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7-Aza Analogs of the Analgetic Agent Azabicyclane. Synthesis and Pharmacologic Analysis†

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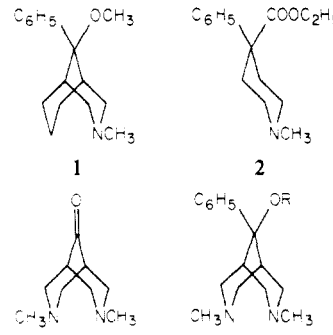
Three 3,7-diazabicyclo[3.3.1]nonane derivatives (4) with a structural similarity to the analgetic agent azabicyclane (1) were prepared. The amino alcohol **4a** was found to prefer a conformation wherein the six-membered ring to which the hydroxyl group is syn is in the boat form. These three compounds had increased basicity in comparison with 1 due to various forces stabilizing their monocationic states. Compounds **4a–c** did not show analgetic activity at the dose levels tested.

The analgetic agent azabicyclane (1) has been reported to be six to eight times as potent as meperidine (2),[1] and related compounds have also been reported to have high analgetic activity and low toxicity.[2] The influence on analgetic activity of an *N*-methyl group, in place of the 7-methylene group, in analogs of 1 was of interest. These compounds (4) feature the two nitrogen atoms in close proximity, and it was anticipated that this would result in increased basicity in relation to 1, due to an increased stability of the monoprotonated state as a result of intramolecular hydrogen bonding.[3] It was thought that the increase in basicity could conceivably result in an increased affinity of the monoprotonated forms of one or more of these compounds at the anionic site of the analgetic receptor, resulting in improved potency and duration of action.

Chemistry. Addition of a solution of amino ketone 3[4] in ether to excess ethereal phenyllithium, followed by aqueous work-up, furnished the amino alcohol **4a**. Alternatively, treatment of the initially formed anion with propionyl chloride[5] gave amino ester **4b**. Attempted synthesis of this ester by treatment of **4a** with propionyl chloride or propionic anhydride in pyridine at elevated temperatures failed, probably due to the restricted nature of the hydroxyl group in this compound. The methyl ether **4c** was prepared in low yield by treatment of the anion with iodomethane. The low yield of this latter reaction was due to the formation of significant amounts of quaternized products, which demonstrates the similarity of nucleophilic character of the oxide anion and the two closely positioned amine functions.

Compounds **4b,c** were not readily amenable to a conformational analysis of their fused six-membered rings. It is reasonable to assume that these ring systems adopt double chair conformations in analogy with the preferred conformation of the bicyclic diamine **5**.[6]



In contrast, compound **4a** was shown by infrared spectrometry to exhibit a strong preference for the chair–boat conformer, with the ring to which the hydroxyl group is syn taking the boat conformation.[7] In the infrared spectrum of **4a** there is a broad, strong band centered at 3230 cm^{-1} due to associated O–H stretch which results from transannular O–H···N bonding; weak absorbance at 3640 cm^{-1} is due to unassociated O–H stretch. Absorbance positions and intensities were invariant with concentration. Examples of compounds displaying 1,4 O–H···X bonding are somewhat rare owing to unfavorable energy differences usually existing between boat and chair conformers; however, a number of examples in mono- and bicyclic systems have been reported.[8] A measure of strength of the intramolecular hydrogen bond in **4a** is obtained from a consideration of the difference, $\Delta\nu$, between the positions of free and associated OH stretch.[9] The usual magnitude of $\Delta\nu$ is 200–250 cm^{-1}; however, in this instance $\Delta\nu$ is 410 cm^{-1} which suggests that the transannular O–H···N hydrogen bond approaches the strength of intermolecular hydrogen bonding observed in neat or concentrated samples of amino alcohols.[10]

Compounds **4a–c** were found to be strong bases with pK_{a_2}* values as high as 11.73. In contrast, the C-7 analog

† This paper is dedicated to the memory of Professor Edward E. Smissman.

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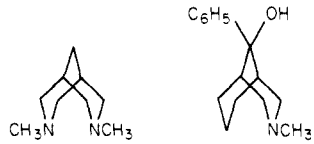
6 has a pK_a^* of 8.16,[5] and its epimer has a pK_a^* of 7.30;[5] presumably azabicyclane (1) is within this range of basicity. This signifies about a fourfold increase in the order of basicity in going from 1 to **4a–c**.



5 6

Pharmacologic Results and Discussion. Compounds **4a–c** were screened for pharmacologic activity in mice (see Experimental Section) by Drs. J. F. Gardocki and H. I. Jacoby, McNeil Laboratories, Ft. Washington, Pa. Preliminary tests for analgetic activity were conducted utilizing the Haffner tail clamp test[11] and the phenylquinone-induced writhing test.[1] The effects on colonic propulsive motility were determined as a test for antidiarrheal activity. Effects on general behavior were also evaluated.

In general, none of the compounds exhibited analgetic or antidiarrheal activity at oral doses of 20–100 mg/kg po. In contrast, azabicyclane (1) had an ED_{50} of 3.9–6.4 mg/kg sc in the Haffner tail clamp test (assessed 30 min after administration of the drug) and caused a significant decrease in colonic propulsive motility at a dose of 10 mg/kg ip.[1] Two of the compounds, **4a,b**, had convulsant activity at 30–100 and 100–300 mg/kg ip, respectively.

It had been speculated that the replacement of the 7-methylene group in 1 with an *N*-methyl group would result in a change in physicochemical characteristics favoring increased binding at the analgetic receptor and enhanced analgetic activity. The observed increase in basicity of **4a–c** in comparison with 1 indicated that the introduction of the second *N*-methyl substituent had significantly affected these characteristics. The preliminary pharmacologic data indicate, however, that the second *N*-methyl substituent introduces features which exert a deleterious effect on analgetic activity. The lack of analgetic effect could not be due entirely to a restriction of distribution into the CNS as a result of increased basicity, since **4a,b** exhibited convulsant effects when administered in high doses.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (ir) were taken on Beckman IR 10 and IR 33 spectrophotometers. Proton magnetic resonance spectra (^{1}H NMR) were obtained on Varian A-60A and T-60 spectrometers using chloroform-*d* as solvent and tetramethylsilane as the internal standard. Electron impact mass spectra (EIMS) were recorded at 70 eV using Finnegan 1015 and Varian CH 5 spectrometers. Elemental analyses were obtained using a F & M 185 CHN analyzer and from Midwest Microlab, Inc., Indianapolis, Ind. Apparent dissociation constants ($pK_{a_2}^*$ values) were determined in 66% aqueous dimethylformamide, at 30°, by potentiometric titration[13] of the respective monoperchlorate salts (**4a–c**) with 0.1 *M* sodium hydroxide, using a Sargent Model D recording titrator equipped with a Beckman combination electrode to make and record pH measurements. Phenyllithium was prepared in ether,[14] or obtained from the Ventron Corp., as a solution in benzene–ether. Work-up of ether or chloroform solutions of reaction products was accomplished by drying with anhydrous sodium sulfate followed by concentration at a rotary evaporator using a Buchler water aspirator at water bath temperatures of 40° or less. The monoperchlorate salts of **4a,c** were converted to the respective free bases by partitioning between chloroform and 10% aqueous sodium hydroxide containing ca. 5% ethanol.

3,7-Dimethyl-9-phenyl-3,7-diazabicyclo[3.3.1]nonan-9-ol (4a). Amino ketone 3 (2.9 g, 17.2 mmol) was dissolved in dry ether (30 ml) and added dropwise to an ice-cold 2.2 *M* solution of ethereal phenyllithium (12 ml) which was stirred magnetically under dry nitrogen. After completion of addition, the resulting suspension was stirred and refluxed for 2.5 hr, allowed to cool, and removed of excess phenyllithium by dropwise addition of 30% aqueous ammonium chloride. To the mixture was added ether (200 ml) and 5% aqueous sodium hydroxide (180 ml). After equilibration, the layers were separated; the organic phase was cooled in ice and treated with cold 40% aqueous ethanolic perchloric acid. The resulting precipitate was crystallized from ethanol as white needles of the monoperchlorate (3.4 g, 44%): mp 250–252° dec; $pK_{a_2}^*$ = 11.69. Anal. ($C_{15}H_{23}ClN_2O_5$) C, H, N.

The free base, prepared from the monoperchlorate, was a white solid: mp 118–120°; ir (KBr) 3.23, 3.39, 3.53, 6.80, 6.90 μ; ir (0.05 *M* is CS_2) ν 3640 (w), 3230 (s, broad), absorbance positions are identical at 0.005 *M* in CS_2; ^{1}H NMR δ 2.1 (s, 3, NCH_3), 2.35 (s, 3, NCH_3), 5.7 (s, 1, $W_{1/2}$ = 8 Hz, D_2O exchangeable, OH), 7.4 (s, 5, C_6H_5); EIMS *m/e* (rel intensity) 246 (m, 80), 170 (93, 1-methyl-4-phenylpyridinium ion), 84 (93), 58 (100, *N,N*-dimethylformimmonium ion), 44 (80).

3,7-Dimethyl-9-phenyl-3,7-diazabicyclo[3.3.1]nonan-9-yl Propionate (4b). To a solution of 2.2 *M* phenyllithium in benzene–ether (12 ml) was added dry ether (40 ml). To this magnetically stirred solution, maintained under nitrogen, was added dropwise a solution of 3 (2.9 g, 17.2 mmol) in dry ether (30 ml). After 1 hr at room temperature, a solution of propionyl chloride (6.5 g, 70 mmol) dissolved in dry ether (40 ml) was added dropwise to the cold (5°) reaction suspension. After stirring for 20 hr at room temperature, water (8 ml) was poured into the reaction flask, the mixture was separated, and the organic layer was discarded. The aqueous layer was adjusted to pH 8–9 with 10% aqueous sodium hydroxide and extracted with three portions of chloroform (40 ml). The combined, concentrated extracts were dissolved in hot acetone (40 ml). The ice-cooled solution afforded three crops of crystals (1.25, 1.10, and 0.45 g): total yield 2.8 g (54%) of the monohydrate; mp 183–186°; ir (fluorolube) 3.33 (w), 3.37 (s), 3.52 (s), 5.73 (s, C=O), 6.85 μ (s); ^{1}H NMR δ 1.00 (t, *J* = 7 Hz, 3, CCH_3), 2.20 (q, *J* = 7 Hz, 2, CH_2CH_3), 2.45 (s, 3, NCH_3), 2.90 (s, 3, NCH_3), 6.00 (s, 2, H_2O), 7.40 (s, 5, C_6H_5); EIMS *m/e* (rel intensity) 302 (M, 27), 229 (18, M – C_2H_5COO–), 170 (98, 1-methyl-4-phenylpiperidinium ion), 58 (100, *N,N*-dimethylformimmonium ion), 44 (54).

The mother liquor from which **4b** crystallized was cooled in ice and treated with excess 40% aqueous ethanolic perchloric acid. The resulting precipitate separated from ethanol–ether as white crystals (0.6 g) of the monoperchlorate: mp 171–176° darkening; $pK_{a_2}^*$ = 11.03. Anal. ($C_{18}H_{27}ClN_2O_6$) C, H, N.

3,7-Dimethyl-9-methoxy-9-phenyl-3,7-diazabicyclo-[3.3.1]nonane (4c). To a 2.2 *M* solution of phenyllithium in ether (8 ml) was added dry ether (50 ml). To this ice-cold solution, magnetically stirred and maintained under nitrogen, was added dropwise a solution of 3 (2.7 g, 16 mmol) dissolved in dry ether. After stirring for 2 hr at room temperature, a solution of iodomethane (2.4 g, 17 mmol) dissolved in dry ether (20 ml) was added dropwise. After stirring overnight, the reaction suspension was poured into 10% aqueous hydrochloric acid (50 ml) and extracted with two portions of ether (75 ml); these extracts were discarded. The aqueous phase was made alkaline with 10% aqueous sodium hydroxide and extracted with three portions of ether (75 ml). The combined extracts gave a brown semisolid. This was dissolved in 1:1 ethanol–acetone (25 ml) and diluted to the point of turbidity with Skellysolve B. After storage at 8° overnight, the suspension was filtered, and the filtrate was concentrated. The residue was dissolved in acetone (15 ml) and neutralized with aqueous ethanolic perchloric acid. The precipitate was filtered and washed with chloroform. The filtrate and washings were concentrated to leave 0.3 g (14%) of the monoperchlorate which crystallized from ethanol as long white needles: mp 224–226° dec; $pK_{a_2}^*$ = 11.73. Anal. ($C_{16}H_{25}ClN_2O_5$) C, H, N. The free base of **4c** was prepared as a yellow solid: ir (0.5 *M* in CS_2) 3.24 (w, C_6H_5), 3.47 μ (s); ^{1}H NMR δ 2.1 (s, 3, NCH_3), 2.5 (s, 3, NCH_3), 2.8 (s, 3, OCH_3), 7.35 (s, 5, C_6H_5).

Water-Soluble Salts of 4a–c. Neither the free bases of **4a–c** nor their monoperchlorate salts were sufficiently soluble for biological testing purposes. For this reason, salts of sufficient solubility were prepared. Treatment of a solution of **4a** (0.4 g,

1.6 mmol) in acetone (25 ml) with a solution of *d*-10-camphorsulfonic acid (0.37 g, 1.6 mmol) in acetone (25 ml) gave 0.7 g (91%) of **4a**·camsylate (crystals from acetone): mp 169–175°. Anal. ($C_{25}H_{38}N_2O_5S$) C, H, N, S. Treatment of a solution of **4b** (0.64 g, 2 mmol) in ethanol (5 ml) with 6 ml of an 0.6 *M* ethanolic solution of methanesulfonic acid furnished 0.72 g (80%) of **4b**·mesylate (white needles from ethanol): mp 117–118°. Anal. ($C_{18}H_{26}N_2O_2 \cdot 1.5CH_4O_3S$) C, H, N. Treatment of **4c** (0.33 g, 1.25 mmol) in acetone (20 ml) with a solution of anhydrous citric acid (0.24 g, 1.25 mmol) in acetone (20 ml), followed by crystallization of the resulting precipitate from acetone, yielded 0.535 g (95%) of **4c**·citrate (white crystals).

Administration of 4a–c. All pharmacologic tests were carried out using groups of ten Swiss–Webster Royal Hart male mice at each dose level, at doses of up to 300 mg/kg per group. The water soluble salts, prepared as described above, were administered po or ip as aqueous solutions (**4a,b**) and as a solution in 30% aqueous propylene glycol (**4c**).

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Adamantanamine Derivatives. Antimicrobial Activities of Certain Mannich Bases†

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A series of Mannich condensation products containing the β-(1-adamantylamino)propiophenone skeleton (type I) and the *o*-(1-adamantylaminomethyl)phenol skeleton (type II) was synthesized and tested for antimicrobial activity against certain bacteria and fungi by the agar diffusion and tube dilution methods. Type I compounds were more active than type II compounds and had a broad-spectrum effect on certain gram-negative and gram-positive bacteria, acid-fast bacteria, a yeast, and a mold.

Previous workers[1-3] have found that certain Mannich bases possessed in vitro antimicrobial activity. Chatten et al.[4] have shown that besides the difference in amine moieties, the substituents in phenyl ketones also exert an influence on activities. Also, Aldrich and workers[5] have reported the effect of structural variations of aminoadamantanes upon antiviral activity. These observations prompted the preparation and testing of the antimicrobial activity of substituted ketone and phenolic Mannich products containing 1-aminoadamantane as the amine moiety. The test organisms were chosen to represent the major types of organism associated with human disease, i.e., the gram-positive and gram-negative bacteria, the acid-fast bacteria, the yeasts, and the filamentous fungi.

Chemistry. Type I and type II Mannich products (Table I) were prepared by the standard Mannich reaction described in the Experimental Section. Compound **7**, which is not a Mannich base, was prepared by the condensation of 2-bromoacetophenone with 1-aminoadamantane.

The major difficulties encountered were poor yields, secondary condensations, and separation of products from unreacted materials, particularly the primary amine.

Microbiological Studies. The results of these studies are presented in Tables II and III as the averages of multiple determinations. The Me_2SO solvent controls did not produce any measurable inhibition of the test organisms. Replicate tests performed with a specific dilution of a test compound on any given day were in excellent agreement and results obtained with a specific dilution of

† This article is dedicated to Dr. Edward E. Smissman, who was an outstanding teacher and research scientist. His innovative philosophy regarding the teaching of medicinal chemistry and its research was given to posterity through his students, all of whom were close to him and loved him.

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