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Structures Related to Morphine. V. Azabicyclodecanes Derived from 2-(*m*-Methoxyphenyl)cyclohexanone

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The synthesis of 6-(*m*-methoxyphenyl)-2-methyl-2-azabicyclo[4.3.1]decan-10-one methobromide (IV) and the corresponding alcohol (VI) from 2-(*m*-methoxyphenyl)cyclohexanone (I) is described. Dry distillation followed by Wolff-Kishner reduction converted IV to 6-(*m*-methoxyphenyl)-2-methyl-2-azabicyclo[4.3.1]decane (V-b) in only 12% over-all yield. Demethylation of V-a with boiling, 48% HBr gave phenolic material refractory to crystallization. On the other hand methyl bromide-cleavage of VI gave a 75% yield of the base VII isolated as the hydrochloride and hydrobromide salts. Compounds IV, VI, and VII had no analgesic activity in mice.

The synthetic compound, 5-(*m*-hydroxyphenyl)-2-methylmorphan (VIII),[1,2] an azabicyclononane containing a piperidine (pentamethyleneimine) portion as a part of the bicyclic system, is comparable to morphine in analgesic effect if administered subcutaneously to mice. Projected shortly after the beginning of the research relevant to VIII were the synthesis and testing (for analgesia) of a homolog (V-b) in which the nitrogen ring may be looked upon as seven-membered, a hexamethyleneimine.[4] Although the methyl ether, 6-(*m*-methoxyphenyl)-2-methyl-2-azabicyclo[4.3.1]decane (V-a),[2] could not be satisfactorily demethylated to V-b, the reactions and intermediates concerned in the synthesis of V-a are herein reported.

Alkylation of 2-(*m*-methoxyphenyl)cyclohexanone (I) with 3-chloro-N,N-dimethylpropylamine in the presence of sodamide gave 2-(3-dimethylaminopropyl)-2-(*m*-methoxyphenyl)cyclohexanone (II) in only 11% yields; a total of 70% of I could be recovered after mild acid hydrolysis of enol ether, the principal competitive product.[8] Bromination of II in boiling acetic acid was effected in 85% yield but the resultant bromo ketone (III) could be cyclized to the azabicyclodecanone (IV) only under fairly vigorous conditions (propanol, 100°), in contrast to the one-carbon-lower homolog[1] which underwent closure rapidly at room temperature. Dry distillation of IV gave, with much destruction of material, the corresponding base which was converted (Wolff-Kishner) to V-a in 40% yield.[9] Demethylation of V-a with boiling 48% HBr yielded phenolic material that was refractory to crystallization either as the base or as a variety of salts. Lack of material prevented exploration of other demethylation procedures.

Hydrogenation of IV (platinum oxide) afforded 90% of diastereomerically pure alcohol methobromide (VI) which, upon dry distillation, gave 60% of VII (isolated as the hydrochloride salt) and 15% of the hydrobromide of VII. Undoubtedly some of the VI suffered dehydrobromination in some fashion (perhaps N→O methyl migration or Hofmann degradation) thus furnishing the hydrogen bromide necessary for the formation of the VII hydrobromide found in the distillate.

Compounds IV, VI, and VII were without analgesic activity at sub-toxic doses in mice.[7]

EXPERIMENTAL

Microanalyses are from the Institutes service analytical laboratory under the direction of Dr. William C. Alford, while pharmacological results are from Dr. N. B. Eddy (Chief of the Section on Analgesics of this Institute) and staff. Melting points were determined in a Hershberg apparatus with total-immersion thermometers.

2-(3-Dimethylaminopropyl)-2-(m-methoxyphenyl)cyclohexanone (II) *hydrobromide.* To a stirred, refluxing mixture of 2.2 g. of sodamide and 50 ml. of benzene (dried over sodium) was added during 5 minutes 11 g. of I[1,10] in 75 ml. of benzene. After 30–45 minutes of refluxing 6.8 g. of 3-chloro-N,N-dimethylpropylamine[11,12] in 75 ml. of benzene was

(1) May and Murphy, *J. Org. Chem.*, **20**, 1197 (1955).

(2) The nomenclature proposed by Barltrop[3] has been used thus far because of its simplicity. The Chemical Abstracts name for VIII would be 5-(*m*-hydroxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonane, while V would be a corresponding [4.3.1] decane. If one extends the Barltrop nomenclature to V it may be named 6-(*m*-methoxyphenyl)-2-methylhomomorphan.

(3) Barltrop, *J. Chem. Soc.*, 399 (1947).

(4) Blicke and Tsao[5] have recently reported seven-membered ring homologs of meperidine, and Seifter, *et al.*,[6] and Eddy[7] have found several such homologs of the meperidine group to have significant analgesic activity.

(5) Blicke and Tsao, *J. Am. Chem. Soc.*, **75**, 3999 (1953).

(6) Seifter, Eckfeld, Letchack, Gore, and Glassman, *Fed. Proc.*, **13**, 403 (1954).

(7) Eddy, Unpublished.

(8) It is curious that C-alkylation of I with 2-chloro-N,N-dimethylethylamine proceeded in 24% yields with apparently less enol ether formation and thus only a 60% recovery of I.

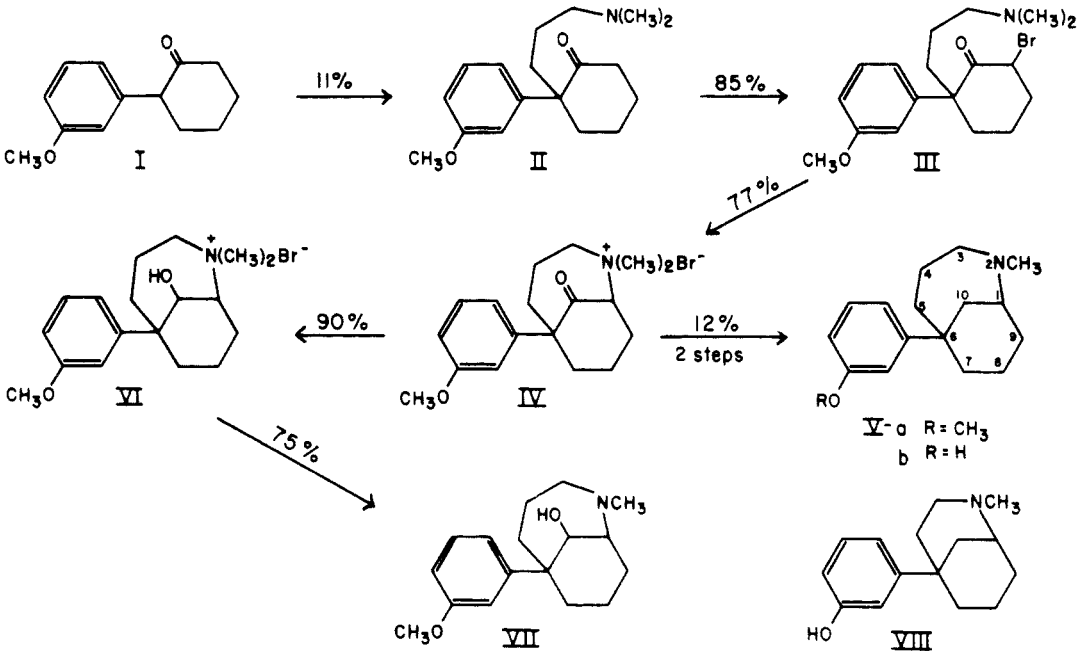
(9) The relatively vigorous conditions necessary to form IV and the extensive destruction of material in subsequent reactions on IV and derivatives as compared with the one-carbon-lower homologs[1] were indicative, qualitatively, of considerably more strain in the 2-azabicyclo[4.3.1]decane system than was expected from examination and comparison of molecular models.

(10) Wildman and Wildman, *J. Org. Chem.*, **17**, 581 (1952).

(11) Dankova, Preobrazhenskiĭ, and Mirapol'skaya, *Zhur. Obscheĭ Khim.* (*J. Gen. Chem.*), **21**, 570 (1951) [*Chem. Abstr.*, **45**, 8484[b] (1951)].

(12) Now available from The Aldrich Chemical Company, Inc., Milwaukee, Wis.

Figure I



added during 1–2 hours. Refluxing and stirring were continued for 48 hours. The cooled benzene was washed twice with water, then twice with 10% HCl in excess. The combined acid extracts were freed of I (from hydrolyzed enol ether) with ether and basified with cold, dilute NH_4OH. The resultant base was dried in ether. Evaporation of the ether left 3.3 g. of liquid which, in dry ether, was acidified to Congo Red with 32% HBr-acetic acid. Cooling overnight gave a semisolid from which solvent was decanted. Trituration with 5 ml. of acetone and cooling to 0° gave 2.2 g. (11%) of *II hydrobromide*, m.p. 174–176°. The analytical sample crystallized from acetone in plates of m.p. 177–178.5°.

Anal. Calc'd for $C_{18}H_{28}BrNO_2$: C, 58.4; H, 7.6. Found: C, 58.5; H, 7.6.

From the combined ether and benzene extracts above, 7.4 g. of evaporatively distilled I, n_D^{20} 1.5490, was obtained.

6-Bromo-2-(3-dimethylaminopropyl)-2-(m-methoxyphenyl)-cyclohexanone (III) *hydrobromide.* Bromine (1.7 g.) in 12 ml. of acetic acid was added during 10–12 minutes to a stirred, refluxing solution of 4.0 g. of II hydrobromide in 45 ml. of acetic acid. The cooled, stirred mixture was diluted to incipient turbidity (to *ca.* 200 ml.) with dry ether and kept at 0° overnight to give 4.1 g. (85%) of III hydrobromide; rosettes from alcohol-acetone-ether, m.p. 180–181° (effervescence).

Anal. Calc'd for $C_{18}H_{27}Br_2NO_2$: C, 48.1; H, 6.1. Found: C, 48.3; H, 6.2.

6-(m-Methoxyphenyl)-2-methyl-2-azabicyclo[4.3.1]decan-10-one methobromide (IV). The hydrobromide (4.1 g.) of III was converted to III (dilute NH_4OH) which was dried briefly in ether and kept on the steam-bath with 10 ml. of propanol for 24 hours. Addition of 10 ml. of acetone and cooling to 0° gave 2.6 g. (77%) of IV, m.p. 212–213.5°; needles from absolute ethanol.

Anal. Calc'd for $C_{18}H_{26}BrNO_2$: C, 58.7; H, 7.1. Found: C, 59.0; H, 7.3.

The *hydrochloride* was prepared by distillation of 0.5 g. of IV at 0.1 mm. and 170–180° (air-bath, 15 hours), acidifying the distillate in ether with dry HCl, and trituration of the resulting viscous sirup (after decantation) with ethyl acetate containing a little acetone; yield 0.12 g. (29%), m.p. 170–171.5°; plates from acetone-ethyl acetate.

Anal. Calc'd for $C_{17}H_{24}ClNO_2$: C, 65.9; H, 7.8; N, 4.5. Found: C, 65.8; H, 7.9; N, 4.5.

Rapid distillation at 220–230° (0.1 mm.) gave almost equally good results, but many other trials, including dry distillation of the methiodide and methochloride, gave inferior yields.

6-(m-Methoxyphenyl)-2-methyl-2-azabicyclo[4.3.1]decane (V-a) *hydrobromide.* A mixture of 0.4 g. of the preceding hydrochloride, 0.4 g. of KOH, 0.4 ml. of 95% hydrazine, and 4 ml. of triethylene glycol was kept at a bath temperature of 175° for 5.5 hours. During the next hour the temperature was gradually raised to 195°. The cooled solution was treated with ether and water. Drying and evaporation of the ether left an oil which was acidified (ether-HBr-acetic acid). Cooling and decantation left a semisolid which crystallized from acetone-ether in a yield of 0.2 g.; hexagonal plates, m.p. 109.5–110.5°.

Anal. Calc'd for $C_{17}H_{26}BrNO$: C, 60.0; H, 7.7. Found: C, 60.0; H, 7.9.

Demethylation of V-a (48% HBr, 30 minutes of refluxing) gave phenolic material which could not be induced to crystallize either as the hydrobromide, hydrochloride, or picrate, or as the free base.

6-(m-Methoxyphenyl)-2-methyl-2-azabicyclo[4.3.1]decan-10-ol methobromide (VI). Methanol (10 ml.), 1.0 g. of IV, and 0.1 g. of platinum oxide absorbed 1.05 molecular equivalents of hydrogen during 0.5 hour. The filtered solution was concentrated *in vacuo* to 5 ml. and diluted gradually (warming) to incipient turbidity with ether to give, after cooling to 0°, 0.9 g. of IV, m.p. 222–224°; flakes. It is slightly hygroscopic.

Anal. Calc'd for $C_{18}H_{28}BrNO_2$: C, 58.4; H, 7.6. Found: C, 58.1; H, 7.6.

6-(m-Methoxyphenyl)-2-methyl-2-azabicyclo[4.3.1]decan-10-ol (VII) *hydrobromide.* Dry distillation of 0.1 g. of VI (air-bath temperature 225–230°) at 0.02 mm. gave a distillate which was triturated with acetone. Filtration yielded 15 mg. (16%) of the hydrobromide of VII. It crystallized from methanol-ether in flakes which melted partially at

208–210° and completely at 222–224°, or in prisms of m.p. 222–224°. When these two modifications were ground together in a mortar only the higher m.p. was observed.

Anal. Calc'd for $C_{17}H_{26}BrNO_2$: C, 57.3; H, 7.4; OCH_3, 8.7. Found: C, 56.9; H, 7.3; OCH_3, 8.1.

The *hydrochloride* crystallized on addition of dry HCl to the acetone filtrate above (from the 0.15 g. of hydrobromide); yield 50 mg. (60%, total 76%). It was also prepared from the VII hydrobromide above; plates from ethanol-ether, m.p. 218° (partially), 235° (completely), prisms from ethanol-acetone, m.p. 236–239°.

Anal. Calc'd for $C_{17}H_{26}ClNO_2$: C, 65.5; H, 8.4; OCH_3, 10.0. Found: C, 65.1; H, 8.4; OCH_3, 10.1.

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