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Azabicycloalkanes as Analgetics. VI.[1] 5-Phenyl-2-azabicyclo[3,2,1]octanes

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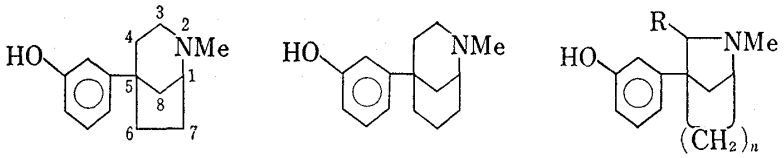
As part of a study on the structure-activity relationships of the partial agonist activity of phenylazabicycloalkane analgetics, the title compound (I), a five membered alicyclic analog of the known analgetic agent (II), has been synthesized. The aminoketone (V) was converted to I *via* the 8-oxo derivative (VII) by the usual method. Alternatively, intramolecular Michael reaction of the amino cyclopentenone derivative generated *in situ* by hydrolysis of the urethane (X) gave the 6-oxo derivative (XII) convertible also to I. Finally and most conveniently, the keto enamines (XVI and XVII), obtained by mercuric acetate oxidation of XIV and XV, were cyclized to XVIII and XII by heating them with aqueous acetic acid, respectively. I was found to be analgetically inactive but exhibited narcotic antagonsit activity comparable to pentazocine. Certain structural correlations between I and other phenylazabicycloalkane analgetics are discussed.

Keywords——azabicycloalkane; piperidine; analgetic activity; narcotic antagonist; partial agonist; structure-activity relationships; cyclization; intramolecular Michael reaction; enamine; phenylmorphan

As part of our study[3] on the structure-activity relationships of the agonist and antagonist actions of phenylazabicycloalkane analgetics, 5-(3-hydroxyphenyl)-2-methyl-2-azabicyclo-[3,2,1]octane (I) has been synthesized. I has a conformationally restricted 4-phenylpiperidine structure similar to that of the phenylmorphan (II), a potent analgetic agent,[4] with a minor change in the size of the alicyclic ring from six to five.



I II XXI a : $n=3$ b : $n=2$

Chart 1

The conventional method[4a,c] of the phenylmorphan synthesis applied equally well to the preparation of the five-membered alicyclic analog (I). Grignard reaction of cyclo pentanone with *m*-methoxyphenylmagnesium bromide followed by dehydration of the resultant carbinol gave the olefin (III). 2-(3-Methoxyphenyl)-cyclopentanone (IV) resulted from III either by *m*-chloroperbenzoic acid oxidation[5] or by hydroboration followed by two successive oxidations with hydrogen peroxide and chromic acid.[6] Reaction of IV with dimethylamino-

1) Part V: M. Takeda, M. Kawamori, H. Inoue, K. Noguchi, and S. Nurimoto, *Chem. Pharm. Bull.* (Tokyo), **25**, 775 (1977).
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3) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, and S. Saito, *Chem. Pharm. Bull.* (Tokyo), **24**, 1002 (1976).
4) *a*) E.L. May and J.G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955); *b*) E.L. May and M. Takeda, *J. Med. Chem.*, **13**, 805 (1970); *c*) M.E. Rogers and E.L. May, *J. Med. Chem.*, **17**, 1328 (1974).
5) J.E. McMurry and L.A. von Beroldingen, *Tetrahedron*, **30**, 2027 (1974).
6) P. de Mayo and R. Suau, *J. Chem. Soc., Perkin I*, **1974**, 2559.

ethyl chloride in dimethylformamide (DMF) in the presence of sodium hydride[4c] gave a mixture of the amino ketone (V), O-alkyl product (enol ether), and the starting material in a ratio of 5: 3: 2, respectively. Acid hydrolysis of this mixture caused regeneration of IV from the O-alkyl product, giving 35% yield of V with a recovery of IV (35%). This paralleled the reported observation in the phenylmorphan series.[4c]. Bromination of the hydrobromide of V in acetic acid followed by basification with ammonium hydroxide gave the quaternary salt (VI) in 83% yield. Dry distillation of VI effected liberation (81.5%) of the free base (VII), from which the deoxo compound (VIII) was obtained in 72% yield by Wolff-Kischner reduction.

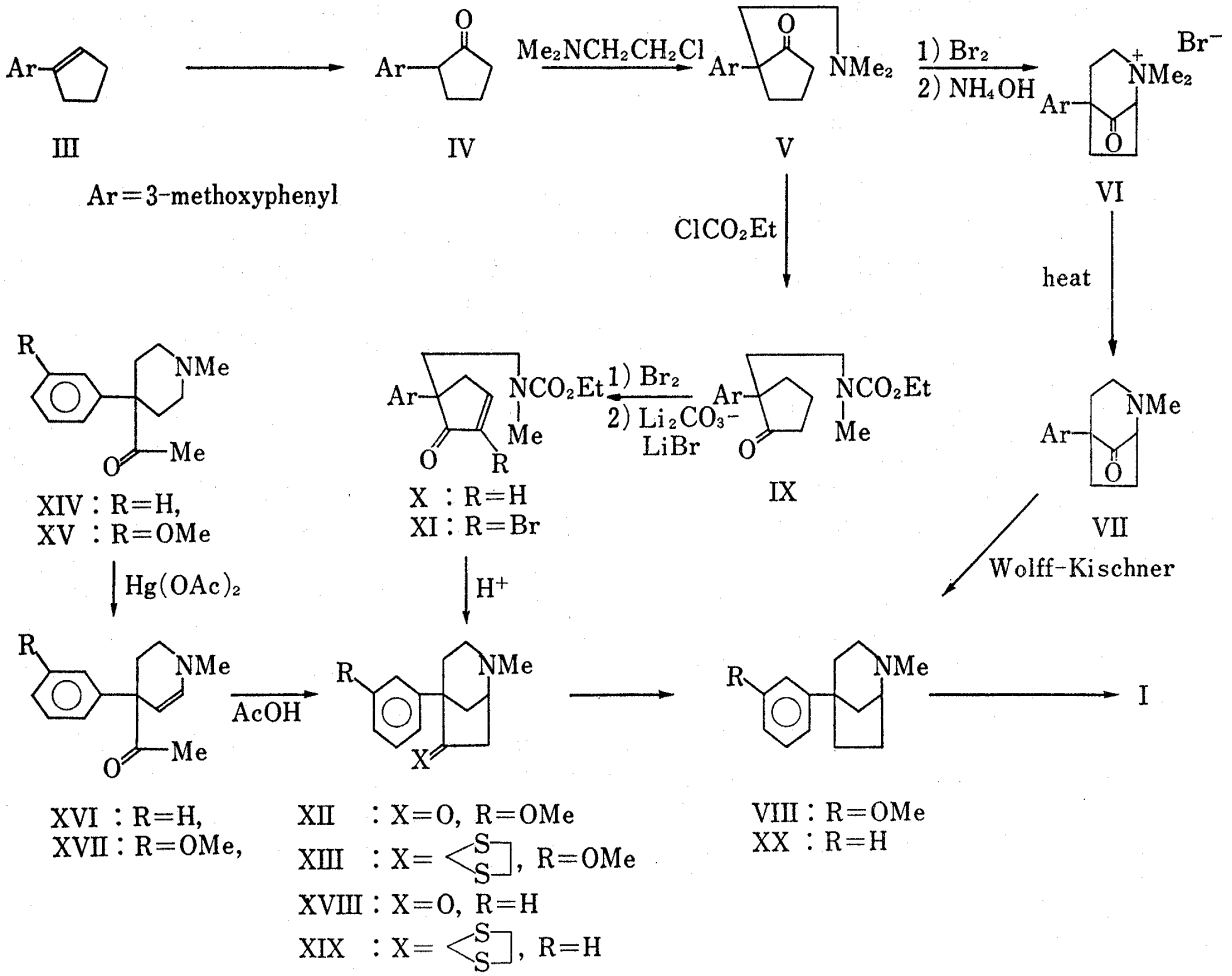

Chart 2

Intramolecular Michael addition of secondary amines to α,β-unsaturated ketones has been reported to be effective entry to various azabicycloalkane systems.[7] As an alternative route to VIII, an application of this type of ring closure was examined by hydrolysis of the urethane (X). Reaction of the amino ketone (V) with ethyl chloroformate in benzene gave the keto urethane (IX) in 95% yield. Bromination of IX in acetic acid followed by dehydrobromination with lithium carbonate and lithium bromide in DMF gave the enone (X, 23.4%) and the bromo enone (XI, 22.1%) with a recovery of IX (12.8%). The structure of XI,

7) *a*) W.J. Gensler, C.D. Gatsonis, and Q.A. Ahmed, *J. Org. Chem.*, **33**, 2968 (1968); *b*) R. Furstoss, P. Teissier, and B. Waegel, *Chem. Comm.*, **1970**, 384; *c*) R. Furstoss, G. Esposito, P. Teissier, and B. Waegell, *Bull. Chem. Soc. Chim. France*, (II) **1974**, 2845; *d*) M. Mokotoff, R.C. Cavestri, *J. Org. Chem.*, **39**, 409 (1974); *e*) J. Adachi, K. Nomura, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **24**, 85 (1976).

probably derived from an α,α-dibrominated ketone intermediate, was deduced from spectral evidence given in the Experimental section. No satisfactory explanation can be offered at present on the different behaviour of the keto urethane (IX) and the hydrobromide of V on bromination. Use of pyridinium hydrobromide perbromide in bromination of IX resulted in little increase in the yield of X (37%) after dehydrobromination, XI still being the by-product.

Heating of X in a 1: 1 mixture of 20% hydrochloric acid and acetic acid effected hydrolysis of the urethane group and gave the bicyclic amino ketone (XII) and its O-demethylated product in yields of 53.4 and 6.4%, respectively, with a recovery of the starting material (21%). The presence of a five-membered ketone absorption at 1740 cm^{-1} and methine proton resonance at 3.55 ppm confirmed the bicyclic structure of XII. It is worth noting that the hydrochloride of XII was directly obtained from the reaction mixture (Experimental section), since this type of cyclization has been tacitly assumed to proceed *via* free secondary amines.[7] Thioketalization of XII followed by desulfurization with Raney Nickel effected reduction of the 6-oxo group of XII and gave VIII in 63% yield. The product proved to be identical with the sample previously obtained from VII.

The two types of cyclization to the 2-azabicyclo[3,2,1]octane system described above involved construction of a piperidine ring from cyclopentane derivatives. Alternatively, construction of a cyclopentane ring from an appropriate piperidine derivative would provide an another route to this system. Intramolecular addition of the active methylene group to the iminium double bond[8,9] in the tetrahydropyridines (the protonated forms of XVI and XVII) appeared to serve for this purpose.

Methyl 1-methyl-4-phenyl-4-piperidylketone (XIV),[10] when allowed to react with an excess of mercuric acetate in 40% aqueous acetic acid under reflux,[11] was readily oxidized, as evidenced by the precipitation of mercurous acetate (86.3% by weight in 5.5 hr). The product obtained after demercuration with hydrogen sulphide was the expected dehydro compound (XVI), from which the crystalline iminium perchlorate was prepared and characterized. Cyclization of XVI was best accomplished by heating it in aqueous acetic acid and the bicyclic ketone (XVIII) was obtained in 67% yield (from XIV). The infrared (IR) spectrum of XVIII had a band at 1745 cm^{-1} characteristic of a five-membered ketone and the nuclear magnetic resonance (NMR) spectrum was also as expected. Similarly, the 3-methoxyphenyl analog (XV)[12] gave XII, identical with the sample previously obtained from X, in 62% yield. In one run, the intermediate enamine (XVII) was isolated in 75% yield and characterized as its iminium perchlorate. XVIII was converted to the deoxo compound (XX) *via* the thioketal (XIX) in the usual manner. Finally, O-demethylation of VIII with 47% HBr gave the phenol (I).

Pharmacology

When tested by the AcOH writhing[13] and hot-plate method,[13] compound (I) and its deoxy relative (XX), five membered alicyclic analogs of II, exhibited no discernible analgesia with doses up to 30 and 10 mg/kg, respectively (mouse, *s.c.*). This parallels our previous experience with the bridged 3-phenylpyrrolidines (XXIa, b) where a change in size of the alicyclic ring from six (XXIa)[3,14] to five (XXIb)[15] caused a marked fall in the agonist (anal-

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10) Chiba, Brit. Patent **614567** (1964) [*C.A.*, **44**, 1545 (1950)].
11) J.W. Lewis and P.A. Mayer, *J. Chem. Soc.*, (*C*), **1970**, 1074.
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13) S. Nurimoto, S. Suzuki, G. Hayashi, and M. Takeda, *Japan J. Pharmacol.*, **24**, 461 (1974).
14) 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).
15) M. Takeda, G. Tsukamoto, K. Noguchi, S. Saito, and S. Nurimoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 2312 (1976).

getic) activity. Thus, a shape of the alicyclic ring is at least one of important structural requisites for the analgetic effectiveness of phenylazabicycloalkanes, though its precise role is not clear. Whatever the role played by this ring size, its effect appears to be a reflection of receptor-related events rather than differential access into the central nervous system, since analgetically inactive I exhibits considerable narcotic antagonist activity.

In fact, when tested by the standard method (inhibition of morphine-induced respiratory depression in rabbit),[13-15] I exhibited antagonist activity (AD_{50}=1.9 mg/kg) comparable to pentazocine (AD_{50}=1.5). May and Takeda have shown[4b] that the antagonist activity of the phenylmorphan (II) resides in its *levo* isomer [(−)-II] and we proposed[14] that the unsubstituted pro-*S* enantiotopic edge of the piperidine ring in (−)-II is responsible for this activity. Therefore, the results obtained with I seem to be in agreement with the above proposal, since I possesses this chiral edge ($N-C_3-C_4-C_5$) identical with that of (−)-II in either of its enantiomers.

Interestingly, compound (XX) without a 3-hydroxy substituent was about twice (AD_{50}= 0.90) as active as I in antagonist activity.

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 are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Mass spectra were measured on a Hitachi RMS-4 mass spectrometer. Gas chromatography (GC) was obtained on a 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*.

1-(3-Methoxyphenyl)-cyclopentene (III)——To a stirred solution of *m*-methoxyphenylmagnesium bromide (prepared from 20.3 g of *m*-bromoanisole, 2.64 g of Mg, and a trace of I_2) in 50 ml of tetrahydrofuran (THF) was added a solution of cyclopentanone (8.4 g) in THF (10 ml) below 5°. The mixture was heated at 53—55° for 1 hr and concentrated. The residue was poured into ice-H_2O containing NH_4Cl (15 g) and the liberated oil was extracted with ether. Evaporation of the ether gave, after washing with saturated NaCl and drying, 20 g of the carbinol as an oil. A mixture of this oil, 3 g of oxalic acid, and 750 ml of toluene was refluxed for 15 hr with a continuous removal of H_2O. The mixture was washed with H_2O, 5% $NaHCO_3$, and H_2O, successively. Evaporation of the dried solvent and distillation of the residue gave 11 g (61%) of III, bp 129—131° (13 mmHg). NMR: 1.65—3.0 (6H, m, CH_2), 3.76 (3H, s, OCH_3), 6.15 (1H, m, CH=C), 6.6—7.5 (4H, m, aromatic protons). Mass Spectrum *m/e*: 174 (M^+, base peak), 159, 143. *Anal.* Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 83.01; H, 7.98.

2-(3-Methoxyphenyl)-cyclopentanone (IV)——A): To a stirred solution of III (3.48 g) in CH_2Cl_2 (10 ml) was added a solution of *m*-chloroperbenzoic acid (3.8 g) in CH_2Cl_2 (45 ml) and $CHCl_3$ (30 ml). The mixture was stirred at 0° for 2 hr and washed with 10% NaOH and H_2O. The organic layer was then shaken with 50 ml of 25% H_2SO_4 for 5 min and washed with 5% $NaHCO_3$ and H_2O. Evaporation of the dried solvent and distillation of the residue gave 2.5 g (65.7%) of IV as pale yellow oil, bp 138—140° (0.5 mmHg). IR ν_{max}^{Liquid} cm^{-1}: 1740 (C=O). NMR: 1.5—2.8 (6H, m, CH_2), 3.27 (1H, m, CH), 3.79 (3H, s, OCH_3), 6.7—7.5 (4H, m, aromatic protons). The oxime prepared in the usual manner was recrystallized from AcOEt and had mp 109—111°. (lit.[16] mp 117—118°). The semicarbazone was recrystallized from MeOH and had mp 194.5—195.5°. *Anal.* Calcd. for $C_{13}H_{17}O_2N_3$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.24; H, 7.08; N, 16.92.

B): To a stirred suspension of III (5.22 g), $NaBH_4$ (1.56 g) in THF (60 ml) was added BF_3·ether (8.4 ml) at 5° and the mixture was stirred at room temperature for 15 hr under N_2. To the mixture was added 15 ml of 3N NaOH and 20 ml of 30% H_2O_2, successively. After being stirred at room temperature for 1 hr, the mixture was extracted with ether. Evaporation of the solvent gave, after washing with H_2O and drying, 7.1 g of an oil. To a stirred solution of this oil in ether (35 ml) was added 25 ml of a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (10 g) in conc. H_2SO_4 (7.5 ml) and H_2O (42.5 ml) at 5—10° and stirring was continued at room temperature for 2 hr. The mixture was extracted with ether and washed with H_2O and 5% $NaHCO_3$. Evaporation of the dried ether and distillation gave 3.5 g (61%) of IV, bp 130° (3 mmHg), identical with the sample previously obtained.

16) T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, and O. Kusama, *J. Chem. Soc.*, (*C*), **1971**, 1051. They prepared IV by the benzyne reaction of *o*-chloroanisole with cyclopentanone. Following this method by us did not give satisfactory results.

2-(3-Methoxyphenyl)-2-(2-dimethylaminoethyl)-cyclopentanone (V) Hydrobromide——To a stirred suspension of 2.58 g of NaH (63% oil dispersion, washed with hexane) in DMF (18 ml) was added a solution of IV (3.8 g) in DMF (4 ml) at 0—5° under N_2 and stirring was continued at the same temperature for 2 hr. To the mixture was added a solution of dimethylaminoethylchloride (2.58 g) in DMF (3 ml) at 5—10° and the mixture was stirred at room temperature for 24 hr, diluted with H_2O, extracted with ether and washed with H_2O. GC analysis of this ether extracts showed a presence of three components (IV, V, and the O-alkylated product) in the ratio of 2: 5: 3,[17] respectively. The ethereal layer was extracted with 10% HCl. The aqueous layer was heated at 40° for 10 min, washed with ether and rendered alkaline with 10% NaOH. The liberated oil was taken in ether and washed with H_2O. Evaporation of the dried solvent left 2.15 g of an oil which was distilled to give 1.81 g (34.6%) of V, bp 155° (0.65 mmHg). IR ν_{max}^{Liquid} cm^{-1}: 1740 (C=O). NMR: 1.5—3.2 (10H, m, CH_2), 2.13 (6H, s, NMe_2), 3.81 (3H, s, OCH_3), 6.6—7.5 (4H, m, aromatic protons). The HBr salt was recrystallized from EtOH and had mp 156.5—157.5°. *Anal.* Calcd. for $C_{16}H_{24}O_2NBr$: C, 56.15; H, 7.07; N, 4.09; Br, 23.35. Found: C, 55.99; H, 6.92; N, 4.26; Br, 23.57. From the neutral fraction (ether, all combined), 1.34 g (35%, practically pure on GC examination) of IV was recovered.

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octan-8-one Methobromide (VI)——To a stirred solution of V·HBr (1.2 g) in AcOH (8 ml) was added a solution of Br_2 (0.674 g) in AcOH (1 ml) at room temperature. Evaporation of the solvent below 35° gave 2 g of an oil. This was dissolved in H_2O (2 ml), basified with 28% NH_4OH (1 ml), and quickly extracted with ether. Evaporation of the ether extracts left an oily residue which was digested with a small amount of acetone and filtered giving 0.34 g of VI. Recrystallization from EtOH gave prisms, mp 260—262° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1760 (C=O). NMR (D_2O): 2.1—2.8 (6H, m, CH_2), 3.32 (3H, s, $\overset{+}{N}CH_3$), 3.39 (3H, s, $\overset{+}{N}CH_3$), 3.91 (3H, s, OCH_3), 3.6—4.1 (3H, m, $\overset{+}{N}CH_2$ and $\overset{+}{N}CH$), 6.85—7.65 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{22}O_2NBr$: C, 56.48; H, 6.52; N, 4.12. Found: C, 56.69; H, 6.74; N, 4.08. Evaporation of the aqueous layer left a white solid which was extracted with hot $CHCl_3$–MeOH (5: 1) and filtered. Evaporation of the filtrate and recrystallization of the residue from H_2O gave an additional amount (0.615 g, total yield; 82.5%) of VI, mp 260—262° (decomp.).

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octan-8-one (VII)——Dry distillation of the methobromide (VI, 0.15 g) at 240—260° (bath temperature) (0.38 mmHg) gave a pale yellow oil. Ethereal solution of this oil was washed with 10% NaOH, dried, and evaporated. Distillation of the residue gave 0.088 g (81.5%) of VII, bp 220° (bath temperature) (0.4 mmHg). IR ν_{max}^{Liquid} cm^{-1}: 1755 (C=O). NMR: 2.40 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 6.7—7.6 (4H, m, aromatic protons). Mass Spectrum *m/e*: 245 (M^+), 217, 189 (base peak). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.16; H, 7.69; N, 5.59. The hydrochloride was recrystallized from EtOH and had mp 195—196° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3180 (OH), no absorption for C=O group. NMR (D_2O): 1.1 (3H, t, $J=7$, $CH_2\underline{CH_3}$), 2.77 (3H, s, $\overset{+}{N}CH_3$), 3.50 (2H, q, $J=7$, OCH_2Me), 3.77 (3H, s, OCH_3), 6.65—7.4 (4H, m, aromatic protons). Mass Spectrum *m/e*: 291 (M^+ for $C_{17}H_{25}O_3N$), 217, 189 (base peak). *Anal.* Calcd. for $C_{17}H_{26}O_3NCl$: C, 62.28; H, 7.99; N, 4.27; Cl, 10.81. Found: C, 62.23; H, 7.95; N, 4.36; Cl, 10.62. These spectral and elemental analyses indicate that this HCl salt is 8-ethoxy-5-(3-methoxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octan-8-ol hydrochloride, a hemiketal form of VII.[18] Regeneration of the free base from this hydrochloride (NH_4OH–ether) gave VII in a quantitative yield.

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octane (VIII) Hydrobromide——A mixture of VII (0.23 g), $NH_2NH_2·H_2O$ (0.2 ml), KOH (0.23 g), and ethyleneglycol (5 ml) was refluxed for 2 hr. The condenser was then removed and the temperature was gradually raised and kept at 180° for 30 min. The mixture was diluted with H_2O (50 ml) and extracted with ether. The extracts were washed with H_2O, dried, and evaporated to leave 0.2 g of an oil. Conversion to the HBr salt and recrystallization from EtOH–ether gave 0.21 g (72%) of VIII·HBr as prisms, mp 178.5—180°. NMR (D_2O): 1.5—2.65 (8H, m, CH_2), 2.90 (3H, s, $\overset{+}{N}CH_3$), 3.2—3.65 (2H, m, $\overset{+}{N}$–CH_2), 3.89 (3H, s, OCH_3), 4.05 (1H, broad peak, $\overset{+}{N}$–CH), 6.8—7.6 (4H, m, aromatic protons). Mass Spectrum *m/e*: 231 (M^+), 203 (base peak), 202. *Anal.* Calcd. for $C_{15}H_{22}ONBr$: C, 57.69; H, 7.10; N, 4.48; Br, 25.59. Found: C, 57.48; H, 7.13; N, 4.39; Br, 25.31.

2-(N-Carbethoxy-N-methylaminoethyl)-2-(3-methoxyphenyl)-cyclopentanone (IX)——To a solution of V (1.4 g) in benzene (20 ml) was added a solution of ethyl chloroformate (1.75 g) in benzene (5 ml) under reflux.[19] The mixture was refluxed for 2.5 hr, washed with 5% HCl and H_2O, and dried. Evaporation of the solvent and distillation of the residue gave 1.62 g (95%) of IX, bp 220° (bath temperature) (0.3 mmHg). IR ν_{max}^{Liquid} cm^{-1}: 1735 (C=O), 1700 (NC=O). NMR: 1.21 (3H, t, $J=7$, $OCH_2\underline{CH_3}$), 2.73 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 4.09 (2H, q, $J=7$, OCH_2Me), 6.7—7.3 (4H, m, aromatic protons). *Anal.* Calcd. for $C_{18}H_{25}O_4N$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.81; H, 7.99; N, 4.21.

17) GC retention time: 1.5, 3.7, and 5.5 min (195°), respectively. The 5.5 min peak disappeared after the acid hydrolysis.

18) Similar formation of a hemiketal during salt formation has been reported in the 9-oxo-6,7-benzomorphan. See, J.G. Murphy, J.H. Ager, and E.L. May, *J. Org. Chem.*, **25**, 1386 (1960).

19) T. Kometani, S. Shiotani, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **24**, 342 (1976).

5-(N-Carbethoxy-N-methylaminoethyl)-5-(3-methoxyphenyl)-cyclopent-2-enone (X)——A): To a stirred solution of IX (0.6 g) in AcOH (5 ml) was added 0.373 g of Br_2 at 20°. The mixture was stirred at room temperature for 2 hr and evaporated below 35°. The residue was dissolved in ether, washed with H_2O and 5% $NaHCO_3$, dried, and evaporated. A mixture of the residue, Li_2CO_3 (0.6 g), LiBr (0.6 g), and DMF (22 ml) was refluxed for 1 hr and evaporated. The residue was diluted with H_2O and extracted with ether. Evaporation of the ether gave, after washing with H_2O and drying, 0.5 g of an oil (TLC three spots). The mixture was separated by preparative TLC [silica gel, developed by benzene–AcOEt (3: 1)]. From the top fraction, 0.165 g (22.1%) of 2-bromo-5-(N-carbethoxy-N-methylaminoethyl)-5-(3-methoxyphenyl)-cyclopent-2-enone (XI) was obtained as an oil. IR ν_{max}^{Liquid} cm^{-1}: 1725 (CO), 1690 (NCO). NMR: 1.24 (3H, t, $J=7$, CH_2-$\underline{CH_3}$), 2.81 (3H, s, NCH_3), 4.10 (2H, q, $J=7$, OCH_2Me), 6.7—7.5 (4H, m, aromatic protons), 7.9 (1H, t, $J=4$, COC=CH). Mass Spectrum *m/e*: 397, 395 (M^+), 267 (base peak), 187. From the middle fraction, 0.077g (12.8%) of IX was recovered. 0.14 g (23.4%) of X, bp 250° (bath temperature) (0.2 mmHg) was obtained from the bottom fraction. IR ν_{max}^{Liquid} cm^{-1}: 1710—1690 (broad, C=O). NMR: 1.24 (3H, t, $J=7$, $CH_2\underline{CH_3}$), 2.83 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 4.11 (2H, q, $J=7$, OCH_2Me), 6.25 (1H, m, COC$\underline{H}$=CH), 6.7—7.5 (4H, m, aromatic protons), 7.83 (1H, m, COCH=C$\underline{H}$). Mass Spectrum *m/e*: 317 (M^+), 272, 201, 188 (base peak). *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.14; H, 7.26; N, 4.42. Found: C, 67.87; H, 7.31; N, 4.43.

B): A mixture of IX (0.319 g), pyridinium hydrobromide perbromide (0.32 g), and AcOH (4 ml) was heated at 40° for 20 min. The mixture was poured into ice-H_2O (150 ml), basified with 5% $NaHCO_3$, and extracted with ether. The combined ether extracts were washed with H_2O, 10% HCl, and H_2O, successively, dried, and evaporated. A mixture of the residue, Li_2CO_3 (0.35 g), LiBr (0.35 g), and DMF (10 ml) was refluxed for 1 hr. The usual work-up gave 0.32 g of an oil. GC analysis indicated the presence of IX, X, and XI in the ratio of 3: 6: 1, respectively. 0.118 g (37%) of X was obtained from this mixture by TLC purification.

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octan-6-one (XII) Hydrochloride from X——A mixture of X (0.4 g), 20% HCl (6 ml), and AcOH (6 ml) was refluxed for 9.5 hr and evaporated. The residue was dissolved in H_2O and washed with ether. Evaporation of the aqueous layer left an crystalline residue which was collected and washed with acetone giving 0.164 g of XII·HCl. Prisms from EtOH, mp 185—186° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1745 (C=O). NMR (D_2O): 2.0—3.8 (8H, m, CH_2), 3.04 (3H, s, $\overset{+}{N}CH_3$), 4.48 (1H, m, $\overset{+}{N}$–CH), 6.9—7.7 (4H, m, aromatic protons). Mass Spectrum *m/e*: 245 (M^+), 203, 202 (base peak), 188. *Anal.* Calcd. for $C_{15}H_{20}O_2NCl$: C, 63.94; H, 7.15; N, 4.97; Cl, 12.77. Found: C, 63.61; H, 7.06; N, 4.98; Cl, 12.72. The regenerated free base had the following spectral data. IR ν_{max}^{Liquid} cm^{-1}: 1740. NMR: 1.8—3.2 (8H, m, CH_2), 2.35 (3H, s, NCH_3), 3.55 (1H, m, NCH), 3.82 (3H, s, OCH_3), 6.7—7.5 (4H, m, aromatic protons).

The mother liquor (acetone) was evaporated and the residue was dissolved in H_2O, basified with 3N–NaOH, and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ left an oil which was converted to the HCl salt giving an additional amount (0.04 g, total yield 53.4%) of XII·HCl, mp 183—185°. The alkaline layer was acidified with 10% HCl, basified with NH_4OH, and extracted with $CHCl_3$–MeOH (5: 1). Evaporation of the extracts left a crystalline residue which was recrystallized from AcOEt gave 0.02 g (6.4%) of 5-(3-hydroxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octan-6-one, mp 153—154°. IR ν_{max}^{Nujol} cm^{-1}: 2300—2200 ($\overset{+}{N}$–H, betaine), 1725 (CO). NMR: 1.8—3.5 (8H, m, CH_2), 2.38 (3H, s, NCH_3), 3.75 (1H, m, N–CH), 6.7—7.5 (4H, m, aromatic protons), 7.95 (1H, s, OH, disappeared on addition of D_2O). Mass Spectrum *m/e*: 231 (M^+), 188 (base peak). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.69; H, 7.41; N, 6.06. Found: C, 72.37; H, 7.61; N, 6.05. This proved to be identical with the sample prepared from XII by O-demethylation with 47% HBr. From the neutral fraction (ether), 0.09 g (21%) of X was recovered.

2-Methyl-5-phenyl-2-azabicyclo[3,2,1]octan-6-one (XVIII) Hydrochloride——A mixture of XIV[10] (regenerated from 1.67 g of the hydrochloride), 14.3 g of yellow mercuric oxide, and 63 ml of 40% AcOH (v/v) was refluxed for 5.5 hr. The precipitate of $Hg_2(OAc)_2$ (2.94 g, 86.3%) was removed and the solution was saturated with H_2S. The mercuric sulfide was removed by filtration and washed with 40% AcOH. A small portion of the filtrate was basified with 20% NaOH and extracted with ether. Evaporation of the dried ether and conversion of the residue to the $HClO_4$ salt gave methyl 1-methyl-4-phenyl-4-(1,2,3,4-tetrahydro)pyridyl ketone (XVI) perchlorate, mp 130—132°. Needles from iso-PrOH. IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O). NMR ($CDCl_3$+DMSO): 1.99 (3H, s, CCH_3), 3.73 (3H, s, $\overset{+}{N}CH_3$), 7.45 (5H, s, Ph), 9.00 (1H, broad peak, $\overset{+}{N}$=CH). *Anal.* Calcd. for $C_{14}H_{18}O_5NCl$: C, 53.25; H, 5.75; N, 4.44. Found: C, 53.03; H, 5.75; N, 4.60. The filtrate[20] (40% AcOH) was refluxed for 17 hr and concentrated. The residue was diluted with H_2O, basified with 20% NaOH and extracted with ether. Evaporation of the dried ether left 1.2 g of an oil which was converted to the HCl salt. Recrystallization from EtOH gave 0.76 g of XVIII·HCl, mp 204—206°. IR ν_{max}^{Nujol} cm^{-1}: 1745 (CO). NMR (D_2O): 2.99 (3H, s, $\overset{+}{N}CH_3$), 4.46 (1H, broad peak, NCH), 7.50 (5H, s, Ph). Mass Spectrum *m/e*: 215 (M^+), 173 (base peak), 172, 96, 70. *Anal.* Calcd. for $C_{14}H_{18}ONCl$: C, 66.79; H, 7.21; N, 5.57. Found: C, 66.59; H, 7.39; N, 5.51. The mother liquor (EtOH) was concentrated and the free base was recovered in the usual manner. This was chromatographed over silica gel. The first part of

20) Concentration of the filtrate caused much decomposition of the enamine and led to the lower yield of XVIII.

elution with $CHCl_3$–MeOH (9: 1) gave 0.24 g of an addition amount of XVIII convertible to 0.245 g (total yield, 66.7%) of the hydrochloride, mp 203—205°. The second part of the elution gave, after conversion to the HCl salt, 0.185 g (13.6%) of XIV·HCl.

4-(3-Methoxyphenyl)-1-methyl-4-(1,2,3,4-tetrahydro)pyridyl Methyl Ketone (XVII) Perchlorate——A mixture of XV[12] (0.37 g), yellow mercuric oxide (3.24 g), and 40% AcOH (13 ml) was refluxed for 8 hr and worked up in the same manner as described above. The filtrate from mercuric sulfide was basified with 20% NaOH (ice-cooling) and extracted with ether. Evaporation of the ether left, after washing with H_2O and drying, 0.355 g of an oil. Conversion to the $HClO_4$ salt and recrystallization from EtOH–acetone gave 0.389 g (75%) of XVII·$HClO_4$, mp 124—125°, as prisms. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR ($CDCl_3$+DMSO): 2.01 (3H, s, $COCH_3$), 3.74 (3H, s, $\overset{+}{N}CH_3$), 3.84 (3H, s, OCH_3), 6.7—7.5 (4H, m, aromatic protons), 8.93 (1H, broad peak, $\overset{+}{N}$=CH). *Anal.* Calcd. for $C_{15}H_{20}O_6NCl$: C, 52.10; H, 5.83; N, 4.05; Cl, 10.25. Found: C, 52.10; H, 5.90; N, 3.99; Cl, 10.13. The regenerated free base had the following spectral data. IR ν_{max}^{Liquid} cm^{-1}: 1705 (C=O), 1635 (N–C=C). NMR: 1.97 (3H, s, $COCH_3$), 2.65 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 4.62 (1H, d, J=8, N–C=CH), 6.2 (1H, d, J=8, N–CH=C), 6.7—7.45 (4H, m, aromatic protons).

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octan-6-one (XII) Hydrochloride from XV——A mixture of XV (1.2 g), yellow mercuric oxide (10.8 g), 50 ml of 40% AcOH was refluxed for 6 hr and worked up in the usual manner. The filtrate (aqueous AcOH) from mercuric sulfide was refluxed for 21 hr and evaporated. The residue was dissolved in H_2O (20 ml), basified with 3N NaOH, and extracted with ether. Evaporation of the dried ether left 1.11 g of an oil which was converted to the HCl salt and recrystallized from EtOH giving 0.674 g of XII·HCl, mp 185—186°, identical with the sample previously obtained from X in all respects (IR, mixed mp, TLC). The free base was recovered from the filtrate (EtOH) and chromatographed over silica gel. The first part of the elution with $CHCl_3$–MeOH (9: 1) gave an additional amount (0.174 g) of XII (total yield, 62.1%). From the second part of the elution, 0.171 g (13.9%) of XV was recovered.

Heating of XVII·$HClO_4$ in 40% AcOH under reflux for 24 hr also gave 73% yield of XII.

2-Methyl-5-phenyl-2-azabicyclo[3,2,1]octane-6-spiro-2′-1,3-dithiolane (XIX)——A mixture of XVIII (regenerated from 1.75 g of the HCl), ethanedithiol (6 ml), BF_3·ether (6 ml), and AcOH (17 ml) was stirred at room temperature for 20 hr. The mixture was poured into ice-H_2O, rendered alkaline with 3N NaOH, and extracted with ether. The ether was extracted with 5% HCl. The acidic layer was washed with ether, basified with NH_4OH, and extracted with $CHCl_3$. Evaporation of the dried $CHCl_3$ and recrystallization of the residue from hexane gave 1.76 g (87%) of XIX, mp 104—106°, as needles. NMR: 2.24 (3H, s, NCH_3), *ca.* 3.3 (4H, m, S–CH_2), 7.3—7.8 (5H, m, Ph). Mass Spectrum *m/e*: 291 (M^+), 174 (base peak), 173, 172, 70. *Anal.* Calcd. for $C_{16}H_{21}NS_2$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.66; H, 7.40; N, 5.11.

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octane-6-spiro-2′-1,3-dithiolane(XIII) Hydrobromide——A mixture of XII (1.23 g), ethandithiol (2.5 ml), BF_3·ether (2.5 ml), and AcOH (15 ml) was stirred at room temperature for 80 hr and worked up in the same manner as described above. The crude product was converted to the HBr salt and recrystallized from EtOH to give 1.77 g (89%) of XIII·HBr, mp 207.5—208.5° (decomp.), as prisms. *Anal.* Calcd. for $C_{17}H_{24}ONS_2Br$: C, 50.74; H, 6.01; N, 3.48; Br, 19.86. Found: C, 50.67; H, 6.20; N, 3.12; Br, 19.94.

2-Methyl-5-phenyl-2-azabicyclo[3,2,1]octane (XX) Hydrochloride——A mixture of XIX (1.6 g), Raney Nickel (W-2, 22 ml), and EtOH (120 ml) was refluxed for 2.5 hr and filtered. Raney Nickel was washed with hot EtOH six times. The combined EtOH was evaporated and the residue was converted to the HCl salt to give, after recrystallization from acetone–EtOH–ether, 0.965 g (74%) of XX·HCl, mp 243—245°. NMR: 2.79 (3H, s, $\overset{+}{N}CH_3$), 3.90 (1H, broad peak, CH), 7.31 (5H, s, Ph). Mass Spectrum *m/e*: 201 (M^+), 173 (base peak), 172, 96, 91, 70, 42. *Anal.* Calcd. for $C_{14}H_{20}NCl$: C, 70.72; H, 8.48; N, 5.89. Found: C, 70.61; H, 8.42; N, 5.87.

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octane (VIII) Hydrobromide from XIII——A mixture of XIII (1.1 g), Raney Nickel (W-2, 15 ml), and EtOH (90 ml) was refluxed for 2.5 hr. The usual work-up and conversion of the oily product to the HBr salt afforded 0.76 g (71.1%) of VIII·HBr, mp 178—180°, identical with the sample previously obtained from VII in every respect (mixed mp, IR, TLC).

5-(3-Hydroxyphenyl)-2-methyl-2-azabicyclo[3,2,1]octane (I) Hydrobromide——A mixture of 0.4 g of VIII·HBr and 10 ml of 47% HBr was refluxed for 1.5 hr and evaporated. The crystalline residue was washed with acetone–ether and recrystallized from MeOH giving 0.332 g (87%) of I·HBr, mp 245.5—247° (decomp.), as prisms. IR ν_{max}^{Nujol} cm^{-1}: 3200 (OH). NMR (D_2O): 2.87 (3H, s, $\overset{+}{N}CH_3$), 3.98 (1H, m, CH), 6.75—7.6 (4H, m, aromatic protons). 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; Br, 26.80. Found: C, 56.27; H, 6.82; N, 4.69; Br, 27.04.

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