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Studies on Novel Type Benzazocine. Syntheses and Pharmacological Properties of Novel Benzazocines

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The cyclization of 1-(substituted-allyl)-1,2,5,6-tetrahydro-2-benzylpyridines with Lewis acid was found to give novel benzomorphans consisted of a new four-ring system. The synthesized compounds have been found to possess a potent analgesic activity with low toxicity in mice in general, and some of them are several times as potent as pentazocine. The relationships between the analgesic activity and the molecular conformation of these compounds were also suggested in this paper.

In several previous papers,[2] it has been reported that the cyclization of 1-allyl-2-benzyltetrahydropyridines with Lewis acid gave the corresponding 6,7-benzomorphans. However, the authors have found that the cyclization of 1-(3′,3′-dimethylallyl)-1,2,5,6-tetrahydro-2-benzyl-3,4-dimethylpyridine IIa with Lewis acid did not give the usually corresponding 6,7-benzomorphan, but another product in high yield. Furthermore, it was found that the compound has a potent analgesic activity with low toxicity in mice. The molecular structure of this compound could be determined by means of nuclear magnetic resonance (NMR), infrared (IR), mass spectra and X-ray diffraction method. The X-ray diffraction studies[3] have shown that the compound has the new molecular structure (IVa) of a four-ring fused system. The derivatives of IVa have been produced by the above method, and both the reaction mechanism and analgesic activity have been studied. The present report is concerned with the syntheses and the pharmacology of the novel compounds (IV) which are obtained by cyclizing the corresponding tetrahydropyridines (II) with Lewis acid, such as PPA, 47%–HBr and $AlBr_3$.

Chemistry

The compounds (IV) were synthesized by the manner which was outlined in Chart 1. The reaction of benzylmagnesium chlorides with quaternary pyridine salts gave a good yield of very unstable dihydro derivatives (I) which were quickly hydrogenated (sodium borohydride in aqueous methanol) to the more stable tetrahydro compounds (II). The Lewis acid-treatment of the reduction mixture containing II gave the desired compounds (IV) in 30—40% of over-all yields based on II. The cyclization reaction was carried out by using polyphosphoric acid (PPA), 47%–HBr or $AlBr_3$ as Lewis acid; the optimal temperature and time are 135—140° and 20—30 hr respectively in case of PPA, 130—135° and 20—25 hr in case of 47%–HBr, or room temperature and 2—3 hr in case of $AlBr_3$ in carbon disulfide. The desired compounds (IV) were obtained directly from II at the reaction condition mentioned above, but when II were treated with Lewis acid under a mild reaction condition (at 125—130° for 15—20 hr with PPA or 47%–HBr), 1-azabicyclo[3,3,1]non-6-enes (III) were obtained. The compounds (III) isolated could also be led to IV by treating again at 130—140° for 15—20 hr with Lewis acid.

1) Location: *Takatsukasa, Takarazuka, Hyogo, 665, Japan.*
2) *a*) T. Kametani and K. Kigasawa, *Yuki Gosei Kagaku Kyokai Shi*, **29**, 227 (1971); *b*) T. Kametani, K. Kigasawa, M. Hiiragi, F. Satoh, H. Sugi, and T. Uryu, *J. Heterocyclic Chem.*, **6**, 43 (1969); *c*) *Idem, ibid.*, **8**, 769 (1971); *d*) *Idem, ibid.*, **9**, 1057, 1065 (1972); *e*) N.F. Albert and W.F. Wettern, *J. Med. Chem.*, **13**, 302 (1970).
3) M. Kimura, T. Nakajima, S. Inaba, and H. Yamamoto, *Bull. Chem. Soc. Japan*, **47**, 1404 (1974).

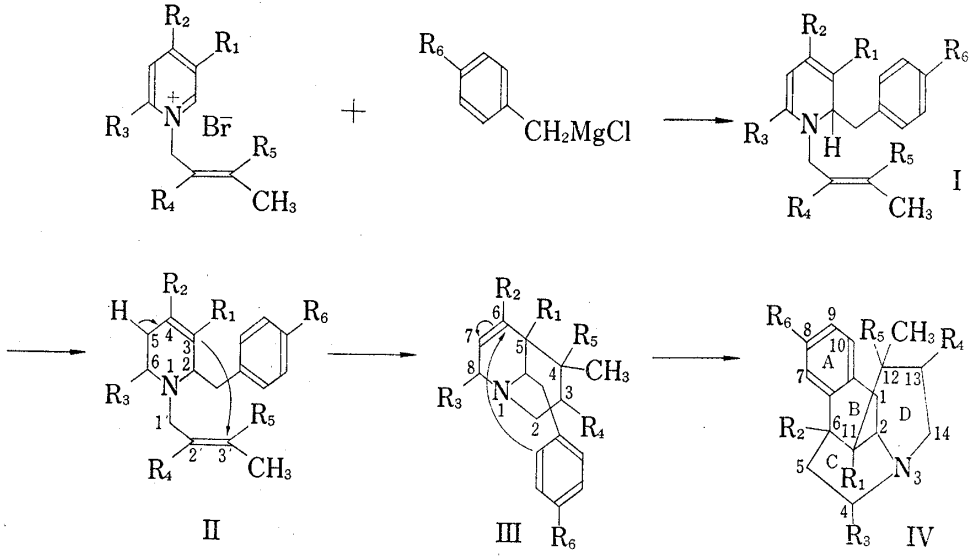

Chart 1 a: $R_1=R_2=R_5=CH_3$, $R_3=R_4=R_6=H$ b: $R_2=R_5=CH_3$, $R_1=R_3=R_4=R_6=H$
c: $R_1=R_2=R_4=R_5=CH$, $R_3=R_6=H$ d: $R_1=R_2=R_5=R_6=CH_3$, $R_3=R_4=H$
e: $R_2=R_3=R_5=CH_3$, $R_1=R_4=R_6=H$ f: $R_1=R_2=CH_3$, $R_5=C_2H_5$, $R_3=R_4=R_6=H$

Therefore the 1-azabicyclo[3,3,1]non-6-enes (III) are considered to be an intermediate in this cyclization reaction. When R_5 is hydrogen atom in II, neither the desired compounds (IV) nor the key intermediates (III) were formed, but the known 6,7-benzomorphan was obtained.[4] From the fact, the formation of IV is suggested to be limited within the case of II of the 3′-carbon atom substituted by two alkyl groups. This is considered to be based on rich electron density of 2′-carbon atom by the hyperconjugation of the alkyl groups. The fact suggests that the cyclization proceeds as the formation of 1-azabicyclo[3,3,1]non-6-enes (III) followed by ring closure to IV (Chart 1). The obtained products (IV) were distilled under reduced pressure or purified by a column chromatography with a silica gel, and characterized as the hydrochlorides, oxalates or picrates.

Kametani, *et al.* previously reported that the cyclization of IIg [$R_1=R_2=R_5=CH_3$, $R_3=R_4=H$ and $R_6=CH_3O$] with Lewis acid (PPA or 47%–HBr) led to the corresponding 1-azabicyclo[3,3,-1]non-6-ene derivative (IIIg) [$R_1=R_2=R_5=CH_3$, $R_3=R_4=H$, and $R_6=CH_3O$]. However, formation of the product related to IV has not been mentioned in their paper.

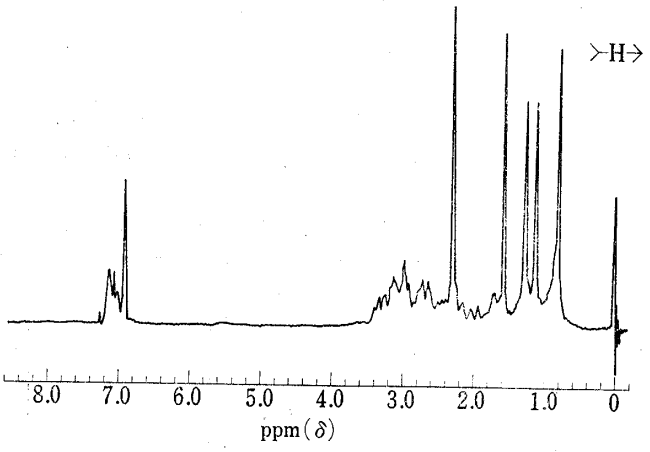

Fig. 1. NMR Spectrum of IVd in $CDCl_3$ (60 MHz)

The NMR spectra (obtained in $CDCl_3$) of IVd and IIIb, are shown in Fig. 1 and 2 respectively. The intense lines in high-field region (at 0.8—2.4 ppm) in Fig. 1 are concluded to be characteristic patterns for the methyl protons. When the results of our X-ray diffraction investigation of IVa[3] were compared with those of morphine,[5] cyclazocine,[6] and 2-allyl-2′-

4) *a*) T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Uryu, and H. Sugi, *J. Heterocyclic Chem.*, **10**, 27 (1973); *b*) Sumitomokagaku, Jap. Patent 45-31664 (1970); Ger Patent 1927724 (1970).
5) L. Gylbert, *Acta Cryst.*, **B29**, 1630 (1973).
6) I.L. Karle, R.D. Gilardi, A.V. Fratin, and J. Karle, *Acta Cryst.*, **B25**, 1469 (1969).

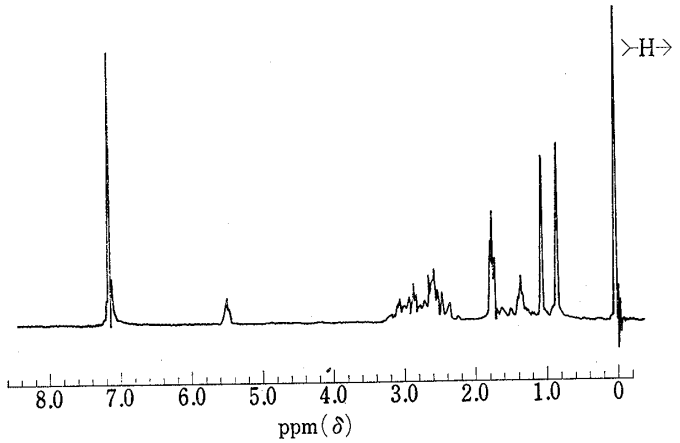

Fig. 2. NMR spectrum of IIIb in $CDCl_3$ (60 MHz)

hydroxy-5,9-dimethyl-6,7-benzomorphan (AHD),[7] the bond lengths and angles of the corresponding parts (rings A, B, and C) has been found to be identical. These facts suggest that C6–CH_3 and C11–CH_3 in IV have the same chemical shift as C5–CH_3 and C9–CH_3 of the known 5,9-dialkyl-6,7-benzomorphans.[8] Accordingly, the five singlet lines at 0.8—2.32 ppm were unequivocally assigned to C11–CH_3, C12–CH_3, C12–CH_3, C6–CH_3, and C8–CH_3 respectively on the basis of the chemical shift of the 5,9-dialkyl-6,7-benzomorphans. The difference of chemical shifts between C6–CH_3 and C11–CH_3 in IV and C9–CH_3 and C5–CH_3 of the known 5,9-dimethyl-6,7-benzomorphan was only 0.1—0.3 ppm.

In case of IIIb, two singlet lines at 0.95 and 1.10 ppm were assigned to C4–$(CH_3)_2$ protons respectively. The lower-field line at 5.5 ppm was assigned to one olefine proton adjacent to C6–CH_3. The C6–CH_3 protons appear at 1.78 ppm as double-doublet (J=2.6 and 2.0 Hz) because of coupling of C6–CH_3 with C7–H and C5–H. The IR spectra of the key intermediates (III) revealed the absorption at 1600—1650 cm^{-1} due to the olefinic bond of the tetrahydropyridine ring.

Pharmacology

The method of assay for analgesic potency is outlined in the experimental part. Table I summarizes the results of acetic acid writhing test for analgesic activity. These compounds have produced typical opiate actions such as Straub's tail, exophthalmus, locomotor hyperactivity and analgesia in mice. The analgesic activity in mice were more potent than that of pentazocine. The compounds, (IVa), (IVb), (IVc), and (IVf) were shown to be long duration analgesic activity. The duration of the effect of these compounds was apparently longer than that of pentazocine. Alkyl substitution of the phenyl group (such as IVd) reduced analgesic potency.

Regarding molecular conformation of IV, the bond distances and angles of the corresponding parts (rings A, B, and C) between IVa and morphine, 5,9-dialkyl-6,7-benzomorphans (such

Table I. Pharmacological Results (ED_{50} in mg/kg, *s.c.* in mice)

Compound	Acetic acid writhing test	Compound	Acetic acid writhing test
IVa[a]	8.9 (6.6—12.5)	IVf[b]	5.6 (2.8—11.2)
IVb[b]	5.6 (2.8—11.2)	Pentazocine[c]	17.3 (10.6—28.2)
IVc[b]	9.4 (6.7—13.2)	Morphine[a]	0.75 (0.49—1.15)
IVe[b]	11.9 (8.5—16.7)		

a) hydrochloride, *b*) oxalate, *c*) lactate

7) W. Fedeli, G. Giacomello, S. Cerrini, and A. Vaciago, *J. Chem. Soc.*, **B 1970**, 1190.
8) S.E. Fullerton, E.L. May, and E.D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

as cyclazocine and AHD), or morphinans (such as 3-hydroxy-N-allylmorphinan) were in good agreement with reasonable errors (supported by the X-ray diffraction investigation).[5-7,9] Hence rings A, B, and C of IV may be found to have the same molecular configuration as morphine or the others. In compounds (IV), there are six asymmetrical centers (at positions 2, 4, 6, 11, 12, and 13), but there is only one racemic pairs, because R_1 and R_2 are always retained in cis-configuration as understood easily from the "*trans*-rule"[10] of addition to olefinic bonds of II and III. On the other hand, R_1 and R_2 in 5,9-dialkyl-6,7-benzomorphans may be *cis*- or *trans*-configulation, and the C—D ring juncture in morphinans may be *cis*- or *trans*-fused, accordingly diastereoisomers (α- and β-forms) are encountered in both[10-13] as shown in Chart 2. That is, as in Chart 2, α-diastereoisomers have a *cis*-5,9-dimethyl configulation with respect to the tetraline ring (rings A and B) and are related to the morphinan, while the β-forms have a *trans*-5,9-dimethyl configulation and are related to the isomorphinan. It has been reported that the β-isomers are much more potent than the α-isomers; the β-isomers of Va is 6—8 times

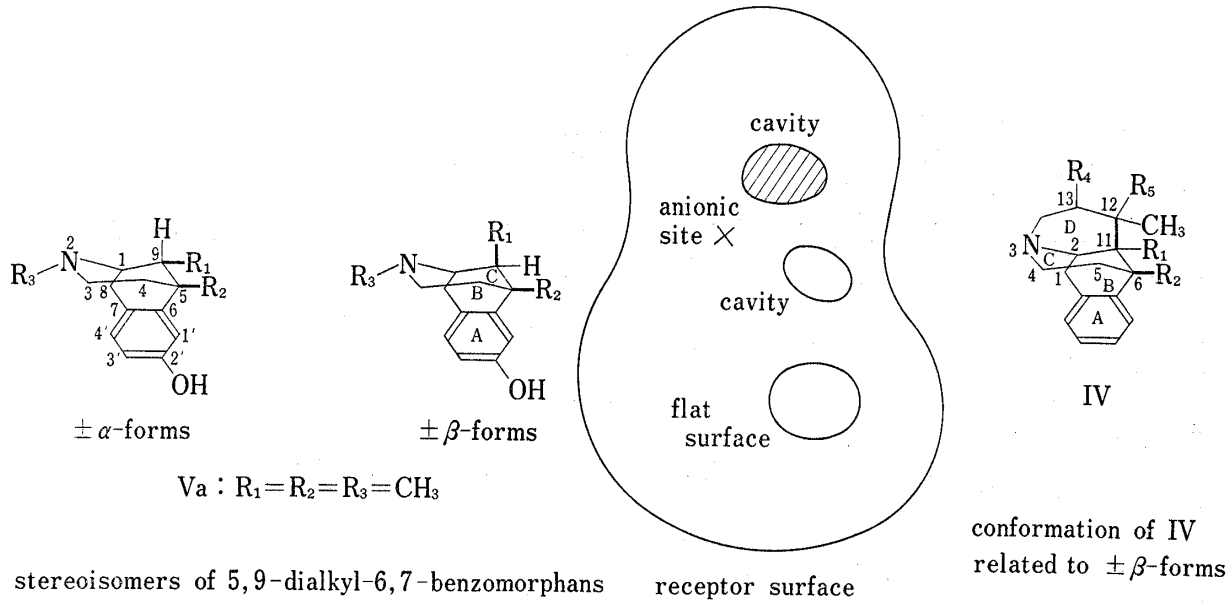

Chart 2. Conformation of IV and 5,9-Dialkyl-6,7-benzomorphans

more active than the α-forms,[13,14] and the 3-hydroxy-N-methyl-iso-morphinan is 8—10 times more active than morphine.[13] In case of IV, since 3- and 11-position of ring C are bridged by a propylene chain substituted by alkyl groups, R_2 always has a *trans*-configulation with respect to the C11—C12 bond. Hence the configulation of IV is analogous to the β-forms ("*trans*-rule" mentioned above). From these examinations with respect to the conformation of IV, it can be expected easily that IV related to the β-forms have potent analgesic activity.

The well-known receptor theory[13,15] of morphines has suggested that 5,9-dialkyl-6,7-benzomorphan or morphinan analgesics have potent activity because of similarity of these molecular structures corresponding to the following three essential receptor sites;

1. A flat portion allowing of van der Waals' forces binding the aromatic ring of the analgesics.

9) J.F. Blount, E. Mohacsi, F.M. Vane, and G.J. Mannering *J. Med. Chem.*, **16**, 352 (1973).
10) M.S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, 1956, p. 242.
11) E.L. May and J.H. Ager, *J. Org. Chem.*, **24**, 1432 (1959).
12) S.E. Fullerton, J.H. Ager, and E.L. May, *J. Org. Chem.*, **27**, 2554 (1962).
13) A.F. Casy, "Stereochemistry and Biology Activity," Med. Chem., 3rd ed. 1970 p. 81.
14) J.H. Ager, S.E. Fullerton, and E.L. May, *J. Med. Chem.*, **6**, 322 (1963).
15) A.H. Beckett and A.F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954).

2. An anionic site.
3. A cavity suitably oriented with sites 1 and 2.

In spite of existence of the ring D, however, compounds (IV) have a remarkable analgesic activity. Therefore, there may be another new analgesic site corresponding to the ring D. The flat aromatic rings A and B in IV lie in almost the same plane, with the –N–C4–C5– part of the piperidine ring C projecting slightly in front, and to the site of the plane. The piperidine ring D is approximately normal to the plane. In addition to the cavity corresponding to ring C, which is one of three essential receptor sites mentioned above, another cavity corresponding to ring D is present in the receptor to accommodate the –C12–C13–C14– portion of IV. Accordingly, the molecules (IV) must be fit to the receptor surface, and the drug-receptor interaction could be reforced by the collective van der Waals' forces between benzene ring A and a flat portion of the receptor surface, and the analgesic activity of IV may be also be enhanced. The fact, that products (IV) having no hydroxy group in the 8-position of the phenyl ring possess a potent analgesic activity, may suggest that there is a new receptor in the receptor surface.

Experimental

Melting points were determined on a Thomas-Hoover Uni-Melt apparatus, and uncorrected. IR spectra were obtained on a Perkin-Elmer Model IR-21 spectrophotometer. NMR spectra were obtained on a Varian A-60 spectrometer. The starting materials, the various pyridine, allylbromide and benzylchloride derivatives were obtained commercially or prepared routinely by literature procedures.

1-(2′,3′,3′-Trimethylallyl)-3,4-dimethyl-pyridinium bromide——To a solution of 15.41 g of 3,4-luthidine in 60 ml of benzene and 30 ml of acetone was added a solution of 19.28 g of 2,3,3-trimethylallylbromide in 30 ml of benzene and 15 ml of acetone at 0—5° with constant stirring. Stirring was continued at 0° for 2 hours and at room temperature for 2 hours. After cooling with ice-cold water, the resulting crystals were filtered and washed with benzene–acetone (2: 1) to give 22.8 g of the pyridinium bromide. mp 160—163°. IR ν_{max}^{Nujol} cm^{-1}: 1630, 1330, 1220, 1130, 1040, 940, 880, 740. This product was used without purification for a next procedure.

1-(2′,3′,3′-Trimethylallyl)-1,2,5,6-tetrahydro-2-benzyl-3,4-dimethylpyridine (IIc)——To a stirred suspension of 22.9 g of 1-(2′,3′,3′-trimethylallyl)-3,4-dimethylpyridinium bromide and 100 ml of dry ether (cooled in ice-water) was added 300 ml of 1.3M ethereal benzylmagnesium chloride at 10—20° during 5 min. The mixture was then stirred without cooling for 2 hours, poured into ice-water ammonium chloride, and basified with ammonium hydroxide. The ethereal layer was extracted three times with 10% hydrochloric acid in *ca.* twofold excess. The combined extracts were basified with cold ammonium hydroxide and the liberated base was extracted three times with ether. The ethereal extracts were dried over sodium sulfate. The air-sensitive residue (10.3 g) obtained from distillation of the ether *in vacuo* was quickly dissolved in 63 ml of methanol and 40 ml of 1N sodium hydroxide and hydrogenated with 2.52 g of sodium borohydride by refluxing for 3 hours. The mixture was diluted with cold water and extracted three times with ether. The combined extracts were washed with water, and dried (sodium sulfate). After removal of ether the residue was distilled under reduced pressure. bp 127—130° (0.1—0.2 mmHg). Yield 7.9 g (32.4%, overall yield from the bromide). IR ν_{max}^{Neat} cm^{-1}: 2700—3100, 1670, 1600, 1490, 1450, 1370, 1100, 780, 750, 720, 690. NMR (in $CDCl_3$) δ: 1.23 (s, 3H, C2′–CH_3), 1.55 (broad s, 3H, C3–CH_3), 1.63 (broad s, 9H, C4-CH_3 and C3′–$(CH_3)_2$). 2.0—3.4 (m. 8H, –CH_2–), 7.2 (s, 5H, aromatic). Other tetrahydropyridines (II) were similary obtained by the reactions of the quaternary ammonium salts with the corresponding Grignard reagents. The results are summarized as follows.

1-(3′,3′-Dimethylallyl)-1,2,5,6-tetrahydro-2-benzyl-3,4-dimethylpyridine (IIa): Yield 27.8%. bp 135—138° (0.31—0.32 mmHg). IR ν_{max}^{Neat} cm^{-1}: 3100—2800, 1660, 1600, 1490, 1450. NMR (in $CDCl_3$) δ: 1.55 (s, 3H, C3–CH_3), 1.60 (broad s, 9H, C4–CH_3, C3′–$(CH_3)_2$), 2.2—3.3 (m, 8H, –CH_2–), 4.8—5.2 (m, 1H, C2′–H), 7.2 (s, 5H, aromatic).

1-(3′,3′-Dimethylallyl)-1,2,5,6-tetrahydro-2-benzyl-4-methylpyridine (IIb): Yield 60.8%. bp 128—132° (0.3 mmHg). IR ν_{max}^{Neat} cm^{-1}: 3100—2700, 1670, 1600, 1490, 1450, 1380, 770, 730. NMR (in $CDCl_3$) δ: 1.63 (s, 6H, C3′–$(CH_3)_2$), 1.75 (broad s, 3H, C4–CH_3), 1.9—3.6 (m, 8H, –CH_2–), 5.0—5.5 (m, 2H, C3–H, C2′–H), 7.2 (s, 5H, aromatic).

1-(3′,3′-Dimethylallyl)-1,2,5,6-tetrahydro-2-(*p*-methylbenzyl)-3,4-dimethylpyridine (IId): yield 26%. bp 137—140° (0.3—0.35 mmHg). IR ν_{max}^{Neat} cm^{-1}: 3100—2700, 1670, 1600, 1500, 1460, 1380, 740, 700. NMR (in $CDCl_3$) δ: 1.55 (s, 3H, C3–CH_3), 1.60—1.62 (3×s, 9H, C3′–$(CH_3)_2$, C4–CH_3), 2.3 (s, 3H, CH_3 of phenyl), 2.4—3.4 (m, 8H, –CH_2–), 4.8—5.3 (m, 1H, C2′–H), 7.1 (s, 5H, aromatic).

1-(3′,3′-Dimethylallyl)-1,2,5,6-tetrahydro-2-benzyl-4,6-dimethylpyridine (IIe): Yield 46.1. bp 128—131° (0.3 mmHg). IR ν_{max}^{Neat} cm^{-1}: 3100—2700, 1670, 1600, 1500, 1460, 1380, 740, 700. NMR (in $CDCl_3$)

δ: 1.15 (d, 3H, J=6.0 Hz, C6–CH_3), 1.5—1.9 (broad s, 9H, C4–CH_3 and C3′–$(CH_3)_2$), 2.1—3.6 (m, 6H, –CH_2–), 5.0—5.5 (m, 2H, C3–H and C2′–H), 7.2 (s, 5H, aromatic).

1-(3′-Methyl-3′-ethylallyl)-1,2,5,6-tetrahydro-2-benzyl-3,4-dimethylpyridine (IIf): Yield 39.6. bp 135—138° (0.2—0.25 mmHg). IR ν_{max}^{Neat} cm^{-1}: 3100—2700, 1670, 1600, 1500, 1460, 750, 730, 700. NMR (in $CDCl_3$) δ: 0.9 (t, 3H, J=9.0 Hz, C3′–Et), 1.5 (s, 3H, C3–CH_3), 1.59 (s, 6H, C4–CH_3 and C3′–CH_3), 1.7—3.4 (m, 10H, –CH_2–), 4.7—5.2 (m, 1H, C2′–H), 7.2 (s, 5H, aromatic).

1,2,3,4,5,6-Hexahydro-6,11,12,12,13-pentamethyl-2,6-methano-3,11-propano-3-benzazocine (IVc)——Cyclization Method A (Using PPA): A mixture of 7.9 g of IIc, 50 g of P_2O_5 and 62.7 g of 85% H_3PO_4 was kept at 135—140° (oil-bath temperature 150—160° for 20 hours under nitrogen atmosphere, cooled, poured into 300 ml of ice-water and basified with ammonium hydroxide. The liberated base was extracted three times with ether and dried over sodium sulfate. After removal of ether, the residue was distilled under reduced pressure. bp 154—156° (0.22 mmHg). Yield 3.92 g (49.6%). IR ν_{max}^{Neat} cm^{-1}: 2800—3100, 1600, 1580, 760, 740, 720, 700, 680. NMR (in $CDCl_3$) δ: 0.82 (s, 3H, C11–CH_3), 0.96 (s, 3H, C12–CH_3), 1.29 (s, 3H, C12–CH_3), 1.55 (s, 3H, C6–CH_3), 0.8 (d, 3H, J=8.0 Hz, C13–CH_3), 1.6—3.5 (m, 8H, –CH_2–), 6.95—7.3 (m, 4H, aromatic). The oxalate was prepared from the free base 1.4 g and oxalic acid 0.44 g in acetone. mp 143—145°. *Anal.* Calcd. for $C_{22}H_{31}O_4N$; C, 70.75; H, 8.37; N, 3.75. Found: C, 70.70; H, 8.39; N, 3.69.

1,2,3,4,5,6-Hexahydro-6,11,12,12-tetramethyl-2,6-methano-3,11-propano-3-benzazocine (IVa)——Cyclization Method A′ (Using PPA and isolating the intermediate IIIa): A mixture of 10 g of IIa, 67 g of P_2O_5 and 84 g of 85% H_3PO_4 was kept at 120° for 6 hours under nitrogen atmosphere, cooled, poured into 300 ml of ice-water and basified with ammonium hydroxide. The liberated base was extracted three times with chloroform and dried over sodium sulfate. After removal of chloroform, the residue was distilled under reduced pressure to give 5 g of 9-benzyl-4,4,5,6-tetramethyl-1-azabicyclo[3,3,1]non-6-ene (IIIa). bp 127—139° (0.09—0.1 mmHg). IR ν_{max}^{Neat} cm^{-1}: 2800—3100, 1650, 1600, 710. NMR (in $CDCl_3$) δ: 0.82 (s, 3H, C4–CH_3), 0.97 (s, 3H, C4–CH_3). 0.95 (s, 3H, C5–CH_3), 1.6—1.8 (m, 3H, C6–CH_3), 2.8—3.8 (m, 8H, –CH_2–), 5.5—5.7 (m, 1H, C7–H), 7.18 (s, 5H, aromatic). A mixture of 2 g of IIIa 13.4 g of P_2O_5 and 17 g of 85% H_3PO_4 was kept 135—140° for 17 hours under nitrogen atmosphere, cooled, poured into 200 ml of ice-water and basified with ammonium hydroxide. The liberated base gave 1.4 g (70%) of IVa. bp 139—143° (0.16 mmHg). IR ν_{max}^{Neat} cm^{-1}: 3100—2800, 1600, 1580, 1490, 1450, 1100, 760, 740, 710, 700. NMR (in $CDCl_3$) δ: 0.76 (s, 3H, C11–CH_3), 1.10 (s, 3H, C12–CH_3), 1.24 (s, 3H, C12–CH_3), 1.55 (s, 3H, C6–CH_3), 1.6—3.5 (m, 10H, –CH_2–), 6.95—7.45 (m, 4H, aromatic).

Cyclization Method B (Using 47% HBr): The tetrahydropyridine (IIa) 5 g and 50 ml of 47% HBr were kept at 135—140° (oil-bath temperature) for 27 hours, cooled, poured into 2 volumes of ice-water and basified with ammonium hydroxide. The liberated base was extracted three times with ether, and dried over sodium sulfate. After removal of ether, the residue was distilled under reduced pressure to give 1.8 g (36%) of IVa. bp 144—147° (0.25—0.28 mmHg).

Cyclization Method C (Using $AlBr_3$): To a solution of 3 g of IIa and 15 ml of carbon disulfide was added during 5 min, 5 g of aluminium bromide at room temperature. The reaction was very exothermic. After a few minutes of a swirling, stirring was continued at room temperature for 3 hours. The mixture was poured into ice-water and, basified with ammonium hydroxide. The liberated base was extracted three times with ether and dried over sodium sulfate. After removal of the ether, the residue was distilled as described for cyclization method B to give 1.95 g (39%) of IVa. bp 145—149° (0.25—0.3 mmHg).

The other 1-azabicyclo[3,3,1]non-6-ene derivatives were similarly obtained by the cyclization method A′ described above. The results are summarized as follows.

9-Benzyl-4,4,6-trimethyl-1-azabicyclo[3,3,1]non-6-ene (IIIb): IR ν_{max}^{Neat} cm^{-1}: 3100—2800, 1650, 1600, 700. NMR (in $CDCl_3$) δ: 0.81 (s, 3H, C4–CH_3), 1.03 (s, 3H, C4–CH_3), 0.7—0.8 (m, 3H, C6–CH_3), 2.3—3.3 (m, 8H, –CH_2–), 5.4—5.6 (m, 1H, C7–H), 7.2 (s, 5H, aromatic).

9-Benzyl-4,4,6,8-tetramethyl-1-azabicyclo[3,3,1]non-6-ene (IIIe): IR ν_{max}^{Neat} cm^{-1}: 3100—2800, 1650, 1600, 700. NMR (in $CDCl_3$) δ: 0.89 (s, 3H, C4–CH_3), 1.10 (s, 3H, C4–CH_3), 0.94 (d, 3H, J=6.0 Hz, C8–CH_3), 1.6—1.8 (m, 3H, C6–CH_3), 2.4—3.5 (m, 6H, –CH_2–), 5.2—5.5 (m, 1H, C7–H), 7.3 (s, 5H, aromatic).

9-Benzyl-4,5,6-trimethyl-4-ethyl-1-azabicyclo[3,3,1]non-6-ene (IIIf): IR ν_{max}^{Neat} cm^{-1}: 3100—2800, 1670, 1600, 700. NMR (in $CDCl_3$) δ: 0.78 (s, 3H, C4–CH_3), 0.95 (s, 3H, C5–CH_3), 1.81 (m, 3H, C6–CH_3), 2.0—3.5 (m, 10H, –CH_2–). 5.4—5.7 (m, 1H, C7–H), 7.2 (s, 5H, aromatic).

1,2,3,4,5,6-Hexahydro-6,12,12-trimethyl-2,6-methano-3,11-propano-3-benzazocine (IVb)——A mixture of 30 g of IIb, 197 g of P_2O_5 and 247 g of 85% H_3PO_4 was kept at 135—140° (oil-bath temperature 150—160°) for 20 hours under nitrogen atmosphere, cooled and basified with ammonium hydroxide. The liberated base was extracted three times with ether and dried over sodium sulfate. After removal of ether, the residue was chromatographed on silica gel using ethylacetate as eluents. The latter fraction of chromatography was a desired compound (IVb). Yield 15 g (50%). IR ν_{max}^{Neat} cm^{-1}: 2850—3100, 1490, 1440, 1100, 740, 700, 650. NMR (in $CDCl_3$) δ: 1.16 (s, 3H, C12–CH_3), 1.25 (s, 3H, C12–CH_3), 1.56 (s, 3H, C6–CH_2), 1.6—3.8 (m, 10H, –CH_2–), 6.90—7.5 (m, 4H, aromatic). The picrate was prepared from the free base 6.0 g and picric acid 6.1 g. mp 213—215°. *Anal.* Calcd. for $C_{24}H_{28}O_7N_4$: C, 59.49; H, 5.82; N, 11.56. Found: C, 59.64; H, 5.96; N, 11.43.

1,2,3,4,5,6-Hexahydro-6,8,11,12,12-pentamethyl-2,6-methano-3,11-propano-3-benzazocine (IVd)——This was synthesized (60%) from IId, as described for cyclization method A above. bp 147—149° (0.2—0.25 mmHg). IR ν_{max}^{Neat} cm^{-1}: 2800—3100, 1600, 1500, 1440, 1380, 1100, 800, 750, 700, 680. NMR (in $CDCl_3$) δ: 0.8 (s, 3H, C11–CH_3), 1.15 (s, 3H, C12–CH_3), 1.28 (s, 3H, C12–CH_3), 1.60 (s, 3H, C6–CH_3), 2.32 (s, 3H, C8–CH_3), 1.7—3.6 (m, 10H, –CH_2–), 6.8—7.2 (m, 3H, aromatic). Oxalate (1/2 $(COOH)_2$): mp 193—195°. *Anal.* Calcd. for $C_{21}H_{30}O_2N$: C, 73.12; H, 8.90; N, 4.27. Found: C, 73.30; H, 9.10; N, 4.31.

1,2,3,4,5,6-Hexahydro-4,6,12,12-tetramethyl-2,6-methano-3,11-propano-3-benzazocine (IVe)——This was synthesized (25%) from IIe as described for cyclization method A above. IR ν_{max}^{Neat} cm^{-1}: 2800—3100, 1600, 1490, 1440, 1200, 1580, 760, 740, 720, 700, 660. NMR (in $CDCl_3$) δ: 1.20 (s, 3H, C12–CH_3), 1.29 (s, 3H, C12–CH_3), 1.59 (s, 3H, C6–CH_3), 1.04 (d, 3H, J=8.0 Hz, C4–CH_3), 1.7—3.9 (m, 8H, –CH_2–), 7.0—7.5 (m, 4H, aromatic).

1,2,3,4,5,6-Hexahydro-6,11,12-trimethyl-12-ethyl-2,6-methano-3,11-propano-3-benzazocine (IVf)——This was synthesized (20%) from IIf, prepared as described for cyclization method A above. IR ν_{max}^{Neat} cm^{-1}: 2800—3000, 1490, 1440, 1100, 760, 740, 710, 690. NMR (in $CDCl_3$) δ: 0.77 (s, 3H, C11–CH_3), 1.60 (s, 3H, C6–CH_3), 1.15 (s, 3H, C12–CH_3), 0.9 (t, 3H, J=8.0 Hz, C12–Et), 1.70—3.5 (m, 10H, –CH_2–), 6.95—7.4 (m, 4H, aromatic). Oxalate mp 174—176°. *Anal.* Calcd. for $C_{22}H_{31}O_4N$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.65; H, 8.46; N, 3.80.

Biological Procedures——Analgesic Activity: Pentazocine (Sosegon inj.——Yamanouchi Pharmaceutical Co., Tokyo) and Morphine hydrochloride (Takeda Chemical Industries, Osaka) were used as the reference compounds. The analgesic activity was determined by the acetic acid writhing test according to the method of Koster, *et al.*[16] Male mice of the dd-strain, weighing 20 to 22 g were used in groups of 5 to 10 animals. At 20 min after a drug administration, 0.1 ml of 0.6% (v/v) acetic acid per 10 g body weight of an animal was injected intraperitoneally. Immediately after an acetic acid injection, the number of writhes was counted for a period of 12 min. The numbers of writhes of the control animals were more than 20. When a mouse showed less than three writhes for that period, the test compound was regarded as positive on an analgesic activity. The ED_{50} values were calculated according to the method of Lichfield-Wilcoxon.

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