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Synthesis of Bridged 2-Phenylcyclohexylamines as Potential Analgetics

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9-Amino-1-(*m*-hydroxyphenyl)bicyclo[3.3.1]nonanes (Va) and their seven-membered homologs (Vb) were synthesized as potential analgetic agents. Condensation of acryloyl chloride with the morpholine enamine of the cyclohexanone (**1a**) gave the diketone (**4a**). Ketalization of **4a** followed by Wolff–Kishner reduction gave the 9-oxo derivative (**11**), which was converted to the 9-amino derivative (**16**) *via* the oxime (**12**). Condensation of acryloyl chloride and the morpholine enamine of the cycloheptanone (**1b**) gave the imminium salt (**3b**). Reaction of **3b** with NH_2OH occurred regiospecifically to give the 9-oxo-10-oxime (**19**). The oxime (**19**) was ultimately converted to the 10-amino derivative (**27**) *via* the amino-alcohol (**21**). $LiAlH_4$ reduction of the 10-*endo*-ethoxycarbamoyl derivative (**25**) and its 9-hydroxy derivative (**23**) anomalously gave epimeric mixtures of the 10-methylamino derivatives. From the primary amines **16** and **27**, various N-substituted derivatives were prepared for pharmacological evaluation. None showed significant activity.

Keywords——analgetic activity; bridged 2-phenylcyclohexylamines; 1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonane-2,9-dione; 1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane-9,10-dione; regioselective protection of diketone

Bridged aminotetralins (I) have been reported to show a combination of analgetic and narcotic antagonist activities with no substantial physical dependence capacity.[2] Tilidine (II), having an exocyclic amino function, is also an effective analgetic agent.[3] Since the benzomorphans (III) have been converted to a 5-phenylmorphan (IV)[4] with retention of analgetic activity, it seemed of interest to synthesize bridged 2-phenylcyclohexylamines (V) as potential analgetic agents. This report describes the synthesis of 9-amino-1-phenylbicyclo[3.3.1]-nonanes (Va) and 10-amino-1-phenylbicyclo[4.3.1]decanes (Vb).

The synthesis of 1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonan-9-one (**11**), a key intermediate for Va, was patterned after the synthesis of its demethoxy analog reported by Baiocchi *et al.*[5,6] Condensation of the morpholine enamine (**2a**) of 2-(*m*-methoxyphenyl)cyclohexanone (**1a**)[7] with acryloyl chloride gave 1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonane-2,9-dione (**4a**) in 75.9% yield after hydrolytic work-up. It was anticipated that the carbonyl group at C_9 in **4a** would be much more reactive than that at C_2 on the basis of the results for the demethoxyl series.[5] Therefore, selective protection of one of the carbonyl groups of **4a** as an ethylene ketal or an oxime afforded the C_9-monoketal (**7**) or the C_9-monoxime (**5**) in good yields, respectively. The structures of these compounds were confirmed by the nuclear magnetic resonance (NMR)

1) Location: *2-2-50, Kawagishi, Toda, Saitama, 335, Japan.*
2) *a*) M.E. Freed, J.R. Potoski, E.H. Freed, G.L. Conklin, and S.C. Bell, *J. Med. Chem.*, **19**, 476 (1976) and references cited therein; *b*) H.H. Swain and M.H. Seevers, Addendum, Minutes of the 36th Meeting of the Committee on Problems of Drug Dependence, National Research Council, National Academy of Sciences, 1974.
3) M. Harrman, W. Steinbrecher, and W. Heldt, *Arzneim.-Forsch.*, **20**, 977 (1970).
4) *a*) E.L. May and J.G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955); *b*) E.L. May and M. Takeda, *J. Med. Chem.*, **13**, 805 (1970); *c*) M.E. Rogers and E.L. May, *J. Med. Chem.*, **17**, 1328 (1974).
5) L. Baiocchi, A. Gambacorta, R. Nicoletti, and V. Petrillo, *Ann. Chim.* (Italy), **1971**, 744.
6) Other attempts to synthesize the ketone (**11**) from **1a** were unsuccessful. These included α,α'-annelation of **1a** or **2a** with various ω,ω'-dihalogeno compounds.
7) T. Kametani, S. Noguchi, I. Agata, T. Aono, K. Kigasawa, M. Hiiragi, T. Hayasaka, and O. Kusama, *J. Chem. Soc.*, **1971** (*C*), 1047; P. Caubere, G. Guillaumet, M.S. Mourad, *Tetrahedron*, **28**, 95 (1972).

spectra of their $NaBH_4$–reduction products (**6** and **14**). The spectra of the alcohols (**6** and **14**) showed the protons α to the hydroxyl groups as pseudo-triplets with $W/2=18$ Hz at 4.30 and 4.80 ppm, respectively, in accordance with the reported observation in the demethoxyl series.[5]

Wolff–Kishner reduction of the monoketal (**7**) yielded a mixture of the ketal (**9**) and its phenolic congener (**10**) in 20.8 and 54.7% yields, respectively. Methylation of this mixture

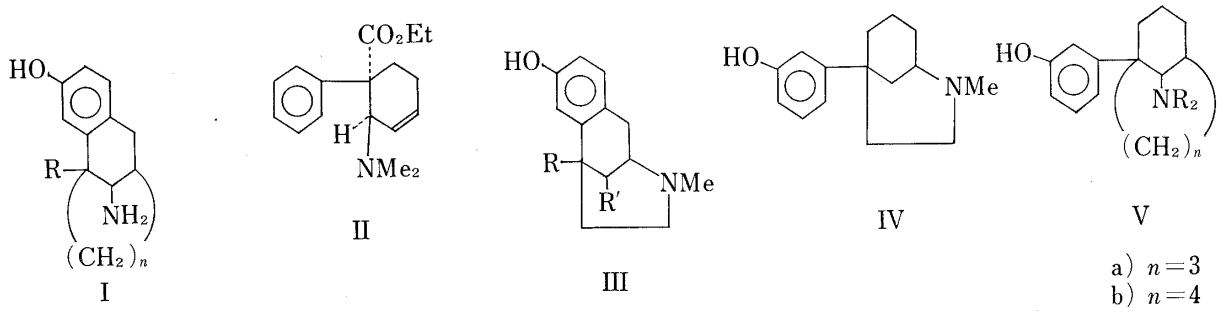


Chart 1

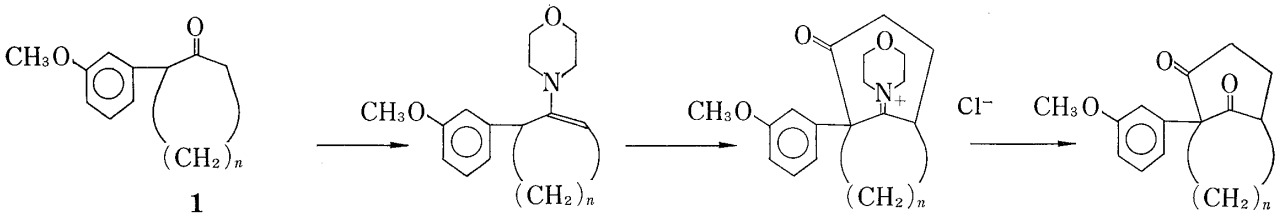
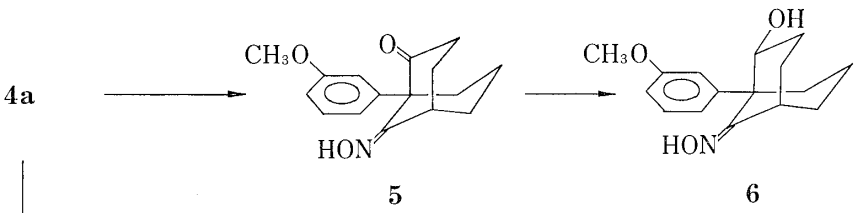


Chart 2



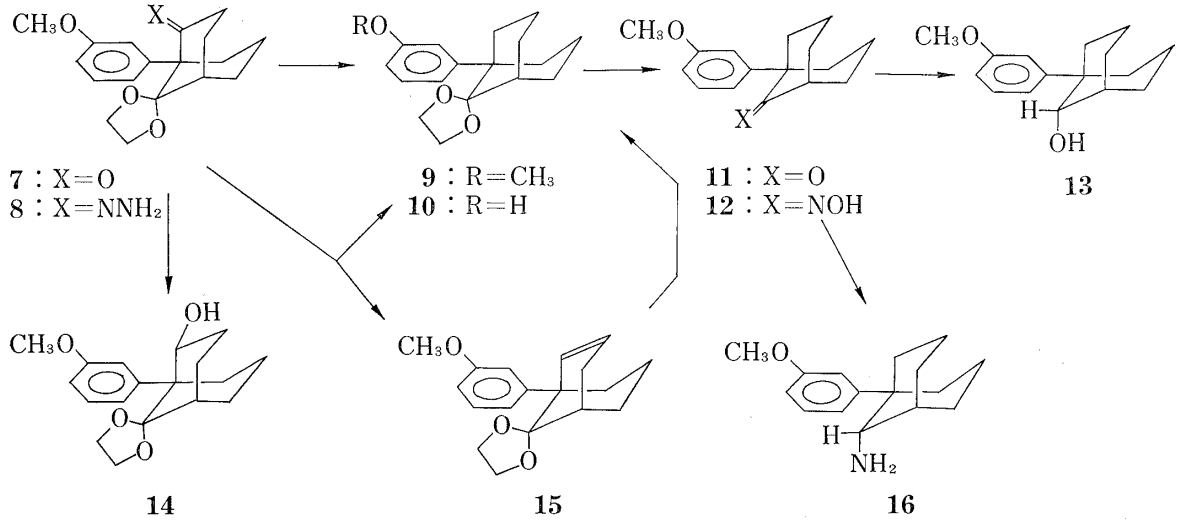


Chart 3

with Me_2SO_4 without separation gave **9** in 80.7% yield.[8] Treatment of the hydrazone (**8**) with *tert*-BuOK in boiling xylene also gave **9** in 60.4% yield together with a small amount (8.8%) of the olefin (**15**), which was convertible to **9** by hydrogenation. Hydroxyimination of the ketone (**11**), produced by acid hydrolysis of **9**, yielded the oxime (**12**), $LiAlH_4$ (LAH) reduction of which gave the 9-amino derivative (**16**). Hydrogenation of the ketone (**11**) in the presence of ammonia resulted in the formation of the 9-hydroxy compound (**13**) instead of **16**.

The morpholine enamine (**2b**) of 2-(*m*-methoxyphenyl)cycloheptanone[9] was prepared using titanium tetrachloride.[10,11]

Condensation of **2b** with acryloyl chloride gave the imminium salt (**3b**). Hydrolysis of **3b** did not occur under the acidic conditions employed for the hydrolysis of the six-membered

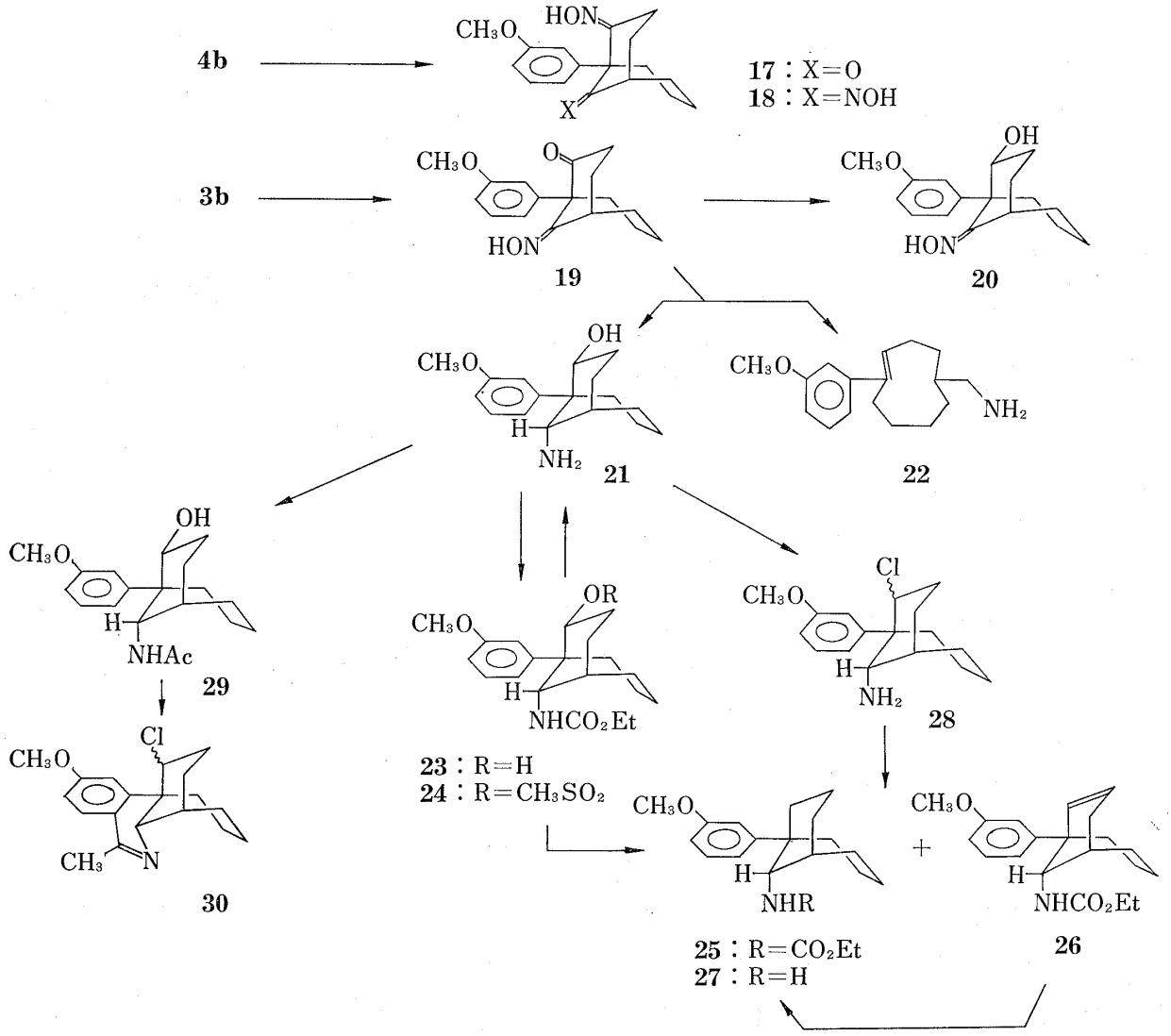


Chart 4

8) In the demethoxyl series, Baiocchi *et al.* removed the C_2 carbonyl group of the monoketal corresponding to **7** by a rather long sequence of reactions involving reduction, formation of the methyl xanthate, pyrolysis, and hydrogenation of the resulting olefin. See ref. 5. Thus, the present method was found to be much more convenient for the removal of the 2-oxo group.

9) C.D. Gutsche and E.F. Jason, *J. Am. Chem. Soc.*, **78**, 1184 (1956).

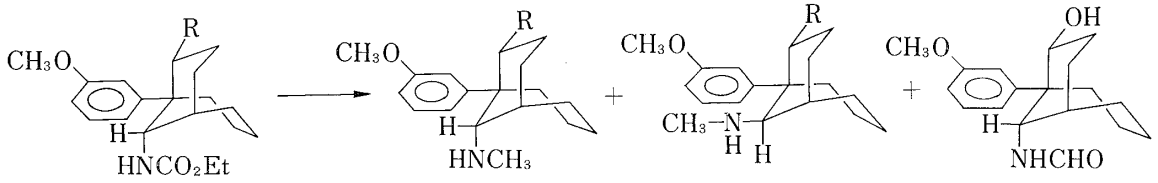
10) Generally, morpholine enamines of 2-substituted cycloheptanones cannot be obtained in satisfactory yield by the usual azeotropic method. I.J. Borowitz, G.J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco, and R.D.G. Rigby, *J. Org. Chem.*, **37**, 581 (1972).

11) W.A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).

analog (**3a**). Accordingly, **3b** was hydrolyzed with aqueous NaOH to the diketone (**4b**) (Chart 2).

Ketalization of **4b** or treatment of the imminium salt (**3b**) with ethylene glycol resulted in recovery of **4b**. Reaction of **4b** with one equivalent of NH_2OH in boiling EtOH gave a mixture of a monoxime (mp 153—155°) and the dioxime (**18**) in 52.5 and 15.2% yields, respectively. Thus, the reactivities of the two carbonyl groups in **4b** were quite different from those of the six-membered analog (**4a**). Treatment of the imminium salt (**3b**) with NH_2OH in dimethylformamide (DMF) at room temperature occurred regiospecifically to give another monoxime (mp 161—162°) in 90% yield. The same treatment of the diketone (**4b**) resulted in recovery of the starting material. The latter monoxime (mp 161—162°) appeared to be the 10-hydroxyimino derivative (**19**) on the basis of the reactions of **3b** and **4b** described above. $NaBH_4$ reduction of **19** gave the hydroxy derivative (**20**) in quantitative yield. In the NMR spectrum, **20** exhibited a quartet with $J=10$ and 6 Hz at 4.14 ppm, assignable to a proton α to an OH group. This confirmed the position as well as the stereochemistry of the hydroxyl group in **20**, the structure of the monoxime (**19**) being thus established. Accordingly, the monoxime having mp 153—155° was assigned the 9-hydroxyimino structure (**17**). Thus, the 10-oxo group of **4b** was found to be much less reactive than the corresponding 9-oxo group of **4a** on ketalization and hydroxyimination. This was also true for the hydrolysis of their respective imminium salts. It appears that the 10-oxo and 10-imino group of **4b** and **3b** are sterically hindered by the butano bridge of the cycloheptane ring, as shown in Chart 4.

Wolff–Kishner reduction of the monoxime (**19**) was unsuccessful. Therefore, **19** was reduced with LAH to the 10-amino-9-hydroxy derivative (**21**) in 81.9% yield. Concomitantly formed in this reduction was a small amount (3.2%) of the fragmentation product (**22**). The *endo* configuration was assigned to the 9-OH group of **21** on the basis of its NMR spectrum (quartet with $J=10$ and 5 Hz at 3.85 ppm). The 10-amino group of **21** was also assumed to be *endo* because the approach of hydride to the oxime group should occur from the less hindered *exo* side. The amino-alcohol (**21**) was treated with $ClCO_2Et$ to afford the urethane (**23**), mesylation of which gave the mesylate (**24**). Treatment of **24** with NaI and Zn powder in glyme[12] gave the reduction product (**25**) and the elimination product (**26**) in 14.9 and 44.3% yields, respectively. The latter was converted to **25** by catalytic hydrogenation. Treatment of the mesylate (**24**) with $NaBH_3CN$ in hexamethylphosphoramide (HMPA)[13] resulted in formation of the elimination product (**26**) in 14% yield. The olefin (**26**) was also obtained in 41.9% yield on treatment of **24** with HMPA alone. Hydrolysis of the urethane (**25**) with 20% alcohol-



23 : R=OH
25 : R=H

37j : R=OH
37h : R=H

32 : R=OH
35 : R=H

33

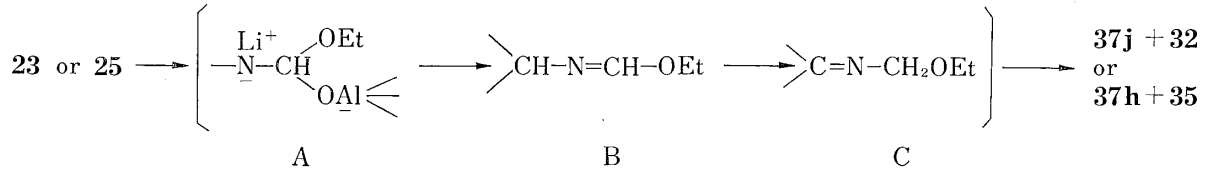


Chart 5

12) Y. Fujimoto and T. Tatsuno, *Tetrahedron Lett.*, **1976**, 3325.
13) R.O. Hutchins, B.E. Maryanoff, and C.A. Milewski, *Chem. Commun.*, **1971**, 1097.

ic KOH gave the 10-amino derivative (**27**). Subsequently, it was found that **27** could also be obtained from the amino-alcohol (**21**) in two steps, chlorination (PCl_5) followed by hydrogenation, in 37.2% overall yield. Chlorination of the N-acetylamino-alcohol (**29**) with $POCl_3$, on the other hand, yielded the cyclized chloride (**30**).

The reduction of the 10-*endo*-ethoxycarbamoyl-9-*endo*-hydroxy derivative (**23**) with LAH gave some anomalous results. The products of this reduction appear to vary with reaction temperature. Reduction in boiling dioxane gave an epimeric mixture of the N-methyl derivatives, **37j** and **32**, in 34.2 and 26.2% yields, respectively. Methylation of the 10-*endo*-amine (**21**) with MeI gave the 10-*endo*-methylamino derivative, identical with **37j**, together with the dimethylamino derivative (**37k**). LAH reduction of **23** in boiling tetrahydrofuran (THF) gave **37j** as a sole product in 75.2% yield. At a lower temperature such as in boiling Et_2O, the N-formyl compound (**33**) was isolated in 22.9% yield in addition to **37j** (56.9%). The 10-*exo*-N-methylamino structure was assigned to **32** on the basis of analytical and spectroscopic data. In the NMR spectrum, the C_9 *exo* proton of **32** appeared at lower field (4.56 ppm) compared with that of **37j** (3.83 ppm). This diamagnetic shift of the C_9 *exo* proton of **32** was apparently due to the anisotropic effect of the amino group which is related to the former in a 1,3-diaxial manner.[14] The 10-*endo*-ethoxycarbamoyl derivative (**25**) behaved similarly in LAH reduction, 10-*endo* and *exo* methylamino derivatives (**37h** and **35**) being isolated. In this reduction, the presence of an equilibrium mixture of the imine intermediates (B and C) can be anticipated[15] and this may cause the formation of epimeric amines.

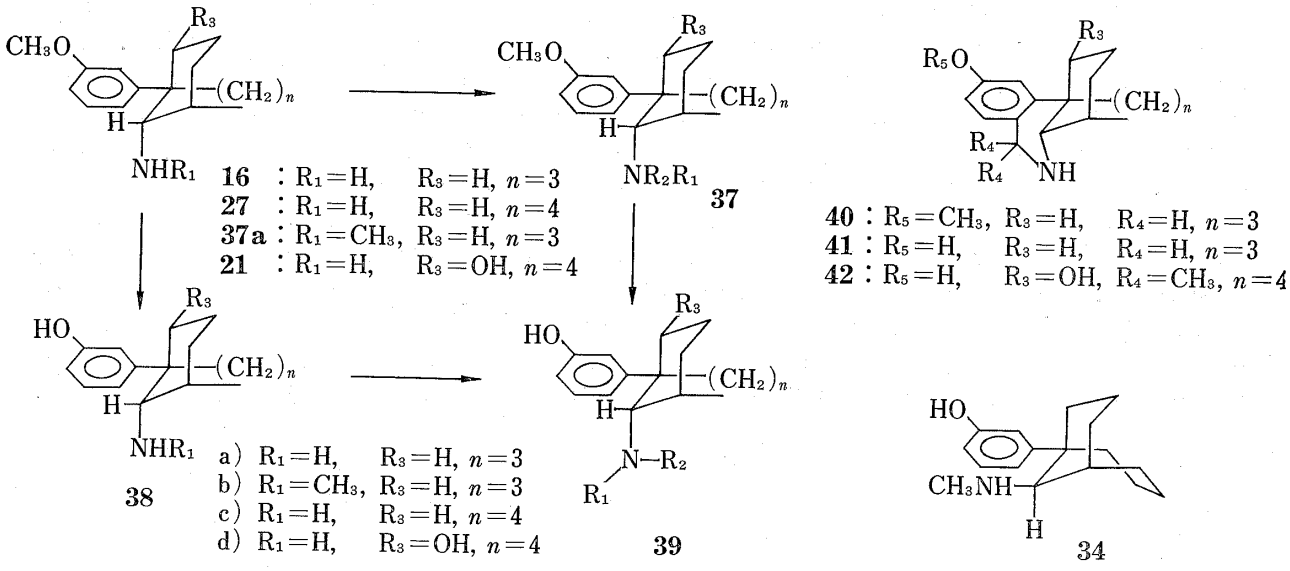


Chart 6

With the desired amines (**16**, **21**, and **27**) at hand, the various N-substituted derivatives listed in Table I were prepared for pharmacological evaluation. This was achieved by diverse routes, depending on the nature of the N-substituents. Compounds (**37b**, **g**, **h**, **j**, **k**, and **39a**, **i**) bearing allyl or methyl groups on the nitrogen were prepared by alkylation with alkyl halides (method A). Compounds (**37c**, **e**, **f**, **i**) bearing a phenethyl group were prepared by acylation with phenylacetyl chloride followed by reduction with B_2H_6 (method B). N-methyl compounds (**37a**, **d**, **39d**) were obtained by acylation with $ClCO_2Et$ followed by LAH reduction (method C). O-Demethylation of the methyl ethers described above with 48% HBr gave the

14) A.F. Casy, *Tetrahedron*, **22**, 2711 (1966).
15) H.O. House, "Modern Synthetic Reactions," second edition, W.A. Benjamin, Inc., Menlo Park, California, 1972, p. 79.

phenols (**39a, b, f, h, j, l, m**) (method D). Compounds (**39c, g, k**) carrying the acid-sensitive cyclopropyl group were prepared by acylation of the phenolic amine (**38**) followed by LAH reduction (method E). When the N-methylation of **16** was attempted with formalin in acidic medium, the cyclized product (**40**) was obtained instead of the N-hydroxymethyl compound. Treatment of crude **38d** (prepared by HBr-O-demethylation of **21**) with Me_2CO also gave the octahydrophenanthridine (**42**).

The compounds prepared in the present study were tested in mice for their analgetic activities by the AcOH-induced writhing method[16] and by the hot-plate method.[16] None of

TABLE I. Bridged 2-Arylcyclohexylamines

Compound	n	R_1	R_2	R_3	Salt	Method	Yield (%)	mp (°C)	Recrystn.[a] solvent	Formula	*Anal.* (%) Calcd (Found) C	H	N
37a	3	CH_3	H	H	HCl	C	81.8	268—270	M-E	$C_{17}H_{26}ClNO$	69.01 (68.91	8.86 8.87	4.73 4.65)
37b	3	CH_2=$CHCH_2$–	H	H	HCl	A	59.4	219—220	A-E	$C_{19}H_{28}ClNO$	70.89 (70.82	8.77 8.65	4.35 4.30)
37c	3	$PhCH_2CH_2$–	H	H	HCl	B	67.2	241—243	M-E	$C_{24}H_{32}ClNO$	74.68 (74.23	8.36 8.21	3.63 3.58)
37d	3	CH_3	CH_3	H	HCl	C	86.8	261—262	B	$C_{18}H_{28}ClNO$	69.76 (69.40	9.11 8.94	4.52 4.59)
37e	3	$PhCH_2CH_2$–	CH_3	H	HCl	B	50.5	192—193	B-E	$C_{25}H_{34}NO\cdot 1/4H_2O$	74.22 (74.38	8.60 8.74	3.46 3.50)
37f	4	$PhCH_2CH_2$–	H	H	HCl	B	51.9	234—236	B-E	$C_{25}H_{34}ClNO$	75.06 (74.95	8.57 8.56	3.50 3.58)
37g	4	CH_3	CH_3	H	HBr	A	20.7	239—241	B-E	$C_{19}H_{30}BrNO$	61.95 (62.01	8.21 8.33	3.80 4.00)
37h	4	CH_3	H	H	HCl	A	55.3	273—275	M-E	$C_{18}H_{28}ClNO$	69.76 (69.77	9.11 9.05	4.52 4.49)
37i	4	$PhCH_2CH_2$–	CH_3	H	HBr	B	39.7[b]	185—187	B-A-E	$C_{26}H_{36}BrNO\cdot 1/2H_2O$	66.91 (67.39	7.99 7.99	3.00 3.06)
37j	4	CH_3	H	OH	HCl	A	20.7	270—273	B-E	$C_{18}H_{28}ClNO_2$	66.34 (66.41	8.66 8.63	4.30 4.33)
37k	4	CH_3	CH_3	OH	HBr	A	36.0	225—227	B-E	$C_{19}H_{30}BrNO_2$	59.37 (59.02	7.87 7.94	3.64 3.77)
38a	3	H	H	H	HBr	D	77.2	203—205	M-A-E	$C_{15}H_{22}BrNO\cdot 1/4H_2O$	56.87 (56.88	7.16 7.14	4.42 4.28)
38b	3	CH_3	H	H	HBr	D	92.3	247—248	M-E	$C_{16}H_{24}BrNO$	58.89 (58.85	7.41 7.29	4.29 4.24)
38c	4	H	H	H	HBr	D	74.8	191—192	A-E	$C_{16}H_{24}BrNO$	58.89 (58.89	7.41 7.41	4.29 4.05)
38d	4	H	H	OH	Oxalate	D	64.8	114—116	B-E	$C_{16}H_{23}NO_2$ $C_2H_2O_4\cdot 3/4H_2O$	59.24 (59.07	7.32 7.44	3.84 3.76)
39a	3	CH_2=$CHCH_2$–	H	H	HCl	A 63.8 / D 25.2[c]		208—210	B-A-E	$C_{18}H_{26}ClNO$	70.22 (70.10	8.51 8.70	4.55 4.59)
39b	3	$PhCH_2CH_2$–	H	H	HBr	D	100	210—211	B-E	$C_{23}H_{30}BrNO$	66.34 (65.91	7.26 7.27	3.36 3.35)
39c	3		H	H	HCl	E	58.4	225—227	B-E	$C_{19}H_{28}ClNO$	70.89 (70.65	8.77 8.81	4.35 4.41)
39d	3	CH_3	CH_3	H	HCl	C	73.5	272—273	B	$C_{17}H_{26}ClNO$	69.01 (69.03	8.86 8.74	4.73 4.82)
39e	3	CH_2=$CHCH_2$–	CH_3	H	Free base	A	40.7	106—108	*n*-Hexane	$C_{19}H_{27}NO$	79.95 (79.83	9.54 9.49	4.91 4.85)
39f	3	$PhCH_2CH_2$–	CH_3	H	Free base	D	86.7	106—108	*n*-Hexane	$C_{24}H_{31}NO$	82.47 (82.44	8.94 8.97	4.01 4.03)
39g	3		CH_3	H	Free base	E	49.7	98—100	*n*-Hexane	$C_{26}H_{29}NO$	80.21 (79.88	9.76 9.67	4.68 4.71)
39h	4	CH_3	CH_3	H	HBr	D	95	255—257	M-E	$C_{18}H_{28}BrNO$	61.01 (60.81	7.96 7.99	3.95 3.92)
39i	4	CH_2=$CHCH_2$–	H	H	HCl	A	70	247—249	B-E	$C_{19}H_{28}ClNO$	70.89 (70.76	8.77 8.71	4.35 4.34)
39j	4	$PhCH_2CH_2$–	H	H	HBr	D	80.2	235—236	M-E	$C_{24}H_{32}BrNO$	66.97 (66.75	7.47 7.55	3.25 3.40)
39k	4		H	H	HCl	E	25.6	219—221	B-E	$C_{20}H_{30}ClNO$	71.51 (71.14	9.00 9.00	4.17 4.13)
39l	4	CH_3	H	OH	HBr	D	72.6	240—242	M-E	$C_{17}H_{26}BrNO_2$	57.30 (57.40	7.36 7.64	3.93 3.82)
39m	4	CH_3	H	H	HBr	D	92.6	281—282	B-E	$C_{17}H_{26}BrNO$	60.00 (59.97	7.70 7.58	4.12 4.00)
34	4	CH_3	H	H	HBr	D	78.1	231—233	M-E	$C_{17}H_{26}BrNO$	60.00 (60.13	7.70 7.73	4.12 4.08)

a) A: Me_2CO, B: EtOH, E: Et_2O, M: MeOH.
b) The starting material was recovered in 38.5% yield.
c) Addition of HBr to the double bond occurred to some extent during O-demethylation. The HBr salt of the HBr-adduct obtained in 16.5% yield gave mp 208—210° (from EtOH–Et_2O). MS *m/e*: 353, 351 (M^+). *Anal.* Calcd for $C_{18}H_{27}Br_2NO\cdot 1/2C_2H_5OC_2H_5$: C, 51.07; H, 6.80; N, 2.98. Found: C, 51.10; H, 6.62; N, 3.22.

16) These tests were performed at the Safety Research Laboratory of this company. For methodology, see S. Nurimoto, S. Suzuki, G. Hayashi, and M. Takeda, *Japan J. Pharmacol.*, **24**, 461, (1974).

the compounds exhibited interesting activity. Only **39k** and **39m** showed marginal activity in the hot-plate test.

Experimental

All melting points (mp) and boiling points (bp) are uncorrected. IR spectra were recorded on a Hitachi IR-215 spectrometer. NMR spectra were taken in $CDCl_3$ (JEOL ME-60) and the chemical shift is given in ppm relative to tetramethylsilane as an internal standard (δ=O), unless otherwise noted. Multiplicities are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad singlet (bs), *etc.* Mass spectra were measured using a Hitachi RMS-4 mass spectrometer. Silica gel PF_{254} (Merck) was used for preparative thick-layer chromatography (preparative TLC).

Morpholine Enamine (2a) of 2-(*m*-Methoxyphenyl)cyclohexanone (1a)——A mixture of **1a** (16.3 g, 79.8 mmol), morpholine (12 ml, 140 mmol), and a catalytic amount of TsOH (300 mg, 1.74 mmol) in toluene (200 ml) was refluxed for 20 hr with continuous removal of water. After cooling, the reaction mixture was washed with 5% $NaHCO_3$ and H_2O and dried. After removal of the solvent, the residual viscous oil was distilled to give **2a** (17.4 g, 80.2%), bp 159—160° (0.7 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 1640. NMR: 4.94 (t, J= 7 Hz, 1H, $-\underset{}{C}=CH-$), 3.80 (s, 3H, OCH_3), 3.53 (t, J=8 Hz, 4H, $-CH_2OCH_2-$), 2.70 (t, J=8 Hz, 4H, $-CH_2NCH_2-$).

1-(*m*-Methoxyphenyl)bicyclo[3.3.1]nonane-2,9-dione (4a)——To a boiling solution of the enamine (**2a**, 41.6 g, 153 mmol) in C_6H_6 (335 ml) was added a solution of acryloyl chloride (16.3 g, 180 mmol) in C_6H_6 (57 ml), and the mixture was heated under reflux for 18 hr. After cooling, the precipitated imminium salt (**3a**) was separated by filtration and washed with C_6H_6. The crude imminium salt was hydrolyzed by stirring with 2 N HCl (120 ml) and C_6H_6 (240 ml) at room temperature for 3 hr and extracted with C_6H_6. After concentration of the dried extracts, the residual solid was recrystallized from EtOH to give 29.5 g of **4a**, mp 94—96°. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1690. MS *m/e*: 258 (M^+). NMR: 3.81 (s, 3H, OCH_3). Analytical sample; mp 99.5—101°. *Anal.* Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.22; H, 7.09. Additional **4a** (510 mg, total yield 75.9%) was obtained from the mother liquor by column chromatography on SiO_2 [elution with C_6H_6-Et_2O (96: 4)]. Further elution with C_6H_6–Et_2O (95: 5) gave 1-(*o*-methoxyphenyl)-bicyclo[3.3.1]nonane-2,9-dione, mp 136—138° (from AcOEt), 390 mg (0.9%). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1695, 740. MS *m/e*: 258 (M^+). *Anal.* Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.15; H, 7.10. This may derived from 2-(*o*-methoxyphenyl)cyclohexanone contaminating the starting material.

9-Hydroxyimino-1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonan-2-one (5)——A mixture of diketone (**4a**, 810 mg, 3.14 mmol), $NH_2OH \cdot HCl$ (252 mg, 3.63 mmol), and $NaOAc \cdot 3H_2O$ (480 mg, 3.53 mmol) in EtOH (20 ml) was heated under reflux for 3 hr and EtOH was removed *in vacuo*. The residual solid was collected on a filter, washed with H_2O, dried (850 mg), and recrystallized from EtOH to give 695 mg (81.1%) of **5**, mp 217—219°. IR ν_{max}^{Nujol} cm^{-1}: 3220, 1720, 1660. *Anal.* Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.29; H, 7.09; N, 5.53.

2-*endo*-Hydroxy-1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonan-9-one Oxime (6)——A mixture of **5** (660 mg, 2.41 mmol) and $NaBH_4$ (200 mg, 5.26 mmol) in EtOH (30 ml) and THF (15 ml) was stirred at room temperature for 18 hr. After removing the solvent, the mixture was dissolved in $CHCl_3$, washed with H_2O, dried, and concentrated. Recrystallization of the residue from EtOH gave 400 mg (60.3%) of **6**, mp 186—188°. IR ν_{max}^{Nujol} cm^{-1}: 3250. NMR: 3.80 (s, 3H, OCH_3), 4.30 (pseudo triplet, $W/2$=18 Hz, 1H, $-\underset{OH}{\underset{|}{C}}H-$). *Anal.* Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.66; H, 7.72; N, 5.28.

9,9-Ethylenedioxy-1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonan-2-one (7)——Diketone (**4a**, 6.0 g, 23 mmol) and ethylene glycol (3.0 g, 62.5 mmol) in C_6H_6 (150 ml) were refluxed in the presence of TsOH (0.1 g) for 75 hr, removing H_2O by means of a Dean–Stark apparatus. After cooling, the mixture was poured into 5% $NaHCO_3$ and extracted with C_6H_6. The extracts were washed with H_2O and purified by column chromatography on SiO_2. Elution with C_6H_6–Et_2O (95: 5) gave a solid (5 g) which was recrystallized from EtOH to give 4.52 g (61.2%) of **7**, mp 101—102°. IR ν_{max}^{Nujol} cm^{-1}: 1700. NMR: 3.0—3.8 (m, 4H, $-OCH_2CH_2O-$), 3.79 (s, 3H, OCH_3). *Anal.* Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.30; H, 7.38. From the second eluate with C_6H_6–Et_2O (95: 5), the starting material (800 mg, 13.3%, mp 93—94°) was recovered.

9,9-Ethylenedioxy-2-*endo*-hydroxy-1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonane (14)——Compound (**7**, 400 mg, 1.32 mmol) was reduced with $LiAlH_4$ (100 mg, 2.6 mmol) in Et_2O (20 ml) for 1 hr at room temperature. The reaction mixture was decomposed with H_2O and then inorganic compounds were removed by filtration and washed with Et_2O. The filtrates were washed with H_2O, dried, and concentrated, and the residue was treated with a small amount of Et_2O to give 325 mg of crude **14**, mp 119—120°. IR ν_{max}^{Nujol} cm^{-1}: 3420. Recrystallization from EtOH afforded 300 mg (74.8%) of **14**, mp 120—121°. NMR: 4.80 (pseudo triplet, $W/2$= 18 Hz, 1H, $-\underset{OH}{\underset{|}{C}}H-$), 3.82 (s, 3H, OCH_3), 3.0—3.9 (m, 4H, $-OCH_2CH_2O-$). *Anal.* Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.17; H, 8.01.

9,9-Ethylenedioxy-1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonane (**9**)——a) Ketal ketone (**7**, 300 mg, 1 mmol) was added to a mixture of triethylene glycol (22 g), hydrazine hydrate (3.7 g, 74 mmol), and conc. HCl (830 mg, 8 mmol). After heating at 130° for 7 hr, KOH (pellets, 1.23 g, 22 mmol) was added to the mixture. The mixture was heated at 210° for 4 hr, poured into ice-water (100 ml) after cooling, and extracted with Et_2O. The dried extracts were concentrated to give an oil (270 mg), which was separated by chromatography on SiO_2.

From the first eluate with C_6H_6–Et_2O (95: 5), 60 mg (20.8%) of **9**, mp 54.5—55.5° (from pet.-ether), was obtained. IR (Nujol): no carbonyl absorption. MS *m/e*: 288 (M^+), 113. NMR: 3.78 (s, 3H, OCH_3), 3.1—3.8 (m, 4H, $-OCH_2CH_2O-$). *Anal.* Calcd for $C_{18}H_{24}O_3$: C, 74.96; H, 8.38. Found: C, 75.27; H, 8.56.

The second eluate with C_6H_6–Et_2O (95: 5) gave 150 mg (54.7%) of **10**, mp 127.5—128.5° (from iso-Pr_2O). IR ν_{max}^{Nujol} cm^{-1}: 3350. MS *m/e*: 274 (M^+), 113, 99. NMR: 3.2—3.9 (m, 4H, $-OCH_2CH_2O-$), 5.92 (s, 1H, OH). *Anal.* Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.21; H, 8.05.

b) O-Methylation of the Mixture of **9** and **10** with $(CH_3)_2SO_4$: A mixture of **9** and **10**, prepared from 3.3 g (10.9 mmol) of **7** as described above, was dissolved in 10% NaOH (15 ml, 37.5 mmol) and Et_2O (5 ml), and $(CH_3)_2SO_4$ (2.4 ml, 25.3 mmol) was added to the solution at 55° during a period of 10 min. After heating at the same temperature for 1 hr, the mixture was diluted with cold water and extracted with Et_2O. The washed and dried extracts were concentrated to give an oil (3.25 g), which was purified by chromatography (SiO_2). The first eluate with C_6H_6–Et_2O (95: 5) gave 2.54 g (80.7%) of **9**. From the second eluate with C_6H_6–Et_2O (95: 5—9: 1), **10** (110 mg, 3.5%) was obtained.

c) Treatment of **8** with *tert*-BuOK in Xylene: The hydrazone (**8**, 700 mg, 2.18 mmol), prepared as described above, was heated with *tert*-BuOK (1 g, 8.91 mmol) in xylene (30 ml) under reflux for 3 hr. After cooling, the mixture was poured into ice-water and extracted with Et_2O. The dried extracts were concentrated and the residual oil (580 mg) was separated by column chromatography on SiO_2. Elution with C_6H_6 gave 380 mg (60.4%) of **9**. The second eluate with the same solvent gave 55 mg (8.8%) of 1-(*m*-methoxyphenyl)-2-bicyclo[3.3.1]nonen-9-one ethylene ketal (**15**) as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3010, 700, 715. MS *m/e*: 286 (M^+), 185, 171, 103, 99. NMR: 6.09 (d-d-d, J=10, 5, and 3 Hz, 1H, C_3–H), 5.55 (d-t, J=10 and 2 Hz, 1H, C_2–H), 3.82 (s, 3H, OCH_3), 3.5—3.8 (m, 2H, $-OCH_2-$), 2.8—3.4 (m, 2H, $-OCH_2-$).

d) Hydrogenation of **15**: The olefin **15** (80 mg, 0.27 mmol) in EtOH (25 ml) was hydrogenated in the presence of 10% Pd–C (40 mg) at 70 kg/cm² (initial pressure of H_2) for 6 hr at 60—80°. After cooling, Pd–C and the solvent were removed to give an oil (75 mg, a mixture of **9** and **15**) which was subjected to preparative TLC with C_6H_6 to give **15** (40 mg, recovered in 50%) and **9** (25 mg, 31%).

1-(*m*-Methoxyphenyl)bicyclo[3.3.1]nonan-9-one Oxime (**12**)——A solution of **9** (690 mg, 2.39 mmol) in EtOH (8.5 ml) and Et_2O (9 ml) was added to conc. HCl (4.2 ml, 4.93 mmol). After stirring at room temperature for 1.5 hr, the mixture was poured into 5% $NaHCO_3$ and extracted with Et_2O. The dried extracts were concentrated to give the crude ketone (**11**, 580 mg, quantitative yield) as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 2910, 2850, 1710. NMR: 1.5—2.8 (m, 13H, $-CH_2-$ and $-\underline{C}H-$), 3.81 (s, 3H, OCH_3), 6.6—7.4 (m, 4H, arom.).

A mixture of the ketone **11** (460 mg, 1.88 mmol), $NH_2OH \cdot HCl$ (230 mg, 3.31 mmol), and $NaOAc \cdot 3H_2O$ (460 mg, 3.38 mmol) in EtOH (14 ml) was heated under reflux for 1 hr and diluted with H_2O. The precipitated oxime (**12**) was collected on a filter (560 mg) and recrystallized from MeOH to give 415 mg (85.0%), mp 190—192°. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1645. *Anal.* Calcd for $C_{16}H_{21}NO_2$: C, 74.09; H, 8.16; N, 5.40. Found: C, 74.02; H, 8.28; N, 5.45.

9-Amino-1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonane (**16**)——The oxime **12** (4.8 g, 18.5 mmol) was reduced with $LiAlH_4$ (1.4 g, 36.8 mmol) in THF (145 ml) under reflux for 3 hr. After cooling, the reaction complex was decomposed by the addition of H_2O under ice-cooling and inorganic compounds were removed. The dried filtrates were concentrated to give an oil (4.6 g), which was converted to the hydrochloride, mp 213—215° (dec.), 4.26 g (81.8%). *Anal.* Calcd for $C_{16}H_{24}ClNO$: C, 68.18; H, 8.58; N, 4.97. Found: C, 67.78; H, 8.68; N, 5.10. Anal. sample mp 215—217° (dec.) (from MeOH–Et_2O). MS *m/e*: 245 (M^+), 187. NMR: 3.99 (s, 3H, OCH_3), 3.50 (bs, 1H, C_9–H).

Hydrogenation of 11 in the Presence of Ammonia——The ketone **11** (100 mg, 0.409 mmol) in conc. NH_4OH (0.2 ml) and EtOH (8 ml) was hydrogenated in the presence of PtO_2 (40 mg) under ordinary pressure and temperature. After removing Pt and the solvent, the residual solid was recrystallized from hexane to give 9-hydroxy-1-(*m*-methoxyphenyl)bicyclo[3.3.1]nonane (**13**, 65 mg, 64.5%), mp 60.5—62°, IR ν_{max}^{Nujol} cm^{-1}: 3400. NMR: 4.12 (d, J=2.5 Hz, $-\underline{C}HOH$), 3.75 (s, 3H, OCH_3); *Anal.* Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.69; H, 9.00.

2-(*m*-Methoxyphenyl)cycloheptanone (**1b**)——a) *m*-Methoxybenzaldehyde (59 g, 0.433 mol) was added to hydrazine hydrate (48 g, 0.959 mol) below 43° under ice-cooling. After stirring at room temperature for 30 min, the mixture was extracted with Et_2O. The extracts were dried over KOH pellets for 2 hr, then anhy. Na_2SO_4 (120 g), sat. alcoholic KOH (18 ml) and yellow mercuric oxide (135 g, 0.623 mol) were added. The mixture was stirred and cooled during the addition of mercuric oxide (30 min) to keep the temperature below 30°. After stirring at room temperature for 5 hr, mercury, mercuric oxide, and Na_2SO_4 were removed by filtration, the filtrates were added to a solution of cyclohexanone (freshly distilled, 305 g, 3.11 mol) in MeOH (220 ml). The initially deep red solution was stirred at room temperature until the color changed

to pale yellow (8 days). After removing volatile materials, the residue was distilled to give 52.67 g (55.7%) of **1b** as an oil, bp 133—139° (0.4 mmHg). [lit.[9] bp 148—152° (0.8 mmHg)].

b) A solution of cycloheptanone (4.6 g, 41 mmol) in THF (6 ml) was added under ice-cooling during a period of 20 min to a Grignard solution, prepared from *m*-bromoanisole (8.34 g, 44.6 mmol) and Mg (1.1 g, 44.6 mmol) in THF (24 ml). After stirring at room temperature for 30 min and at 50—55° for 1 hr, work up of the reaction mixture in the usual manner gave crude 1-(*m*-methoxyphenyl)cycloheptanol (7.49 g) as an oil. The crude cycloheptanol was dehydrated by heating with oxalic acid (1 g, 11.1 mmol) and toluene (280 ml) for 16 hr. The reaction mixture was distilled, after removal of the solvents, to give 1-(*m*-methoxyphenyl)cycloheptene (6.07 g, 73%), bp 135—140° (4 mmHg). NMR: 3.76 (s, 3H, OCH_3), 6.11 (t, J=6.5 Hz, 1H, olefinic proton).

Under an N_2 atmosphere, a mixture of the above cycloheptene (6.07 g, 30 mmol) and $NaBH_4$ (2.10 g, 55.5 mmol) in THF (60 ml) was treated with $BF_3 \cdot Et_2O$ (10.5 g, 74 mmol) under ice-cooling during a period of 20 min. After stirring at room temperature for 15 hr, 10% NaOH (30 ml, 75 mmol) and 30% H_2O_2 (20 ml) were added to the reaction mixture under ice-cooling. After stirring at room temperature for 1 hr, the reaction mixture was concentrated *in vacuo* and extracted with Et_2O. The dried extracts were evaporated to give crude 2-(*m*-methoxyphenyl)cycloheptanol (7.2 g) as an oil. To a stirred solution of this cycloheptanol in Et_2O (35 ml) was added 35 ml of a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (10 g) in conc. H_2SO_4 (7.5 ml) and H_2O (50 ml) at 5—13°, and stirring was continued at room temperature for 2 hr. The mixture was extracted with Et_2O and washed with H_2O, 5% $NaHCO_3$, and H_2O. Concentration of the dried extracts followed by distillation gave 4.0 g of crude **1b**, bp 155—165° (3 mmHg). Purification by chromatography on SiO_2 (eluted with pet.ether-Et_2O (9: 1)) gave pure **1b** (2.2 g, 33.6%).

Morpholine Enamine (2b) of 1b——Under an N_2 atmosphere, a solution of $TiCl_4$ (26.4 g, 0.139 mol) in C_6H_6 (280 ml) was added to a solution of **1b** (53.97 g, 0.247 mol) and morpholine (72.6 g, 0.833 mol) in C_6H_6 (1.3 l) at 3—6° during a period of 40 min. After stirring at room temperature overnight, the mixture was heated at 75—80° for 8 hr, then filtered after cooling. After removing the solvent, the oil obtained was distilled to give 53.8 g (75.8%) of enamine (**2b**) as an oil, bp 155—164° (0.3 mmHg).

1-(*m*-Methoxyphenyl)bicyclo[4.3.1]decane-9,10-dione (4b)——A solution of acryloyl chloride (5.05 g, 55.8 mmol) in C_6H_6 (25 ml) was added to a solution of the enamine **2b** (15.89 g, 55.8 mmol) in C_6H_6 (124 ml) under reflux during a period of 20 min. After refluxing for 20 hr, the imminium salt (**3b**) was filtered and washed with C_6H_6 to give 16.4 g (78%), mp 237—240°. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1620. MS *m/e*: 341 (M^+), 259 (base peak). NMR: 3.82 (s, 3H, OCH_3).

The crude imminium salt (**3b**, 1g, 2.64 mmol) in $CHCl_3$ (30 ml) was stirred with 10% NaOH (15 ml, 37.5 mmol) at room temperature for 1 hr and extracted with Et_2O. The washed and dried extracts were concentrated to give 600 mg (83.4%) of **4b**, mp 108—110°. Analytical sample: mp 111—112° (from EtOH). MS *m/e*: 272 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1730, 1695. NMR: 1.1—3.2 (m, 13H, $-CH_2-$, $-\underset{|}{C}H-$), 3.81 (s, 3H, OCH_3). *Anal.* Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.83; H, 7.23.

9-Hydroxyimino-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decan-10-one (17)——The diketone **4b** (136 mg, 0.5 mmol) was heated with $NaOAc \cdot 3H_2O$ (70 mg, 0.5 mmol) and $NH_2OH \cdot HCl$ (35 mg, 0.5 mmol) in EtOH (3 ml) for 6 hr. After removal of EtOH by evaporation, the residue was diluted with H_2O and extracted with Et_2O. The dried extracts were concentrated to give a mixture (110 mg) of the starting material, **17**, and **18** which were separated by preparative TLC with AcOEt–C_6H_6 (1:4). Starting material (18 mg, 13%) was recovered from extracts of the upper fraction. The monoxime (**17**, 90 mg), was obtained from extracts of the middle fraction and recrystallized from EtOH to give 75 mg (52.5%) as prisms, mp 153—155°. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1715, 1640. MS *m/e*: 287 (M^+), 270 (base peak), 242, 214, 200, 186. *Anal.* Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.02; H, 7.49; N, 4.87. Extraction of the lower fraction gave dioxime (**18**, 23 mg, 15.2%), mp 239—242° (dec.) (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3250, 1640. MS *m/e*: 302 (M^+), 285 (base peak), 268, 253, 214. *Anal.* Calcd for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.34; N, 9.27. Found: C, 67.51; H, 7.30; N, 9.20.

10-Hydroxyimino-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decan-9-one (19)——The imminium salt 3b (51.8 g, 0.137 mol) was added to a solution of anhyd. NaOAc (11.7 g, 0.143 mol) and $NH_2OH \cdot HCl$ (9.5 g, 0.137 mol) in dry DMF (250 ml) at room temperature. After stirring overnight, the mixture was diluted with H_2O. The precipitated crude **19** was collected, washed with H_2O, and recrystallized from MeOH to give prisms, 35.53 g (90.3%), mp 161—162°. IR ν_{max}^{Nujol} cm^{-1}: 3290, 1705, 1655. MS *m/e*: 287 (M^+), 270 (base peak), 215, 200, 186. *Anal.* Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.90; H, 7.36; N, 4.88.

9-*endo*-Hydroxy-10-hydroxyimino-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane (20)——The monoxime **19** (132 mg, 0.5 mmol) was reduced with $NaBH_4$ (80 mg, 2.1 mmol) in EtOH (2 ml) and MeOH (1 ml) at room temperature for 3 hr. After removing the solvent, the residue was extracted with Et_2O. The extracts were washed with H_2O, dried, and evaporated to dryness to give a solid (150 mg, mp 161—163°), which was recrystallized from (iso-Pr)$_2O$ to give 130 mg (97.3%) of **20**, mp 164—165°. IR ν_{max}^{Nujol} cm^{-1}: 3430, 3270, 1630. NMR: 3.77 (s, 3H, OCH_3), 3.70 (m, 1H, C_6–H), 4.14 (d-d, J=11 and 6 Hz, 1H, C_9–H). *Anal.* Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.41; H, 8.06; N, 4.85.

Reduction of 19 with $LiAlH_4$——The monoxime **19** (35.15 g, 0.122 mol) was added to a solution of $LiAlH_4$ (17 g, 0.439 mol) in dioxane (1 l) and THF (300 ml) at room temperature. The reaction mixture was heated

under reflux until it became clear and worked up in the usual manner to give an oil, which was dissolved in a small amount of $CHCl_3$ and allowed to stand at room temperature to give 25.7 g of 10-*endo*-amino-9-*endo*-hydroxy-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane (**21**), mp 97—99° (turbid melt at 89—91°).

The mother liquor was concentrated and the residue was separated by column chromatography on SiO_2 (eluted with $CHCl_3$–MeOH (98: 2)).

The 9-*endo*-hydroxy-10-hydroxyimino compound **20** (344 mg, 1.0%) was obtained from the first eluate.

The second eluate gave additional **21** (1.87 g, mp 98—100° (turbid melt at 90—92°) (from $CHCl_3$-hexane), total yield 81.9%), IR $\nu_{max}^{liq.}$ cm^{-1}: 3380. NMR (free base): 3.03 (d, J=5.5 Hz, 1H, C_{10}–H), 3.79 (s, 3H, OCH_3), 3.85 (d-d, J=10 and 5 Hz, 1H, C_9–H). *Anal.* Calcd for $C_{17}H_{25}NO_2 \cdot 1/5CHCl_3$: C, 69.02; H, 8.49; N, 4.68. Found: C, 68.68; H, 8.34; N, 4.68.

The hydrochloride of **21** showed mp 224—226° after recrystallization from MeOH–Et_2O. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3000—2400. MS *m/e*: 275 (M^+), 258, 240. NMR (HCl salt, D_2O): 3.74 (d, J=5 Hz, 1H, C_{10}–H), 3.87 (s, 3H, OCH_3), 4.20 (d-d, J=10 and 5 Hz, 1H, C_9–H). *Anal.* Calcd for $C_{17}H_{26}ClNO_2 \cdot 1/4H_2O$: C, 64.52; H, 8.48; N, 4.43. Found: C, 64.79; H, 8.47; N, 4.45.

The third eluate (2.0 g, a mixture of unknown compounds) was discarded.

The fourth eluate gave an oil (2.25 g) of 5-aminomethyl-1-(*m*-methoxyphenyl)-1-cyclononene (**22**), which was converted to the picrate and recrystallized from EtOH–Et_2O to give 1.88 g (3.2%) of **22**·picrate, mp 185—187°. IR (free base) $\nu_{max}^{liq.}$ cm^{-1}: 3380, 3300, 1610, 1598, 1580, 1575; (picrate) ν_{max}^{Nujol} cm^{-1}: 3230, 3100; (HCl salt) ν_{max}^{Nujol} cm^{-1}: 3000, 2650, 2000, 1610, 1598, 1580, 1575. MS *m/e*: 259 (M^+), 242. NMR (picrate, DMSO-d_6): 3.76 (s, 3H, OCH_3), 5.57 (t, J=8 Hz, 1H, olefinic proton). *Anal.* Calcd for $C_{17}H_{25}NO \cdot C_6H_3N_3O_7$: C, 56.55; H, 5.78; N, 11.47. Found: C, 56.67; H, 6.05; N, 11.42.

10-*endo*-Ethoxycarbamoyl-9-*endo*-hydroxy-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane (23)——A mixture of the amino-alcohol **21** (25.7 g, 93.3 mmol), 5% $NaHCO_3$ (800 ml), and CH_2Cl_2 (650 ml) was treated with $ClCO_2Et$ (19.2 g, 177 mmol). After stirring at room temperature for 4 hr, the reaction mixture was extracted with $CHCl_3$. The extracts were washed with H_2O, dried, and concentrated to give an oil, which was treated with a small amount of Et_2O and hexane. The obtained **23**, mp 88—92°, 23.76 g (73.3%), had a half-mol of Et_2O of crystallization. NMR: 1.10 (t, J=7 Hz, 3H, CH_3 of ester), 1.21 (t, J=7 Hz, 3H, CH_3, of Et_2O), 3.49 (q, J=7 Hz, 2H, OCH_2– of Et_2O), 3.97 (q, J=7 Hz, 2H, –OCH_2– of ester), 3.81 (s, 3H, OCH_3), 4.21 (d–d, J=10 and 5 Hz, 1H, C_9–H), 4.82 (d, J=9 Hz, 1H, C_{10}–H). Recrystallization of this hemietherate from (iso-Pr)$_2$O gave prisms of mp 89—91°; these were hemiisopropyl etherate. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1690, 1665. MS *m/e*: 347 (M^+), 329, 301, 214, 121. NMR: 3.81 (s, 3H, OCH_3), 3.97 (q, J=7 Hz, 2H, OCH_2–), 4.21 (q, J=10 and 5 Hz, 1H, C_9–H), 4.82 (d, J=9 Hz, 1H, C_{10}–H), 1.10 (t, J=7 Hz, 3H, CH_3), 3.62 (septet, J=6 Hz, 1H, $(Me)_2CH$–), 1.14 (d, J=6 Hz, 6H, $CH(C\underline{H}_3)_2$). *Anal.* Calcd for $C_{20}H_{29}NO_4 \cdot 1/2C_6H_{14}O$: C, 69.31; H, 9.11; N, 3.51. Found: C, 69.43; H, 8.95; N, 3.62.

10-*endo*-Ethoxycarbamoyl-9-*endo*-mesyloxy-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane (24)——A solution of **23** (22.0 g, 63.3 mmol) in pyridine (88 ml) was treated with CH_3SO_2Cl (16.1 g, 140 mmol) under ice-cooling. After stirring at room temperature for 4 hr, the reaction mixture was poured into ice-water and the separated crystalline solid was filtered off, washed with Et_2O, and recrystallized from $CHCl_3$–hexane to give 21.6 g (80.2%) of **24**, mp 159—161°. IR ν_{max}^{Nujol} cm^{-1}: 3450, 1715, 1360, 1180. MS *m/e*: 425 (M^+), 329, 300. *Anal.* Calcd for $C_{21}H_{31}NO_6S$: C, 59.27; H, 7.34; N, 3.29. Found: C, 58.86; H, 7.16; N, 3.18.

Hydrolysis of 24——A mixture of **24** (100 mg, 0.29 mmol), 10% NaOH (10 ml), and EtOH (40 ml) was heated under reflux for 20 hr, concentrated *in vacuo*, and extracted with $CHCl_3$–EtOH (3: 1). The extracts were dried and concentrated to give an oil (80 mg), which was purified by preparative TLC with $CHCl_3$–MeOH (9: 1) to give 44 mg (55.6%) of **23**.

Reaction of Mesylate (24) with Zn-NaI——A mixture of the mesylate **24** (10 g, 23.5 mmol), NaI (18 g, 120 mmol), and Zn powder (18 g, 275 mmol) in glyme (200 ml) was heated under reflux for 48 hr, and heating was continued for a further 28 hr after addition of NaI (18 g) and Zn powder (18 g). After cooling, the mixture was diluted with H_2O and Et_2O and inorganic compounds were removed by filtration. The filtrates were concentrated *in vacuo*. The obtained oil (9.75 g) was separated by column chromatography on SiO_2 (eluted with C_6H_6–AcOEt 98: 2).

10-*endo*-Ethoxycarbamoyl-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane (**25**, 1.16 g, 14.9%) was obtained from the first eluate as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3460, 3350, 1710. MS *m/e*: 331 (M^+), 242, 240. NMR: 1.17 (t, J=7 Hz, 3H, $CH_2C\underline{H}_3$), 3.80 (s, 3H, OCH_3), 4.04 (q, J=7 Hz, $OC\underline{H}_2Me$), 4.86 (bd, J=11 Hz, 1H, C_{10}–H).

From the second eluate 10-*endo*-ethoxycarbamoyl-1-(*m*-methoxyphenyl)-9-bicyclo[4.3.1]decene (**26**, 3.43 g, 44.3%, mp 70—72°) was obtained after recrystallization from hexane. IR ν_{max}^{Nujol} cm^{-1}: 3460, 3350, 1700. MS *m/e*: 329 (M^+), 300, 240. NMR: 1.07 (t, J=8 Hz, 3H, $CH_2C\underline{H}_3$), 3.78 (s, 3H, OCH_3), 4.04 (q, J=8 Hz, 2H, OCH_2Me), 5.4—6.1 (m, 2H, olefinic protons). *Anal.* Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.24; H, 8.27; N, 4.26.

Reaction of 24 with HMPA——Heating of **24** (200 mg, 0.47 mmol) with HMPA (2 ml) at 120° for 30 hr followed by preparative TLC with C_6H_6–AcOEt (10: 1) afforded **26** (65 mg, 41.9%).

Reduction of 26——The olefin **26** (3.45 g, 10.5 mmol) in EtOH (100 ml) was hydrogenated in the presence of 10% Pd–C (600 mg) under high pressure (65 kg/cm^2 initial pressure of H_2) at 70—90° for 7.5 hr. After removal of the catalyst and solvent, 3.4 g (97.7%) of **25** was obtained.

Hydrogenation of crude **26**, without purification by chromatography, did not proceed completely, probably because of poisoning of the catalyst.

10-*endo*-Amino-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane (27)——a) The urethane **25** (3.4 g, 10.3 mmol) was refluxed with 20% KOH (80 ml, 400 mmol) and EtOH (200 ml) for 3 days. After removal of the solvent, the residue was diluted with water and extracted with $CHCl_3$. The dried extracts were concentrated to give an oil (2.88 g), which was converted to the hydrobromide (3.03 g, 86.8%, mp 206—208°). Recrystallization of the hydrobromide from MeOH–Et_2O gave needles of mp 208—210°, **27**·hydrobromide. IR ν_{max}^{Nujol} cm^{-1}: 3200—2500. MS *m/e*: 259 (M^+), 242. NMR (free base): 3.26 (d, J=3.8 Hz, 1H, C_{10}–H), 3.81 (s, 3H, OCH_3). *Anal.* Calcd for $C_{17}H_{26}BrNO$: C, 60.00; H, 7.70; N, 4.12. Found: C, 59.97; H, 7.75; N, 4.17.

b) A suspension of **21**·hydrochloride (190 mg, 0.609 mmol) in CH_2Cl_2 (3 ml) was treated with PCl_5 (250 mg, 1.20 mmol) at room temperature and the mixture was refluxed for 21 hr. After removing the solvent, the residue (287 mg) in EtOH (30 ml) was hydrogenated in the presence of 10% Pd–C (150 mg) at 80 kg/cm^2 (initial pressure of H_2) for 5 hr at 80—100°. After removal of the catalyst and solvent, the residual oil (250 mg) was dissolved in H_2O, made basic with K_2CO_3, and extracted with Et_2O. The extracts were washed with H_2O, dried, and concentrated to give an oil (170 mg) which was separated by preparative TLC (SiO_2) with $CHCl_3$–EtOH (10: 1).

The oil (32 mg) which was obtained by extraction of the upper fraction was converted to the hydrobromide (mp 185—187°, 30 mg). Recrystallization of the crude hydrobromide from EtOH–Et_2O gave 10-*endo*-amino-9-chloro-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane hydrobromide (**28**) (28 mg, 12.3%) of mp 187—189°. MS *m/e*: 295, 293 (M^+), 257. *Anal.* Calcd for $C_{17}H_{25}BrClNO$: C, 54.48; H, 6.72; N, 3.74. Found: C, 54.59; H, 6.91; N, 3.66.

The amine (**27**) obtained from the lower fraction of TLC was converted to the hydrobromide (70 mg, 37.2%).

4,10b-Butano-1-chloro-1,2,3,4,4a,10b-hexahydro-9-methoxy-6-methylphenanthridine (30)——The amino-alcohol **21** (275 mg, 1 mmol) was stirred with Ac_2O (150 mg, 1.5 mmol), CH_2Cl_2 (20 ml), and 5% $NaHCO_3$ (15 ml) at room temperature for 3 hr and extracted with $CHCl_3$. The extracts were washed with H_2O, dried, and concentrated to give 10-*endo*-acetamino-9-*endo*-hydroxy-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane (**29**, 310 mg, 97.7%) as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3350, 1650. A solution of **29** (145 mg, 0.457 mmol) in pyridine (0.7 ml) was treated with $POCl_3$ (125 mg, 0.914 mmol) under ice-cooling. After stirring at room temperature for 3 hr and then at 80° for 4 hr, the mixture was poured into ice-water and extracted with Et_2O. The dried extracts were concentrated to give an oil (130 mg), which was purified by preparative TLC with C_6H_6–AcOEt (4: 1) and converted to the hydrochloride. The solid (50 mg) was recrystallized from hexane to give 35 mg (24.1%) of **30**·HCl, mp 161—162°. IR ν_{max}^{Nujol} cm^{-1}: 1615. MS *m/e*: 319, 317 (M^+). *Anal.* Calcd for $C_{19}H_{25}Cl_2NO$: C, 71.79; H, 7.61; N, 4.41. Found: C, 71.74; H, 7.67; N, 4.41.

$LiAlH_4$ Reduction of 23——a) The urethane **23** (800 mg, 2.08 mmol) was refluxed overnight with $LiAlH_4$ (350 mg, 9.21 mmol) in THF (30 ml) and worked up in the usual manner to give an oil (600 mg), which was converted to the hydrochloride. Recrystallization of the crude hydrochloride from EtOH–Et_2O gave 510 mg (75.2%) of **37j**·HCl, mp 270—273°. IR ν_{max}^{Nujol} cm^{-1}: 3330, 2750—2500. MS *m/e*: 289 (M^+), 271. 258. NMR (free base): 3.83 (1H, C_9–H),[17] 3.81 (s, 3H, OCH_3), 2.72 (d, J=5 Hz, 1H, C_{10}–H), 2.16 (s, 3H, N–CH_3), 1.5—2.5 (m, 13H). *Anal.* Calcd for $C_{18}H_{28}ClNO_2$: C, 66.34; H, 8.66; N, 4.30. Found: C, 66.41; H, 8.63; N, 4.33.

b) When **23** (500 mg, 1.30 mmol) was reduced with $LiAlH_4$ (230 mg, 6.05 mmol) in dioxane (20 ml) under reflux for 7 hr, two kinds of N-methyl derivatives (**37j** and **32**) were obtained in 34.2 and 26.2% yields, respectively, after separation by preparative TLC with $CHCl_3$–MeOH (9: 1). The latter gave mp 109—111° after recrystallization from (iso-Pr)$_2$O. Hydrochloride, mp 271—273° (from MeOH–Et_2O). IR (HCl salt) ν_{max}^{Nujol} cm^{-1}: 3320, 2800—2300. MS *m/e*: 289 (M^+), 271, 258.[18] NMR (free base): 4.56 (distorted triplet, 1H, C_9–H), 3.79 (s, 3H, OCH_3), 2.78 (bs, 1H, C_{10}–H), 2.01 (s, 3H, N–CH_3), 1.5—2.3 (m, 13H). *Anal.* Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.41; H, 9.23; N, 4.69.

c) The urethane **23** (116 mg, 0.302 mmol) was reduced overnight with $LiAlH_4$ (60 mg, 1.58 mmol) in boiling Et_2O (5 ml) and worked up in the usual manner. The oil obtained was converted to the HCl salt to give **37j**·HCl (56 mg, 56.9%), mp 269—271°. The mother liquor was purified by preparative TLC with AcOEt to give the N–CHO compound **33** (21 mg, 22.9%), mp 145—146° (from AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3380, 1655, 1540. MS *m/e*: 303 (M^+), 258, 214, 201. NMR (free base, $CDCl_3$–DMSO-d_6): 3.76 (s, 3H, OCH_3), 3.3—3.8 (m, 1H, C_9–H), 4.43 (bd, 1H, C_{10}–H), 7.86 (s, 1H, CHO). *Anal.* Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.05; H, 8.19; N, 4.57.

9-*endo*-Hydroxy-1-(*m*-methoxyphenyl)-10-*endo*-methylaminobicyclo[4.3.1]decane (37j) (Method A)——A mixture of **21** (143 mg, 0.520 mmol), CH_3I (103 mg, 0.726 mmol), and $NaHCO_3$ (200 mg, 2.38 mmol) in DMF

17) In the NMR spectrum of **37j**·hydrochloride (D_2O), the signal of C_9–H was observed at 4.19 ppm as a distorted triplet.

18) The mass spectrum of **32** was superimposable on that of **37j**.

(3 ml) was stirred at 150° for 5 hr, diluted with H_2O after cooling, and extracted with Et_2O. The extracts were dried and concentrated to give an oil (160 mg), which was separated by preparative TLC with C_6H_6–AcOEt (9: 1). The oil (88 mg) obtained from the extracts of the upper fraction was converted to the hydrobromide to give 10-*endo*-dimethylamino-9-*endo*-hydroxyl-1-(*m*-methoxyphenyl)bicyclo[4.3.1]decane hydrobromide (**37k**, 72 mg, 36.0%), mp 225—227° after recrystallization from EtOH–Et_2O. IR (free base) $\nu_{max}^{liq.}$ cm^{-1}: 3550, 3450, 2810, 2760. MS *m/e*: 303 (M^+), 288, 286. *Anal.* Calcd for $C_{19}H_{30}BrNO_2$: C, 59.37; H, 7.87; N, 3.64. Found: C, 59.02; H, 7.94; N, 3.77.

An oil (40 mg) obtained by extraction from the lower fraction was converted to the hydrochloride to give **37j**·HCl (35 mg, 20.7%) after recrystallization from Et_2O–EtOH.

$LiAlH_4$ Reduction of 25——a) The urethane **25** (135 mg, 0.407 mmol) was reduced with $LiAlH_4$ (60 mg, 1.58 mmol) in boiling Et_2O (5 ml) for 8 hr as described above to give 95 mg (75.4%) of **37h**·HCl, mp 273—275° after recrystallization from MeOH–Et_2O. MS *m/e*: 273 (M^+), 258, 245, 242. NMR (free base): 3.84 (s, 3H, OCH_3), 2.94 (d, J=5 Hz, 1H, C_{10}–H), 2.28 (s, 3H, N–CH_3), 2.1—2.6 (m, 3H), 1.4—2.1 (m, 12H). *Anal.* Calcd for $C_{18}H_{28}ClNO$: C, 69.76; H, 9.11; N, 4.52. Found: C, 69.77; H, 9.05; N, 4.49.

b) When **25** (510 mg, 1.54 mmol) was reduced with $LiAlH_4$ (320 mg, 8.4 mmol) in THF (20 ml) under reflux for 18 hr and worked up as described above, **37h**·HCl, mp 273—275° (from MeOH–Et_2O), and **35**·HBr, mp 212—213° (from MeOH–Et_2O), were obtained in 47.1 and 17.4% yields, respectively.

The latter gave the following physical data. MS *m/e*: 273 (M^+), 258, 242. NMR (free base): 3.85 (s, 3H, OCH_3), 2.97 (t, J=5 Hz, 1H, C_{10}–H),[19] 2.43 (s, 3H, N–CH_3), 2.7—2.9 (m, 1H), 2.2—2.5 (m, 2H), 1.3—2.1 (m, 12H); *Anal.* Calcd for $C_{18}H_{28}BrNO$: C, 61.01; H, 7.97; N, 3.95. Found: C, 61.21; H, 7.97; N, 3.88.

9-Amino-1-(*m*-hydroxyphenyl)bicyclo[3.3.1]nonane (38a)·Method D——The amine **16**·HCl (1.4 g, 4.98 mmol) was hydrolyzed by heating with 48% HBr (18 ml) and HOAc (5 ml) under reflux for 1 hr. After concentration, the residue was crystallized by treatment with EtOH. The resulting solid (1.22 g, mp 200—203°) was recrystallized from MeOH–acetone–Et_2O to give 1.20 g (77.2%) of **38a**·hydrobromide, mp 203—205°. IR ν_{max}^{Nujol} cm^{-1}: 3150, 2800—2300. *Anal.* Calcd for $C_{15}H_{22}BrNO \cdot 1/4H_2O$: C, 56.87; H, 7.16; N, 4.42. Found: C, 56.88; H, 7.14; N, 4.28. The free base showed mp 230—231° (from MeOH).

1-(*m*-Methoxyphenyl)-9-phenethylaminobicyclo[3.3.1]nonane (37c)·Method B——A mixture of **16** (450 mg, 1.83 mmol) and K_2CO_3 (450 mg, 3.26 mmol) in THF (9 ml) and H_2O (3 ml) was treated with phenylacetyl chloride (380 mg, 2.46 mmol). After stirring at room temperature for 1.5 hr, the mixture was concentrated *in vacuo*. The residual crystals were collected on a filter to give the amide, mp 164—166°, 530 mg (78.7%). IR ν_{max}^{Nujol} cm^{-1}: 3320, 1630.

The crude amide was reduced overnight with $NaBH_4$ (160 mg, 4.2 mmol) and $BF_3 \cdot Et_2O$ (0.72 ml, 5.6 mmol) in THF (20 ml) at room temperature. The mixture was decomposed by the addition of H_2O and concentrated *in vacuo*. The residue was diluted with H_2O, made basic with K_2CO_3, and extracted with $CHCl_3$. The dried extracts were concentrated to give the amine-borane (600 mg) as an oil.

The crude amine-borane was treated with 23% HCl–EtOH (9 ml) and Et_2O (18 ml) at room temperature for 3 hr. After concentration of the reaction mixture, the residual solid was collected, washed with small amounts of H_2O and Et_2O, and recrystallized from MeOH–Et_2O to give **37c**·HCl (475 mg, 67.2% from **16**), mp 241—243°. *Anal.* Calcd for $C_{24}H_{32}ClNO$: C, 74.68; H, 8.36; N, 3.63. Found: C, 74.23; H, 8.21; N, 3.58.

1-(*m*-Methoxyphenyl)-9-(methylamino)bicyclo[3.3.1]nonane (37a)·Method C——A mixture of **16** (628 mg, 2.48 mmol), sat. aq. $NaHCO_3$ (15 ml), $ClCO_2Et$ (1 ml, 10.5 mmol), and CH_2Cl_2 (20 ml) was stirred at room temperature for 4 hr then the CH_2Cl_2 layer was separated, washed with H_2O, dried, and concentrated to give urethane (870 mg). IR $\nu_{max}^{liq.}$ cm^{-1}: 3430, 3340, 1700.

The crude urethane was reduced by heating under reflux with $LiAlH_4$ (300 mg, 7.9 mmol) in THF (8 ml) and Et_2O (2 ml) for 15 hr. After work up in the usual manner, the oily product was converted to the hydrochloride which was recrystallized from MeOH–Et_2O to give **37a**·HCl (600 mg, 81.8%, mp 268—270°). *Anal.* Calcd for $C_{17}H_{26}ClNO$: C, 69.01; H, 8.86; N, 4.73. Found; C, 68.91; H, 8.87; N, 4.65.

9-(Cyclopropylmethyl)amino-1-(*m*-hydroxyphenyl)bicyclo[3.3.1]nonane (39c)·Method E——The phenolic amine **38a** (400 mg, 1.73 mmol) was allowed to react with cyclopropyl carbonyl chloride (0.5 ml), NEt_3 (0.8 ml), and DMF (8 ml) at room temperature overnight. The mixture was then concentrated and extracted with Et_2O. The extracts were washed with H_2O, dried, and concentrated to give the crude amide (770 mg) as an oil. This amide was reduced with $LiAlH_4$ (300 mg, 7.9 mmol) in THF (10 ml) and Et_2O (2 ml) under reflux (20 hr) and the $LiAlH_4$–complex was decomposed by the addition of H_2O. The mixture was acidified with dil·HCl and then made basic with conc. NH_4OH. After the removal of inorganic compounds by filtration, the filtrates were extracted with $CHCl_3$. The dried extracts were concentrated to give an oil, which was converted to the HCl salt. Recrystallization of the crude hydrochloride from EtOH–Et_2O gave 325 mg (58.4%) of pure **39c**·HCl, mp 225—227°. IR ν_{max}^{Nujol} cm^{-1}: 3160, 2800—2300. *Anal.* Calcd for $C_{19}H_{28}ClNO$: C, 70.89; H, 8.77; N, 4.35. Found: C, 70.65; H, 8.81; N, 4.41.

19) In the NMR spectrum of the HBr salt (MeOH-d_4), the signal of this proton also appeared as a triplet (J=5 Hz) at 3.62 ppm. A long-range coupling between the C_{10}- and *endo*-C_9-protons may be present.

The mother liquor was purified by column chromatography (silica gel, eluted with $CHCl_3$). From the first eluate, the amide was recovered (50 mg, 10%), mp 190—191° (from AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 3370, 3180, 1630. MS *m/e*: 299 (M^+), 230. *Anal.* Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.12; H, 8.46; N, 4.68.

9-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-4,10b-propanophenanthridine (**40**)——A mixture of **16**·HCl (500 mg, 1.78 mmol), 38% HCHO (4.7 ml, 64.3 mmol), conc. HCl (0.39 ml, 4.44 mmol), and EtOH (4.7 ml) was heated under reflux for 4 hr and concentrated. The residual solid was recrystallized from EtOH to give **40**·hydrochloride (335 mg, 64.1%), mp 267—268°. NMR (HCl salt, D_2O): 4.45 (bs, 2H, C_6–H), 3.82 (s, 3H, OCH_3), 3.51 (d, J=2 Hz, C_{4a}–H). *Anal.* Calcd for $C_{17}H_{24}ClNO$: C, 69.49; H, 8.23; N, 4.77. Found: C, 69.33; H, 8.31; N, 4.66.

9-Hydroxy-1,2,3,4,4a,5,6,10b-octahydro-4,10b-propanophenanthridine (**41**)——A solution of **40**·hydrochloride (400 mg, 1.36 mmol) in 48% HBr (4 ml) was heated under reflux for 1.5 hr. After standing at room temperature, the precipitated **41**·hydrobromide was filtered off (360 mg) and recrystallized from EtOH–Et_2O to give colorless prisms, 320 mg (72.6%), mp 300—303° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3250, 2600—2300. *Anal.* Calcd for $C_{16}H_{22}BrNO$: C, 59.26; H, 6.84; N, 4.32. Found: C, 59.34; H, 6.87; N, 4.22.

4,10b-Butano-1,9-dihydroxy-6,6-dimethyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (**42**)——A mixture of **21** (430 mg, 1.56 mmol) and 48% HBr (4 ml) was heated under reflux for 1.5 hr then concentrated *in vacuo*. Treatment of the residual gummy product with acetone gave **42**·hydrobromide (325 mg, 54.5%), mp 273—275° (from MeOH–Et_2O). IR ν_{max}^{Nujol} cm^{-1}: 3180. MS *m/e*: 301 (M^+). NMR (HBr salt, DMSO-d_6): 6.76 and 7.06 (AB-q, 2H, J=8 Hz, C_7 and C_8–H), 6.64 (s, 1H, C_{10}–H), 3.3—3.5 (m, 1H, C_1–H), 3.18 (s, 1H, C_{4a}–H), 1.36 and 1.45 (each s, 3H×2, $C(CH_3)_2$). *Anal.* Calcd for $C_{19}H_{28}BrNO_2$: C, 59.68; H, 7.38; N, 3.66. Found: C, 59.84; H, 7.49; N, 3.83.

10-*endo*-Amino-9-*endo*-hydroxy-1-(*m*-hydroxyphenyl)bicyclo[4.3.1]decane (**38d**)——After O-demethylation of **21** (400 mg, 1.45 mmol) with boiling 48% HBr (4 ml) for 1.5 hr, the reaction mixture was concentrated *in vacuo*. The residue was converted to the free base with aq. NH_4OH and extracted with Et_2O. The extracts were converted to the oxalate (mp 105—110°, 350 mg), and recrystallization of the oxalate from EtOH–Et_2O gave 330 mg (mp 114—116°, 64.8%) of **38d**·oxalate. MS *m/e*: 261 (M^+). *Anal.* Calcd for $C_{18}H_{25}NO_6 \cdot 3/4H_2O$: C, 59.24; H, 7.32; N, 3.84. Found: C, 59.07; H, 7.44; N, 3.76.

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