[Chem. Pharm. Bull. 24(5)1002—1012(1976)]

UDC 547.895.04 : 547.298.1.04

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

Mikio Takeda,[1a] Hirozumi Inoue, Katsuyuki Noguchi, Yasushi Honma, Masatoshi Kawamori, Goro Tsukamoto, and Seiichi Saito

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd.[1]

(Received August 23, 1975)

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 (XIa, b) respectively. A number of drivatives bearing various substituents on nitrogen and C_7 have been prepared from (XIa, b) for pharmacological evaluation.

6,7-*endo*-Dimethyl-1-(3-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 agoinst 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 benzomorphan[2] (I), phenylmorphan[3] (II), pyrrolidine[4] (III), and hexamethylenimine[5] (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.
2) *a*) E.L. May and N.B. Eddy, *J. Med. Chem.*, **9**, 851 (1966); *b*) J.H. Ager, A.E. Jacobson, and E.L. May, *J. Med. Chem.*, **12**, 288 (1969); *c*) F.H. Clarke, R.T. Hill, J.K. Saelens, and N. Yokoyama, "Narcotic Antagonists," ed. by M.C. Braude, L.S. Harris, E.L. May, J.P. Smith, and J.E. Villarreal, Advances in Biochemical Psychopharmacology, Vol. 8, Raven Press, New York, 1974, pp. 80—89.
3) *a*) E.L. May and M. Takeda, *J. Med. Chem.*, **13**, 805 (1970); *b*) M.E. Rogers and E.L. May, *J. Med. Chem.*, **17**, 1328 (1974).
4) R.E. Bowman, *Chem. Ind.* (London), **1969**, 1077.
5) P.G. Goode and A.C. White, *Brit. J. Pharmacol.*, **43**, 462P (1971).
6) *a*) D.R. Jasinski, "Agonist and Antagonist Actions of Narcotic Analgestic Drugs," ed. by H.W. Kosterlitz, H.O.J. Collier, and J.E. Villarreal, Macmillan Press, 1972, pp. 94—103; *b*) D.R. Jasinski, *Clin. Pharmacol. and Ther.*, **12**, 613 (1971); *c*) J.E. Villarreal, "Recent Advances in the Pharmacology of Morphine-like Drugs, Advances in Mental Science, Volume II," ed. by R.T. Harris, W. McIsac, and C.R. Schuste, University of Texas Press, Houston, Texas, 1970, pp. 83—116.

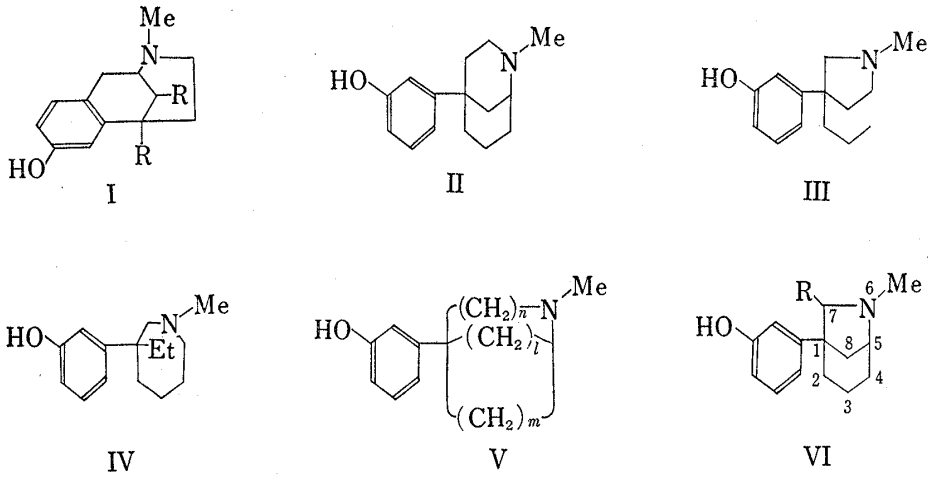


Chart 1

To gain greater insight into the steric requirements for the partial agonist activity and to search an ideal analgetic 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[7] (VIIa) yielded the ketal amide

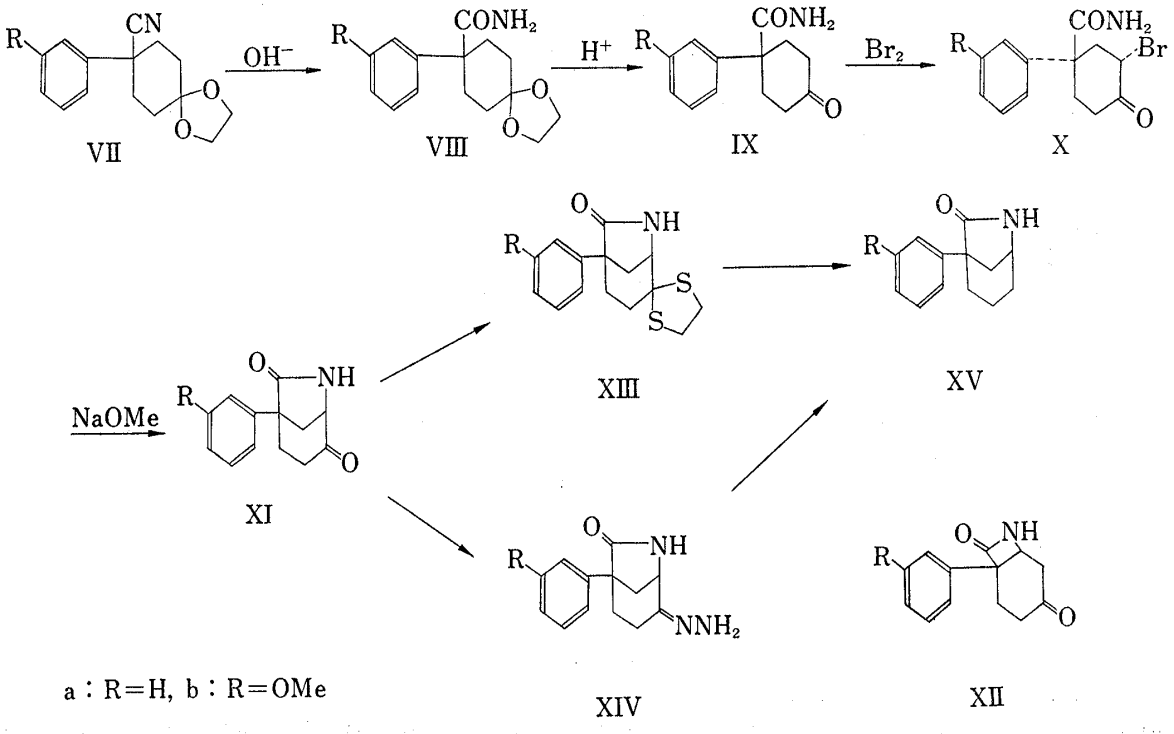


Chart 2

7) E.C. Horning, M.G. Horning, M.S. Fish, and M.W. Rutenburg, *J. 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[8] at room temperature afforded 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,[8] one is led to assign the *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.[8b] By a sequence of similar reactions, the 3-methoxyphenyl analog (XIb) was obtained from 1-(3-methoxyphenyl)-4-oxocyclohexanecarbonitrile ethylene ketal (VIIb)[9] 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[10] minimized this

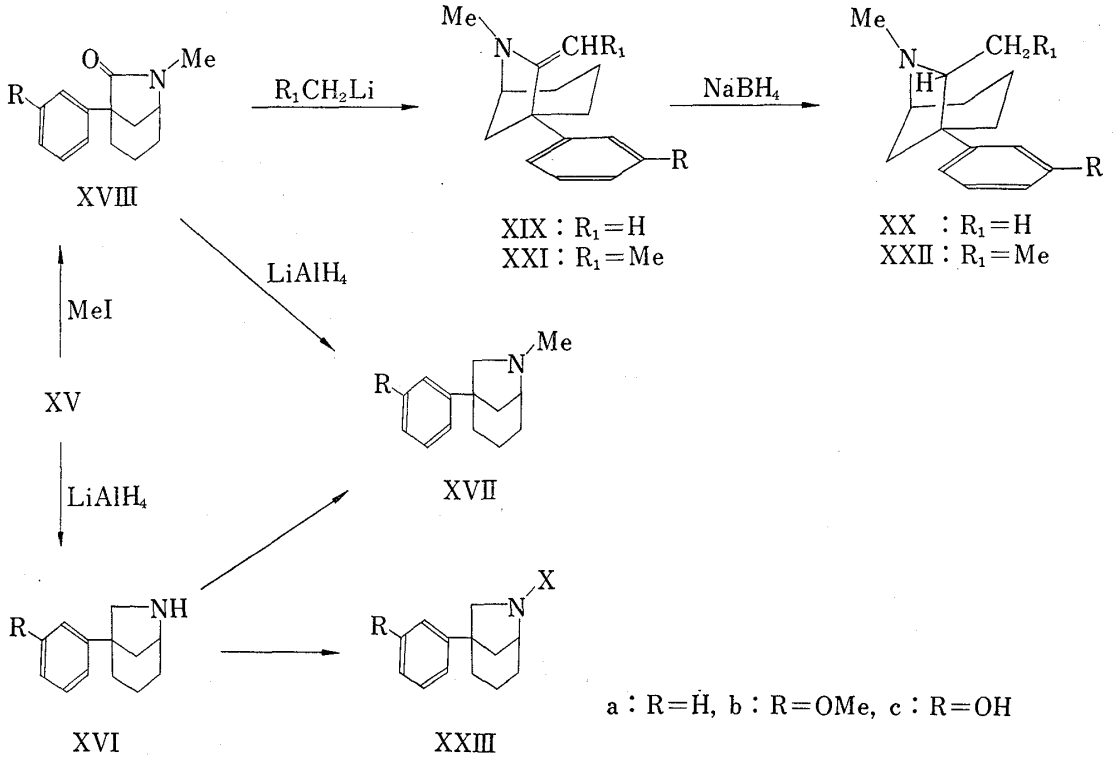


Chart 3

8) *a*) G.N. Walker and D. Alkalay, *J. Org. Chem.*, **31**, 1905 (1966); *b*) W.L. Nelson and K.F. Nelson, *J. Org. Chem.*, **36**, 607 (1971).
9) S. Uyeo, H. Shiraki, A. Koshiro, T. Yashiro, and K. Kagei, *Chem. Pharm. Bull.*, (Tokyo) **14**, 1033 (1966).
10) M.F. Grundon, H.B. Henbest, and M.D. Scott, *J. Chem. Soc.*, **1963**, 1855.

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 C_7 was carried out by the method described by Walker, *et al.*[11] Thus, treatment of the N-methyl lactam (XVIII) with methyllithium 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

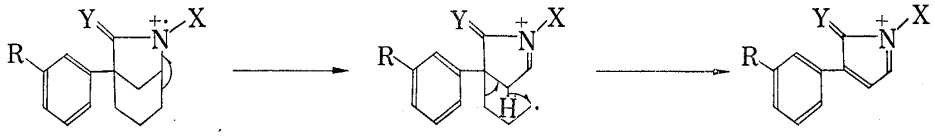
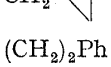
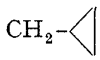
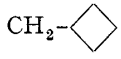


Chart 4

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

R	X	Method[a]	Salt	Crystn[b] solvent	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
H	$CH_2CH=CH_2$	A	picrate	A	129—130	$C_{22}H_{24}O_7N_4$	57.87 (57.83)	5.30 (5.28)	12.28 (12.31)
H	CH_2- 	B	base	—	240[c]	$C_{17}H_{23}N$	84.59 (84.73)	9.61 (9.53)	5.80 (5.81)
H	$(CH_2)_2Ph$	B	oxalate	A	207—209	$C_{23}H_{26}O_4N$	72.41 (72.11)	7.13 (7.20)	3.67 (3.66)
H	$(CH_2)_2COPh$	C	HCl	C-D	166—168	$C_{22}H_{26}ONCl \cdot 1/2H_2O$	72.41 (72.65)	7.46 (7.53)	3.84 (4.04)
H	$(CH_2)_3COPh$-F(*p*)	A	HBr	A-C	212—214	$C_{23}H_{27}ONBrF$	63.90 (63.75)	6.30 (6.26)	3.24 (3.16)
OMe	$(CH_2)_3COPh$-F(*p*)	A	HCl	A-C	195—196	$C_{24}H_{29}O_2NClF$	68.96 (68.68)	6.99 (6.96)	3.35 (3.29)
OMe	$(CH_2)_3COPh$	A	HCl	A-C	167—169	$C_{24}H_{30}O_2NCl$	72.06 (72.46)	7.56 (7.72)	3.50 (3.56)
OH	$CH_2CH=CH_2$	A	picrate	A	163—165	$C_{22}H_{24}O_8N_4$	55.93 (55.68)	5.12 (5.10)	11.86 (11.88)
OH	$CH_2C\equiv CH$	A	oxalate	B	218—219	$C_{17}H_{20}O_3N$	71.34 (70.98)	7.00 (7.12)	4.89 (4.84)
OH	CH_2- 	B	base	—	220[d]	$C_{17}H_{23}ON$	79.33 (78.91)	9.01 (8.89)	5.44 (5.38)
OH	CH_2- 	B	base	—	240[c]	$C_{18}H_{25}ON$	79.66 (79.38)	9.29 (9.01)	5.16 (5.09)
OH	$(CH_2)_5CH_3$	B	base	—	250[c]	$C_{19}H_{29}ON$	79.39 (78.99)	10.17 (10.08)	4.87 (4.86)
OH	$(CH_2)_2Ph$	B	oxalate	A-C	230—232	$C_{21}H_{25}ON \cdot 1/2(CO_2H) \cdot 1/2H_2O$	73.31 (73.20)	7.55 (7.34)	3.89 (3.73)
OH	$CH_2CH=CHPh$	A	picrate	B	180—183	$C_{28}H_{28}O_8N_4 \cdot 1/2H_2O$	60.32 (60.54)	5.20 (5.16)	10.05 (10.01)
OH	$(CH_2)_2COPh$	C	HCl	B-C	187—189	$C_{22}H_{26}O_2NCl$	71.05 (70.86)	7.05 (7.05)	3.77 (3.59)

a) See Experimental section.
b) A, EtOH; B, MeOH; C, ether; D, acetone
c) bp (bath temperature) (0.1 mmHg)
d) bp (bath temperature) (0.2 mmHg)

11) G.N. Walker and D. Alkalay, *J. Org. Chem.*, **36**, 491 (1971).

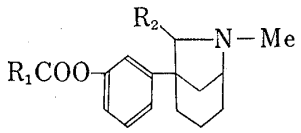
were given in the Experimental section. *endo* Configuration of the 7-Me group was unequivocally established on the basis of X-ray analysis of the hydrobromide of the corresponding phenol (XXc).[12] This result parallels the preferential formation of the *endo* alcohol from bicyclo[3,2,1]octan-6-one 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/e* (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 Furstoss, *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



R_1	R_2	Optical rotation	Method[a]	Salt	Crystn[b] solvent	mp, °C	Formula	Analysis (%) Calcd. (Found) C	H	N
CH_3	CH_3	±	A	HCl	A-B	250—252	$C_{17}H_{24}O_2NCl$	65.90 (65.45)	7.81 (7.83)	4.52 (4.47)
CH_3	CH_3	+	A	HCl[c]	A-B	207—211	$C_{17}H_{24}O_2NCl\cdot H_2O$	62.25 (62.51)	7.99 (7.91)	4.27 (4.26)
CH_3	CH_3	−	A	HCl[d]	A-B	208—211	$C_{17}H_{24}O_2NCl\cdot H_2O$	62.25 (62.51)	7.99 (7.89)	4.27 (4.28)
CH_3	C_2H_5	±	A	HBr	A-B	237—240	$C_{18}H_{26}O_2NBr$	58.70 (58.75)	7.12 (7.15)	3.80 (3.90)
C_2H_5	CH_3	±	A	HBr	B-C	226—228	$C_{18}H_{26}O_2NBr$	58.70 (58.36)	7.12 (7.00)	3.80 (3.70)
C_5H_{11}	CH_3	±	A	HBr	B-C	95—97	$C_{21}H_{32}O_2NBr\cdot H_2O$	58.89 (58.46)	7.71 (7.47)	3.27 (3.17)
Ph	CH_3	±	B	HCl	D-E	207—209	$C_{22}H_{26}O_2NCl$	71.05 (70.82)	7.05 (7.02)	3.77 (3.86)
3-Pyridyl	CH_3	±	B	2HCl	A-B-E	210—218	$C_{21}H_{26}O_2N_2Cl\cdot 1/2\ H_2O$	60.24 (59.94)	6.50 (6.36)	6.69 (6.87)

a) See Experimental section
b) A, EtOH; B, ether; C, $CHCl_3$; D, AcOEt; E, acetone
c) $[\alpha]_D^{24}$ +9.9° (*c*=0.46, MeOH)
d) $[\alpha]_D^{24}$ −9.9° (*c*=0.38, MeOH)

12) These analytical data including the absolute stereochemistry of (+)-XXc will be appeared in a later communication.
13) R.A. Appleton, J.C. Fairlie, R. McCrindle, and W. Parker, *J. Chem. Soc.* (C), **1968**, 1716.
14) R. Furstoss, A. Heumann, B. Waegell, and J. Gore, *Org. Mass Spectrom.*, **6**, 1207 (1972).

bromo-8-camphorsulfonic acid ammonium salt and then with (−)-dibenzoyltartaric acid. The (−)- and (+)-XXb isomers were demethylated to the (+)- and (−)-phenols (XXc),[12] respectively.

1-Phenyl-6-azabicyclo[3,2,1]octane derivatives prepared were tested for their analgetic activities.[15] In the mouse writhing method,[16] analgetic activities of XXc and its dextro isomer were comparable to meperidine and morphine, respectively. Introduction of methyl substituent on C_7 apparently enhanced the activity. XXc and its (+)-isomer also exhibited nalorphine-like antagonism in morphine-dependent monkeys.[17] 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.[17] 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 $CDCl_3$ (containing tetramethylsilane at δ 0.00 as an internal standard) at 60 MHz, unless otherwise stated.[18] Mass spectra were measured using Hitachi RMS-4 mass spectrometer. Gas chromatography were 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 Na_2SO_4 and all evaporations were carried out *in vacuo*.

1-Phenyl-4-oxo-cyclohexanecarboxamide Ethylene Ketal (VIIIa)——A mixture of VIIa[7] (16 g), KOH (16 g), ethylene glycol (320 ml) and H_2O (320 ml) was refluxed for 12 hr. The mixture was diluted with H_2O (300 ml) and extracted with $CHCl_3$. Evaporation of the dried extracts gave, after recrystallization from AcOEt-*n*-hexane, 8.5 g (50%) of VIIIa as needles, mp 138—140°.[19] IR ν_{max}^{Nujol} cm^{-1}: 1650 ($CONH_2$). Mass Spectrum *m/e*: 261 (M^+). *Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.95; 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 (29.7%) of 1-phenyl-4-oxo-cyclohexanecarboxylic acid ethylene ketal, mp 142—144°. IR ν_{max}^{Nujol} cm^{-1}: 2800—3000 (COOH), 1710 (C=O), 1100, 1040 (ketal). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.41; H, 6.86.

1-(3-Methoxylphenyl)-4-oxo-cyclohexanecarboxamide Ethylene Ketal (VIIIb)——A mixture of VIIb[9] (3.5 g), KOH (3.5 g), EtOH (70 ml) and H_2O (70 ml) was refluxed for 22 hr. The mixture was concentrated and extracted with $CHCl_3$. Evaporation of the dried extracts gave the residue which was digested with small amount of ether and filtered to give 2.3 g (62.3%) of VIIIb. Prisms from AcOEt, mp 136—137°. IR ν_{max}^{Nujol} cm^{-1}: 3430, 3340, 3290, 3200 (NH_2), 1670 (C=O). *Anal.* Calcd. for $C_{16}H_{21}O_4N$: 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 VIIb. From the aqueous layer, 0.58 g of 1-(3-methoxyphenyl)-4-oxo-cyclohexanecarboxylic acid ethylene ketal,[9] 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% $NaHCO_3$, dried and evaporated. Recrystallization of the residue from AcOEt gave 10.4 g (81.8%) of IXa as needles, mp 146—147°.[20] IR ν_{max}^{Nujol} cm^{-1}: 3350, 3100 (NH), 1705 (C=O), 1680 (NH_2CO). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; 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. Nurimoto and their associates in the Safety Research Laboratory of this company.
16) S. Nurimoto, S. Suzuki, G. Hayashi, and M. Takeda, *Japan. J. Pharmacol.*, **24**, 461 (1974).
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, VIIIa 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 $CHCl_3$) and NMR spectra of both samples were identical.

1-(3-Methoxyphenyl)-4-oxo-cyclohexanecarboxamide (IXb)——This compound was prepared from VIIIb in 73.5% yield in the same manner as that described above. Prisms from AcOEt–*n*-hexane, mp 120—122°. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3160 (NH_2), 1700 (C=O), 1685 ($CONH_2$). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: 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-cyclohexanecarboxamide (Xa)——To a solution of IXa (6 g) in AcOH (60 ml) was added a solution of Br_2 (4.44 g) in AcOH (60 ml) at 20—25° under stirring. The mixture was poured into ice-H_2O, extracted with $CHCl_3$, and washed with H_2O. 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}^{Nujol} cm^{-1}: 1670 (C=O), 3100, 3350 (NH_2). Mass Spectrum *m/e*: 297, 295 (M^+), 173 (base peak). *Anal.* Calcd. for $C_{13}H_{14}O_2NBr$: 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 (XIa)——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 H_2O and extracted with $CHCl_3$. Evaporation of the dried extracts gave, after recrystallization from AcOEt, 2.65 g of (XIa) as prisms, mp 204—205°. IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH), 1720 (C=O), 1680 (NHCO). NMR: 2.1—3.2 (6H, m, $-CH_2-$), 3.89 (1H, d, J=6, C_5–H), 7.48 (5H, s, aromatic protons). Mass Spectrum *m/e*: 215 (M^+, base peak), 159. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: 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) gave an oil which was chromatographed over silica gel (20 g) and eluted with C_6H_6–AcOEt (1: 1). Evaporation of the eluate gave an additional amount (0.31 g, total yield 86%) of XIa, mp 201—204°.

A mixture of XIa (0.05 g), NaOMe (0.1 g), 1 ml of D_2O and 3 ml of dioxane was stirred at 25° for 45 hr. The mixture was acidified with 10% HCl, extracted with $CHCl_3$ and washed with H_2O. Evaporation of the dried extracts gave 0.03 g of deuterated XIa, mp 199—201°. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1725 (C=O), 1690 (NHCO). NMR: 1.9—3.15 (4H, m, $-CH_2-$), 3.85 (1H, d, J=6, C_5–H), 7.5 (5H, s, aromatic protons).

1-(3-Methoxyphenyl)-6-azabicyclo[3,2,1]octane-4,7-dione (XIb)——To a stirred solution of IXb (50.46 g) in AcOH (500 ml) was added a solution of Br_2 (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 XIb. Needles from AcOEt, mp 138—140°. IR ν_{max}^{Nujol} cm^{-1}: 3230, 3100 (NH), 1715 (C=O), 1680 (NHCO). Mass Spectrum *m/e*: 245 (M^+, base peak), 189. NMR (in $CDCl_3$–C_6H_6, 100 MHz): 1.4—2.7 (6H, m, $-CH_2-$), 3.33 (1H, J=6, d, C_5–H), 3.54 (3H, s, OCH_3). *Anal.* Calcd. for $C_{14}H_{15}O_3N$: 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 XIa (4.4 g), ethandithiol (3.5 ml) and BF_3·ether (4 ml) was stirred at 22° for 2 hr. The mixture was poured into 10% NaOH (50 ml), extracted with $CHCl_3$, and washed with 10% NaOH. Evaporation of the dried extracts gave 5 g (84%) of XIIIa, mp 170—195°. Pillars from EtOH, mp 194—196°. IR ν_{max}^{Nujol} cm^{-1}: 3190, 3070 (NH), 1695 (NHCO). Mass Spectrum *m/e*: 291 (M^+), 131 (base peak). NMR: 3.30 (4H, s, S–CH_2CH_2–S), 3.77 (1H, d, J=5, C_5–H). *Anal.* Calcd. for $C_{15}H_{17}ONS_2$: 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) 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 (69.6%) of XVa as needles, mp 139—141°. IR ν_{max}^{Nujol} cm^{-1}: 3170, 3060 (NH), 1685 (NHCO). Mass Spectrum *m/e*: 201 (M^+), 158 (base peak), 130. *Anal.* Calcd. for $C_{13}H_{15}ON$: C, 77.56; H, 7.51; N, 6.96. Found: C, 77.16, H, 7.63; N, 6.80.

B) A mixture of XIa (0.9 g), KOH (1.2 g), NH_2NH_2·H_2O (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 H_2O (20 ml) and extracted with ether. Evaporation of the extracts gave, after washing with H_2O 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) A mixture of XIb (21.73 g), NH_2-NH_2·H_2O (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 hydrazone (XIVb), mp 140—143°. A mixture of this hydrazone, 17.1 g of *tert*-BuOK and 400 ml of toluene was refluxed for 2 hr. The mixture was washed with H_2O, dried, and evaporated. The residue was recrystallized from AcOEt–*n*-hexane affording 17.54 g (85% from XIb) of XVb as pillars, mp 109—111°. IR ν_{max}^{Nujol} cm^{-1}: 3180, 3070 (NH), 1695 (NHCO). Mass Spectrum *m/e*: 231 (M^+, base peak), 188, 173, 159. NMR: 3.78 (3H, s, OCH_3), *ca.* 3.80 (1H, m, C_5–H). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.83; H, 7.51; N, 6.19.

B) Wolff-Kischner reduction of XIb (1 g) in ethylene glycol in the same manner as that described for XVa afforded 0.34 g (36%) of XVb, mp 102—104°.

1-Phenyl-6-azabicyclo[3,2,1]octane (XVIa) Hydrochloride——A mixture of XVa (1.2 g), LAH (1.2 g) and 60 ml of THF was refluxed for 5 hr. The mixture was diluted with ether (100 ml), decomposed by

addition of H_2O (2 ml) and filtered from inorganic material. Evaporation of the filtrate and conversion of the residue to the hydrochloride gave, after recrystallization from EtOH, 1.2 g (89.4%) of XVIa·HCl, mp 234—235° (decomp.). *Anal.* Calcd. for $C_{13}H_{18}NCl$: C, 69.79; H, 8.11; N, 6.26. Found: C, 69.49; H, 8.11; N, 6.20.

1-(3-Methoxyphenyl)-6-azabicyclo[3,2,1]octane (XVIb) 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 XVIb oxalate, mp 173—175°. Mass Spectrum *m/e*: 217 (M^+), 174 (base peak). *Anal.* Calcd. for $C_{16}H_{21}O_5N$: C, 62.52; H, 6.89; N, 4.56. Found: C, 62.43; H, 6.92; N, 4.60.

6-Methyl-1-phenyl-6-azabicyclo[3,2,1]octan-7-one (XVIIIa)——To 10 ml of dimethylsulfoxide was added NaH (0.11 g, 65% oil dispersion) under N_2. The mixture was stirred at 70—72° for 30 min. After cooling, XVa (0.5 g) was added at 10—15° and the mixture was stirred for 1 hr at room temperature. CH_3I (0.43 g) was then added and stirring was continued for 2 hr. The mixture was poured into ice-H_2O, extracted with ether, and washed with H_2O. Evaporation of the dried extracts gave, after recrystallization from *n*-hexane, 0.44 g (81.8%) of XVIIIa, mp 71—72°. IR ν_{max}^{Nujol} cm^{-1}: 1695 (C=O). *Anal.* Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.50. Found: C, 77.60; H, 7.96; N, 6.51.

1-(3-Methoxylphenyl)-6-methyl-6-azabicyclo[3,2,1]octan-7-one (XVIIIb)——XVIIIb was obtained in 94.4% yield from XVb by the method described above. Prisms from iso-Pr_2O, mp 68—70°. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). NMR: 3.81 (3H, s, NCH_3), 3.62 (1H, m, C_5–H). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.22; H, 8.03; N, 5.78.

6-Methyl-1-phenyl-6-azabicyclo[3,2,1]octane (XVIIa) Hydrochloride ——A) N-Methylation of XVIa: To a solution of XVIa (regenerated from 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, $NaBH_4$ (0.2 g) was added at 10—15° and stirring was continued for 2 hr at room temperature. The mixture was evaporated, diluted with H_2O, and extracted with $CHCl_3$. The residue left from drying and evaporation of the $CHCl_3$ was converted to the hydrochloride giving 0.31 g (60.3%) of XVIIa·HCl. Needles from acetone, mp 184—186°. *Anal.* Calcd. for $C_{14}H_{20}NCl$: C, 70.71; H, 8.48; N, 5.89. Found: C, 70.60; H, 8.61; N, 5.73.

B) LAH Reduction of XVIIIa: A mixture of XVIIIa (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-azabicyclo[3,2,1]octane (XVIIb) Hydrobromide—A) N-Methylation of XVIb: XVIIb was obtained from XVIb in 73% yield by the method described above (formalin-$NaBH_4$). Hydrobromide was recrystallized from EtOH–ether as pillars and had mp 171—173°. NMR[21]: 2.9 (1H, q, $J_{gem}=11$, $J_{NH}=4$, C_7–H), 2.95 (3H, d, $J_{NH}=4$, N^+–CH_3), 3.80 (3H, s, OCH_3), 4.0 (1H, m, C_5–H), 4.35 (1H, q, $J_{gem}=11$, $J_{NH}=6$, C_7–H), 10.8 (broad peak, N^+–H) free base: 2.50 (3H, s, N–CH_3), 2.88 (1H, d, $J_{gem}=10$, C_7–H), 3.20 (1H, d, $J_{gem}=10$, C_7–H), *ca.* 3.2 (1H, m, C_5–H). *Anal.* Calcd. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.51; H, 7.08; N, 4.54.

B) LAH Reduction of XVIIIb: A mixture of XVIIIb (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 Al_2O_3 (50 g) and eluted with ether. Evaporation of the eluate and conversion 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-azabicyclo[3,2,1]octane] dipicrate by the following evidence. IR spectrum (free base in $CHCl_3$) had no absorptions atributable to OH and C=O groups. NMR (free base): 2.54 (6H, s, N–CH_3), 3.20 (2H, m, C_5–H), 3.65 (6H, s, OCH_3), 4.14 (2H, s, –CH–O–). Analytical sample had mp 156—158° (EtOH). *Anal.* Calcd. for $C_{30}H_{38}O_3N_2 \cdot 2C_6H_3O_7N_3$: 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 eluate into the hydrobromide gave 0.12 g (10.6%) of 1-(3-methoxyphenyl)-3-methylaminocyclohexanemethanol hydrobromide, mp 183—185°. IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH). NMR (free base): 2.66 (3H, s, N–CH_3), 3.80 (3H, s, OCH_3), 3.44 (2H, s, CH_2O). *Anal.* Calcd. for $C_{15}H_{24}O_2NBr$: C, 54.55; H, 7.32; N, 4.24. Found: C, 54.20; H, 7.34; N, 4.25.

1-(3-Hydroxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octane (XVIIc)——A mixture of XVIIb·HBr (0.4 g) and 47% HBr (4 ml) was refluxed for 1 hr and evaporated. The residue was basified with NH_4OH and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ gave, after recrystallization from AcOEt, 0.245 g (88%) of XVIIc, mp 144.5—145.5°. Mass Spectrum *m/e*: 217 (M^+), 174 (base peak). *Anal.* Calcd. for $C_{14}H_{19}ON$: 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-azabicyclo[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 XVIIIa (0.8 g) in C_6H_6 (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 H_2O and extracted with ether. Evaporation of the dried extracts gave 0.78 g of oil, a portion of which was converted to the picrate and recrystallized from EtOH giving 6-methyl-7-methylene-1-phenyl-6-azabicyclo[3,2,1]octane picrate, mp 161—163°. *Anal.* Calcd. for $C_{15}H_{19}N \cdot C_6H_3O_7N_3$: 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 $NaBH_4$ (0.3 g) and the mixture was stirred at room temperature for 20 hr. EtOH was removed and the residue was diluted with H_2O and extracted with $CHCl_3$. 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–CH_3), 2.50 (3H, s, N–CH_3), 2.63 (1H, q, J=6.5, C_7–H). *Anal.* Calcd. for $C_{15}H_{22}NCl$: 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[21] (in $CDCl_3$–D_2O): 1.64 (3H, d, J=7, C–CH_3), 3.02 (3H, s, N^+–CH_3), 3.28 (1H, q, J=7, C_{7exo}–H), 3.81 (3H, s, O–CH_3), 3.85 (1H, m, C_5–H). Free base: 1.24 (3H, d, J=7, C–CH_3), 2.50 (3H, s, N–CH_3), 2.70 (1H, q, J=7, C_7–H), 3.15 (1H, m, C_5–H). *Anal.* Calcd. for $C_{16}H_{24}ONBr$: 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 $C_{16}H_{24}ONCl \cdot H_2O$: 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[21]: 1.64 (3H, d, J=7.5, C–CH_3), 3.52 (3H, s, N^+–CH_3), 3.78 (3H, s, N^+–CH_3), 3.84 (3H, s, O–CH_3), *ca.* 3.9 (1H, q, J=7.5, C_{7exo}–H), 4.67 (1H, m, C_5–H). *Anal.* Calcd. for $C_{17}H_{26}ONBr$: 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 XVIIIb, followed by reduction with $NaBH_4$ by the method described above, gave XXIIb in 61% yield. The hydrochloride crystallized from EtOH–ether had mp 176—178°. NMR (D_2O): 0.93 (3H, t, J=7, CH_2Me), 3.09 (3H, s. N^+–CH_3), 3.45 (1H, t, J=7, C_7–H), 3.84 (3H, s, O–CH_3). *Anal.* Calcd. for $C_{17}H_{26}ONCl \cdot H_2O$: C, 65.04; 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 acetone and filtered. Recrystallization from EtOH–ether gave 3.02 g (96%) of XXc·HBr, mp 231—233°. Mass Spectrum *m/e*: 231 (M^+), 216, 188 (base peak). *Anal.* Calcd. for $C_{15}H_{22}ONBr$: 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 AcOEt and had mp 182—183°. *Anal.* Calcd. for $C_{15}H_{21}ON$: 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 $C_{15}H_{22}ONCl$: 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 (XXIIc) Hydrobromide——O-Demethylation of XXIIb in the same manner as that described above gave XXIIc·HBr in 83.3% yield, mp 245—247°, needles from MeOH–ether. *Anal.* Calcd. for $C_{16}H_{24}ONBr$: C, 58.89; H, 7.41; N, 4.29. Found: C, 58.83; H, 7.59; N, 4.30.

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), K_2CO_3 (0.4 g), allylbromide (0.22 g) and 8 ml of DMF was heated at 70—80° for 1.5 hr. The mixture was evaporated, diluted with H_2O and extracted with ether. Evaporation of the dried extracts gave a residue, which was converted to 0.465 g (57.0%) of 6-allyl-1-phenyl-6-azabicyclo[3,2,1]octane (XXIIIa, X=$CH_2CH=CH_2$) picrate, 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), K_2CO_3 (0.3 g), H_2O (1 ml) and MeOH (5 ml) was added a solution of phenylacetylchloride (0.22 g) in ether (2 ml) at 5—10°. The mixture was stirred at room temperature for 1 hr, evaporated, diluted with H_2O, and extracted with ether. The extracts were washed with 10% HCl and H_2O, dried and evaporated. The crystalline residue and LAH (0.3 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 (68.5%) of 6-phenethyl-1-phenyl-6-azabicyclo[3,2,1]-octane (XXIIIa, X=CH_2CH_2Ph) oxalate, mp 207—209° (from EtOH).

Method C: A mixture of XVIc (0.4 g), N-(2-benzoylethyl)-N,N,N-trimethylammonium iodide (0.69 g), K_2CO_3 (0.24 g) and DMF (5 ml) was stirred at room temperature for 2 hr under N_2. The mixture was diluted with H_2O 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-benzoylethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (XXIIIc, X=CH_2CH_2COPh)·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 $CHCl_3$–ether gave 0.25 g (85%) of 6,7-*endo*-dimethyl-1-(3-propionyloxyphenyl)-6-azabicyclo-[3,2,1]octane hydrobromide, mp 226—228°.

Method B: To a stirred solution of XXc (0.35 g) in pyridine (4 ml) was added a solution of benzoyl-chloride (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)-6,7-*endo*-dimethyl-6-azabicyclo[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-azabicyclo[3,2,1]octane (XVIb)——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 (−)-XVIb, mp 190—192°. *Anal.* Calcd. for $C_{18}H_{25}O_7N$: C, 58.84; H, 6.86; N, 3.81. Found: C, 58.80; H, 7.02; N, 3.83. $[\alpha]_D^{23}$ +10.1° (c=0.268, MeOH). The regenerated free base had $[\alpha]_D^{23}$ −15.3° (c=0.64, MeOH). The mother liquor from the tartrate salt of (−)-XVIb (all combined) was evaporated, diluted with H_2O, basified with NH_4OH and extracted with ether. Evaporation of the dried extracts gave 6.5 g of (+) enriched base. To a solution of this oil in EtOH (15 ml) was added a solution of 4.25 g of (−)-malic acid in EtOH (25 ml). After standing overnight, crystalline precipitate was collected and recrystallized from EtOH to give 5.2 g (74.5%) of the malate salt of (+)-XVIb, mp 132—133°. *Anal.* Calcd. for $C_{18}H_{25}O_6N$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.11; H, 7.08; N, 3.85. The regenerated free base had $[\alpha]_D^{23}$ +15.3° (c=0.69, MeOH). The combined filtrate (EtOH) from the malate salts of (+)-XVIb was evaporated and the free base was recovered in the usual manner. Treatment of this (−) enriched base again with *d*-tartaric acid in the same manner as that described above afforded an additional amount (2.45 g, total yield 76%) of the tartrate salt of (−)-XVIb, mp 190—192°.

(+)-1-(3-Methoxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octane (+)-(XVIIb) Picrate——This compound was obtained from (−)-XVIb in 89% yield by the method described for its racemate. Needles from EtOH, mp 140—142°. *Anal.* Calcd. for $C_{21}H_{24}O_8N_4$: C, 54.78; H, 5.25; N, 12.17. Found: C, 54.94; H, 5.34; N, 12.02. $[\alpha]_D^{23}$ +67.5° (c=0.4, $CHCl_3$).

(−)-1-(3-Methoxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octane (−)-(XVIIb) Picrate——The procedure was made as mentioned above. Yield was 89.5% from (+)-XVIb. Needles from EtOH, mp 140—142°. *Anal.* Calcd. for $C_{21}H_{24}O_8N_4$: C, 54.78; H, 5.25; N, 12.17. Found: C, 54.75; H, 5.33; N, 11.98. $[\alpha]_D^{23}$ −68.4° (c=0.39, $CHCl_3$).

(+)-1-(3-Hydroxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octane (+)-(XVIIc)——O-Demethylation of (+)-XVIIb by the method described previously for its racemate gave (+)-XVIIc in 93% yield. Pillars from AcOEt, mp 150—152°. *Anal.* Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.21; H, 8.82; N, 6.27. $[\alpha]_D^{23}$ +19.5° (c=0.37, 1N HCl).

(−)-1-(3-Hydroxyphenyl)-6-methyl-6-azabicyclo[3,2,1]octane (−)-(XVIIc)——The procedure was made as described above. Yield was 92% from (−)-XVIIb. Pillars from AcOEt, mp 150—152°. *Anal.* Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.30; H, 8.36; N, 6.36. $[\alpha]_D^{23}$ −19.0° (c=0.4, 1N HCl).

Optical Resolution of 6,7-*endo*-Dimethyl-1-(3-methoxyphenyl)-6-azabicyclo[3,2,1]octane (XXb)——A mixture of 17.4 g of (+)-3-bromo-8-camphorsulfonic acid NH_4 salt, 13 g of (±)-XXb and 120 ml of H_2O 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°. *Anal.* Calcd. for $C_{26}H_{38}O_5NBrS$: C, 56.11; H, 6.88; N, 2.52. Found: C, 56.04; H, 6.79; N, 2.65. $[\alpha]_D^{20}$ +61.7° (c=1.26, MeOH). The free base regenerated from the sulfonate salt had $[\alpha]_D^{20}$ −10.4° (c=1.13, MeOH). Methobromide was crystallized from iso-PrOH as flakes, mp 251—252° (decomp.). *Anal.* Calcd. for $C_{17}H_{26}ONBr$: C, 60.00; H, 7.70; N, 4.12. Found: C, 59.94, H, 7.72; N, 4.06. $[\alpha]_D^{20}$ +23.9° (c=0.67, MeOH). The mother liquor (EtOH) from the sulfonate salt was evaporated, diluted with H_2O, basified with NH_4OH and extracted with benzene. Evaporation of the dried extracts gave 7.43 g of the (+) enriched base. This oil, 10.8 g of (−)-dibenzoyltartaric acid and 52 ml of EtOH were boiled to solution, concentrated to *ca.* 25 ml and allowed to stand overnight. The precipitate was filtered and recrystallized from MeOH giving 15.1 g (94.5%) of the dibenzoyltartrate salt of (+)-XXb, mp 144—146° (decomp.). *Anal.* Calcd. for $C_{34}H_{37}O_9N$: C, 67.65; H, 6.18; N, 2.32. Found: C, 67.52; H, 6.19; N, 2.42. $[\alpha]_D^{27}$ −76.85° (c=1.22, MeOH). The free base regenerated from this salt had $[\alpha]_D^{20}$ +10.5° (c=1.11, MeOH). The methobromide was crystallized from iso-PrOH, mp 251—253° (decomp.). *Anal.* Calcd. for $C_{17}H_{26}ONBr$: C, 60.00; H, 7.70; N, 4.12. Found: C, 60.11; H, 7.79; N, 4.09. $[\alpha]_D^{20}$ −23.6° (c=0.41, MeOH).

(+)-6,7-*endo*-Dimethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (+)-(XXc) Hydrobromide——O-Demethylation of (−)-XXb was carried out as described for its racemate giving 95% yield of (+)-XXc·HBr. Plates from EtOH, mp 245—248°. *Anal.* Calcd. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.74; H, 6.79; N, 4.61. $[\alpha]_D^{25}$ +8.7° (c=0.61, H_2O). The free base was crystallized from AcOEt as needles, mp 152—153°. *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.93; H, 9.22; N, 6.16. The hydrochloride was recrystallized from EtOH and had mp 264—267°. *Anal.* Calcd. for $C_{15}H_{22}ONCl$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.30; H, 8.26; N, 5.32. $[\alpha]_D^{23}$ +12.9° (c=2.07, MeOH).

(−)-6,7-*endo*-Dimethyl-1-(3-hydroxyphenyl)-6-azabicyclo[3,2,1]octane (−)-(XXc) Hydrobromide——Plates from EtOH, mp 245—248°. $[\alpha]_D^{25}$ −8.9° (c=0.52, H_2O). Yield was 93% from (+)-XXb. *Anal.* Calcd. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.49. Found: C, 57.54; H, 6.90; N, 4.64.

Acknowledgement——The authors express their gratitude to Dr. Everette L. May, National Institutes of Health, for his aid in determination of the physical dependence capacity in monkeys. They also thank Director Michio Yamazaki of this laboratory, Professor Emeritus S. Sugasawa of the Tokyo University, Drs. N. Sugimoto and H. Kugita for their interest and encouragement. Thanks are extended to the staff of the analytical section presided over by Dr. K. Kotera for elemental and spectral analyses.