Azabicycloalkanes as Analgetics. I. Synthesis of 1-Phenyl-6-azabicyclo[3,2,1]octane Derivatives

Mikio Takeda,1,2) Hirozumi Inoue, Katsuyuki Noguchi, Yasushi Honma, Masatoshi Kawamori, Goro Tsukamoto, and Seichi Saito

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd.1)

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As part of studies on azabicycloalkanes as analgetics with narcotic antagonist activity, 1-phenyl-6-azabicyclo[3,2,1]octane derivatives have been synthesized. Bromination of the keto amide (IXa, b) followed by treatment with sodium methoxide gave the bicyclic keto lactam (XIIa, b) respectively. A number of derivatives bearing various substituents on nitrogen and C4 have been prepared from (XIIa, b) for pharmacological evaluation. 6,7-endo-Dimethyl-1-(8-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (XXc) and its dextro isomers exhibited analgetic activities on the order of meperidine and morphine, respectively. They also had narcotic antagonist activity with a low grade of abuse potential.

Since the discovery that the narcotic antagonist, nalorphine, also has analgetic (agonist) properties and especially since the emergence of the weak antagonist, pentazocine, as an analgetic agent without appreciable abuse liability, the general trend of research to develop improved analgetics has centered on structures possessing a mixture of agonist and antagonist components (partial agonist). Numerous N-methyl derivatives of morphine, morphinan and 6,7-benzomorphan have been converted to nalorphine-like antagonists by appropriate substitution (allyl and related groups) on nitrogen. These "classical" narcotic antagonists, however, produced, very often, bizarre, disturbing, psychotomimetic side effects which preclude their clinical utility.

Recently, certain N-methyl compounds of the benzomorphan2) (I), phenylmorphinan3) (II), pyrrolidine4) (III), and hexamethylenimine5) (IV) series have been reported to display antagonist properties with low grade of addiction liability especially in monkeys.

Although quantitative carryover of these pharmacological profiles from monkey to man has not been achieved so far,6) this new type of partial agonists still seems to be interesting field for exploration. Structural requirements for the antagonist activity in these compounds have not well established yet. Stereochemical factors including absolute spacial geometry, however, may be of most importance because some of these compounds do not display the antagonist activity until they were resolved into their enantiomers.2,3)

1) Location: 2-2-50, Kawagishi, Toda, Saitama; a) To whom correspondence should be addressed.
To gain greater insight into the steric requirements for the partial agonist activity and to search for an ideal analogic agent with no substantial addiction liability, we initiated a study on the azabicycloalkane derivatives represented by the general formula (V). Structure V has (a) a benzene nucleus linked to quaternary carbon (b) a tertiary amino group and (c) a phenolic hydroxyl situated meta to the quaternary carbon attachment, which are common chemical features in structures I—IV. By varying $n$, $m$ and $l$, structure V would provide various, rather rigidly held, relative spatial orientations of nitrogen and a benzene ring.

Described herein is the synthesis of 1-phenyl-6-azabicyclo[3.2.1]octane derivative (VI), which can be regarded not only as a five-membered analog of II but also as a “bridged” version of III and IV with increased rigidity of the molecules. Base-catalyzed cyclization of the bromo keto amide (X) was chosen as a route to this skeleton in the present study. Alkaline hydrolysis of 1-phenyl-4-oxo-cyclohexanecarbonitrile ethylene ketal\textsuperscript{7)} (VIIa) yielded the ketal amide

\[
\text{NaOMe} \quad \text{R} \quad \text{O} \quad \text{NM} \quad \text{O} \\
\text{XI} \quad \text{XIII} \quad \text{XV} \quad \text{XIV} \quad \text{XII}
\]

\[
a : R=H, \quad b : R=\text{OMe}
\]

\text{Chart 2}

\text{7) E.C. Horning, M.G. Horning, M.S. Fish, and M.W. Rutenberg, } J. \text{ Am. Chem. Soc. 74 773 (1952).}
(VIIia), which in turn was heated in acetic acid to afford the keto amide (IXa). Bromination of IXa in acetic acid gave the crystalline bromo keto amide (Xa) in 58% yield. Cyclization of Xa with sodium methoxide in methanol to afford 1-phenyl-6-azabicyclo[3.2.1]octane-4,7-dione (XIa) in 86% yield. The oily residue obtained from the filtrate of Xa was found to contain about 30% of additional Xa on gas chromatographic examination and gave XIa in 23% yield on treatment with sodium methoxide. Considering that intramolecular displacement of bromine with the anion of the amide nitrogen would involve backside (S_n2 type) attack, one is led to assign the \textit{trans} Br-amide structure to Xa. Infrared spectrum of the bicyclic keto lactam (XIa) showed bands at 3270 (NH), 1720 (C=O), and 1680 cm\(^{-1}\) (NHCO), respectively. The nuclear magnetic resonance spectrum (NMR) of XIa exhibited a doublet (\(J=6\) Hz) at 3.89 ppm attributable to C\(_5\) methine proton. Thus, the coupling between C\(_5\) and C\(_8\) exo protons was not observed because the corresponding dihedral angle was about 90°. Deuterium exchange did not alter the pattern of this methine proton but removed two exchangeable protons on C\(_3\). These results were consistent onyl with the structure XIa and ruled out an alternate structure XII which may result from elimination of HBr, followed by conjugate addition of the amide nitrogen. By a sequence of similar reactions, the 3-methoxyphenyl analog (XIIb) was obtained from 1-\{(3-methoxyphenyl)-4-oxo-cyclohexanecarbonitrile ethylene ketal (VIIib) in a comparable yield (Chart 2).

Removal of the 4-oxo group of XIa, b was carried out in two ways. Thioketalization of XIa followed by desulfurization with Raney Ni gave the lactam (XVa) in 65% yield. Alternatively, Wolff-Kishner reduction of XIa, b with hydrazine hydrate and potassium hydroxide in ethylene glycol gave XVa, b in rather low yields (52% and 36%, respectively), possibly because of the concomitant hydrolysis of the lactam moiety. An application of a modified Wolff-Kishner reduction using potassium tert-butoxide in boiling toluene minimized this

\[ R\text{CH}_2\text{Li} \xrightarrow{\text{MeI}} \overset{\text{LiAlH}_4}{\longrightarrow} \overset{\text{NaBH}_4}{\longrightarrow} \overset{\text{CH}_3\text{R}_1}{\longrightarrow} \overset{\text{R}}{\longrightarrow} \overset{\text{Me}}{\longrightarrow} \overset{\text{N}}{\longrightarrow} \overset{\text{Me}}{\longrightarrow} \overset{\text{C}}{\longrightarrow} \overset{\text{H}}{\longrightarrow} \overset{\text{R}}{\longrightarrow} \overset{\text{Me}}{\longrightarrow} \]

\[ \text{XVIII} \xrightarrow{\text{XIX: } R_1=H} \overset{\text{XX: } R_1=H}{\longrightarrow} \overset{\text{XXII: } R_1=Me}{\longrightarrow} \]

\[ \text{Me} \overset{\text{H}}{\longrightarrow} \overset{\text{R}}{\longrightarrow} \overset{\text{Me}}{\longrightarrow} \overset{\text{C}}{\longrightarrow} \overset{\text{H}}{\longrightarrow} \overset{\text{R}}{\longrightarrow} \overset{\text{Me}}{\longrightarrow} \]

a: R=H, b: R=OMe, c: R=OH

Chart 3


side reaction and gave an excellent yield of the desired lactam. Thus, by this method, XVb was obtained from the hydrazone (XIVb) in 91% yield. Lithium aluminum hydride (LAH) reduction of the lactam (XV) afforded the secondary amine (XVI) which was N-methylated to give XVII. XVII also resulted from LAH reduction of the N-methyl lactam (XVIII). O-Demethylation of XVIIb with 47% hydrobromic acid gave the phenol (XVIIc).

Introduction of alkyl substituent on C₁ was carried out by the method described by Walker, et al.¹¹ Thus, treatment of the N-methyl lactam (XVIII) with methylithium gave a good yield of the enamine (XIX) which was reduced with sodium borohydride to the single epimer of the 6,7-dimethyl derivative (XX). NMR spectral data compatible with the structure

![Chart 4]

**Table I. N-Substituted Derivatives of 1-Phenyl-6-azabicyclo[3,2,1]octane (XXIII)**

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Method(Ⅲ)</th>
<th>Salt</th>
<th>Crystln(b) solvent</th>
<th>mp (°C)</th>
<th>Formula</th>
<th>Analysis (%)(Calcd.)(Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CH₂=CH₂</td>
<td>A</td>
<td>picrate</td>
<td>A</td>
<td>129–130</td>
<td>C₁₂H₂₂O₄N₄</td>
<td>57.87 (57.83) 5.30 12.28</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>B</td>
<td>base</td>
<td>—</td>
<td>240°</td>
<td>C₁₃H₂₃N</td>
<td>84.59 (84.73) 9.61 5.80</td>
</tr>
<tr>
<td>H</td>
<td>(CH₃)₂Ph</td>
<td>B</td>
<td>oxalate</td>
<td>A</td>
<td>207–209</td>
<td>C₁₂H₁₆O₄N₂</td>
<td>72.41 (72.11) 7.13 3.67</td>
</tr>
<tr>
<td>H</td>
<td>(CH₃)₂COPh</td>
<td>C</td>
<td>HCl</td>
<td>C–D</td>
<td>166–168</td>
<td>C₁₂H₁₆ONCl–1/2H₂O</td>
<td>72.41 (72.65) 7.46 3.84</td>
</tr>
<tr>
<td>H</td>
<td>(CH₃)₂COPh–F(p)</td>
<td>A</td>
<td>HBr</td>
<td>A–C</td>
<td>212–214</td>
<td>C₁₂H₁₆ONBrF</td>
<td>63.90 (63.75) 6.30 3.24</td>
</tr>
<tr>
<td>OMe</td>
<td>(CH₃)₂COPh–F(p)</td>
<td>A</td>
<td>HCl</td>
<td>A–C</td>
<td>195–196</td>
<td>C₁₂H₁₆O₄NCIF</td>
<td>68.96 (68.68) 6.99 3.35</td>
</tr>
<tr>
<td>OMe</td>
<td>(CH₃)₂COPh</td>
<td>A</td>
<td>HCl</td>
<td>A–C</td>
<td>167–169</td>
<td>C₁₂H₁₆O₄NCI</td>
<td>72.06 (72.46) 7.56 3.50</td>
</tr>
<tr>
<td>OH</td>
<td>CH₂=CH₂</td>
<td>A</td>
<td>picrate</td>
<td>A</td>
<td>163–165</td>
<td>C₁₂H₁₆O₄N₄</td>
<td>55.93 (55.69) 5.12 11.86</td>
</tr>
<tr>
<td>OH</td>
<td>CH₃</td>
<td>A</td>
<td>oxalate</td>
<td>B</td>
<td>218–219</td>
<td>C₁₃H₂₃O₄N</td>
<td>71.34 (70.98) 7.00 4.89</td>
</tr>
<tr>
<td>OH</td>
<td>CH₃</td>
<td>B</td>
<td>base</td>
<td>—</td>
<td>220°</td>
<td>C₁₃H₂₃ON</td>
<td>79.33 (78.91) 9.01 5.44</td>
</tr>
<tr>
<td>OH</td>
<td>CH₃</td>
<td>B</td>
<td>base</td>
<td>—</td>
<td>240°</td>
<td>C₁₃H₂₃ON</td>
<td>79.66 (79.38) 9.29 5.16</td>
</tr>
<tr>
<td>OH</td>
<td>(CH₃)₂CH₃</td>
<td>B</td>
<td>base</td>
<td>—</td>
<td>250°</td>
<td>C₁₃H₂₃ON</td>
<td>79.39 (78.99) 10.17 4.87</td>
</tr>
<tr>
<td>OH</td>
<td>(CH₃)₂Ph</td>
<td>B</td>
<td>oxalate</td>
<td>A–C</td>
<td>230–232</td>
<td>C₁₃H₂₃ON–1/2(CO₂H)·1/2H₂O</td>
<td>73.31 (73.20) 7.55 3.89</td>
</tr>
<tr>
<td>OH</td>
<td>CH₂=CH₂=CH₂</td>
<td>A</td>
<td>picrate</td>
<td>B</td>
<td>180–183</td>
<td>C₁₂H₁₆O₄N₄·1/2H₂O</td>
<td>60.32 (60.54) 5.20 10.05</td>
</tr>
<tr>
<td>OH</td>
<td>(CH₃)₂COPh</td>
<td>C</td>
<td>HCl</td>
<td>B–C</td>
<td>187–189</td>
<td>C₁₂H₁₆O₄N₂Cl</td>
<td>71.05 (70.86) 7.05 3.77</td>
</tr>
</tbody>
</table>

(a) See Experimental section.
(b) bp (bath temperature) (0.1 mm Hg)
(c) bp (bath temperature) (0.2 mm Hg)

were given in the Experimental section. *endo* Configuration of the 7-Me group was unequivocally established on the basis of X-ray analysis of the hydrobromide of the corresponding phenol (XXc).\(^{12}\) This result parallels the preferential formation of the *endo* alcohol from bicyclo[3,2,1]octan-6-one on LAH reduction.\(^{13}\) Similarly, the 7-ethyl derivative (XXIIc) was obtained from XVIIIb. Stereochemistry of XXII was assigned by analogy with XX (Chart 3).

For pharmacological evaluation, introduction of various substituents on the nitrogen of XVIa, b, c was carried out by the usual method furnishing the tertiary amines (XXIIIa, b, c). O-Acyl derivatives were prepared from the phenols (XVIIc, XXc, and XXIIc), respectively. The N- and O-substituted derivatives thus prepared are listed in Table I and II, respectively.

All 6-azabicyclo[3,2,1]octane derivatives obtained in the present study invariably showed an intense peak at *m/z* (M-43) in their mass spectra. The formation of this ion is apparently associated with the loss of a propano bridge of the molecules and is depicted in the following manner (Chart 4). Similar observation has been reported by Furstost, *et al.*\(^{14}\)

Finally, the two N-methyl phenols (XVIIc and XXc) were selected for resolution into their optical isomers. Because direct resolution of these racemates with various optically active acids were unsuccessful, it was necessary to resolve their precursors. Thus, the secondary amine (XVIb) was resolved into (+)- and (−)-isomers *via* their d-tartrate and l-malate. N-methylation of (+)- and (−)-XVIb, followed by O-demethylation, afforded (−)- and (+) -XVIIc, respectively. Resolution of the methoxy racemate (XXb) was effected with (+)-3-

**Table II. O-Acyl Derivatives of 1-Phenyl-6-azabicyclo[3,2,1]octane**

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>Optical rotation</th>
<th>Method(^a)</th>
<th>Salt</th>
<th>Crystn.(^b) solvent</th>
<th>mp, °C</th>
<th>Formula</th>
<th>Analysis (%), (Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>± A</td>
<td>HCl</td>
<td>A - B</td>
<td>250–252</td>
<td>C₁₁H₁₄O₂NCl</td>
<td>65.90 (65.49 (7.83) 4.47)</td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>+ A</td>
<td>HCl(^c)</td>
<td>A - B</td>
<td>207–211</td>
<td>C₁₁H₁₄O₂NCl·H₂O</td>
<td>62.25 (7.99) 4.27</td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>− A</td>
<td>HCl(^d)</td>
<td>A - B</td>
<td>208–211</td>
<td>C₁₁H₁₄O₂NCl·H₂O</td>
<td>62.25 (7.99) 4.27</td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>C₂H₅</td>
<td>± A</td>
<td>HBr</td>
<td>A - B</td>
<td>237–240</td>
<td>C₁₁H₁₄O₂NBr</td>
<td>58.70 (7.12) 3.80</td>
<td></td>
</tr>
<tr>
<td>C₂H₅</td>
<td>CH₃</td>
<td>± A</td>
<td>HBr</td>
<td>B - C</td>
<td>226–228</td>
<td>C₁₁H₁₄O₂NBr</td>
<td>58.70 (7.12) 3.80</td>
<td></td>
</tr>
<tr>
<td>C₂H₅</td>
<td>CH₃</td>
<td>± A</td>
<td>HBr</td>
<td>B - C</td>
<td>95–97</td>
<td>C₁₁H₁₄O₂NBr·H₂O</td>
<td>58.89 (7.71) 3.27</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>CH₃</td>
<td>± B</td>
<td>HCl</td>
<td>D - E</td>
<td>207–209</td>
<td>C₁₁H₁₄O₂NCl</td>
<td>71.05 (7.05) 3.77</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) See Experimental section
\(^b\) | A, EtOH; B, ether; C, CHCl₃; D, AcOEt; E, acetone
\(^c\) | [a]D + 9.9° (c=0.46, MeOH)
\(^d\) | [a]D − 9.9° (c=0.38, MeOH)

12) These analytical data including the absolute stereochemistry of (+)-XXc will be appeared in a later communication.
bromo-8-camphorsulfonic acid ammonium salt and then with (–)-dibenzoyl tartaric acid. The (–)- and (+)-XXb isomers were demethylated to the (+)- and (–)-phenols (XXc), respectively.

1-Phenyl-6-azabicyclo[3,2,1]octane derivatives prepared were tested for their analgetic activities. In the mouse writhing method, analgetic activities of XXc and its dextro isomer were comparable to meperidine and morphine, respectively. Introduction of methyl substituent on C₂ apparently enhanced the activity. XXc and its (–)-isomer also exhibited nalorphine-like antagonism in morphine-dependent monkeys. Further, in the test for the capacity to produce physical dependence in Rhesus monkeys (chronic study for 33 days), abuse potential of the racemate (XXc) appeared to be very slight. Detailed pharmacological data with 1-phenyl-6-azabicyclo[3,2,1]octane derivatives will be presented in a later communication.

Experimental

All melting points were determined with a Yanagimoto capillary melting point apparatus (Model MP-1) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrophotometer. NMR spectra were taken in CDCl₃ (containing tetramethylsilane at δ 0.00 as an internal standard) at 60 MHz, unless otherwise stated. Mass spectra were measured using Hitachi RMS-4 mass spectrometer. Gas chromatography was obtained on a Shimadzu GC-1C instrument using an EGA column. Optical rotations were measured on a JASCO DIP-180 polarimeter. The organic solutions were dried over Na₂SO₄ and all evaporations were carried out in vacuo.

1-Phenyl-4-oxo-cyclohexanecarboxamide Ethylene Ketal (VIIa) — A mixture of VIIa(16 g), KOH (16 g), ethylene glycol (320 ml) and H₂O (320 ml) was refluxed for 12 hr. The mixture was diluted with H₂O (300 ml) and extracted with CHCl₃. Evaporation of the dried extracts gave, after recrystallization from AcEt-n-hexane, 8.5 g (50%) of VIIa as needles, mp 138—140°. IR ν<sub>max</sub> cm⁻¹: 1650 (CONH₂). Mass Spectrum m/e: 261 (M⁺). Anal. Calcd. for C₁₉H₂₂O₄N: C, 68.96; H, 7.33; N, 5.36. Found: C, 68.58; H, 7.22; N, 5.23. The aqueous layer was acidified with AcOH and extracted with ether. Evaporation of the dried extracts gave 5.1 g (20.7%) of 1-phenyl-4-oxo-cyclohexanecarboxylic acid ethylene ketal, mp 142—144°. IR ν<sub>max</sub> cm⁻¹: 2800—3000 (COOH), 1710 (C=O), 1100, 1040 (ketal). Anal. Calcd. for C₁₉H₂₁O₄: C, 68.68; H, 6.92. Found: C, 68.41; H, 6.86.

1-(3-Methoxyphenyl)-4-oxo-cyclohexanecarboxamide Ethylene Ketal (VIIIb) — A mixture of VIIIb (3.5 g), KOH (3.5 g), EtOH (70 ml) and H₂O (70 ml) was refluxed for 22 hr. The mixture was concentrated and extracted with CHCl₃. Evaporation of the dried extracts gave the residue which was digested with small amount of ether and filtered to give 2.3 g (82.5%) of VIIIb. Prisms from AcOEt, mp 136—137°. IR ν<sub>max</sub> cm⁻¹: 3430, 3340, 3290, 3200 (NH₂), 1670 (C=O). Anal. Calcd. for C₁₉H₂₁O₄N: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.01; H, 7.21; N, 4.72. The mother liquor (ether) was evaporated to give 0.8 g of recovered VIIIb. From the aqueous layer, 0.58 g of 1-(3-methoxyphenyl)-4-oxo-cyclohexanecarboxylic acid ethylene ketal, mp 119—121°, was obtained.

1-Phenyl-4-oxo-cyclohexanecarboxamide (IXa) — A mixture of VIIIa (15.3 g) and AcOH (300 ml) was refluxed for 4 hr and evaporated. The residue was taken in ether, washed with 5% NaHCO₃, dried and evaporated. Recrystallization of the residue from AcOEt gave 10.4 g (81.8%) of IXa as needles, mp 146—147°. IR ν<sub>max</sub> cm⁻¹: 3350, 3100 (NH), 1705 (C=O), 1680 (NH₂CO). Anal. Calcd. for C₁₉H₂₄O₄N: C, 71.88; H, 6.95; N, 6.44. Found: C, 71.46; H, 6.88; N, 6.35.

15) The tests were conducted by Drs. G. Hayashi and S. Nuriimoto and their associates in the Safety Research Laboratory of this company.
17) Private communication from Dr. H.H. Swain, University of Michigan. We are grateful to Dr. E.L. May, National Institutes of Health for transmitting the results to us. See also addendum in the Minutes of the 37th Meeting of the Committee on Problems of Drug Dependence, National Research Council, National Academy of Sciences, 1975.
18) Coupling constants (J) are given in Hz and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Spectra were recorded on a Model JOEL ME-60 instrument.
19) In another instance, VIIa crystallized as prisms, mp 149—151°. NMR spectra of both samples were superimposable.
20) IXa was obtained, in another run, as needles, mp 139—141°. IR (in CHCl₃) and NMR spectra of both samples were identical.
1-(3-Methoxyphenyl)-4-oxo-cyclohexancarboxamide (IXb)—This compound was prepared from VIIIb in 73.5% yield in the same manner as that described above. Prisms from AcOEt-ν-hexane, mp 120—122°. IR ν_max cm⁻¹: 3580, 3160 (NH₂), 1700 (C=O), 1685 (CONH₂). Anal. Calcd. for C₁₇H₁₈O₃N: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.73; H, 7.03; N, 5.78.

3-Bromo-1-phenyl-4-oxo-cyclohexancarboxamide (Xa)—To a solution of IXb (6 g) in AcOEt (60 ml) was added a solution of Br₂ (4.44 g) in AcOH (60 ml) at 20—25° under stirring. The mixture was poured into ice-H₂O, extracted with CHCl₃, and washed with H₂O. Evaporation of the dried extracts gave the residue, which was crystallized from tetrahydrofuran (THF)-ether to give 4.75 g (58.1%) of Xa as prisms, mp 149—150°. IR ν_max cm⁻¹: 1670 (C=O), 3100, 3350 (NH₂). Mass Spectrum m/e: 297, 295 (M⁺), 173 (base peak). Anal. Calcd. for C₁₇H₁₅Br₂NBr: C, 52.71; H, 4.76; N, 4.72. Found: C, 53.02; H, 4.90; N, 4.86. Evaporation of the mother liquor (THF-ether) gave 3 g of oil, which was found to contain about 30% of Xa on gas chromatographic examination.

1-Phenyl-6-azabicyclo[3,2,1]octane-4,7-dione (Xla)—To a stirred solution of NaOMe (prepared from 1.41 g of Na and 50 ml of MeOH) was added Xa (4.7 g) at 20—26°. Stirring was continued for 1 hr at 22° and the mixture was concentrated, diluted with H₂O and extracted with CHCl₃. Evaporation of the dried extracts gave, after recrystallization from AcOEt, 2.65 g of (Xla) as prisms, mp 204—205°. IR ν_max cm⁻¹: 3270 (NH), 1720 (C=O), 1650 (NHCO). NMR: 2.1—3.2 (6H, m, —CH₂—), 3.89 (1H, d, J=6, C₆—H), 7.48 (5H, s, aromatic protons). Mass Spectrum m/e: 325 (M⁺, base peak), 159. Anal. Calcd. for C₁₇H₁₄O₂N: C, 72.53; H, 6.08; N, 6.50. Found: C, 72.49; H, 6.04; N, 6.45. Evaporation of the mother liquor (AcOEt) which was an oil which was chromatographed over silica gel (20 g) and eluted with C₂H₅—AcOEt (1:1). Evaporation of the eluate gave an additional amount (0.31 g, total 86%) of Xla, mp 201—204°.

A mixture of Xa (0.05 g), NaOMe (0.1 g), 1 ml of D₂O and 3 ml of dioxane was stirred at 25° for 45 hr. The mixture was acidified with 10% HCl, extracted with CHCl₃ and washed with H₂O. Evaporation of the dried extracts gave 0.03 g of deuterated Xla, mp 199—201°. IR ν_max cm⁻¹: 3300 (NH), 1725 (C=O), 1690 (NHCO). NMR: 1.9—3.15 (4H, m, —CH₂—), 3.85 (1H, d, J=6, C₆—H), 7.5 (5H, s, aromatic protons).

1-(3-Methoxyphenyl)-6-azabicyclo[3,2,1]octane-4,7-dione (Xlb)—To a stirred solution of IXb (50.46 g) in AcOH (500 ml) was added a solution of Br₂ (32.7 g) in AcOH (500 ml) at 20—23°. The mixture was worked up in the same manner as that described above to give 69.83 g of the crude bromo keto amide (Xb) as an oil. Without further purification, this was cyclized with NaOMe (prepared from 18.8 g of Na and 750 ml of MeOH) giving 25.2 g (50.4%), from IXb) of Xlb. Needles from AcOEt, mp 138—140°. IR ν_max cm⁻¹: 3230, 3100 (NH), 1715 (C=O), 1680 (NHCO). Mass Spectrum m/e: 245 (M⁺, base peak), 189. NMR (in CDCl₃-CD₃OD, 100 MHz): 1.4—2.7 (6H, m, —CH₂—), 3.33 (1H, J=6, C₆—H), 3.54 (3H, s, OCH₃). Anal. Calcd. for C₁₇H₂₀O₂N: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.76; H, 6.34; N, 5.72.

1-Phenyl-6-azabicyclo[3,2,1]octane-4,7-dione 4-Ethylene Thioketal (XIIIa)—A mixture of Xla (4.4 g), ethanethiol (3.5 ml) and BF₃-ether (4 ml) was stirred at 22° for 2 hr. The mixture was poured into 10% NaOH (50 ml), extracted with CHCl₃, and washed with 10% NaOH. Evaporation of the filtrate gave, after recrystallization from AcOEt, 2.4 g (66.9%) of XIIIa as needles, mp 170—195°. Pillars from EtOH, mp 194—196°. IR ν_max cm⁻¹: 3190, 3070 (NH), 1695 (NHCO). Mass Spectrum m/e: 291 (M⁺), 131 (base peak). NMR: 3.30 (4H, s, S—CH₂CH₂S—), 3.77 (1H, d, J=5, C₆—H). Anal. Calcd. for C₁₈H₂₁ONS₂: C, 61.82; H, 5.88; N, 4.80. Found: C, 61.40; H, 5.84; N, 4.66.

1-Phenyl-6-azabicyclo[3,2,1]octan-7-one (XVa)—A mixture of XIIIa (5 g), Raney Nickel (W-7, 25 ml) and 200 ml of EtOH was refluxed for 7 hr. The catalyst was filtered and washed with hot EtOH. Evaporation of the filtrate gave, after recrystallization from AcOEt, 2.4 g (66.9%) of XVIa as needles, mp 139—141°. IR ν_max cm⁻¹: 3170, 3060 (NH), 1685 (NHCO). Mass Spectrum m/e: 201 (M⁺), 158 (base peak), 130. Anal. Calcd. for C₁₇H₁₅N₂O: C, 77.76; H, 5.17; N, 6.96. Found: C, 77.16; H, 7.63; N, 6.80.

B) A mixture of Xla (0.9 g), KOH (1.2 g), NH₂NH₂·H₂O (1.2 ml) and 11 ml of ethylene glycol was refluxed for 2 hr. Then, the condenser was removed and the temperature was gradually raised and kept at 185° for 1 hr. The mixture was diluted with H₂O (20 ml) and extracted with ether. Evaporation of the extracts gave, after washing with H₂O and drying, the residue which on recrystallization from AcOEt afforded 0.41 g (52.4%) of XVa.

1-(3-Methoxyphenyl)-6-azabicyclo[3,2,1]octan-7-one (XVb)—A mixture of Xlb (21.73 g), NH₂NH₂·H₂O (4.9 g) and 170 ml of EtOH was refluxed for 1 hr. The mixture was concentrated, digested with benzene and filtered to afford 21.64 g (94%) of the hydroxazone (XVb), mp 140—143°. A mixture of this hydroxazone, 17.1 g of test-BuOK and 400 ml of toluene was refluxed for 2 hr. The mixture was washed with H₂O, dried, and evaporated. The residue was recrystallized from AcOEt-ν-hexane affording 17.54 g (85%) of XVb as pills, mp 109—111°. IR ν_max cm⁻¹: 3180, 3070 (NH), 1695 (NHCO). Mass Spectrum m/e: 231 (M⁺, base peak), 188, 173, 159. NMR: 3.78 (3H, s, OCH₃), ca. 3.80 (1H, m, C₆—H). Anal. Calcd. for C₁₇H₁₄O₂N: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.83; H, 7.51; N, 6.19.

B) Wolff-Kishner reduction of Xlb (1 g) in ethylene glycol in the same manner as that described for XVa afforded 0.34 g (56%) of XVb, mp 102—104°.

1-Phenyl-6-azabicyclo[3,2,1]octane (XVla) Hydrochloride—A mixture of XVa (1.2 g), LAH (1.2 g) and 80 ml of THF was refluxed for 5 hr. The mixture was diluted with ether (100 ml), decomposed by
addition of H₂O (2 ml) and filtered from inorganic material. Evaporation of the filtrate and concentration of the residue to the hydrochloride gave, after recrystallization from EtOH to give XVIIb oxalate, mp 173—175°. Mass Spectrum m/e: 217 (M⁺), 174 (base peak). Anal. Calcd. for C₁₃H₁₂ON: C, 78.10; H, 7.96; N, 6.50. Found: C, 78.10; H, 7.96; N, 6.51.

1-(3-Methoxyphenyl)-6-azacyclo[3,2,1]octane (XVIIb) Oxalate—This compound was prepared from XVb in the same manner as that described above. The crude base was converted to the oxalate and recrystallized from EtOH to give XVIIb oxalate, mp 173—175°. Mass Spectrum m/e: 217 (M⁺), 174 (base peak). Anal. Calcd. for C₁₃H₁₂ON: C, 78.10; H, 7.96; N, 6.50. Found: C, 78.10; H, 7.96; N, 6.51.

6-Methyl-1-phenyl-6-azacyclo[3,2,1]octan-7-one (XVIIIa)—To 10 ml of dimethylsulfoxide was added NaOH (0.11 g, 65% oil dispersion) under N₂. The mixture was stirred at 70—72° for 30 min. After cooling, XV (0.5 g) was added at 10—15° and the mixture was stirred for 1 hr at room temperature. CH₁ (0.43 g) was then added and stirring was continued for 2 hr. The mixture was poured into ice-H₂O, extracted with ether, and washed with H₂O. Evaporation of the dried extracts gave, after recrystallization from n-hexane, 0.44 g (81.8%) of XVIIIa, mp 71—72°. IR νmax cm⁻¹: 1695 (C=O). Anal. Calcd. for C₁₃H₁₂ON: C, 78.10; H, 7.96; N, 6.50. Found: C, 78.10; H, 7.96; N, 6.51.

1-(3-Methoxyphenyl)-6-methyl-6-azacyclo[3,2,1]octan-7-one (XVIIIb)—XVIIIb was obtained in 94.4% yield from XVb by the method described above. Prisms from iso-Pr₂O, mp 68—70°. IR νmax cm⁻¹: 1690 (C=O). NMR: 3.81 (3H, s, NCH₃), 3.62 (1H, m, C=H). Anal. Calcd. for C₁₃H₁₄O₂N: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.22; H, 8.05; N, 5.78.

6-Methyl-1-phenyl-6-azacyclo[3,2,1]octane (XVIIa) Hydrochloride—A N-Methylation of XVIa: To a solution of XVIa (0.5 g of the hydrochloride) in 10 ml of EtOH was added 37% formalin (0.34 g) and the mixture was heated at 60—70° for 30 min. After cooling, NaBH₄ (0.2 g) was added at 10—15° and stirring was continued for 2 hr at room temperature. The mixture was evaporated, diluted with H₂O, and extracted with CHCl₃. The residue left from drying and evaporation of the CHCl₃ was converted to the hydrochloride giving 0.31 g (60.3%) of XVIIa-HCl. Needles from acetone, mp 184—186°. Anal. Calcd. for C₁₃H₁₂ON: C, 70.71; H, 8.48; N, 5.89. Found: C, 70.60; H, 8.61; N, 5.73.

B) LAH Reduction of XVIIa: A mixture of XVIIa (0.5 g), LAH (0.5 g) and THF (25 ml) was refluxed for 5 hr. The usual procedure and work-up gave an oil which was converted to the hydrochloride giving 0.465 g (84.4%) of XVIIa-HCl, mp 184—186°.

1-(3-Methoxyphenyl)-6-methyl-6-azacyclo[3,2,1]octane (XVIIb) Hydrobromide—A N-Methylation of XVIIb: XVIIb was obtained from XVb in 73% yield by the method described above (formalin-NaBH₄). Hydrobromide was recrystallized from EtOH—ether as pillars and had mp 171—173°. NMR: 2.9 (1H, q, J=7Hz), 2.95 (3H, d, J=7Hz), 3.80 (3H, s, OCH₃), 4.0 (1H, m, C=H), 4.35 (1H, q, J=7Hz), 6.0 (1H, s, N-CH₃), 7.88 (1H, d, J=7Hz), 7.20 (1H, s, N=CH₂), 8.02 (1H, d, J=7Hz), 8.02 (1H, d, J=7Hz). Anal. Calcd. for C₁₃H₁₄O₂NBr: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.51; H, 7.08; N, 4.54.

B) LAH Reduction of XVIIb: A mixture of XVIIb (0.84 g), LAH (0.65 g) and 40 ml of THF was refluxed for 5 hr. The usual work-up gave an oil (0.85 g), which was found to be a mixture of three components by thin-layer chromatography (TLC). The mixture was chromatographed over Al₂O₃ (50 g) and eluted with ether. Evaporation of the elute and concentration of the residue into the hydrobromide gave 0.44 g (41.5%) of XVIIb-HBr, mp 170—172°. Elution with ether—MeOH (96:4) gave 0.14 g of oil. Conversion of this oil to the picrate and recrystallization from EtOH gave 0.18 g (11.3%) of picrate, mp 152—153°. This was found to be 7,7’-oxybis[1-(3-methoxyphenyl)-6-methyl-6-azacyclo[3,2,1]octane] dipicrate by the following evidence. IR spectrum (free base in CHCl₃) had no absorptions attributable to OH and C=O groups. NMR (free base): 2.54 (6H, s, N-CH₃), 3.20 (2H, m, C=H), 3.65 (6H, s, OCH₃), 4.14 (2H, s, -CH₂-). Analytical sample had mp 150—158° (EtOH). Anal. Calcd. for C₂₅H₂₆O₁₂N₂·2CH₂O₂Nₗ₂: C, 54.07; H, 4.76; N, 12.01. Found: C, 54.13; H, 4.82; N, 12.04.

Elution with MeOH and conversion of the elute into the hydrobromide gave 0.12 g (10.6%) of 1-(3-methoxyphenyl)-3-methylaminocyclohexanemethyl hydrobromide, mp 183—185°. IR νmax cm⁻¹: 3450 (OH). NMR (free base): 2.66 (6H, s, N-CH₃), 3.80 (3H, s, OCH₃), 3.44 (2H, s, CH₂O). Anal. Calcd. for C₁₃H₁₄O₂NBr: C, 54.55; H, 7.32; N, 4.24. Found: C, 54.20; H, 7.34; N, 4.25.

1-(3-Hydroxybenzyl)-6-methyl-6-azacyclo[3,2,1]octane (XVIIc)—A mixture of XVIIb·HBr (4.9 g) and 47% HBr (4 ml) was refluxed for 1 hr and evaporated. The residue was basified with NH₄OH and extracted with CHCl₃. Evaporation of the dried CHCl₃ gave, after recrystallization from AcOEt, 0.245 g (88%) of XVIIc, mp 145.5—145°. Mass Spectrum m/e: 217 (M⁺), 174 (base peak). Anal. Calcd. for C₁₃H₁₅ON: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.06; H, 8.71; N, 6.27.

6,7-endo-Dimethyl-1-phenyl-6-azacyclo[3,2,1]octane (XXa) Hydrochloride—To a ethereal solution of MeLi (prepared from 0.71 g of Li, 1.6 g of MeI and 11 ml of ether) was added a solution of XVIIa (0.8 g) in C₆H₆ (30 ml) at room temperature. The mixture was gently refluxed for 3 hr, decomposed by addition

21) These data were obtained by double irradiation technique at 100 MHz. We are indebted to Mr. N. Takeda for the experiment.
of H₂O and extracted with ether. Evaporation of the dried extracts gave 0.78 g of oil, a portion of which was converted to the picate and recrystallized from EtOH giving 6-methyl-7-methylene-1-phenyl-6-azabicyclo[3,2,1]octane picate, mp 161—163°. **Anal.** Calcd. for C₁₄H₁₈N·C₂H₆O₂N·H₂O: C, 57.01; H, 5.01; N, 12.67. Found: C, 56.79; H, 5.04; N, 12.49.

To a solution of the above oil in EtOH (60 ml) was added NaBH₄ (0.3 g) and the mixture was stirred at room temperature for 20 hr. EtOH was removed and the residue was diluted with H₂O and extracted with CHCl₃. The extracts gave, after drying and evaporation, a residue which was converted to 0.62 g (66%) of XXa-hydrochloride. It was crystallized from acetone-EtOH—ether as needles, mp 261—263°. **NMR** (free base): 1.19 (3H, d, J = 6.5, C-CH₃), 2.50 (3H, s, N-CH₂), 2.63 (1H, q, J = 6.5, C₅-H). **Anal.** Calcd. for C₁₄H₂₄NCl: C, 71.54; H, 8.81; N, 5.56. Found: C, 71.30; H, 8.64; N, 5.42.

6,7-endo-Dimethyl-1-(3-methoxyphenyl)-6-azabicyclo[3,2,1]octane (XXb) Hydrobromide—This compound was prepared from XVIIIb in 90% yield in the same manner as that described above. The hydrobromide was crystallized from EtOH—ether and had mp 175—177°. **NMR** (in CDCl₃-D₂O): 1.64 (3H, d, J = 7, C-CH₃), 3.02 (3H, s, N°CH₂), 3.28 (1H, q, J = 7, C₅exo-H), 3.81 (3H, s, O-CH₃), 3.85 (1H, m, C₆-H). Free base: 1.24 (3H, d, J = 7, C-CH₃), 2.50 (3H, s, N-CH₂), 2.70 (1H, q, J = 7, C₅-H), 3.15 (1H, m, C₆-H). **Anal.** Calcd. for C₁₄H₂₄NOCl·H₂O: C, 58.89; H, 7.41; N, 4.29. Found: C, 58.55; H, 7.65; N, 4.28. The hydrochloride was crystallized from iso-ProH and had mp 193—195°. **Anal.** Calcd. for C₁₄H₂₄NOCl·H₂O: C, 63.90; H, 8.83; N, 4.65. Found: C, 64.04; H, 8.67; N, 4.66. Methobromide was crystallized from EtOH, mp 230—231°. **NMR** (in CDCl₃-D₂O): 1.64 (3H, d, J = 7.5, C-CH₃), 3.52 (3H, s, N°-CH₂), 3.78 (3H, s, N°-CH₂), 3.84 (3H, s, O-CH₃), ca. 3.0 (1H, q, J = 7.5, C₅exo-H), 4.67 (1H, m, C₆-H). **Anal.** Calcd. for C₁₄H₂₄NOCl·H₂O: C, 60.00; H, 7.70; N, 4.12. Found: C, 59.89; H, 7.77; N, 4.14.

7-endo-Ethyl-6-methyl-1-(3-methoxyphenyl)-6-azabicyclo[3,2,1]octane (XXIIb) Hydrochloride—EtLi treatment of XVIIb, followed by reduction with NaBH₄ by the method described above, gave XXIIb in 61% yield. The hydrochloride was crystallized from EtOH—ether and had mp 176—178°. **NMR** (D₂O): 0.93 (3H, t, J = 7, CH₃), 3.09 (3H, s, N°-CH₂), 3.45 (1H, t, J = 7, C₆-H), 3.84 (3H, s, O-CH₃). **Anal.** Calcd. for C₁₄H₂₄NOCl·H₂O: C, 63.04; H, 8.99; N, 4.46. Found: C, 65.09; H, 8.93; N, 4.47.

6,7-endo-Dimethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (XXc) Hydrobromide—A mixture of XXb-HBr (3.3 g) and 47% HBr (33 ml) was refluxed for 1 hr and evaporated. The residue was digested with acetic and filtered. Recrystallization from EtOH—ether gave 3.02 g (96%) of XXc·HBr, mp 231—233°. Mass Spectrum m/z: 251 (M⁺), 216, 188 (base peak). **Anal.** Calcd. for C₁₄H₂₄NOBr·H₂O: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.49; H, 7.18; N, 4.48. The free base was recrystallized from AcOH and had mp 182—183°. **Anal.** Calcd. for C₁₄H₂₀ON: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.92; H, 9.09; N, 6.10. The hydrochloride recrystallized from EtOH—ether had mp 238—240° (decomp.). **Anal.** Calcd. for C₁₄H₂₄NOCl: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.30; H, 8.26; N, 5.32.

7-endo-Ethyl-1-(3-hydroxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octane (XXIIb) Hydrobromide—O-Demethylation of XXIIb in the same manner as that described above gave XXIIb·HBr in 83.3% yield, mp 245—247°, needles from MeOH—ether. **Anal.** Calcd. for C₁₄H₂₄NOBr·C₂H₅: C, 58.89; H, 7.41; N, 4.29. Found: C, 58.83; H, 7.59; N, 4.50.

N-Substituted Derivatives of 1-Phenyl-6-azabicyclo[3,2,1]octane (XXIII) —Method A: In a typical procedure, a mixture of XVIa (regenerated from 0.4 g of the hydrochloride), K₂CO₃ (0.3 g), H₂O (1 ml) and MeOH (5 ml) was added a solution of phenylacetylene (0.22 g) and 8 ml of DMF was heated at 70—80° for 1.5 hr. The mixture was evaporated, diluted with H₂O and extracted with ether. The extracts were washed with 10% HCl and H₂O dried and evaporated. The crystalline residue and LAH (0.5 g) in THF (20 ml) were refluxed for 2 hr. The usual work-up gave an oil, which was converted to the oxalate giving 0.35 g (65.5%) of 6-phenethyl-1-phenyl-6-azabicyclo[3,2,1]octane (XXIIIa, X = CH₂CH₂CH₃) picate, mp 129—130° (from EtOH).

Method B: In a typical procedure, to a stirred mixture of XVIa (regenerated from 0.3 g of the hydrochloride), K₂CO₃ (0.3 g), H₂O (1 ml) and MeOH (5 ml) was added 0.05 g of phenylacetylene (0.22 g) in ether (2 ml) at 5°. The mixture was stirred at room temperature for 1 hr, evaporated, diluted with H₂O and extracted with ether. The extracts were washed with 10% HCl and H₂O dried and evaporated. The crystalline residue was dissolved in benzene (0.5 g) in THF (20 ml) and refluxed for 2 hr. The usual work-up gave an oil, which was converted to the oxalate giving 0.35 g (65.5%) of 6-phenethyl-1-phenyl-6-azabicyclo[3,2,1]octane (XXIIIa, X = CH₂CH₂CH₃) picate, mp 129—130° (from EtOH).

Method C: A mixture of XVIb (0.4 g), N,N-(2-benzoyl-ethyl)-N,N,N-trimethylammonium iodide (0.69 g), K₂CO₃ (0.24 g) and DMF (5 ml) was stirred at room temperature for 2 hr under N₂. The mixture was diluted with H₂O and extracted with ether. Evaporation of the dried extracts gave an oil which was converted to the hydrochloride and recrystallized from MeOH—ether to give 0.635 g (86.5%) of 6-benzoyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (XXIIIb, X = CH₂CH₂COHP)-HCl.

The N-substituted derivatives prepared are listed in Table I.

O-Acyl Derivatives of 1-(3-Hydroxyphenyl)-6-azabicyclo[3,2,1]octane—Method A: In a typical procedure, a mixture of XXc·HBr (0.25 g), propionic anhydride (5 ml) and 2 drops of pyridine was heated at 80—90° for 2 hr. After cooling, the precipitated crystals were filtered and washed with acetone. Recrystallization from CHCl₃—ether gave 0.25 g (85%) of 6,7-endo-dimethyl-1-(3-propionyloxyphenyl)-6-azabicyclo[3,2,1]octane, mp 226—228°.
Method B: To a stirred solution of XXc (0.35 g) in pyridine (4 ml) was added a solution of benzoylchloride (0.28 g) in benzene (2 ml) at 5–10°. The mixture was stirred at room temperature for 45 min and evaporated. The residue was digested with AcOEt and filtered. Recrystallization from acetone–AcOEt gave 0.43 g (77%) of 1-(3-benzoyloxyphenyl)-6-endo-dimethyl-6-azacycloc[3,2,1]octane hydrochloride, mp 207–209°.

The O-acyl derivatives prepared are listed in Table II.

Optical Resolution of 1-(3-Methoxyphenyl)-6-azacycloc[3,2,1]octane (XVIlb)—To a solution of (±)-XVIb (regenerated from 12.26 g of the oxalate) in EtOH (15 ml) was added a solution of d-tartaric acid (6.2 g) in EtOH (85 ml) and the mixture was allowed to stand overnight. Filtration gave 13.4 g of crystals, mp 139–166°. Two recrystallizations from MeOH gave 3.2 g of the tartrate salt of (−)-XVIIb, mp 190–192°.

Optical Resolution of 1-(3-Methoxyphenyl)-6-azacycloc[3,2,1]octane (±)-XVIIb Picare—This compound was obtained from (−)-XVIIb by recrystallized from EtOH mp 190–192°. Anal. Calcd. for C_{19}H_{18}O_{2}N_{4}: C; 54.78; H; 5.25; N; 12.17. Found: C; 54.74; H; 5.34; N; 12.02. [x]_{D}^{23} + 67.5° (c = 0.4, CHCl_{3}).

Optical Resolution of 6,7-endo-Dimethyl-1-(3-methoxyphenyl)-6-azacycloc[3,2,1]octane (XXb)—A mixture of 17.4 g of (−)-bromo-8-camphorsulfonic acid NH_{2} salt, 13 g of (−)-XXb and 120 ml of MeOH was heated at 95–100° for 1 hr. The mixture was evaporated to dryness giving a crystalline residue, which was recrystallized from 60 ml of EtOH to afford 12.3 g (83%) of the sulfonate salt of (−)-XXb, mp 223–226°.

Optical Resolution of 6,7-endo-Dimethyl-1-(3-methoxyphenyl)-6-azacycloc[3,2,1]octane (XVIIIb)—The procedure was made as mentioned above. Yield was 92% from (−)-XVIIIb. Needles from EtOH, mp 150–152°. Anal. Calcd. for C_{19}H_{18}O_{2}N_{4}: C; 54.78; H; 5.25; N; 12.17. Found: C; 54.77; H; 5.33; N; 11.98. [x]_{D}^{23} - 68.4° (c = 0.39, CHCl_{3}).

Optical Resolution of 1-(3-Hydroxyphenyl)-6-azacycloc[3,2,1]octane (−)-XVIIb)—The procedure was made as described above. Yield was 92% from (−)-XVIIb. Needles from AcOEt, mp 150–152°. Anal. Calcd. for C_{19}H_{18}O_{2}N_{4}: C; 54.78; H; 5.25; N; 12.17. Found: C; 54.77; H; 5.33; N; 11.98. [x]_{D}^{23} - 19.0° (c = 0.4, In HCl).

Optical Resolution of 6,7-endo-Dimethyl-1-(3-hydroxyphenyl)-6-azacycloc[3,2,1]octane (−)-XVIIIb)—The procedure was made as described above. Yield was 92% from (−)-XVIIIb. Needles from AcOEt, mp 150–152°. Anal. Calcd. for C_{19}H_{18}O_{2}N_{4}: C; 54.78; H; 5.25; N; 12.17. Found: C; 54.77; H; 5.33; N; 11.98. [x]_{D}^{23} - 19.0° (c = 0.4, In HCl).

Optical Resolution of 6,7-endo-Dimethyl-1-(3-hydroxyphenyl)-6-azacycloc[3,2,1]octane (−)-XVIIIb)—The procedure was made as described above. Yield was 92% from (−)-XVIIIb. Needles from AcOEt, mp 150–152°. Anal. Calcd. for C_{19}H_{18}O_{2}N_{4}: C; 54.78; H; 5.25; N; 12.17. Found: C; 54.77; H; 5.33; N; 11.98. [x]_{D}^{23} - 19.0° (c = 0.4, In HCl).
(-)-6,7-endo-Dimethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (-)-(XXc) Hydrobromide——
Plates from EtOH, mp 245—246. [α]D 29° –8.9° (c=0.52, H2O). Yield was 93% from (+)-XXb. Anal. Calcd. for C18H24ONBr: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.54; H, 6.90; N, 4.64.

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