[Chem. Pharm. Bull. 24(10)2312—2316(1976)]

UDC 547.892.04.09 : 615.31.015.11

Azabicycloalkanes as Analgetics. IV.[1] 4-Phenyl-2-azabicyclo[2,2,1]heptanes

Mikio Takeda,[2a] Goro Tsukamoto, Katsuyuki Noguchi, Seiichi Saito and Seiichi Nurimoto[2]

Research Laboratories, Tanabe Seiyaku Co., Ltd.[2]

(Received November 22, 1975)

As part of studies on the structure–activity relationships of azabicycloalkane antagonist-analgetics, the title compound (II), a five membered alicyclic analog of I (a good mixture of analgetic and antagonist properties), was synthesized. The phenols (XII and XIII) with a bridged 3-phenylpyrrolidine moiety similar to that of I were found to be analgetically inactive. Thus, a shape of the alicyclic ring may also play an important role on the analgetic effectiveness of these derivatives. Interestingly, however, XII and XIII displayed apparent properties of narcotic antagonism on the order of I and pentazocine, the result suggesting that the structural requisite for the antagonist activity in these derivatives, differing from those for analgesia, may be a N-methylphenylethanamine chain.

The preceding paper of this series[3,4] described the synthesis of 1-phenyl-6-azabicyclo-[3,2,1]octane derivative (I), a good mixture of analgetic and narcotic antagonist activities with a low grade of physical dependence capacity. In continuation of our research designed to examine structure–analgetic activity relationships of azabicycloalkanes,[3] we have synthesized 4-phenyl-2-azabicyclo[2,2,1]heptanes (II). Structure II has a bridged 3-phenylpyrrolidine moiety similar to that of I with a minor change in the size of the alicyclic ring from six to five.

As outlined in Chart 2, synthesis of II was carried out essentially in the same manner as that described for I previously.[4] Thus, heating of 3-cyano-3-(3-methoxyphenyl)cyclopentan-1-one (III)[5] in methanolic hydrogen chloride gave the keto ester (IV) in 71% yield. Platinum-catalyzed hydrogenation of IV in the presence of aqueous methylamine followed by heating the reduction product afforded the bicyclic lactam (V) together with the non-cyclizing *trans*-amino ester (VI) in yields of 61 and 36.4%, respectively. V was reduced with lithium aluminum hydride (LAH) to the amine (VII). Treatment of the lactam (V) with methyllithium (MeLi) followed by reduction with sodium borohydride gave a single epimer of the 2,3-dimethyl derivative (X) in 74% yield and a small amount of the diastereoisomeric mixture of the carbinol amine (XI).

Since the reduction of enamines with $NaBH_4$ has been believed to proceed *via* the imminium form,[6] the approach of hydride in this reduction would occur from the sterically more accessible *exo* side of the structure A.[7] From this consideration, one is led to tentatively assign the 3-*endo*-methyl structure to X in parallel with our previous experience in the 6-

1) Part III: 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.*, "in press."
2) Location: *2–2–50, Kawagishi, Toda, Saitama, Japan*; *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, and S. Saito, *Chem. Pharm. Bull.* (Tokyo), **24**, 1514 (1976).
5) H. Shirai, T. Yashiro, and T. Kuwayama, *Yakugaku Zasshi*, **93**, 1371 (1973).
6) R.E. Lyle and P.S. Anderson, "Advances in Heterocyclic Chemistry," Vol. 6, ed. by A.R. Katritzky and A. J. Boulton, Academic Press, New York and London, 1966, p. 45.
7) Norbornene has been reported to yield very great predominance (99%) of *exo* norborneol on the hydroboration-oxidation reaction: H.C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544, (1961).

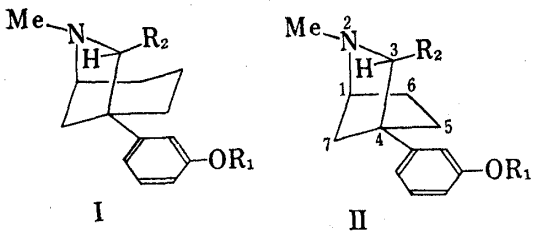

Chart 1

azabicyclo[3,2,1]octane system.[3] The carbinol amine (XI) obtained in 5.5% yield[8] as a mixture of diastereoisomers might arise from the amino ketone (IX) formed by hydrolysis of the intermediate enamine. In agreement with this assumption, infrared (IR) spectrum of the crude product obtained from the MeLi treatment of V showed bands at 1700 (C=O) and 1640 cm^{-1} (C=C–N), respectively. Because no formation of a carbinol amine was observed in the same reaction of 6-azabicylco[3,2,1]octane series.[3,4] above result might be due to the highly strained structure of the 2-azabicyclo[2,2,1]heptane system. O-Demethylation of VII and X with 47% HBr gave the corresponding phenols (XII and XIII), respectively.

All 4-phenyl-2-azabicyclo[2,2,1]-heptane derivatives obtained in the present study generally exhibited a characteristic pair of peaks at *m/e* (M−28) and (M−29) in their mass spectra. Formation of these ions is apparently associated with a loss of the ethano bridge of the molecule as depicted in the following manner (Chart 3). As an evidence of the path a, metastable ion at *m/e* 163 (calculated M* 162.9) was observed in the spectrum of VII.

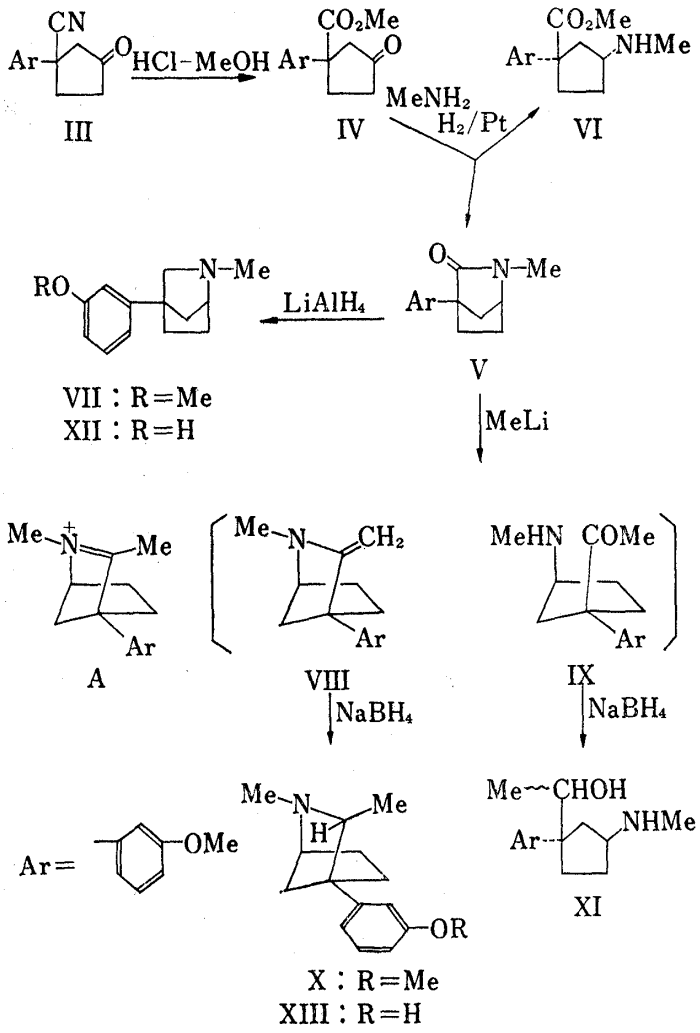

Chart 2

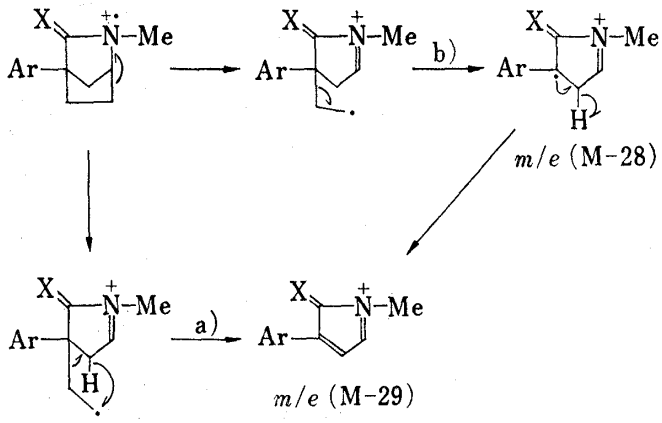

Chart 3

Pharmacology

In Table I are given analgetic activities (mouse writhing method[9]),

8) The yield was increased to 14.5% with decrease of the yield of X when the reaction mixture was decomposed with H_2O at elevated temperature. See Experimental section.

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

narcotic antagonist activities (antagonism of morphine-induced respiratory depression in rabbit[9]), and maximum tolerant doses (24 hr) of the 4-phenyl-2-azabicyclo[2,2,1]heptane derivatives. Comparative data for morphine, meperidine, and pentazocine are also presented. Rather weak analgetic activities (about one third that of meperidine) were observed only for the methoxy derivatives (VII and X). Thus, the phenols (XII and XIII) with the same relative orientation of nitrogen and a benzene ring as I were found to be analgetically inactive. In our previous paper,[1] we stressed that a presence of properly situated phenylpropanamine chain is an important structural requirement for the azabicycloalkane analgetics. The present finding, however, suggests that a shape of the alicyclic ring also plays an important role for the analgetic effectiveness of these derivatives.[10]

TABLE I. Analgetic and Antagonist Activities of 4-Phenyl-2-azabicyclo[2,2,1]heptane Derivatives

Compound	Toxicity MTD. mg/kg[a]	Analgetic activity ED_{50}, mg/kg[b]	Antagonist activity AD_{50}, mg/kg[c]
VII[d]	30	15.0(10.6—21.3)[e]	—[f]
X[g]	30	15.1(10.2—22.4)	—[f]
XII[h]	>100	none[i]	2.9
XIII[d]	>100	none[i]	1.4
Morphine[g]	>100	0.8 (0.6— 1.1)	none[j]
Meperidine[g]	>100	4.5 (2.6— 7.8)	none[j]
Pentazocine[g]	>100	4.5 (3.2— 6.4)	1.5

a) maximum tolerant dose in mice (24 hr, *s.c.*)
b) tested *s.c.* in mice by the AcOH-induced writhing method[9]
c) antagonism of morphine-induced respiratory depression; tested *i.v.* in rabbits. See reference 9.
d) hydrobromide
e) confidence interval (95%)
f) not tested
g) hydrochloride
h) free base in dil. HCl
i) no effect with doses up to 22.5 mg/kg
j) no effect with doses up to 5 mg/kg

Interestingly, as seen in Table I, however, XII and XIII displayed apparent properties of narcotic antagonism on the order of pentazocine and I (R_1=H, R_2=H or Me).[1] In parallel to our previous observation with I,[1] the 2,3-dimethyl derivative (XIII) is about twice as potent as the 3-desmethyl relative (XII) in this property.

The results described above with XII and XIII and the previous experience with the enantiomeric difference in the pharmacological profiles of I[1] (dextro-isomers are antagonist-analgetics, while the levo-isomers are antagonists without analgetic activities) indicate that the structural requisite for the narcotic antagonism in these derivatives, differing from those for analgesia, may be a N-methylphenylethanamine chain probably without antipodal stereoselectivity. Further studies on other series of phenyl-azabicycloalkanes being in progress in this laboratory would shed more light on this point.

Experimental

All melting points were determined with a Yanagimoto capillary melting point apparatus (Model MP-1) and are uncorrected. IR spectra were recorded on a Hitachi IR-215 spectrophotometer. 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

10) The analgetic activity of the 3-alkyl-3-phenylpyrrolidine derivatives are known to be significantly affected by the size of the 3-alkyl group. See reference 11.
11) J.F. Cavalla, D.C. Bishop, R.A. Selway, N.E. Webb, C V. Winter, and M. Welford, *J. Med. Chem.*, **8**, 316 (1965).

are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Mass spectra were measured on a Hitachi 323 spectrometer. The organic solutions were dried over Na_2SO_4 and all evaporations were carried out *in vacuo*.

Methyl 1-(3-Methoxyphenyl)-3-oxocyclopentanecarboxylate (IV)——A solution of III[5] (22 g) in MeOH (200 ml) was saturated with dry hydrogen chloride and refluxed for 5 hr. The mixture was evaporated, diluted with H_2O and extracted with benzene. The extracts were washed with H_2O and 5% $NaHCO_3$, dried, and evaporated. Distillation of the residue gave 18.1 g (71%) of IV as a pale yellow oil, bp 178—180° (0.9 mmHg). IR ν_{max}^{Liquid} cm^{-1}: 1740, 1730 (both C=O). NMR: 2.3—3.5 (6H, m, $-CH_2-$), 3.70 (3H, s, CO_2CH_3), 3.87 (3H, s, $ArOCH_3$), 6.8—7.6 (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, 67.51; H, 6.36.

4-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[2,2,1]heptan-3-one (V)——A mixture of IV (17 g), 40% aqueous $MeNH_2$ (20 ml), PtO_2 (0.8 g) and MeOH (300 ml) was hydrogenated in a Paar apparatus with an initial pressure of 2 kg/cm^2. The mixture was heated at 50° for 3 hr, filtered from the catalyst, and evaporated. The residue was heated at 110° under a reduced pressure (25 mmHg) for 1.5 hr, dissolved in benzene and washed with dil. HCl and H_2O. Evaporation of the dried benzene left 9.6 g (61%) of V, mp 80—83°. Recrystallization from isopropyl ether gave prisms, mp 82—83°. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). NMR: 2.80 (3H, s, NCH_3), 3.80 (3H, s, OCH_3). Mass Spectrum *m/e*: 231 (M^+), 203 (base peak). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.77; H, 7.56; N, 5.94. The acidic layer was basified with NH_4OH and extracted with benzene. Evaporation of the dried extracts gave 6.5 g (36.4%) of the *trans*-amino ester (VI) as an oil. The hydrochloride was crystallized from acetone as needles and had mp 204—206°. IR ν_{max}^{Nujol} cm^{-1}: 1730 (C=O). NMR: 2.59 (3H, s, NCH_3), 3.63 (3H, s, CO_2CH_3), 3.79 (3H, s, $ArOCH_3$). Mass Spectrum *m/e*: 263 (M^+). *Anal.* Calcd. for $C_{15}H_{22}O_3NCl$: C, 60.10; H, 7.06; N, 4.67. Found: C, 59.97; H, 7.40; N, 4.36.

4-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[2,2,1]heptane (VII) Hydrobromide——A mixture of V (2.2 g), $LiAlH_4$ (1.9 g) and THF (50 ml) was refluxed for 4.5 hr. The mixture was diluted with ether (50 ml), decomposed by addition of H_2O (4 ml), and filtered from inorganic materials. Evaporation of the filtrate gave, after conversion of the residue to the hydrobromide and recrystallization from acetone–AcOEt–ether, 2.21 g (77.5%) of VII·HBr, mp 99—103° as needles. NMR: 2.85 (3H, s, N^+CH_3), 3.80 (3H, s, OCH_3). Free base: 2.40 (3H, s, NCH_3), 2.65 (1H, d, $J_{gem}=11$, C_3-H), 2.96 (1H, d, $J_{gem}=11$, C_3-H), 3.30 (1H, broad peak, C_1-H), 3.80 (3H, s, OCH_3). Mass Spectrum *m/e*: 217 (M^+), 189, 188 (base peak). *Anal.* Calcd. for $C_{14}H_{20}ONBr$: C, 56.38; H, 6.76; N, 4.70. Found: C, 56.27; H, 6.74; N, 4.75.

2,3-*endo*-Dimethyl-4-(3-methoxyphenyl)-2-azabicyclo[2,2,1]heptane (X) Hydrochloride——To an ethereal solution of MeLi (prepared from 10.35 g of MeI, 1.25 g of Li and 30 ml of ether) was added a solution of V (7 g) in benzene (200 ml) at room temperature under stirring. After being stirred at room temperature for 2 hr, the mixture was decomposed by addition of H_2O below 10°. The organic layer was separated, washed with H_2O, dried and evaporated to give the oily residue. IR spectrum of this oil (liquid) exhibited bands at 1700 (C=O) and 1640 cm^{-1} (C=C–N), respectively. To a solution of this oil in EtOH (100 ml) was added $NaBH_4$ (2.3 g) and the mixture was stirred at room temperature overnight. EtOH was removed and the residue was diluted with H_2O, extracted with benzene, and washed with H_2O. The organic layer was extracted with dil. HCl. The acidic layer was basified with NH_4OH and extracted with benzene. Evaporation of the extracts gave an oil, which was converted to 5.16 g of X·HCl, mp 185—187°. Needles from acetone–AcOEt. NMR: 1.52 (3H, d, $J=7$, C-CH_3), 2.95 (3H, d, $J_{N^+H}=5$, N^+CH_3), 3.82 (3H, s, OCH_3). Free base: 1.00 (3H, d, $J=7$, C-CH_3), 2.40 (3H, s, NCH_3), 3.05 (1H, broad peak, C_1-H), 3.80 (3H, s, OCH_3). Mass Spectrum *m/e*: 231 (M^+), 203, 202, 84. *Anal.* Calcd. for $C_{15}H_{22}ONCl$: C, 67.28; H, 8.28; N, 5.23. Found: C, 67.34; H, 8.35; N, 5.26. The mother liquor from X·HCl was evaporated and the free base recovered in the usual manner from the residue was chromatographed over Al_2O_3 (100 g). Elution with $CHCl_3$ and conversion of the eluate to the hydrochloride gave an additional amount of X·HCl (0.73 g, total yield 73.5%). The eluate with $CHCl_3$–MeOH (5: 1) was distilled to give 0.4 g (5.5%) of the diastereoisomeric mixture of the amino alcohol (XI), bp 180° (bath temperature, 0.1 mmHg). IR ν_{max}^{Liquid} cm^{-1}: 3300 (OH). NMR: 0.80 (*ca.* 1.5 H, d, $J=6$, C-CH_3), 0.85 (*ca.* 1.5H, $J=6$, C-CH_3), 2.35 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), ca. 3.8 (1H, CH-O). Mass Spectrum *m/e*: 249 (M^+), 205 (base peak). *Anal.* Calcd. for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.03; H, 9.41; 5.58.

When the MeLi mixture was decomposed by addition of H_2O at 15—35°, the yields of X and XI, after reduction with $NaBH_4$, were 58.3 and 14.5%, respectively.

4-(3-Hydroxyphenyl)-2-methyl-2-azabicyclo[2,2,1]heptane (XII)——A mixture of VII (1.1 g) and 47% HBr (15 ml) was refluxed for 1.5 hr and evaporated. The residue was basified with NH_4OH and the crystalline precipitate was collected to give 0.83 g (77.5%) of XII. Needles from benzene, mp 140—142°. NMR: 2.40 (3H, s, NCH_3), 2.56 (1H, d, $J_{gem}=11$, C_3-H), 2.96 (1H, d, $J_{gem}=11$, C_3-H), 3.30 (1H, broad peak, C_1-H). 9.8 (1H, s, OH, disappeared on addition of D_2O). Mass Spectrum *m/e*: 203 (M^+), 175, 174 (base peak). *Anal.* Calcd. for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.80; H, 8.45; N, 6.80.

2,3-*endo*-Dimethyl-4-(3-hydroxyphenyl)-2-azabicyclo[2,2,1]heptane (XIII) Hydrobromide——A mixture of X·HCl (1.8 g) and 47% HBr (19 ml) was refluxed for 1.5 hr and evaporated. Recrystallization of the residue from acetone–EtOH–ether gave 1.88 g (94%) of XIII·HBr, mp 187—189°, as prisms. NMR (D_2O): 1.30 (3H, d, $J=7$, C-CH_3), 3.00 (3H, s, N^+CH_3), 3.35 (1H, q, $J=7$, C_3-H), 4.00 (1H, broad peak, C_1-H). Mass Spectrum

m/e: 217 (M^+), 188, 187, 84. *Anal.* Calcd. for $C_{14}H_{20}ONBr$: C, 56.38; H, 6.76; N, 4.70. Found: C, 56.44; H, 6.86; N, 4.86.

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