 for 13 hr and washed with diluted aqueous NaHCO₃. The C_6H_6 solution was concentrated to give an oily residue, which was crystallized on cooling its $(C_2H_5)_2O$ solution yielding 19.6 g of IV as colorless solid. The mother liquor was diluted with C_6H_6 and washed with diluted HCl. The organic layer was washed with H_2O , and evaporated to dryness. The oily residue was purified by silica gel column chromatography with C_6H_6 /AcOEt (5:1) and AcOEt, yielding 15.6 g of IV. The dilute HCl washings were made basic with 28% NH₄OH, and extracted with C_6H_6 . The extract was washed with H_2O , dried, and evaporated to give 9.5 g of an oily product. This oily product was combined with 7 g of the same fractions which obtained from the preceding column chromatography, and dissolved with 25 ml of C_6H_6 . The solution was refluxed for 20 hr, and concentrated. The residue was added with Et₂O, and left at room temperature. IV (6.1 g) was collected by filtration and washed with $(C_2H_5)_2O$. Total yield: 41.3 g (27.2%), mp 198–200° (from MeOH/CHCl₃). IR ν_{max}^{KBr} cm^{-1} : 3200 (NH), 1735 (CO₂Et), 1670 (CONH). NMR (d_6 -DMSO) δ : 1.18 (3H, t, $J=7.0$ Hz, C- CH_3), 1.90–2.60 (2H, m, C-CH₂-C), 3.20–3.55 (4H, m, -CH-CO $\times 2$ and C-CH₂-N), 3.72 (3H, s, OCH₃), 4.07 (2H, q, $J=7.0$ Hz, -CH₂-Me), 6.75–7.20 (4H, m, aromatic protons), 7.60 (1H, broad singlet, NH). Anal. Calcd. for C₁₈H₁₉O₄N: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.94; H, 7.03; N, 5.09. On the other hand, when the purified III was treated in a similar manner as described above, the yield of IV was 56%.

5-(1-Hydroxy-1-methylethyl)-3-(4-methoxyphenyl)-2-piperidinone (V)—To the Grignard reagent prepared from 14.7 g of Mg and 86 g of CH₃I in 500 ml of dry $(C_2H_5)_2O$ was added dropwise a solution of 70 g of IV in 500 ml of dry C_6H_6 with stirring at 60–70° over a 1.5 hr period and $(C_2H_5)_2O$ was evaporated at the same time. The solution was refluxed for 2 hr, cooled, and decomposed with dilute HCl and C_6H_6 layer was separated. The aqueous layer was extracted with CHCl₃. The combined organic layer was washed with H_2O , dried and concentrated. The residue was crystallized on cooling its C_6H_6 /AcOEt (1:1) solution, yielding

9) All melting points were uncorrected. IR spectra were taken with a Hitachi EPI-S2. NMR spectra were taken with a Hitachi Perkin-Elmer R-20 spectrometer using TMS as an internal standard.

26.4 g (39.7%) of V. Recrystallization from MeOH gave colorless crystals, mp 201—203°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1635 (CONH). NMR (d_6 -DMSO) δ : 1.07 (6H, s, C-CH₃ × 2), 1.55—2.30 (3H, m, $\text{C}_5\text{-H}$ and C-CH₂-C), 2.90—3.50 (3H, m, $\text{C}_2\text{-H}_2$ and C-CH₂-N), 3.70 (3H, s, OCH₃), 6.73—7.17 (4H, m, aromatic protons), 7.47 (1H, broad singlet, NH). *Anal.* Calcd. for C₁₅H₂₁O₃N: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.61; H, 8.28; N, 5.38. Furthermore, the filtrate was concentrated to give 40 g (60.2%) of an oily product. The crystalline product (V) and the oily product (V') were separately used for the next reaction.

1,2,3,4,5,6-Hexahydro-8-methoxy-6,6-dimethyl-1,5-methano-3-benzazocin-2-one (VI)—a) V (37.5 g) was added with stirring into 400 g of 80% H₂SO₄ at room temperature for 3 hr. The cold solution was poured into 500 g of a mixture of ice and H₂O. The product was crystallized by scratching the flask, and left overnight. The crystals of VI were collected and dried. Yield: 21.2 g (60.5%), mp 254—256° (from CHCl₃/MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1680 (CONH). NMR (CF₃CO₂H) δ : 1.48 (3H, s, C-CH₃), 1.52 (3H, s, C-CH₃), 2.10—2.60 (3H, m, C₅-H and C₁₁-H₂), 3.75—4.00 (3H, m, C₁-H and C₄-H₂), 4.00 (3H, s, OCH₃), 6.89 (1H, q, $J=2$ Hz, $J=9$ Hz, C₉-H), 7.15 (1H, d, $J=2$ Hz, C₇-H), 7.36 (1H, d, $J=9$ Hz, C₁₀-H), 8.88 (1H, broad singlet, NH). *Anal.* Calcd. for C₁₅H₁₉O₂N: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.24; H, 8.14; N, 5.87. The aqueous layer was washed with CHCl₃ and left at room temperature, yielding 14.0 g of 1,2,3,4,5,6-hexahydro-8-methoxy-6,6-dimethyl-9-sulfo-1,5-methano-3-benzazocin-2-one (VII) as colorless crystals, mp 260°. NMR (D₂O + NaOD) δ : 1.18 (3H, s, C-CH₃), 1.38 (3H, s, C-CH₃), 3.97 (3H, s, OCH₃), 7.15 and 7.52 (each 1H, s, aromatic protons). The Na salt of VII was recrystallized from aqueous EtOH. mp 267—270° (decomp.). *Anal.* Calcd. for C₁₅H₁₈O₅NNaS·3H₂O: C, 44.88; H, 6.03; N, 3.49; S, 7.99; H₂O, 13.46. Found: C, 44.51; H, 6.16; N, 3.46; S, 8.27; H₂O, 13.3. V' (40 g) was treated with 400 g of 80% H₂SO₄ in a similar manner as described above, yielding 10.6 g (29%) of VI.

b) V (5.0 g) was added with stirring into 50 g of polyphosphoric acid at 80° and heated with stirring at 85—95° for 15 hr. The warm solution was poured into a mixture of ice and H₂O and stirred. Precipitates were collected by filtration and washed with successive, H₂O, (C₂H₅)₂O, and CHCl₃/MeOH, yielding 4.0 g (86%). The NMR spectrum agreed with that of the sample obtained at a).

1,2,3,4,5,6-Hexahydro-8-methoxy-6,6-dimethyl-1,5-methano-3-benzazocine (VIII)—The suspended solution of 31.6 g of VI and 7.4 g of LiAlH₄ in 300 ml of dry dioxane was refluxed for 6 hr. After cooling, the saturated (NH₄)₂SO₄ solution (230 ml) was added. The dioxane layer was decanted and aqueous layer was extracted thoroughly with (C₂H₅)₂O. The organic layers were combined, and evaporated *in vacuo*. The residue was dissolved in (C₂H₅)₂O and the solution was washed with H₂O, dried, and evaporated, yielding 27.0 g of VIII as an oily product. VIII·HCl (colorless crystal): mp 265—268° (decomp.) (from AcOH/MeOH). NMR (D₂O) δ : 1.29 (3H, s, C-CH₃), 1.45 (3H, s, C-CH₃), 1.80—2.25 (3H, m, C₅-H and C₁₁-H₂), 3.30—3.40 (4H, m, C₂-H₂ and C₄-H₂), 3.60 (1H, m, C₁-H), 3.84 (3H, s, OCH₃), 6.99 (1H, q, $J=2.5$ Hz, $J=9.0$ Hz, C₉-H), 7.04 (1H, d, $J=2.5$ Hz, C₇-H), 7.14 (1H, d, $J=9.0$ Hz, C₁₀-H). *Anal.* Calcd. for C₁₅H₂₁ON·HCl: C, 67.28; H, 8.28; N, 5.23. Found: C, 67.58; H, 8.31; N, 5.22.

1,2,3,4,5,6-Hexahydro-8-methoxy-3,6,6-trimethyl-1,5-methano-3-benzazocine (IX)—A mixture of 13.0 g of VIII, 14.3 g of HCO₂H, and 9.0 g of 37% HCHO was heated on a water bath for 3.5 hr. The reaction mixture was diluted with 35 ml of 10% HCl, and concentrated to give a solid mass. Recrystallization from AcOEt/MeOH afforded 14.9 g of IX as colorless crystals. mp 237—240°. NMR (D₂O) δ : 1.31 (3H, s, C-CH₃), 1.48 (3H, s, C-CH₃), 1.95—2.30 (3H, m, C₅-H and C₁₁-H₂), 2.77 (3H, s, N-CH₃), 3.10—3.45 (4H, m, C₂-H₂ and C₄-H₂), 3.60—4.00 (1H, m, C₁-H), 3.85 (3H, s, OCH₃), 6.88 (1H, q, $J=2.5$ Hz, $J=8.5$ Hz, C₉-H), 7.04 (1H, d, $J=2.5$ Hz, C₇-H), 7.20 (1H, d, $J=8.5$ Hz, C₁₀-H). *Anal.* Calcd. for C₁₆H₂₃ON·HCl: C, 68.19; H, 8.58; N, 4.97. Found: C, 68.05; H, 8.92; N, 4.87.

1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,6-trimethyl-1,5-methano-3-benzazocine (X)—A solution of 14.4 g of IX·HCl in 100 ml of 47% HBr was heated under reflux for 2.5 hr. Removal of the solvent *in vacuo* gave the residue, which was made basic with 28% NH₄OH, and extracted with (C₂H₅)₂O. The extract was washed with H₂O, dried, and evaporated to give a syrup, which was purified by silica gel column chromatography with AcOEt, yielding 9.0 g of X, mp 114—116° (from petroleum ether/(C₂H₅)₂O). *Anal.* Calcd. for C₁₅H₂₁ON: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.69; H, 9.30; N, 6.02. X·HCl was hygroscopic. NMR (D₂O) δ : 1.29 (3H, s, C-CH₃), 1.44 (3H, s, C-CH₃), 1.90—2.20 (3H, broad singlet, C₅-H and C₁₁-H₂), 2.77 (3H, s, N-CH₃), 2.95—3.40 (4H, m, C₂-H₂ and C₄-H₂), 3.55—3.95 (1H, m, C₁-H), 6.73 (1H, q, $J=8$ Hz, $J=2$ Hz, C₉-H), 6.90 (1H, d, $J=2$ Hz, C₇-H), 7.10 (1H, d, $J=8$ Hz, C₁₀-H). *Anal.* Calcd. for C₁₅H₂₁ON·HCl·0.8H₂O: C, 63.84; H, 8.43; N, 4.96. Found: C, 63.85; H, 8.58; N, 4.98.

1,2,3,4,5,6-Hexahydro-8-methoxy-6,6-dimethyl-3-phenethyl-1,5-methano-3-benzazocine (XI)—A suspended solution of 2.53 g of VIII, 1.9 g of NaHCO₃ and 2.3 g of phenethyl bromide in 30 ml of DMF was heated with stirring at 90—100° for 3 hr. After cooling, the reaction mixture was diluted with H₂O and extracted with C₆H₆. The extract was washed with H₂O, dried, and evaporated to give 4.0 g of an oily product. This was purified by silica gel column chromatography with successive, C₆H₆, and C₆H₆/AcOEt (5:1), yielding 3.5 g of XI as an oily product. Recrystallization of XI·HCl from AcOEt/MeOH gave 3.4 g, mp 213.5—215.0°. *Anal.* Calcd. for C₂₃H₂₉ON·HCl: C, 74.27; H, 8.13; N, 3.77. Found: C, 74.18; H, 8.11; N, 3.73.

1,2,3,4,5,6-Hexahydro-8-hydroxy-6,6-dimethyl-3-phenethyl-1,5-methano-3-benzazocine (XII)—A solution of 2.1 g of XI·HCl in 20 ml of 47% HBr was heated at 135—145° on an oil bath for 2 hr. After cooling, the precipitated crystals were collected, yielding 2.3 g of XII·HBr, which was slightly soluble in H₂O. XII·HCl: 2.0 g, mp 273—275°. NMR (*d*₆-DMSO) δ : 1.23 (3H, s, C-CH₃), 1.43 (3H, s, C-CH₃), 1.80—2.20 (3H, broad singlet, C₈-H and C₁₁-H₂), 2.60—3.70 (9H, m, C₁-H and CH₂×4), 6.62 (1H, q, *J*=2 Hz, *J*=8 Hz, C₉-H), 6.80 (1H, d, *J*=2 Hz, C₇-H), 6.94 (1H, d, *J*=8 Hz, C₁₀-H), 7.20 (5H, s, C₆H₅). *Anal.* Calcd. for C₂₂H₂₇ON·HCl: C, 73.83; H, 7.89; N, 3.91. Found: C, 73.70; H, 7.89; N, 3.82.

1,2,3,4,5,6-Hexahydro-8-hydroxy-6,6-dimethyl-1,5-methano-3-benzazocine (XIII)—A solution of 11.0 g of VIII·HCl in 80 ml of 47% HBr was heated at 138—143° for 2.5 hr and evaporated *in vacuo*. The crystalline residue was recrystallized from H₂O, yielding XIII·HBr, mp 282—293° (decomp.). NMR (*d*₆-DMSO) δ : 1.23 (3H, s, C-CH₃), 1.39 (3H, s, C-CH₃), 1.65—2.10 (3H, m, C₅-H and C₁₁-H₂), 2.70—3.40 (5H, m, C₁-H and CH₂×2), 6.75 (1H, q, *J*=2.5 Hz, *J*=8 Hz, C₉-H), 6.89 (1H, d, *J*=2.5 Hz, C₇-H), 7.09 (1H, d, *J*=8 Hz, C₁₀-H). *Anal.* Calcd. for C₁₄H₁₉ON·HBr: C, 56.38; H, 6.76; N, 4.70. Found: C, 56.41; H, 6.89; N, 4.70. The solution of XIII·HBr in H₂O was made basic with 28% NH₄OH, and cooled. The precipitates were collected and recrystallized from MeOH, yielding 8.1 g of XIII as colorless crystals, mp 212—214°. *Anal.* Calcd. for C₁₄H₁₉ON: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.26; H, 8.84; N, 6.41.

1,2,3,4,5,6-Hexahydro-8-hydroxy-6,6-dimethyl-3-(3-methyl-2-butenyl)-1,5-methano-3-benzazocine (XIV)—To a suspended solution of 8.1 g of XIII, 9.4 g of NaHCO₃ in 80 ml of DMF was added dropwise with stirring a solution of 6.1 g of 1-bromo-3-methyl-2-butene in 5 ml of DMF. The solution was heated with stirring at 90—100° for 2 hr. After the inorganic substance and solvent were removed, the residue was diluted with H₂O, and extracted with C₆H₆. The extract was washed with H₂O, dried, and concentrated *in vacuo*, yielding 11.5 g of XIV as an oily product. XIV·HCl: 8.6 g. When XIV·HCl was recrystallized from EtOH or EtOH/(CH₃)₂CO, it included EtOH of crystallization. mp 110—112°. NMR (D₂O) δ : 1.20 (3H, t, *J*=7.5 Hz, O-C-CH₃), 1.31 (3H, s, C-CH₃), 1.41 (3H, s, C-CH₃), 1.75 (3H, s, =C-CH₃), 1.81 (3H, s, =C-CH₃), 2.05 (3H, m, C₅-H and C₁₁-H₂), 3.1—3.4 (4H, m, C₂-H₂ and C₄-H₂), 3.59 (2H, d, *J*=8 Hz, N-CH₂-C-C<), 3.65 (2H, q, *J*=7.5 Hz, O-CH₂-Me), 3.75 (1H, m, C₁-H), 5.15 (1H, t, *J*=7.5 Hz, C-CH=C), 6.75 (1H, q, *J*=2.5 Hz, *J*=8 Hz, C₉-H), 6.89 (1H, d, *J*=2.5 Hz, C₇-H), 7.09 (1H, d, *J*=8 Hz, C₁₀-H). *Anal.* Calcd. for C₁₉H₂₇ON·HCl·C₂H₅OH: C, 68.55; H, 9.31; N, 3.81. Found: C, 68.40; H, 9.46; N, 3.79.

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