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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 NH₂OH 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**). LiAlH₄ 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-phenylmorphane (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 C₉ in **4a** would be much more reactive than that at C₂ 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 C₉-monoketal (**7**) or the C₉-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' -annulation 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)cycloheptanone⁹⁾ 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 C₂ 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. Suci, 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 $153\text{--}155^\circ$) 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 $161\text{--}162^\circ$) in 90% yield. The same treatment of the diketone (**4b**) resulted in recovery of the starting material. The latter monoxime (mp $161\text{--}162^\circ$) 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 $153\text{--}155^\circ$ 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 glyme¹²⁾ 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-

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 anticipated¹⁵ 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 Me₂CO 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 method¹⁶⁾ 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
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 ₂ CH 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 ₂ CH ₂ -	CH ₃	H	HCl	B	50.5	192—193	B-E	C ₂₅ H ₃₄ NO·1/4H ₂ O	74.22 (74.38)	8.60 8.74	3.46 3.50
37f	4	PhCH ₂ CH 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		55.3	273—275	M-E	C ₁₈ H ₂₆ ClNO	69.76 (69.77)	9.11 9.05	4.52 4.49
37i	4	PhCH ₂ CH ₂ -	CH ₃	H	HBr	B	39.7 ^{b)}	185—187	B-A-E	C ₂₆ H ₃₆ BrNO·1/2H ₂ O	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		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·1/4H ₂ O	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 ₂₂ NO ₂ C ₂ H ₂ O ₄ ·3/4H ₂ O	59.24 (59.07)	7.32 7.44	3.84 3.76
39a	3	CH ₂ =CHCH ₂ -	H	H	HCl	{ A D }	63.8 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 ₂ CH ₂ -	H	H	HBr		100				66.34 (65.91)	7.26 7.27	3.36 3.35
39c	3	-CH ₂ -	H	H	HCl	E	58.4	225—227	B-E	C ₁₉ H ₂₆ 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 ₂ CH 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 ₂ -	CH ₃	H	Free base	E	49.7	98—100	n-Hexane	C ₂₀ 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 ₂₆ 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 ₂ CH 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	-CH ₂ -	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: Me₂CO, B: EtOH, E: Et₂O, 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-Et₂O). MS m/e: 353, 351 (M⁺). Anal. Calcd for C₁₈H₂₄Br₂NO·1/2C₂H₅OC₂H₅: 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 ($\delta=0$), 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 PF₂₅₄ (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 $\nu_{\text{max}}^{\text{liq}}$ cm^{-1} : 1640. NMR: 4.94 (t, $J=7$ Hz, 1H, $-\dot{\text{C}}=\text{CH}-$), 3.80 (s, 3H, OCH_3), 3.53 (t, $J=8$ Hz, 4H, $-\text{CH}_2\text{OCH}_2-$), 2.70 (t, $J=8$ Hz, 4H, $-\text{CH}_2\text{NCH}_2-$).

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 2N 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 $\nu_{\text{max}}^{\text{Nujol}}$ 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 $\text{C}_{16}\text{H}_{18}\text{O}_3$: 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 -Et₂O (96:4)]. Further elution with C_6H_6 -Et₂O (95:5) gave 1-(*o*-methoxyphenyl)-bicyclo[3.3.1]nonane-2,9-dione, mp 136–138° (from AcOEt), 390 mg (0.9%). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1720, 1695, 740. MS m/e : 258 (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{O}_3$: C, 74.39; H, 7.02. Found: C, 74.15; H, 7.10. This may be 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), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (252 mg, 3.63 mmol), and $\text{NaOAc}\cdot 3\text{H}_2\text{O}$ (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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3220, 1720, 1660. Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3$: 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3250. NMR: 3.80 (s, 3H, OCH_3), 4.30 (pseudo triplet, $W/2=18$ Hz, 1H, $-\dot{\text{C}}\text{H}-$). Anal. OH

Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$: 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 -Et₂O (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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1700. NMR: 3.0–3.8 (m, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 3.79 (s, 3H, OCH_3). Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4$: C, 71.50; H, 7.34. Found: C, 71.30; H, 7.38. From the second eluate with C_6H_6 -Et₂O (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 Et₂O (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 Et₂O. The filtrates were washed with H_2O , dried, and concentrated, and the residue was treated with a small amount of Et₂O to give 325 mg of crude **14**, mp 119–120°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3420. Recrystallization from EtOH afforded 300 mg (74.8%) of **14**, mp 120–121°. NMR: 4.80 (pseudo triplet, $W/2=$

OH
18 Hz, 1H, $-\dot{\text{C}}\text{H}-$), 3.82 (s, 3H, OCH_3), 3.0–3.9 (m, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$). Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{O}_4$: 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 Et₂O. The dried extracts were concentrated to give an oil (270 mg), which was separated by chromatography on SiO₂.

From the first eluate with C₆H₆-Et₂O (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, OCH₃), 3.1–3.8 (m, 4H, –OCH₂CH₂O–). Anal. Calcd for C₁₈H₂₄O₃: C, 74.96; H, 8.38. Found: C, 75.27; H, 8.56.

The second eluate with C₆H₆-Et₂O (95:5) gave 150 mg (54.7%) of **10**, mp 127.5–128.5° (from iso-Pr₂O). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3350. MS *m/e*: 274 (M⁺), 113, 99. NMR: 3.2–3.9 (m, 4H, –OCH₂CH₂O–), 5.92 (s, 1H, OH). Anal. Calcd for C₁₇H₂₂O₃: C, 74.42; H, 8.08. Found: C, 74.21; H, 8.05.

b) O-Methylation of the Mixture of **9** and **10** with (CH₃)₂SO₄: 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 Et₂O (5 ml), and (CH₃)₂SO₄ (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 Et₂O. The washed and dried extracts were concentrated to give an oil (3.25 g), which was purified by chromatography (SiO₂). The first eluate with C₆H₆-Et₂O (95:5) gave 2.54 g (80.7%) of **9**. From the second eluate with C₆H₆-Et₂O (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 Et₂O. The dried extracts were concentrated and the residual oil (580 mg) was separated by column chromatography on SiO₂. Elution with C₆H₆ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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, C₃-H), 5.55 (d-t, *J*=10 and 2 Hz, 1H, C₂-H), 3.82 (s, 3H, OCH₃), 3.5–3.8 (m, 2H, –OCH₂–), 2.8–3.4 (m, 2H, –OCH₂–).

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 H₂) 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 C₆H₆ 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 Et₂O (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% NaHCO₃ and extracted with Et₂O. The dried extracts were concentrated to give the crude ketone (**11**, 580 mg, quantitative yield) as an oil. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2910, 2850, 1710. NMR: 1.5–2.8 (m, 13H, –CH₂– and –CH–), 3.81 (s, 3H, OCH₃), 6.6–7.4 (m, 4H, arom.).

A mixture of the ketone **11** (460 mg, 1.88 mmol), NH₂OH·HCl (230 mg, 3.31 mmol), and NaOAc·3H₂O (460 mg, 3.38 mmol) in EtOH (14 ml) was heated under reflux for 1 hr and diluted with H₂O. 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3230, 1645. Anal. Calcd for C₁₆H₂₁NO₂: 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 LiAlH₄ (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 H₂O 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 C₁₆H₂₄ClNO: 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-Et₂O). MS *m/e*: 245 (M⁺), 187. NMR: 3.99 (s, 3H, OCH₃), 3.50 (bs, 1H, C₉-H).

Hydrogenation of 11 in the Presence of Ammonia—The ketone **11** (100 mg, 0.409 mmol) in conc. NH₄OH (0.2 ml) and EtOH (8 ml) was hydrogenated in the presence of PtO₂ (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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3400. NMR: 4.12 (d, *J*=2.5 Hz, –CHOH), 3.75 (s, 3H, OCH₃); Anal. Calcd for C₁₆H₂₂O₂: 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 Et₂O. The extracts were dried over KOH pellets for 2 hr, then anhy. Na₂SO₄ (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 Na₂SO₄ 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, OCH₃), 6.11 (t, *J* = 6.5 Hz, 1H, olefinic proton).

Under an N₂ atmosphere, a mixture of the above cycloheptene (6.07 g, 30 mmol) and NaBH₄ (2.10 g, 55.5 mmol) in THF (60 ml) was treated with BF₃·Et₂O (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% H₂O₂ (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 Et₂O. 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 Et₂O (35 ml) was added 35 ml of a solution of Na₂Cr₂O₇·2H₂O (10 g) in conc. H₂SO₄ (7.5 ml) and H₂O (50 ml) at 5–13°, and stirring was continued at room temperature for 2 hr. The mixture was extracted with Et₂O and washed with H₂O, 5% NaHCO₃, and H₂O. Concentration of the dried extracts followed by distillation gave 4.0 g of crude **1b**, bp 155–165° (3 mmHg). Purification by chromatography on SiO₂ (eluted with pet.ether-Et₂O (9:1)) gave pure **1b** (2.2 g, 33.6%).

Morpholine Enamine (2b) of 1b—Under an N₂ atmosphere, a solution of TiCl₄ (26.4 g, 0.139 mol) in C₆H₆ (280 ml) was added to a solution of **1b** (53.97 g, 0.247 mol) and morpholine (72.6 g, 0.833 mol) in C₆H₆ (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 C₆H₆ (25 ml) was added to a solution of the enamine **2b** (15.89 g, 55.8 mmol) in C₆H₆ (124 ml) under reflux during a period of 20 min. After refluxing for 20 hr, the imminium salt (**3b**) was filtered and washed with C₆H₆ to give 16.4 g (78%), mp 237–240°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1720, 1620. MS *m/e*: 341 (M⁺), 259 (base peak). NMR: 3.82 (s, 3H, OCH₃).

The crude imminium salt (**3b**, 1g, 2.64 mmol) in CHCl₃ (30 ml) was stirred with 10% NaOH (15 ml, 37.5 mmol) at room temperature for 1 hr and extracted with Et₂O. 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1730, 1695. NMR: 1.1–3.2 (m, 13H, -CH₂-, -CH-), 3.81 (s, 3H, OCH₃). Anal. Calcd for C₁₇H₂₀O₃: 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·3H₂O (70 mg, 0.5 mmol) and NH₂OH·HCl (35 mg, 0.5 mmol) in EtOH (3 ml) for 6 hr. After removal of EtOH by evaporation, the residue was diluted with H₂O and extracted with Et₂O. 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-C₆H₆ (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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3230, 1715, 1640. MS *m/e*: 287 (M⁺), 270 (base peak), 242, 214, 200, 186. Anal. Calcd. for C₁₇H₂₁NO₃: 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3250, 1640. MS *m/e*: 302 (M⁺), 285 (base peak), 268, 253, 214. Anal. Calcd for C₁₇H₂₃N₂O₃: 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 NH₂OH·HCl (9.5 g, 0.137 mol) in dry DMF (250 ml) at room temperature. After stirring overnight, the mixture was diluted with H₂O. The precipitated crude **19** was collected, washed with H₂O, and recrystallized from MeOH to give prisms, 35.53 g (90.3%), mp 161–162°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3290, 1705, 1655. MS *m/e*: 287 (M⁺), 270 (base peak), 215, 200, 186. Anal. Calcd for C₁₇H₂₁NO₃: 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 NaBH₄ (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 Et₂O. The extracts were washed with H₂O, 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3430, 3270, 1630. NMR: 3.77 (s, 3H, OCH₃), 3.70 (m, 1H, C₆-H), 4.14 (d-d, *J* = 11 and 6 Hz, 1H, C₉-H). Anal. Calcd for C₁₇H₂₃NO₃: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.41; H, 8.06; N, 4.85.

Reduction of 19 with LiAlH₄—The monoxime **19** (35.15 g, 0.122 mol) was added to a solution of LiAlH₄ (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 $\nu_{\text{max}}^{\text{liq}}$ 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 $\text{C}_{17}\text{H}_{25}\text{NO}_2 \cdot 1/5\text{CHCl}_3$: 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 $\nu_{\text{max}}^{\text{Nujol}}$ 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 $\text{C}_{17}\text{H}_{26}\text{ClNO}_2 \cdot 1/4\text{H}_2\text{O}$: 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) $\nu_{\text{max}}^{\text{liq}}$ cm^{-1} : 3380, 3300, 1610, 1598, 1580, 1575; (picrate) $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3230, 3100; (HCl salt) $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3000, 2650, 2000, 1610, 1598, 1580, 1575. MS m/e : 259 (M^+), 242. NMR (picrate, $\text{DMSO}-d_6$): 3.76 (s, 3H, OCH_3), 5.57 (t, $J=8$ Hz, 1H, olefinic proton). Anal. Calcd for $\text{C}_{17}\text{H}_{25}\text{NO} \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$: 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, $-\text{OCH}_2-$ 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) $_2\text{O}$ gave prisms of mp 89–91°; these were hemiisopropyl etherate. IR $\nu_{\text{max}}^{\text{Nujol}}$ 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, $(\text{Me})_2\text{CH}-$), 1.14 (d, $J=6$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$). Anal. Calcd for $\text{C}_{20}\text{H}_{29}\text{NO}_4 \cdot 1/2\text{C}_6\text{H}_{14}\text{O}$: 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 $\text{CH}_3\text{SO}_2\text{Cl}$ (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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3450, 1715, 1360, 1180. MS m/e : 425 (M^+), 329, 300. Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{NO}_6\text{S}$: 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 $\nu_{\text{max}}^{\text{liq}}$ cm^{-1} : 3460, 3350, 1710. MS m/e : 331 (M^+), 242, 240. NMR: 1.17 (t, $J=7$ Hz, 3H, CH_2CH_3), 3.80 (s, 3H, OCH_3), 4.04 (q, $J=7$ Hz, OCH_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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3460, 3350, 1700. MS m/e : 329 (M^+), 300, 240. NMR: 1.07 (t, $J=8$ Hz, 3H, CH_2CH_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 $\text{C}_{20}\text{H}_{27}\text{NO}_3$: 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 CHCl₃. 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–Et₂O gave needles of mp 208–210°, **27**·hydrobromide. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3200–2500. MS m/e : 259 (M⁺), 242. NMR (free base): 3.26 (d, $J=3.8$ Hz, 1H, C₁₀-H), 3.81 (s, 3H, OCH₃). Anal. Calcd for C₁₇H₂₆BrNO: 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 CH₂Cl₂ (3 ml) was treated with PCl₅ (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/cm² (initial pressure of H₂) for 5 hr at 80–100°. After removal of the catalyst and solvent, the residual oil (250 mg) was dissolved in H₂O, made basic with K₂CO₃, and extracted with Et₂O. The extracts were washed with H₂O, dried, and concentrated to give an oil (170 mg) which was separated by preparative TLC (SiO₂) with CHCl₃–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–Et₂O 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 C₁₇H₂₅BrClNO: 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 Ac₂O (150 mg, 1.5 mmol), CH₂Cl₂ (20 ml), and 5% NaHCO₃ (15 ml) at room temperature for 3 hr and extracted with CHCl₃. The extracts were washed with H₂O, 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 $\nu_{\text{max}}^{\text{H}_2\text{O}}$ cm⁻¹: 3350, 1650. A solution of **29** (145 mg, 0.457 mmol) in pyridine (0.7 ml) was treated with POCl₃ (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 Et₂O. The dried extracts were concentrated to give an oil (130 mg), which was purified by preparative TLC with C₆H₆–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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1615. MS m/e : 319, 317 (M⁺). Anal. Calcd for C₁₉H₂₅Cl₂NO: C, 71.79; H, 7.61; N, 4.41. Found: C, 71.74; H, 7.67; N, 4.41.

LiAlH₄ Reduction of 23—a) The urethane **23** (800 mg, 2.08 mmol) was refluxed overnight with LiAlH₄ (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–Et₂O gave 510 mg (75.2%) of **37j**·HCl, mp 270–273°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3330, 2750–2500. MS m/e : 289 (M⁺), 271, 258.¹⁸ NMR (free base): 3.83 (1H, C₉-H),¹⁷ 3.81 (s, 3H, OCH₃), 2.72 (d, $J=5$ Hz, 1H, C₁₀-H), 2.16 (s, 3H, N-CH₃), 1.5–2.5 (m, 13H). Anal. Calcd for C₁₈H₂₈ClNO₂: 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 LiAlH₄ (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 CHCl₃–MeOH (9:1). The latter gave mp 109–111° after recrystallization from (iso-Pr)₂O. Hydrochloride, mp 271–273° (from MeOH–Et₂O). IR (HCl salt) $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3320, 2800–2300. MS m/e : 289 (M⁺), 271, 258.¹⁸ NMR (free base): 4.56 (distorted triplet, 1H, C₉-H), 3.79 (s, 3H, OCH₃), 2.78 (bs, 1H, C₁₀-H), 2.01 (s, 3H, N-CH₃), 1.5–2.3 (m, 13H). Anal. Calcd for C₁₈H₂₇NO₂: 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 LiAlH₄ (60 mg, 1.58 mmol) in boiling Et₂O (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 $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3400, 3380, 1655, 1540. MS m/e : 303 (M⁺), 258, 214, 201. NMR (free base, CDCl₃–DMSO-*d*₆): 3.76 (s, 3H, OCH₃), 3.3–3.8 (m, 1H, C₉-H), 4.43 (bd, 1H, C₁₀-H), 7.86 (s, 1H, CHO). Anal. Calcd for C₁₈H₂₅NO₃: 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), CH₃I (103 mg, 0.726 mmol), and NaHCO₃ (200 mg, 2.38 mmol) in DMF

17) In the NMR spectrum of **37j**·hydrochloride (D₂O), the signal of C₉-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 H₂O after cooling, and extracted with Et₂O. The extracts were dried and concentrated to give an oil (160 mg), which was separated by preparative TLC with C₆H₆-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-Et₂O. IR (free base) $\nu_{\max}^{\text{liq}}$ cm⁻¹: 3550, 3450, 2810, 2760. MS m/e : 303 (M⁺), 288, 286. Anal. Calcd for C₁₉H₃₀BrNO₂: 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 Et₂O-EtOH.

LiAlH₄ Reduction of 25—a) The urethane **25** (135 mg, 0.407 mmol) was reduced with LiAlH₄ (60 mg, 1.58 mmol) in boiling Et₂O (5 ml) for 8 hr as described above to give 95 mg (75.4%) of **37h**·HCl, mp 273–275° after recrystallization from MeOH-Et₂O. MS m/e : 273 (M⁺), 258, 245, 242. NMR (free base): 3.84 (s, 3H, OCH₃), 2.94 (d, $J=5$ Hz, 1H, C₁₀-H), 2.28 (s, 3H, N-CH₃), 2.1–2.6 (m, 3H), 1.4–2.1 (m, 12H). Anal. Calcd for C₁₈H₂₈ClNO: 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 LiAlH₄ (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-Et₂O), and **35**·HBr, mp 212–213° (from MeOH-Et₂O), 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, OCH₃), 2.97 (t, $J=5$ Hz, 1H, C₁₀-H),¹⁹ 2.43 (s, 3H, N-CH₃), 2.7–2.9 (m, 1H), 2.2–2.5 (m, 2H), 1.3–2.1 (m, 12H); Anal. Calcd for C₁₈H₂₈BrNO: 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-Et₂O to give 1.20 g (77.2%) of **38a**·hydrobromide, mp 203–205°. IR $\nu_{\max}^{\text{liq}}$ cm⁻¹: 3150, 2800–2300. Anal. Calcd for C₁₅H₂₂BrNO·1/4H₂O: 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 K₂CO₃ (450 mg, 3.26 mmol) in THF (9 ml) and H₂O (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 $\nu_{\max}^{\text{liq}}$ cm⁻¹: 3320, 1630.

The crude amide was reduced overnight with NaBH₄ (160 mg, 4.2 mmol) and BF₃·Et₂O (0.72 ml, 5.6 mmol) in THF (20 ml) at room temperature. The mixture was decomposed by the addition of H₂O and concentrated *in vacuo*. The residue was diluted with H₂O, made basic with K₂CO₃, and extracted with CHCl₃. 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 Et₂O (18 ml) at room temperature for 3 hr. After concentration of the reaction mixture, the residual solid was collected, washed with small amounts of H₂O and Et₂O, and recrystallized from MeOH-Et₂O to give **37c**·HCl (475 mg, 67.2% from **16**), mp 241–243°. Anal. Calcd for C₂₄H₃₂ClNO: 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. NaHCO₃ (15 ml), ClCO₂Et (1 ml, 10.5 mmol), and CH₂Cl₂ (20 ml) was stirred at room temperature for 4 hr then the CH₂Cl₂ layer was separated, washed with H₂O, dried, and concentrated to give urethane (870 mg). IR $\nu_{\max}^{\text{liq}}$ cm⁻¹: 3430, 3340, 1700.

The crude urethane was reduced by heating under reflux with LiAlH₄ (300 mg, 7.9 mmol) in THF (8 ml) and Et₂O (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-Et₂O to give **37a**·HCl (600 mg, 81.8%, mp 268–270°). Anal. Calcd for C₁₇H₂₆ClNO: 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), NEt₃ (0.8 ml), and DMF (8 ml) at room temperature overnight. The mixture was then concentrated and extracted with Et₂O. The extracts were washed with H₂O, dried, and concentrated to give the crude amide (770 mg) as an oil. This amide was reduced with LiAlH₄ (300 mg, 7.9 mmol) in THF (10 ml) and Et₂O (2 ml) under reflux (20 hr) and the LiAlH₄-complex was decomposed by the addition of H₂O. The mixture was acidified with dil. HCl and then made basic with conc. NH₄OH. After the removal of inorganic compounds by filtration, the filtrates were extracted with CHCl₃. The dried extracts were concentrated to give an oil, which was converted to the HCl salt. Recrystallization of the crude hydrochloride from EtOH-Et₂O gave 325 mg (58.4%) of pure **39c**·HCl, mp 225–227°. IR $\nu_{\max}^{\text{liq}}$ cm⁻¹: 3160, 2800–2300. Anal. Calcd for C₁₉H₂₈ClNO: 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 C₁₀- and *endo*-C₉-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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3370, 3180, 1630. MS m/e : 299 (M^+), 230. Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_2$: 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, $\text{C}_6\text{-H}$), 3.82 (s, 3H, OCH_3), 3.51 (d, $J=2$ Hz, $\text{C}_{4a}\text{-H}$). Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{ClNO}$: 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3250, 2600—2300. Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{BrNO}$: 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 $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3180. MS m/e : 301 (M^+). NMR (HBr salt, $\text{DMSO}-d_6$): 6.76 and 7.06 (AB-q, 2H, $J=8$ Hz, C_7 and $\text{C}_8\text{-H}$), 6.64 (s, 1H, $\text{C}_{10}\text{-H}$), 3.3—3.5 (m, 1H, $\text{C}_1\text{-H}$), 3.18 (s, 1H, $\text{C}_{4a}\text{-H}$), 1.36 and 1.45 (each s, $3\text{H} \times 2$, $\text{C}(\text{CH}_3)_2$). Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{BrNO}_2$: 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 $\text{C}_{18}\text{H}_{25}\text{NO}_6 \cdot 3/4\text{H}_2\text{O}$: C, 59.24; H, 7.32; N, 3.84. Found: C, 59.07; H, 7.44; N, 3.76.

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