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Azabicycloalkanes as Analgetics. V.[1] 4-Phenyl-2-azabicyclo[2,2,2]octanes

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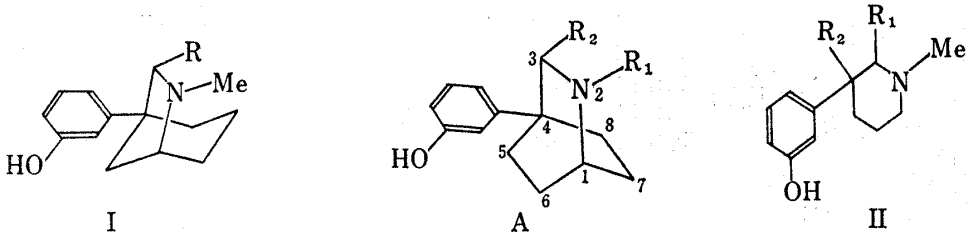
As part of a study on the steric aspects of the partial agonist activity of phenylazabicycloalkane analgetics, the title compound (A), a skeletal isomer of the known partial agonist (I), was synthesized. The keto ester (IV) was converted to the lactam (VIII) either by hydrogenation of the oxime (V) or by reductive amination. VIII gave A bearing various substituents. Alternatively, A was obtained from the unsaturated amine (XVI) *via* the bridged aziridine (XVII). Generally, no discernible analgetic activity was observed for A. However, the two N-methyl compounds (Xf and XIc) exhibited narcotic antagonist activity on the order of I and pentazocine. The simple N-methyl-3-phenylpiperidines (II), a prototype of both I and A, also showed comparable antagonist activity. These results support the idea that the N-methylphenethylamine fragment in I is responsible for its antagonist activity. Replacement of the N-methyl group of Xf by an allyl and a propyl group conferred increased antagonist activity. This shift of the potency parallels that observed for II previously.

Keywords——azabicycloalkane; piperidine; analgetic activity; narcotic antagonist; partial agonist; structure-activity relationship; cyclization; synthesis; bridged aziridine

The previous papers[3,4] of this series disclosed the synthesis of the 1-phenyl-6-azabicyclo-[3,2,1]octane derivative (I), a good mixture of analgetic and narcotic antagonist components (partial agonist), with a low grade of physical dependence capacity.[5] In continuation of our study[3] on the steric aspects of the partial agonist activity of phenylazabicycloalkane analgetics, we have synthesized 4-phenyl-2-azabicyclo[2,2,2]octanes(A). Structure (A) is a skeletal isomer of I with respect to a position of nitrogen ring closure and can be regarded as a conformationally constrained analog of the 3-phenylpiperidine analgetics (II).[6]



I A II

Chart 1

1) Part IV: M. Takeda, G. Tsukamoto, K. Noguchi, S. Saito, and S. Nurimoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 2312 (1976).
2) Location: *2-2-50, Kawagishi, Toda, Saitama, Japan.*
3) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, and S. Saito, *Chem. Pharm. Bull.* (Tokyo), **24**, 1002 (1976).
4) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, Y. Yamawaki, and S. Saito, *Chem. Pharm. Bull.* (Tokyo), **24**, 1514 (1976).
5) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, Y. Yamawaki, S. Saito, K. Aoe, T. Date, S. Nurimoto, and G. Hayashi, *J. Med. Chem.*, **20**, 221 (1977).
6) *a*) H. Kugita and T. Oine, *Chem. Pharm. Bull.* (Tokyo), **11**, 253 (1963); *b*) H. Kugita, T. Oine, H. Inoue, and G. Hayashi, *J. Med. Chem.*, **8**, 313 (1965).

Cyclization of *cis*-4-amino-1-phenylcyclohexanecarboxylic acid (VI, $R_1=R_2=R_3=H$) to the bicyclic lactam (VIIIa) described by Koelsch[7] appeared to be the most feasible entry to structure (A). Methyl 4-hydroxyimino-1-phenylcyclohexanecarboxylate (Va), prepared from the ketal acid (IIIa)[3] by the usual method, was hydrogenated over Raney Nickel to afford a mixture of the *cis* and *trans* amino esters (VI and VII, $R_1=R_3=H$, $R_2=Me$). Treatment of this mixture with sodium hydroxide in aqueous ethanol at room temperature gave the lactam (VIIIa) in 42.4% yield (from Va). The non-cyclizing *trans* amino acid (IXa) was recovered in 32.3% yield. This procedure was more satisfactory than the use of phosphorus oxychloride in the cyclization step described by Koelsh.[7] Similarly, the 3-methoxyphenyl lactam (VIIIb) resulted from Vb. Methylation of VIIIa,b gave the N-methyl lactam (VIIIc,d), respectively.

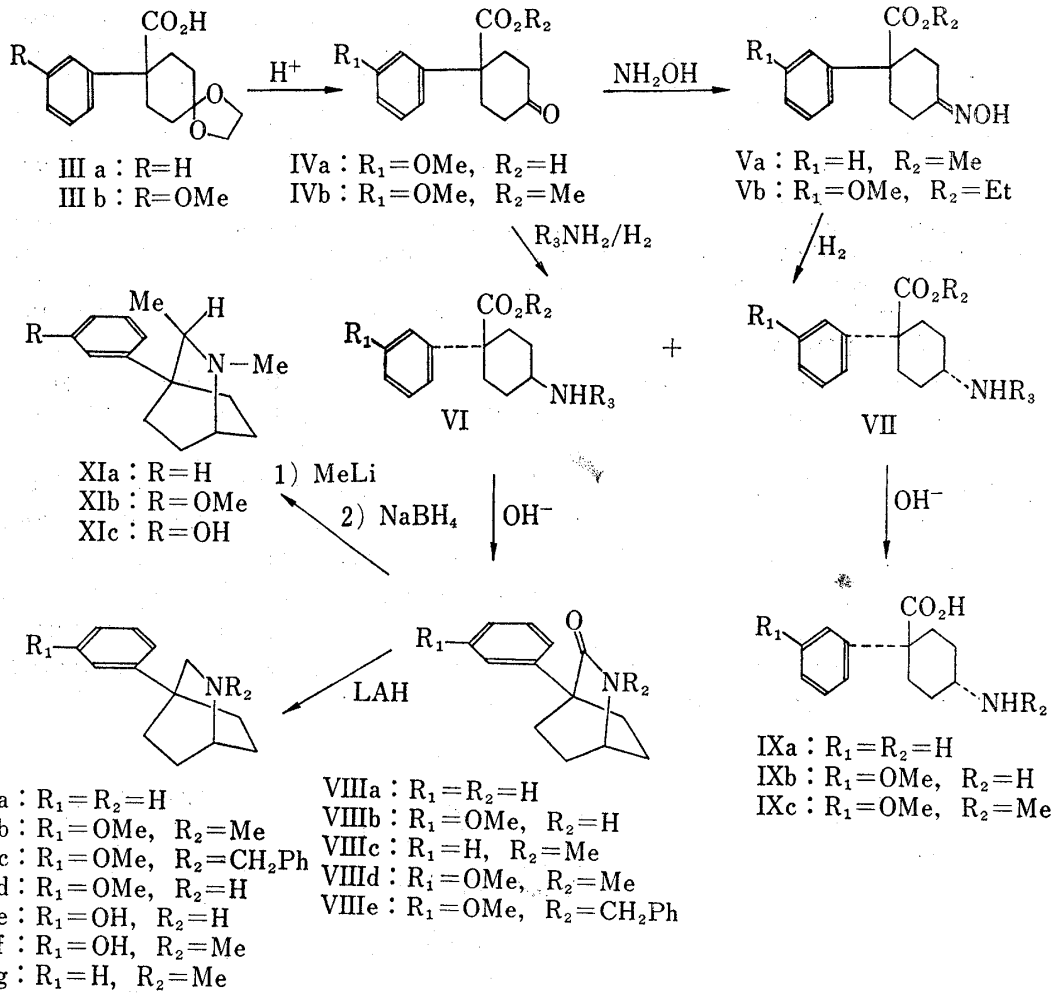


Chart 2

Alternatively, reductive amination of the keto ester (IVb) with methylamine in the presence of PtO_2 afforded the *cis* and *trans* amino esters (VI and VII, $R_1=OMe$, $R_2=R_3=Me$) in a ratio of 3:1 [gas chromatography (GC)], respectively. On prolonged heating with sodium methoxide in methanol, this mixture gave the lactam (VIIId) and the *trans* amino acid (IXc) in yields of 50.2 and 15.9%, respectively. Similar reductive amination of IVb with benzylamine gave the *cis* and *trans* benzylamino esters (VI and VII, $R_1=OMe$, $R_2=Me$, $R_3=CH_2Ph$) in 58 and 26% yields. The *cis* ester cyclized to the N-benzyl lactam (VIIIe) in 90% yield on treatment with sodium methoxide. Lithium aluminum hydride (LAH) reduction

7) C.F. Koelsch, *J. Org. Chem.*, **25**, 164 (1960).

of the bicyclic lactams (VIII) gave the corresponding amines (X). Hydrogenolysis of the N-benzylamine (Xc) over colloidal palladium gave the secondary amine (Xd). The 2,3-dimethyl derivatives (XIa, b) resulted from the N-methyllactams (VIIIc,d) by treatment with methyllithium followed by sodium borohydride reduction.[3]

Nagata, *et al.* reported[8] that 4-aminomethylcyclohexenes can be oxidized to bridged aziridines and that the latter affords 2-azabicyclo[2,2,2]octane system either by catalytic hydrogenation or nucleophilic cleavage. Application of this method to the 4-phenyl analog was examined as an alternate route to structure A. 4-Aminomethyl-4-(3-methoxyphenyl) cyclohexene (XVI) was prepared by the sequence outlined in Chart 3. Thus, the unsaturated nitrile (XIV) was obtained from 4-hydroxy-1-(3-methoxyphenyl)-cyclohexanecarbonitrile (XII)[9] in 37.2% yield *via* the tosylate (XIII). Alternatively and more conveniently, treatment of the tosylhydrazone of the cyano ketone (XV)[9] with sodium methoxide in boiling diglyme[10] affforded XIV in 59% yield. XIV was reduced with LAH to the unsaturated amine (XVI) in 70% yield. Oxidation of XVI was carried out in benzene with excess lead tetraacetate in the presence of potassium carbonate. Isolation of the bridged aziridine (XVII) was difficult due to its instability and the failure to prepare its crystalline salt.

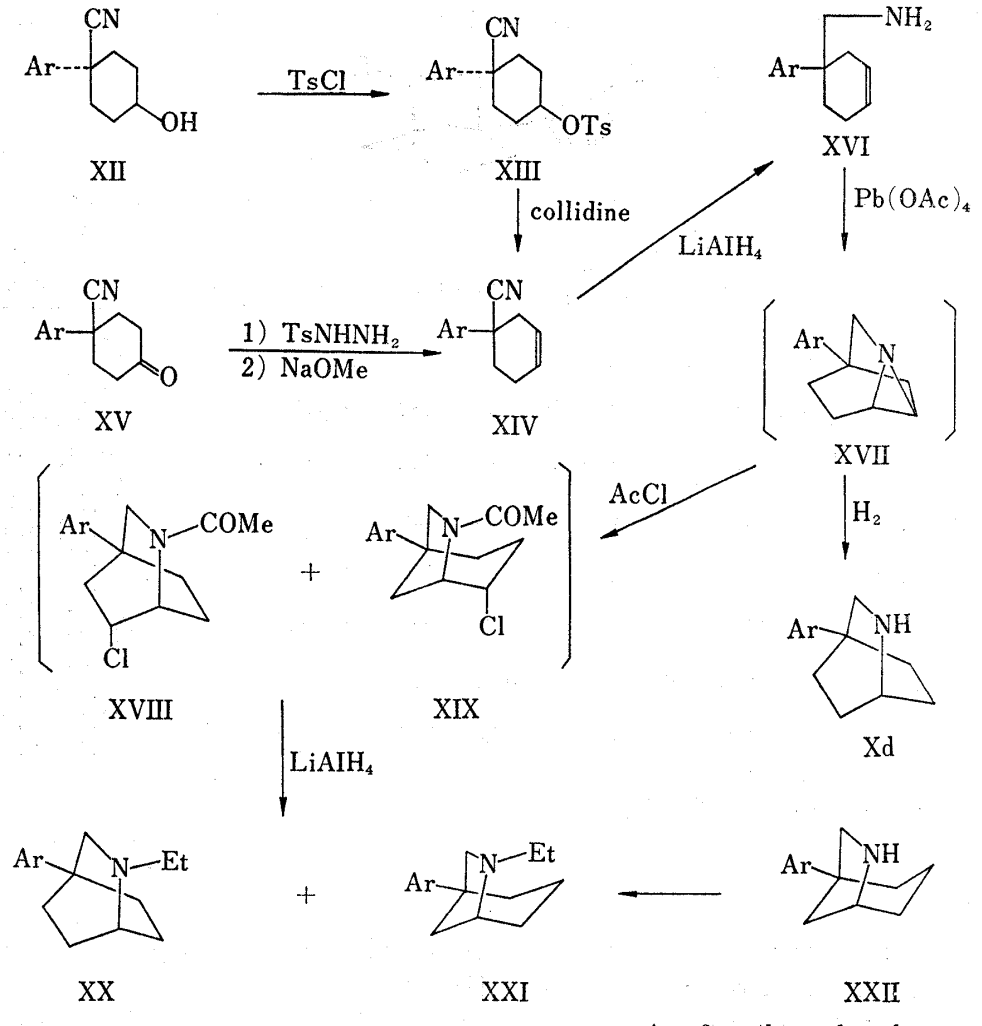


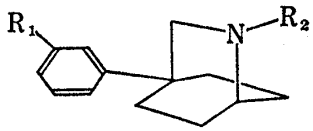
Chart 3

8) *a*) W. Nagata, S. Hirai, K. Kawata, and T. Aoki, *J. Am. Chem. Soc.*, **89**, 5045 (1967); *b*) W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *J. Am. Chem. Soc.*, **89**, 5046 (1967).
9) H. Shirai, T. Yashiro, and T. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1564 (1969).
10) L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959).

Immediate hydrogenation of the crude oxidation product in acetic acid in the presence of colloidal palladium, however, gave the secondary amine (Xd) in 32% yield as a sole product, identical with the sample previously obtained from Xc. Exclusive formation of the 2-azabicyclo[2,2,2]octane system from the aziridine (XVII) by catalytic hydrogenation is consistent with the reported observation.[8b] Reaction of crude XVII with acetyl chloride in ether followed by LAH reduction gave a mixture of the N-ethyl compounds (XX and XXI) in a ratio of 4:1 (GC), respectively. XX and XXI were separated by thin-layer chromatography (TLC) on silica gel in yields of 32.6 and 9.2% and identified with the authentic samples prepared from Xd and XXII[3], respectively. Preferential formation of the 2-azabicyclo[2,2,2]octane system (XX) appears to parallel with the reported observation,[8b] but the ratio of the intermediates (XVIII and XIX) was not ascertained because of a failure in separation either by TLC or GC.[11]

Finally, all the methoxy compounds were converted to the respective phenols with boiling 47% HBr. From the secondary amines (Xa,e), various N-substituted derivatives (XXIII) listed in Table I were prepared by the usual method for pharmacological evaluation.

Table I. N-Substituted Derivatives of 4-phenyl-2- azabicyclo[2,2,2]octane (XXIII)



Compd	R_1	R_2	Salt	Crystn Solvent[a]	mp, (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
a	H	$CH_2CH=CH_2$	HCl	A + B	181—182	$C_{16}H_{22}NCl$	72.84 (72.98)	8.41 (8.50)	5.31 (5.29)
b	H	CH_2-	HCl	B + C	208—212	$C_{17}H_{24}NCl$	73.49 (73.49)	8.71 (8.69)	5.04 (5.06)
c	HO	C_3H_7	HCl	C + D	226—228	$C_{16}H_{24}ONCl$	68.19 (68.14)	8.58 (8.69)	4.97 (4.92)
d	HO	C_5H_{11}	HCl	B + C	135—140	$C_{18}H_{28}ONCl$	69.77 (69.74)	9.11 (8.93)	4.52 (4.55)
e	HO	$CH_2CH=CH_2$	HCl	C + D	220—224	$C_{16}H_{22}ONCl$	68.68 (68.44)	7.93 (8.04)	5.00 (4.92)
f	HO	$(CH_2)_2Ph$	free base	D	163.5—165	$C_{21}H_{25}ON$	82.04 (81.69)	8.20 (8.16)	4.56 (4.46)
g	HO	CH_2-	HCl	C + D	203—206	$C_{17}H_{24}ONCl \cdot 1/2\ H_2O$	67.40 (67.11)	8.27 (8.07)	4.63 (4.45)

a) A, MeOH; B, Et_2O; C, EtOH; D, *iso*-PrOH

Pharmacology

In general, no discernible analgesia (mouse writhing method[12]) was observed for the 4-phenyl-2-azabicyclo[2,2,2]octanes (A) (Table II). In this series only the N-allyl compound (XXIIIe) was marginally active. Thus, the transposition of nitrogen ring closure from C_3 (I) to C_4 (A) in a phenylcyclohexane ring resulted in a marked fall in the agonist (analgetic) activity.

11) Since the skeletal rearrangement of XVIII and/or XIX during LAH reduction may occur, the ratio of XX and XXI does not represent that of XVIII and XIX.

12) S. Nurimoto, S. Suzuki, G. Hayashi, and M. Takeda, *Japan J. Pharmacol.*, **24**, 461 (1974).

Table II. Analgetic and Antagonistic Activities of 4-Phenyl-2-azabicyclo[2,2,2]octanes

Compound	Analgetic activity ED_{50}, mg/kg, *s.c.*[a]	Antagonistic activity AD_{50}, mg/kg, *i.v.*[b]
Xf[c]	—[d]	2.2
XIc[c]	—[d]	0.65
XXIIIc[e]	—[d]	0.62
XXIIIe[e]	10.1(6.8—15.0)[f]	0.25
XXIIIf[g]	—[d,h]	
I(R=H)[c,i]	12.3(8.2—18.6)	3.1
I(R=Me)[c,i]	4.5(3.4—6.0)	2.6
II(R_1=H, R_2=Me)[c,j]		1.1
II(R_1=R_2=Me)[c,k]		0.2
Pentazocine[e]	4.5(3.2—6.4)	1.5
Nalorphine[e]	4.5(1.8—11.1)	0.16

a) The inhibition of AcOH-induced writhing response was determined in groups of six mice by the method described previously[12] and the ED_{50} for analgetic activity was calculated according to the Weil's method.[13]
b) The inhibition of morphine-induced respiratory depression determined in groups of three rabbits. The AD_{50} was defined as the dose which produced a 50% antagonism of morphine-induced depression in the respiratory frequency per min. For methodology, see reference 12.
c) Hydrobromide.
d) No effect with doses up to 10 mg/kg.
e) Hydrochloride.
f) Confidence interval (95%).
g) Free base in 0.3% CMC suspension.
h) Tested *p.o.*
i) See reference 3.
j) See reference 6a.
k) See reference 6b.

On the contrary, the two N-methyl compounds (Xf and XIc) exhibit narcotic antagonist activity (inhibition of morphine-induced respiratory depression in rabbit[12]) comparable to pentazocine and I.[5] This provides an additional evidence for our earlier proposal[1,5] that the N-methylphenethylamine fragment incorporated in I is responsible for its antagonist activity. In parallel to our previous experience with I,[5] the 2,3-dimethyl derivative (XIc) is a more potent antagonist than its 3-unsubstituted relative (Xf).

Further evidence for the importance of a phenethylamine moiety is provided by the antagonist activity (Table II) of the simple 3-phenylpiperidines (II) prepared in our earlier work,[6] a prototype of both I and A. Again in this series the 1,2,3-trimethyl derivative is more potent than its 2-unsubstituted relative.

Replacement of the N-methyl group of Xf by a propyl and an allyl group (XXIIIc,e) confers increased antagonist activity. XXIIIe is about half as active as nalorphine. This shift of the potency appears to be quite similar to that produced by the identical change in the N-substituent of II as described in our previous paper.[14]

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. Nuclear magnetic resonance (NMR) spectra were determined on a Model JEOL ME-60 instrument in $CDCl_3$ (containing tetramethylsilane at δ 0.00 as an internal standard), unless otherwise specified. Coupling constants (J) are given in Hz and the following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Mass spectra were measured on a Hitachi RMS-4 mass spectrometer. Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrophotometer. Gas chromatography (GC) was obtained on a

13) C.S. Weil, *Biometrics*, **8**, 249 (1952).
14) S. Nurimoto and G. Hayashi, *Japan J. Pharmacol.*, **23**, 742 (1973).

Shimadzu GC-4BPF instrument using a 3% OV-17 column. The organic solutions were dried over Na_2SO_4 and all evaporations were carried out *in vacuo*.

Methyl 4-Hydroxyimino-1-phenylcyclohexanecarboxylate (Va)——A solution of IIIa[3] (36.1 g) in MeOH (200 ml) was saturated with dry HCl and the mixture was refluxed for 4 hr. MeOH was removed and the residue was taken in ether and washed with 5% $NaHCO_3$ and H_2O, successively. Evaporation of the dried ether left 36.4 g of an oil which was dissolved in AcOH (400 ml) and refluxed for 4 hr to complete ketal hydrolysis. AcOH was removed and the residue was taken in benzene and washed with H_2O. Evaporation of the dried solvent gave 31.2 g of the oily keto ester. A mixture of this oil, $NH_2OH \cdot HCl$ (12.3 g), $NaOAc \cdot 3H_2O$ (24 g), H_2O (100 ml) and EtOH (250 ml) was kept at room temperature for 48 hr. Usual work-up gave an oil which was treated with a small amount of ether and filtered to give 15.1 g of Va. Recrystallization from AcOEt–hexane gave needles, mp 132—134°. IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH), 1725 (C=O), 1675 (C=N). NMR: 1.7—3.3 (8H, m, CH_2), 3.63 (3H, s, OCH_3), 7.30 (5H, s, Ph). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.62; H, 7.01; N, 5.52. An additional amount (3.5 g) of Va (total yield; 54.6% from IIIa) was obtained from the mother liquor (ether) by chromatography on Al_2O_3.

1-(3-Methoxyphenyl)-4-oxocyclohexanecarboxylic Acid (IVa)——A mixture of IIIb[3] (17.1 g) and AcOH (170 ml) was refluxed for 21 hr. The usual work-up and recrystallization from benzene gave 11.1 g (76.5%) of IVa, mp 104—105.5°. IR ν_{max}^{Nujol} cm^{-1}: 1690, 1720 (both C=O). NMR: 2.1—2.9 (8H, m, CH_2), 3.8 (3H, s, OCH_3), 6.7—7.4 (4H, m, aromatic protons). Mass Spectrum *m/e*: 248 (M^+). *Anal.* Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.59; H, 6.51.

Methyl 1-(3-Methoxyphenyl)-4-oxocyclohexanecarboxylate (IVb)——To a solution of IVa (38.3 g), NaOH (6.9 g), EtOH (155 ml), and hexamethylphosphoramide (155 ml) was added MeI (43.6 g). The mixture was heated at 40—50° for 1.5 hr and poured into ice-H_2O. The resultant oil was extracted with ether and washed with H_2O. Evaporation of the dried ether left a crystalline residue which was recrystallized from iso-Pr_2O to give 34.2 g (84.5%) of IVb, mp 81.5—82.5°. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR: 1.9—2.9 (8H, m, CH_2), 3.70 (3H, s, CO_2CH_3), 3.79 (3H, s, $ArOCH_3$), 6.7—7.5 (4H, m, aromatic protons). Mass Spectrum *m/e*: 262 (M^+). *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.87; H, 6.99.

4-Phenyl-2-azabicyclo[2,2,2]octan-3-one (VIIIa)——A mixture of Va (10.3 g), Raney Ni (W-7, 10 ml), 28% NH_4OH (30 ml) and EtOH (400 ml) was hydrogenated in an autoclave at 40—50° with an initial pressure of 55 kg/cm^2 for 4 hr and filtered. Evaporation of the solvent left 10.3 g of a mixture of the amino ester as an oil. A mixture of this oil, 5% NaOH (100 ml), and EtOH (100 ml) was stirred at room temperature for 5 days, diluted with H_2O (500 ml), and extracted with $CHCl_3$. Evaporation of the dried extracts left an oil which was treated with a small amount of ether and filtered to give 3.55 g (42.4%) of VIIIa, mp 257—260° (lit.[7] mp 263—264°). The aqueous layer was acidified with conc. HCl and evaporated. The residue was extracted with hot $CHCl_3$–EtOH (5: 1) and filtered. Evaporation of the filtrate and recrystallization of the residue from EtOH–ether gave 3.44 g (32.3%) of IXa·HCl, mp 294—297° (lit.[7] mp>285°).

4-(3-Methoxyphenyl)-2-azabicyclo[2,2,2]octan-3-one (VIIIb)——A mixture of IVa (30.2 g), EtOH (250 ml) and conc. H_2SO_4 (10 ml) was refluxed for 5 hr and evaporated. The residue was taken in ether and washed with H_2O, 5% $NaHCO_3$, and H_2O, successively. Evaporation of the dried solvent left 23.3 g of the oily keto ester. A mixture of this oil, hydroxylamine hydrochloride (6.96 g), $NaOAc \cdot 3H_2O$ (13.7 g), H_2O (50 ml), and EtOH (150 ml) was stirred at room temperature overnight and concentrated. The residue was diluted with H_2O and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ left an oil which was dissolved in $CHCl_3$ and chromatographed over Al_2O_3. Evaporation of the eluate with $CHCl_3$–MeOH (95: 5) gave 9 g of the oxime ester (Vb) as an oil. IR ν_{max}^{liquid} cm^{-1}: 3400 (OH), 1720 (C=O), 1660 (C=N). NMR: 1.20 (3H, t, $J=7$, C–CH_3), 1.6—3.3 (8H, m, CH_2), 3.76 (3H, s, OCH_3), 4.14 (2H, q, $J=7$, OCH_2), 6.7—7.4 (4H, m, aromatic protons). Mass Spectrum *m/e*: 291 (M^+). A mixture of this oil, Raney Ni (13 ml), 28% NH_4OH (27 ml) and EtOH (360 ml) was hydrogenated in the same manner as described above. The usual work-up and cyclization in the same manner as described above gave 1.5 g of VIIIb, mp 215—216°. Plates from benzene–AcOEt. IR ν_{max}^{Nujol} cm^{-1}: 3170 (NH), 1660 (C=O). NMR: 1.7—2.4 (8H, m, CH_2), 3.75 (1H, broad peak, CH), 3.81 (3H, s, OCH_3), 6.7—7.3 (4H, m, aromatic protons). 7.75 (1H, broad peak, NH, disappeared on addition of D_2O). Mass Spectrum *m/e*: 231 (M^+). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.56; H, 7.32; N, 5.81.

From the acidic portion, 1.4 g of IXb·HCl was obtained. Small prisms from EtOH–ether, mp 263—265°. Mass Spectrum *m/e*: 249 (M^+). *Anal.* Calcd. for $C_{14}H_{20}O_3NCl$: C, 58.84; H, 7.05; N, 4.90. Found: C, 58.52; H, 6.89; N, 4.56.

2-Methyl-4-phenyl-2-azabicyclo[2,2,2]octan-3-one (VIIIc)——To 15 ml of dimethyl sulfoxide (DMSO) was added NaH (0.13 g, 69% oil dispersion) under N_2. The mixture was stirred at 50—60° for 1 hr. After cooling, VIIIa (0.6 g) was added at 10—15° and the mixture was stirred at room temperature for 1.5 hr. CH_3I (0.7 g) was then added and stirring was continued for 1.5 hr. The mixture was poured into ice-H_2O and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ and recrystallization of the residue from AcOEt gave 0.54 g (84.4%) of VIIIc, mp 157—159°. *Anal.* Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.92; H, 8.02; N, 6.48.

4-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[2,2,2]octan-3-one (VIIId)——a. N-Methylation of VIIIb: The procedure was made as described above. Yield was 81.6%. Needles from iso-PrOH–iso-Pr_2O, mp

143—146°. NMR: 1.7—2.3 (8H, m, CH_2), 3.02 (3H, s, NCH_3), 3.5—3.7 (1H, broad peak, CH), 3.80 (3H, s, OCH_3), 6.65—7.35 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.31; H, 7.69; N, 5.59.

b. Reductive Amination of IVb: A mixture of IVb (0.33 g), PtO_2 (0.04 g), 40% aqueous $MeNH_2$ (0.25 ml) and MeOH (20 ml) was hydrogenated in a Paar apparatus with an initial pressure of 2 kg/cm² at room temperature for 3 hr. The catalyst was filtered and the filtrate was concentrated. The residue was taken in ether and extracted with 10% HCl. The acidic layer was basified with NH_4OH and extracted with ether. Evaporation of the dried ether gave 0.3 g of a mixture of the amino ester VI and VII (R_1=OMe, R_2=R_3=Me). GC analysis showed a presence of two isomers (3: 1). NMR spectrum of this mixture exhibited the two sets of signals for the N-Me (2.42 and 2.36) and the CO_2Me group (3.63 and 3.58) in 3: 1 ratio, respectively. A mixture of this oil (0.3 g) and methanolic NaOMe solution (prepared from 0.03 g of Na and 1 ml of MeOH) was refluxed for 20 hr. The mixture was evaporated, diluted with H_2O, and extracted with AcOEt. The organic solution was washed with H_2O, 10% HCl, and H_2O, successively. Evaporation of the dried solvent and recrystallization of the residue from iso-PrOH–iso-Pr_2O gave 0.155 g (50.2%) of VIIId, mp 143—145.5°, identical with the sample previously obtained in all respects (mixed mp and IR).

The alkaline solution was acidified with 10% HCl and evaporated. The residue was extracted with hot $CHCl_3$–MeOH (9: 1) and filtered. Evaporation of the filtrate gave, after recrystallization from EtOH–ether, 0.06 g (15.9%) of the *trans* amino acid (IXc) hydrochloride, mp 265—268° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 2460 (N^+H_2), 1720 (C=O). NMR (D_2O): 2.65 (3H, s, NCH_3), 3.85 (3H, s, OCH_3). *Anal.* Calcd. for $C_{15}H_{22}O_3NCl$: C, 60.09; H, 7.40; N, 4.67. Found: C, 59.73; H, 7.28; N, 4.56.

2-Benzyl-4-(3-methoxyphenyl)-2-azabicyclo[2,2,2]octan-3-one (VIIIe)——A mixture of IVb (2 g), benzylamine (0.9 g), PtO_2 (0.1 g) and MeOH (30 ml) was hydrogenated in the same manner as described for VIIId. Treatment of the oily product with 10% HCl caused precipitation of a crystalline solid which was collected and washed with acetone to give 1.72 g (58%) of the hydrochloride of the *cis* benzylamino ester (VI, R_1=OMe, R_2=Me, R_3=$CH_2C_6H_5$), mp 223—225.5°. The regenerated free base was recrystallized from iso-Pr_2O and had mp 81—83°. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O). NMR: 3.65 (3H, s, CO_2CH_3), 3.78 (3H, s, $ArOCH_3$), 3.82 (2H, s, $CH_2C_6H_5$), 6.7—7.5 (4H, m, aromatic protons), 7.30 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{22}H_{27}O_3N$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.49; H, 7.80; N, 3.99.

Evaporation of the filtrate (acetone) and recrystallization of the residue from $CHCl_3$–ether gave 0.78 g (26%) of the hydrochloride of the *trans* benzylamino ester (VII, R_1=OMe, R_2=Me, R_3=$CH_2C_6H_5$), mp 174.5—176°. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O). NMR: 3.60 (3H, s, CO_2CH_3), 3.80 (3H, s, $ArOCH_3$), 3.97 (2H, s, $CH_2C_6H_5$). Mass Spectrum *m/e*: 353 (M^+). *Anal.* Calcd. for $C_{22}H_{28}O_3NCl \cdot 1/2H_2O$: C, 66.24; H, 7.33; N, 3.51. Found: C, 66.49; H, 7.22; N, 3.40.

A mixture of the *cis* benzylamino ester (0.38 g) and methanolic solution of NaOMe (prepared from 0.075 g of Na and 7.5 ml of MeOH) was refluxed for 47 hr. The usual work-up gave 0.31 g (90.2%) of VIIIe, mp 68—71°. Plates from ether. IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O). NMR: 3.6 (1H, broad peak, C_1–H), 3.83 (3H, s, OCH_3), 4.61 (2H, s, $CH_2C_6H_5$). Mass Spectrum *m/e*: 321 (M^+). *Anal.* Calcd. for $C_{21}H_{23}O_2N$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.35; H, 7.24; N, 4.43.

4-Phenyl-2-azabicyclo[2,2,2]octane (Xa) Hydrochloride——A mixture of VIIIa (3.3 g), $LiAlH_4$ (LAH) (3.3 g) and tetrahydrofuran (THF) (140 ml) was refluxed for 5 hr. The mixture was decomposed by addition of H_2O and filtered. Evaporation of the filtrate and conversion of the residue to the HCl salt gave 2.8 g (75.3%) of Xa·HCl. Recrystallization from EtOH–ether gave needles, mp 186—188°. NMR (D_2O): 1.96 (8H, s, CH_2), 3.34 (2H, s, NCH_2), 3.58 (1H, m, CH), 7.32 (5H, s, C_6H_5). Mass Spectrum *m/e*: 187 (M^+). *Anal.* Calcd. for $C_{13}H_{18}NCl$: C, 69.79; H, 8.11; N, 6.26. Found: C, 69.48; H, 8.37; N, 6.27.

4-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[2,2,2]octane (Xb) Hydrobromide——This compound was obtained from VIIId by the same method as described above. Plates from EtOH, mp 205—209°. *Anal.* Calcd. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.48. Found: C, 57.41; H, 7.10; N, 4.50.

2-Benzyl-4-(3-methoxyphenyl)-2-azabicyclo[2,2,2]octane (Xc) Picrate——The procedure was made as described above. Yield was 94.8% from VIIIe. The picrate was crystallized from acetone–MeOH and had mp 173—176.5°. *Anal.* Calcd. for $C_{21}H_{25}ON \cdot C_6H_3O_7N_3$: C, 60.44; H, 5.26; N, 10.44. Found: C, 60.18; H, 5.42; N, 10.19.

4-(3-Methoxyphenyl)-2-azabicyclo[2,2,2]octane (Xd) Hydrobromide——A mixture of Xc (8.2 g), colloidal palladium (1.15 g), and AcOH (190 ml) was hydrogenated in a Paar apparatus with an initial pressure of 2 kg/cm² at room temperature for 4.5 hr. The usual work-up and conversion of the oily product to the HBr salt gave 6.52 g (82%) of Xd·HBr. Needles from EtOH–ether, mp 137.5—138.5°. *Anal.* Calcd. for $C_{14}H_{20}ONBr$: C, 56.38; H, 6.76; N, 4.69. Found: C, 56.53; H, 6.83; N, 4.60.

2-Methyl-4-phenyl-2-azabicyclo[2,2,2]octane (Xg) Oxalate——A mixture of Xa (0.47 g), 37% formalin (0.2 g) and EtOH (20 ml) was heated at 80° for 45 min. After cooling, 10% Pd–C (0.15 g) was added to the solution and the mixture was shaken in H_2 atomosphere at room temperature for 5 hr. The usual work-up and conversion of the oily product to the oxalate gave 0.67 g (92%) of Xg·oxalate. Needles from MeOH–ether, mp 136—138°. Mass Spectrum *m/e*: 201 (M^+, base peak), 173, 172. *Anal.* Calcd. for $C_{14}H_{19}N \cdot 3/2\ C_2H_2O_4$: C, 60.70; H, 6.60; O, 28.54; N, 4.16. Found: C, 60.99; H, 6.75; O, 28.71; N, 4.18.

In the same manner as described above, Xd was N-methylated to give Xb·HBr, in 70% yield, identical with the sample previously obtained from VIIId.

2,3-Dimethyl-4-phenyl-2-azabicyclo[2,2,2]octane (XIa) Hydrochloride——To an ethereal solution of MeLi (prepared from 0.11 g of Li, 1 g of CH_3I, and 7 ml of ether) was added a solution of VIIIc (0.5 g) in dry benzene (20 ml) at 0—5° (N_2, stirring). The mixture was refluxed for 1 hr, decomposed by addition of H_2O at −10—0°, and extracted with ether. Evaporation of the dried extracts left an oil (0.5 g). To a solution of this oil in EtOH (20 ml) was added $NaBH_4$ (0.2 g) at 5—10° and the mixture was stirred at room temperature overnight. The mixture was concentrated, diluted with H_2O, and extracted with ether. Evaporation of the dried ether and conversion of the residue to the HCl salt gave, after recrystallization from EtOH–ether 0.48 g (79%) of XIa·HCl, mp 184—186°. IR ν_{max}^{Nujol} cm^{-1}: 3430, 1640 (hydrate H_2O). *Anal.* Calcd. for $C_{15}H_{22}NCl \cdot 1/2H_2O$: C, 69.07; H, 8.89; N, 5.37. Found: C, 68.86; H, 8.89; N, 5.37.

4-(3-Methoxyphenyl)-2,3-dimethyl-2-azabicyclo[2,2,2]octane (XIb) Hydrochloride——This compound was obtained from VIIId in 50% yield by the same method as described above. The hydrochloride was recrystallized from acetone–ether and had mp 213—215°. NMR (regenerated free base): 0.70 (3H, d, $J=9$, C–CH_3), 2.44 (3H, s, NCH_3), 3.79 (3H, s, OCH_3). Mass Spectrum *m/e*: 245 (M^+), 230 (base peak). *Anal.* Calcd. for $C_{16}H_{24}ONCl \cdot H_2O$: C, 64.31; H, 8.43; N, 4.69. Found: C, 64.69; H, 8.44; N, 4.70.

1-(3-Methoxyphenyl)-cyclohex-3-enecarbonitrile (XIV)——a. From XII: A mixture of XII[9] (5 g), TsCl (4.95 g), and pyridine (25 ml) was kept in a refrigerator overnight. The mixture was poured into ice-H_2O and extracted with ether. The ether was washed with 10% HCl, H_2O, 5% $NaHCO_3$, and H_2O, successively, dried, and evaporated. The residue was treated with a small amount of ether and filtered giving 4.9 g of the tosylate (XIII), mp 96—98°. A mixture of XIII (4.9 g) and 20 ml of 2,4,6-collidine was refluxed for 8 hr under N_2 and evaporated. The residue was taken in benzene and washed with 10% HCl, H_2O, 5% $NaHCO_3$, and H_2O, successively. Evaporation of the dried benzene left 2.3 g of an oil, which was chromatographed over silica gel (100 g). The eluate with benzene was concentrated and distilled to give 1.7 g (37.2% from XII) of XIV, as an oil, bp 138° (3 mmHg). IR ν_{max}^{liquid} cm^{-1}: 2230 (CN), 1650 (C=C). NMR: 2.1—2.7 (6H, m, CH_2), 3.85 (3H, s, OCH_3), 5.85 (2H, broad peak, CH=CH). 6.8—7.5 (4H, m, aromatic protons). Mass Spectrum *m/e*: 213 (M^+), 159 (base peak). *Anal.* Calcd. for $C_{14}H_{15}ON$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.58; H, 6.99; N, 6.51.

b. From XV: A mixture of XV[9] (2 g), $TsNHNH_2$ (1.8 g) and EtOH (10 ml) was refluxed for 18 hr and evaporated. The residue was treated with iso-Pr_2O and filtered giving 3.39 g of the tosylhydrazone as an amorphous powder. To a stirred suspension of NaOMe (prepared from 0.24 g of Na) in 30 ml of diglyme was added a solution of the above tosylhydrazone (3.39 g) in 15 ml of diglyme at room temperature. The mixture was refluxed for 2 hr and evaporated. The residue was diluted with H_2O and extracted with ether. The ether was washed with H_2O, 10% HCl, H_2O, 5% $NaHCO_3$, and H_2O, successively, dried, and evaporated. Distillation of the residue gave 1.1 g (59.1%) of XIV, bp 135—138° (3 mmHg). This proved to be identical with the sample previously obtained from XII in all respects (IR and NMR).

4-Aminomethyl-4-(3-methoxyphenyl)-cyclohexene (XVI) Hydrochloride——A mixture of XIV (17 g), LAH (5.44 g), and THF (1000 ml) was refluxed for 6 hr. The mixture was decomposed by addition of H_2O (15 ml) and filtered. Evaporation of the filtrate and conversion of the residue to the HCl salt gave 14.36 g (70.9%) of XVI·HCl, mp 130—134°. Recrystallization from EtOH–ether gave needles, mp 131—134°. NMR: 3.82 (3H, s, OCH_3), 5.7 (2H, broad peak, CH=CH). 6.7—7.5 (4H, m, aromatic protons). 7.9 (3H, broad peak, $\overset{+}{N}H_3$). *Anal.* Calcd. for $C_{14}H_{20}ONCl$: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.24; H, 7.96; N, 5.47.

4-(3-Methoxyphenyl)-2-azabicyclo[2,2,2]octane (Xd) Hydrobromide *via* the Aziridine (XVII)——To a stirred solution of XVI (0.5 g) in benzene (20 ml) was added 0.55 g of K_2CO_3 and 1.25 g of $Pb(OAc)_4$ at 30—35°. After being stirred at the same temperature for 1 hr, to the mixture was added the second portion of K_2CO_3 (0.55 g) and $Pb(OAc)_4$ (1.25 g). Addition of K_2CO_3 and $Pb(OAc)_4$ was repeated in the same manner four times. After cooling, the mixture was decomposed by addition of cold sat.K_2CO_3 (4 ml) and filtered. The filtrate was extracted with ice-cold tartaric acid solution. The aqueous layer was basified with K_2CO_3 (ice-cooling) and extracted with benzene. Evaporation of the dried benzene at room temperature left 0.27 g of crude XVII as an oil. A mixture of this oil, colloidal palladium (0.1 g), and 10 ml of AcOH was hydrogenated in a Paar apparatus with an initial pressure of 2 kg/cm^2 at room temperature for 0.5 hr. The usual work-up gave 0.18 g of an oil which was converted into the HBr salt and recrystallized from EtOH–ether giving 0.19 g (32.1% from XVI) of Xd·HBr, mp 135—137°, identical with the sample previously obtained from Xc in all respects (IR, mixed mp, and TLC).

2-Ethyl-4-(3-methoxyphenyl)-2-azabicyclo[2,2,2]octane (XX) Hydrobromide and 6-Ethyl-1-(3-methoxyphenyl)-6-azabicyclo[3,2,1]octane (XXI) Picrate *via* the Aziridine (XVII)——To an ethereal solution (15 ml) of the aziridine (XVII, prepared from 1 g of XVI·HCl in the same manner as that described above) was added AcCl (1 ml) at −5° and the mixture was stirred at the same temperature for 1 hr and then at room temperature for 2 hr. The mixture was decomposed by addition of H_2O and the organic layer was separated and washed with 5% K_2CO_3. Evaporation of the dried solvent left 0.7 g of an oil. A mixture of this oil and LAH (0.68 g) in THF (30 ml) was refluxed for 2 hr and worked up in the usual manner to give 0.5 g of an oil.

GC analysis showed two peaks (4: 1). The mixture was separated by preparative TLC [silica gel, developed by $CHCl_3$–MeOH (9: 1) containing little NH_4OH]. From the lower fraction, 0.31 g (31.6%) of 2-ethyl-4-(3-methoxyphenyl)-2-azabicyclo[2,2,2]octane (XX) was obtained. Conversion to the HBr salt and recrystallization from EtOH–ether gave XX·HBr, mp 150—151°. NMR: 1.56 (3H, t, J=7, C–CH_3), 3.25 (2H, q, J=7, $\underline{CH_2}$–Me), 3.5 (1H, broad peak, CH). Mass Spectrum *m/e*: 245 (M^+). *Anal.* Calcd. for $C_{16}H_{24}ONBr$: C, 58.88; H, 7.42; N, 4.29. Found: C, 58.63; H, 7.34; N, 4.45. From the upper fraction of the TLC, 0.09 g (9.2%) of 6-ethyl-1-(3-methoxyphenyl)-6-azabicyclo[3,2,1]octane (XXI) was isolated as an oil. NMR: 1.11 (3H, t, J=7, C–CH_3), 2.67 (2H, q, J=7, $\underline{CH_2}$–Me), 3.3 (1H, m, CH). The picrate was recrystallized from MeOH and had mp 142—145°. *Anal.* Calcd. for $C_{16}H_{23}ON \cdot C_6H_3O_7N_3$: C, 55.68; H, 5.48; N, 11.79. Found: C, 55.79; H, 5.63; N, 11.90. Both XX and XXI proved to be identical with the authentic samples prepared by N-ethylation of Xd and XXII[3] in the following manner, respectively.

A mixture of Xd (regenerated from 0.15 g of the HBr salt), EtI (0.085 g), $NaHCO_3$ (0.1 g), and dimethylform amide (DMF) (5 ml) was heated at 70° for 3.5 hr. The usual work-up and conversion of the product to the HBr salt gave 0.055 g of XX·HBr, mp 151—152° (from EtOH–ether).

XXII[3] (regenerated from 0.15 g of the oxalate) was N-ethylated with EtI in the same manner as that described above to give 0.06 g of XXI. The picrate had mp 142—145°.

4-(3-Hydroxyphenyl)-2-azabicyclo[2,2,2]octane (Xe) Hydrobromide——A mixture of Xd·HBr (5.8 g) and 47% HBr (60 ml) was refluxed for 1.5 hr and evaporated. The residue was digested with acetone and filtered giving 5.34 g (97%) of Xe·HBr. Plates from iso-PrOH, mp 203—204°. *Anal.* Calcd. for $C_{13}H_{18}ONBr$: C, 54.93; H, 6.38; N, 4.93. Found: C, 54.92; H, 6.54; N, 4.84.

The following phenols were obtained from the corresponding methoxy derivatives in the same manner as described above. 4-(3-Hydroxyphenyl)-2-methyl-2-azabicyclo[2,2,2]octane (Xf)·HBr, mp 213—216°. Plates from iso-PrOH–EtOH. *Anal.* Calcd. for $C_{14}H_{20}ONBr$: C, 56.38; H, 6.76; N, 4.69. Found: C, 56.31; H, 6.82; N, 4.78. 4-(3-Hydroxyphenyl)-2,3-dimethyl-2-azabicyclo[2,2,2]octane (XIc)·HBr, mp 230—232°. Needles from iso-PrOH–ether. *Anal.* Calcd. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.48. Found: C, 57.66; H, 7.15; N, 4.48.

N-Substituted 4-Phenyl-2-azabicyclo[2,2,2]octanes (XXIII)——In a typical procedure, a mixture of Xe (0.3 g), PrI (0.306 g), $NaHCO_3$ (0.3 g), and DMF (10 ml) was heated at 90—110° for 3 hr. The mixture was diluted with H_2O and extracted with AcOEt. Evaporation of the solvent left, after washing with H_2O and drying, an oil. Conversion of this oil to the HCl salt and recrystallization from iso-PrOH–EtOH gave 0.33 g (78.2%) of 4-(3-hydroxyphenyl)-2-propyl-2-azabicyclo[2,2,2]octane (XXIIIc)·HCl, mp 226—228°. Analytical data are given in Table I. N-Substituted 4-phenyl-2-azabicyclo[2,2,2]octanes (XXIII) prepared in essentially the same manner are listed in Table I.

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