Azabicycloalkanes as Analgetics. VII.¹⁾

1-Phenyl-3-azabicyclo[3.3.1]nonanes

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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 study³⁾ 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).
- 2) Location: 2-2-50, Kawagishi, Toda, Saitama; a) To whom inquiries should be addressed.
- 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, S. Saito, K. Aoe, T. Date, S. Nurimoto, and G. Hayashi, *J. Med. Chem.*, **20**, 221 (1977).
- 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).

to the intermediate iminium double bond⁷⁾ from the sterically more accessible *exo* side⁸⁾ 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 Jensen⁹⁾ 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 test¹⁰⁾ in doses up to 20 mg/kg s.c. Thus, a methylene insertion between the C₅ 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	XVIIIId ^{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 III⁶⁾ (27 g), ether (250 ml), KCN (29.1 g), and H₂O (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 H₂O. Evaporation of the dried ether left 28.9 g (97%) of the crude cyanohydrine (IV) as a mixture of diastereoisomers. IR $\nu_{\text{max}}^{\text{liquid}}$ cm⁻¹: 3420 (OH), 2230 (CN), 1720 (CO). MS *m/e*: 289 (M⁺). NMR: 3.68 (*ca.* 1H, s, CO₂CH₃), 3.71 (*ca.* 2H, s, CO₂CH₃), 3.81 (3H, s, ArOCH₃), 3.95 (1H, broad peak, OH, disappeared on addition of D₂O).

- 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. Baggeley, J.R. Dixon, J.M. Evans, and S.H. Graham, *Tetrahedron*, **23**, 299 (1967).
- 9) K. Clauss and H. Jensen, *Angew. Chem. Intern. Ed. Engl.*, **12**, 918 (1973).
- 10) S. Nurimoto, S. Suzuki, G. Hayashi, and M. Takeda, *Japan J. Pharmacol.*, **24**, 461 (1974).
- 11) M. Takeda, M. Kawamori, H. Inoue, K. Noguchi, and S. Nurimoto, *Chem. Pharm. Bull.* (Tokyo), **25**, 775 (1977).

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 $\nu_{\text{max}}^{\text{liquid}} \text{ cm}^{-1}$: 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 $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 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 $\text{C}_{15}\text{H}_{19}\text{NO}_2$: 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 $\text{C}_{16}\text{H}_{24}\text{BrNO}_3$: 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 $\text{C}_{15}\text{H}_{21}\text{NO}_3$: 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 $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 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 $\text{C}_{16}\text{H}_{21}\text{NO}_2$: 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 $\text{C}_{15}\text{H}_{22}\text{ClNO}$: 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 $\text{C}_{16}\text{H}_{24}\text{ClNO}$: 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, $J=6.2$, $\text{C}-\text{CH}_3$), 2.15 (3H, s, NCH_3), 3.81 (3H, s, ArOCH_3). MS m/e : 259 (M^+). Anal. Calcd. for $\text{C}_{17}\text{H}_{26}\text{ClNO}$: 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 $\nu_{\text{max}}^{\text{Liquid}} \text{ cm}^{-1}$: 3300 (OH). NMR (free base): 0.96 (3H, d, $J=6.1$, $\text{C}-\text{CH}_3$), 1.74 (2H, broad s, NH and OH, disappeared on addition of D_2O), 2.41 (3H, s, NCH_3), 3.65 (1H, q, $J=6.1$, $\text{CH}-\text{Me}$), 3.87 (3H, s, ArOCH_3). MS m/e : 277 (M^+), 259 ($\text{M}-\text{H}_2\text{O}$). Anal. Calcd. for $\text{C}_{19}\text{H}_{29}\text{NO}_6$: 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 $\text{C}_{15}\text{H}_{22}\text{BrNO}$: 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 hydrogenated⁹⁾ in a Parr apparatus with an initial pressure of 2 kg/cm² 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.

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