Chem. Pharm. Bull. 25(7)1777—1781(1977)

UDC 547.895.04.09 : 615.212.011.5.015.11

Azabicycloalkanes as Analgetics. VII.[1) 1-Phenyl-3-azabicyclo[3.3.1]nonanes

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(Received November 18, 1976)

As part of study on the structure–activity relationships of phenylazabicycloalkane analgetics, the title compound (I) has been synthesized. Structure (I) could be regarded as a piperidine analog of 1-phenyl-6-azabicyclo[3.2.1]octane (II), a known partial agonist, and also as a conformationally constrained analog of the 3-phenyl-piperidine analgetics (XIX). From the keto ester (III), I was obtained by the sequence of reactions outlined in Chart 2. Neither by the AcOH writhing nor by the hot-plate method, I exhibited appreciable analgetic activity. In contrast, the N-methyl compounds (XIV and XV) showed narcotic antagonist activity, with the former being the more active. Replacement of the N-methyl group of XV by a propyl and an allyl group (XVIIIa, d) resulted in an increase in the antagonist activity. Their activity was about one-tenth that of nalorphine.

Keywords——azabicycloalkane; analgetic activity; narcotic antagonist; partial agonist; structure–activity relationship; phenylpiperidine; lactam

In continuation of our study[3)] on the structure–activity relationships of phenylazabicycloalkane analgetics, 1-phenyl-3-azabicyclo[3.3.1]nonane (I) has been synthesized. Structure (I) can be regarded as a homolog of 1-phenyl-6-azabicyclo[3.2.1]octane (II), a good mixture of analgetic and antagonist components (partial agonist),[3,4)] and also as a conformationally constrained analog of the 3-phenylpiperidine analgetics (XIX).[5)]

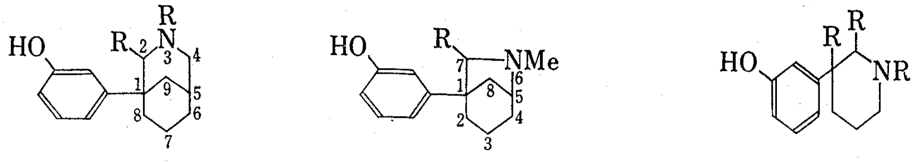

Chart 1

Reaction of methyl 1-(3-methoxyphenyl)-3-oxocyclohexanecarboxylate (III)[6)] with potassium cyanide and hydrochloric acid gave the cyanohydrine (IV) as a mixture of diastereoisomers. Dehydration of IV with thionyl chloride and pyridine gave the unsaturated nitrile (V) as a 2:1 mixture of position isomers of the double bond. Hydrogenation of V over Raney Nickel effected both saturation of the double bond and reduction of the cyano group, giving the bicyclic lactam (VI) in 50% yield (from III). In this reaction, the non-cyclizing *trans*

1) Part VI: K. Noguchi, M. Takeda, and S. Nurimoto, *Chem. Pharm. Bull.* (Tokyo), **25**, 890 (1977).
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5) *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).
6) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, Y. Yamawaki, and S. Saito, *Chem. Pharm. Bull.* (Tokyo), **24**, 1514 (1976).

amino ester and acid (VII and VIII) were also isolated in 6 and 9.8% yields, respectively. VI was methylated to the N-methyllactam (IX). Lithium aluminum hydride (LAH) reduction of the lactams (VI and IX) gave the corresponding amines (X and XI).

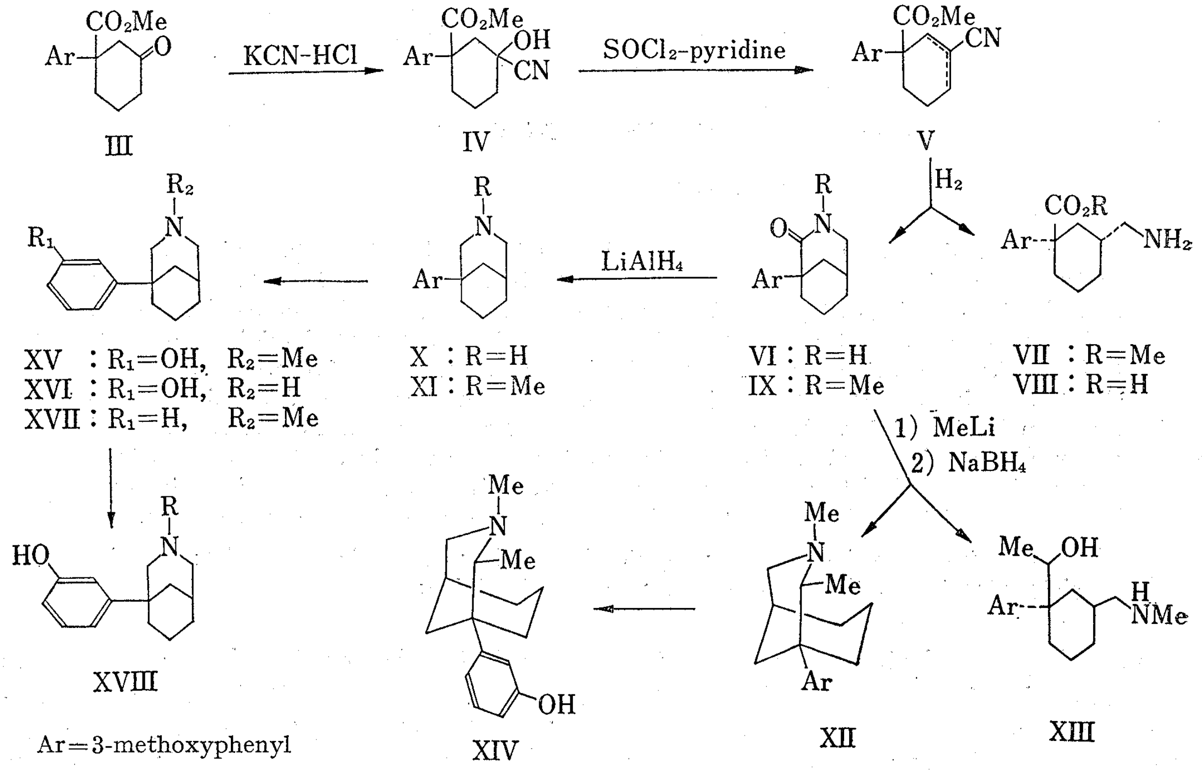

Chart 2

The 2,3-dimethyl compound (XII) was prepared by the method described previously.[3] Methyllithium treatment of the lactam (IX) followed by reduction with sodium borohydride gave XII and the carbinol amine (XIII) in yields of 42 and 12.4%, respectively. *endo* Configuration was tentatively assigned to the 2-methyl group of XII, since an approach of hydride

Table I. N-Substituted 1-(3-Hydroxyphenyl)-3-azabicyclo[3.3.1]nonanes (XVIII)

Compd.	R	Salt	Crystn solvent[a]	mp(°C)	Formula	Analysis(%) Calcd. (Found) C	H	N
a	C_3H_7	HCl	A+B	205—209	$C_{17}H_{26}ClNO$	69.01 (69.05)	8.86 (8.82)	4.73 (4.95)
b	C_5H_{11}	Picrolonate	A	204—206.5[b]	$C_{29}H_{37}N_5O_7$	63.14 (63.07)	6.76 (6.89)	12.70 (12.72)
c	CH_2-cyclopropyl	Picrate	A	169—171	$C_{24}H_{28}N_4O_8$	57.59 (57.59)	5.64 (5.85)	11.20 (11.15)
d	$CH_2CH=CH_2$	HCl	A+B	196—200[b]	$C_{17}H_{24}ClNO$	69.49 (69.64)	8.23 (8.42)	4.76 (4.85)
e	$CH_2CH=CMe_2$	HCl	A+B	215—217[b]	$C_{19}H_{28}ClNO$	70.90 (70.54)	8.77 (8.69)	4.35 (4.50)
f	CH_2CH_2Ph	HCl	A+B	244—247	$C_{22}H_{28}ClNO$	73.83 (73.53)	7.88 (7.94)	3.91 (3.97)

a) A, EtOH; B, ether. *b*) With decomposition.

to the intermediate iminium double bond[7] from the sterically more accessible *exo* side[8] might be expected in this reduction. Formation of a ring fission product similar to XIII was observed also in our previous case.[7]

O-Demethylation of X, XI, and XII gave their respective phenols (XVI, XV, and XIV). Certain N-substituted derivatives (XVIII) listed in Table I were prepared from XVI by the usual method. Removal of the phenolic hydroxy group of XV was effected by the method described by Clauss and Jensen[9] and furnished XVII.

Pharmacology

When tested by the AcOH writhing method,[10] none of the 1-phenyl-3-azabicyclo[3.3.1]-nonanes prepared in the present study exhibited discernible analgesia in doses up to 10 mg/kg *s.c.* in mice. They were inactive also in the hot-plate test[10] in doses up to 20 mg/kg *s.c.* Thus, a methylene insertion between the C_5 and the nitrogen of II led to a marked decrease in the agonist (analgetic) activity. This cannot be attributed simply to their inaccessibility into the central nervous system, because they showed considerable narcotic antagonist activity (inhibition of morphine-induced respiratory depression in rabbit)[10] (Table II).

Table II. Narcotic Antagonist Activity of 1-Phenyl-3-azabicyclo[3.3.1]nonanes

Compound	AD_{50} mg/kg[a]	Compound	AD_{50} mg/kg[a]
XIV[b]	1.7	XVIIId[c]	1.9
XV[b]	(35.6% at 5 mg/kg)	Pentazocine[c]	1.5
XVIIIa[c]	1.8	Nalorphine[c]	0.16

a) Inhibition of morphine-induced respiratory depression. Tested *i.v.* in rabbits. For methodology, see reference 10.
b) Hydrobromide.
c) Hydrochloride.

In fact, in agreement with our earlier proposal,[4,7,11] the N-methyl compounds (XIV and XV) with a N-methylphenethylamine fragment exhibited this property. The 2,3-dimethyl derivative (XIV), equipotent to pentazocine, was a much stronger antagonist than its 2-unsubstituted relative (XV). This parallels our earlier experiences with other bicyclic systems and the simple piperidines (XIX).[4,7,11] Replacement of the N-methyl group of XV by a propyl and an allyl group (XVIIIa, d) resulted in an increase in the antagonist activity. However, their activity is about one-tenth that of nalorphine.

Experimental

Instruments and standard techniques used are the same as that described previously.[6]

1-(3-Methoxyphenyl)-3-azabicyclo[3.3.1]nonan-2-one (VI)——To a stirred mixture of III[6] (27 g), ether (250 ml), KCN (29.1 g), and H_2O (200 ml) was added conc. HCl (32.5 g) during 0.5 hr at 25° and stirring was continued for 4 hr. The organic layer was separated and washed with H_2O. Evaporation of the dried ether left 28.9 g (97%) of the crude cyanohydrine (IV) as a mixture of diastereoisomers. IR ν_{max}^{Liquid} cm^{-1}: 3420 (OH), 2230 (CN), 1720 (CO). MS *m/e*: 289 (M^+). NMR: 3.68 (*ca.* 1H, s, CO_2CH_3), 3.71 (*ca.* 2H, s, CO_2CH_3), 3.81 (3H, s, $ArOCH_3$), 3.95 (1H, broad peak, OH, disappeared on addition of D_2O).

7) M. Takeda, G. Tsukamoto, K. Noguchi, S. Saito, and S. Nurimoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 2312 (1976).
8) Approach of reagents to the double bond of bicyclo[3.3.1]nonan-2-ene system has been reported to occur from the *exo* side. See K.H. Baggaley, J.R. Dixon, J.M. Evans, and S.H. Graham, *Tetrahedron*, 23, 299 (1967).
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To a solution of crude IV (28.9 g) in pyridine (250 ml) was added 28 g of $SOCl_2$ under ice-cooling and stirring was continued for 1 hr at room temperature. The mixture was diluted with H_2O (500 ml), acidified with conc. HCl, and extracted with benzene. The benzene was washed with H_2O, dried, and evaporated giving 25.4 g (93%) of the unsaturated nitrile (V) as a mixture of position isomers of the double bond. GC analysis showed two peaks in a ratio of 2: 1. IR ν_{max}^{Liquid} cm^{-1}: 2220 (CN), 1730 (CO). NMR: 1.6—3.0 (6H, m, CH_2), 3.68 (*ca.* 2H, s, CO_2CH_3), 3.73 (*ca.* 1H, s, CO_2CH_3), 3.82 (3H, s, $ArOCH_3$), 6.7—7.3 (5H, m, aromatic and olefinic protons). MS *m/e*: 271 (M^+), 212 (base peak).

A mixture of V (24.8 g), Raney Ni (W-7, 25 ml), 28% NH_4OH (80 ml), and dioxane (200 ml) was hydrogenated in an autoclave at 150—160° with an initial pressure of 100 kg/cm^2 for 24 hr. The catalyst was removed and the filtrate was concentrated. The residue was dissolved in AcOEt and washed with 10% HCl, and H_2O. Evaporation of the dried AcOEt left a crystalline residue which was collected and washed with ether giving 11.17 g (50%) of the lactam (VI). Needles from isopropyl ether, mp 142—143°. IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1660 (CO). NMR: 1.35—3.50 (10H, m, CH_2), *ca.* 3.4 (1H, m, CH), 3.80 (3H, s, OCH_3), 6.7—7.45 (4H, m, aromatic protons). MS *m/e*: 245 (M^+). *Anal.* Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.36; H, 7.90; N, 5.74.

The HCl washings were basified with 28% NH_4OH and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ left 4.7 g of an oil. Conversion of this oil to the HBr and recrystallization from iso-PrOH–ether gave 1.98 g (6%) of the *trans* amino ester (VII)·HBr, mp 187—189°. NMR (free base): 1.29 (2H, s, NH_2), 3.64 (3H, s, CO_2CH_3), 3.78 (3H, s, $ArOCH_3$), 6.7—7.4 (4H, m, aromatic protons). MS *m/e*: 277 (M^+). *Anal.* Calcd. for $C_{16}H_{24}BrNO_3$: C, 53.64; H, 6.75; N, 3.91. Found: C, 53.47; H, 6.69; N, 3.99.

The basic layer (aqueous NH_4OH) was concentrated to dryness and the crystalline residue was washed with a small amount of H_2O and filtered giving 2.15 g (9.8%) of the *trans* amino acid (VIII), mp 312—315° (dec.). The analytical sample was reprecipitated from its 50% AcOH solution with conc. NH_4OH and had mp 315—317° (dec.). MS *m/e*: 263 (M^+). *Anal.* Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.01; H, 8.03; N, 5.18.

1-(3-Methoxyphenyl)-3-methyl-3-azabicyclo[3.3.1]nonan-2-one (IX)——To 20 ml of dimethyl sulfoxide was added 0.203 g of NaH (69% oil dispersion, washed with hexane) and the mixture was heated at 60—70° for 30 min (N_2, stirring). VI (1.3 g) was added to the mixture under ice-cooling and stirring was continued for 30 min at 25°. To the mixture was then added 1.35 g of MeI and the mixture was stirred for 3 hr at 25°. The mixture was poured into ice-H_2O and extracted with ether. Evaporation of the dried ether gave, after recrystallization from isopropyl ether–hexane, 0.97 g (70.6%) of IX, mp 71.5—72.5°. IR $\nu_{max}^{Nujol}$$cm^{-1}$: 1630 (CO). NMR: 3.01 (3H, s, NCH_3), 3.81 (3H, s, OCH_3). MS *m/e*: 259 (M^+), 187 (base peak). *Anal.* Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.92; H, 8.22; N, 5.45.

1-(3-Methoxyphenyl)-3-azabicyclo[3.3.1]nonane (X) Hydrochloride——A mixture of VI (8.9 g), $LiAlH_4$ (4 g), and tetrahydrofuran (THF) (170 ml) was refluxed for 5 hr. The usual work-up and conversion of the product to the HCl salt gave 8.1 g (83.5%) of X·HCl. Needles from EtOH–ether, mp 217—219°. *Anal.* Calcd. for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.23; H, 8.25; N, 5.19.

1-(3-Methoxyphenyl)-3-methyl-3-azabicyclo[3.3.1]nonane (XI) Hydrochloride——$LiAlH_4$ reduction of IX in the same manner as described above gave XI in 83.1% yield. The hydrochloride crystallized from EtOH–ether in prisms had mp 192—193°. *Anal.* Calcd. for $C_{16}H_{24}ClNO$: C, 68.19; H, 8.58; N, 4.97. Found: C, 68.48; H, 8.32; N, 5.24. XI also resulted from X in 70% yield by N-methylation (HCHO–$NaBH_4$).

1-(3-Methoxyphenyl)-2,3-dimethyl-3-azabicyclo[3.3.1]nonane (XII) Hydrochloride——To an ethereal solution of MeLi (prepared from 0.21 g of Li, 1.92 g of MeI, and 20 ml of ether) was added a solution of IX (1.17 g) in benzene (10 ml) at −5—0°. The mixture was stirred at 25° for 1 hr and decomposed by addition of H_2O below 5°. The organic layer was separated, dried, and evaporated giving 1.21 g of an oil. To a solution of this oil in EtOH (20 ml) was added $NaBH_4$ (0.4 g) below 10° and stirring was continued at 25° overnight. The mixture was evaporated, diluted with H_2O, and extracted with benzene. Evaporation of the dried extracts left 0.97 g of an oil which was converted to the HCl and recrystallized from acetone giving 0.42 g of XII·HCl. Needles from iso-PrOH, mp 250—254° (dec.). NMR (free base): 0.78 (3H, d, J=6.2, C–CH_3), 2.15 (3H, s, NCH_3), 3.81 (3H, s, $ArOCH_3$). MS *m/e*: 259 (M^+). *Anal.* Calcd. for $C_{17}H_{26}ClNO$: C, 69.01; H, 8.86; N, 4.73. Found: C, 69.05; H, 8.82; N, 4.95. From the mother liquor of XII·HCl (iso-PrOH), a free base was recovered in the usual manner and purified by preparative TLC [silica gel, developed by $CHCl_3$–MeOH (9: 1)]. From the upper fraction, additional XII convertible to 0.14 g of the HCl (total yield, 42%) was obtained. From the lower fraction, 1-(3-methoxyphenyl)-α-methyl-3-methylaminomethylcyclohexanemethanol (XIII) was isolated as an oil and converted to 0.205 g (12.4%) of its oxalate, mp 164.5—166° (dec.). IR ν_{max}^{Liquid} cm^{-1}: 3300 (OH). NMR (free base): 0.96 (3H, d, J=6.1, C–CH_3), 1.74 (2H, broad s, NH and OH, disappeared on addition of D_2O), 2.41 (3H, s, NCH_3), 3.65 (1H, q, J=6.1, $\underline{C}$H–Me), 3.87 (3H, s, $ArOCH_3$). MS *m/e*: 277 (M^+), 259 ($M-H_2O$). *Anal.* Calcd. for $C_{19}H_{29}NO_6$: C, 62.10; H, 7.96; N, 3.81. Found: C, 61.78; H, 8.04; N, 4.11.

1-(3-Hydroxyphenyl)-3-methyl-3-azabicyclo[3.3.1]nonane (XV) Hydrobromide——A mixture of XI·HCl (0.6 g) and 5 ml of 47% HBr was refluxed for 1 hr and evaporated. The residue was digested with acetone and filtered giving 0.595 g (89.5%) of XV·HBr. Needles from EtOH–ether, mp 191—193°. *Anal.* Calcd. for $C_{15}H_{22}BrNO$: C, 57.69; H, 7.10; N, 4.48. Found: C, 57.59; H, 7.22; N, 4.52.

1-(3-Hydroxyphenyl)-3-azabicyclo[3.3.1]nonane (XVI) Hydrobromide——O-Demethylation of X by the same method described above gave XVI·HBr in 98.2% yield. Pillars from EtOH–ether, mp 252—255°. *Anal.* Calcd. for $C_{14}H_{20}BrNO$: C, 56.38; H, 6.76; N, 4.69. Found: C, 56.11; H, 6.82; N, 4.59.

1-(3-Hydroxyphenyl)-2,3-dimethyl-3-azabicyclo[3.3.1]nonane (XIV) Hydrobromide——XIV·HBr was obtained by O-demethylation of XII in 90.6% yield. Needles from EtOH–ether, mp 242—246°. *Anal.* Calcd. for $C_{16}H_{24}BrNO$: C, 58.90; H, 7.41; N, 4.29. Found: C, 58.65; H, 7.72; N, 4.26.

3-Methyl-1-phenyl-3-azabicyclo[3.3.1]nonane (XVII) Hydrochloride——A mixture of XV (regenerated from 1.03 g of the HBr), methanesulfonyl chloride (1 ml), and pyridine (5 ml) was stirred at 25° overnight and evaporated. The residue was diluted with H_2O, basified with NH_4OH, and extracted with benzene. The extracts were washed with H_2O, dried, and evaporated. The residue was dissolved in ether, filtered from insoluble material and the filtrate was evaporated giving 1 g of the O-mesylate of XV as an oil. A mixture of this oil, Et_3N (0.326 g), colloidal palladium (0.35 g), and 20 ml of MeOH was hydrogenated[9] in a Parr apparatus with an initial pressure of 2 kg/cm^2 at 25°. The usual work-up and conversion of the oily product to the HCl salt gave 0.54 g (65% from XV) of XVII·HCl. Plates from EtOH–ether, mp 256.5—257.5°. *Anal.* Calcd. for $C_{15}H_{22}ClN$: C, 71.55; H, 8.81; N, 5.56. Found: C, 71.47; H, 8.79; N, 5.56.

N-Substituted 1-(3-Hydroxyphenyl)-3-azabicyclo[3.3.1]nonanes (XVIII)——In a typical procedure, a mixture of 0.35 g of XVI, 0.33 g of propyl iodide, 0.33 g of $NaHCO_3$, and 10 ml of N,N-dimethylformamide (DMF) was heated at 90—100° for 4.5 hr. The mixture was evaporated, diluted with H_2O, and extracted with ether. Evaporation of the dried extracts left an oil which was converted to 0.38 g (80%) of the hydrochloride of 1-(3-hydroxyphenyl)-3-propyl-3-azabicyclo[3.3.1]nonane (XVIIIa), mp 205—209°. Analytical data are given in Table I. N-Substituted 1-(3-hydroxyphenyl)-3-azabicyclo[3.3.1]nonanes listed in Table I were prepared in essentially the same manner as described above.

Acknowledgement The authors thank Professor H. Tomisawa of the Tohoku College of Pharmacy, Director M. Yamazaki of this laboratory, Dr. S. Sugasawa, Professor Emeritus of the Tokyo University, Drs. N. Sugimoto, H. Kugita, and S. Saito for their encouragement and helpful discussions throughout this series of work. Thanks are also extended to the staff of the analytical section of this laboratory presided over by Dr. K. Kotera for elemental and spectral analyses.