Azabicyclo Chemistry III. Reduction and Concomitant Hydrogenolysis of 1-Methyl-7-methoxyindole. Stereochemical Assignments (1).

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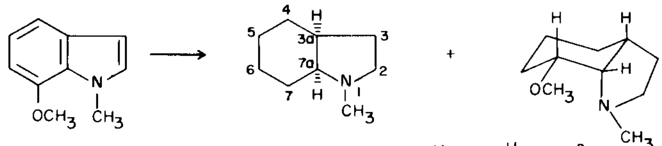
In the course of a study (2) aimed at preparing 2-methyl-9-methoxy-2-azabicyclo[3.3.1]nonane (**6**) it became necessary to ascertain whether or not we had obtained compound **6** or an isomeric 1-methyl-7-methoxy-octahydroindole, for example, compound **3**. The text of this note thus deals with the synthesis and structure proof of the octahydroindole compound by an unequivocal route.

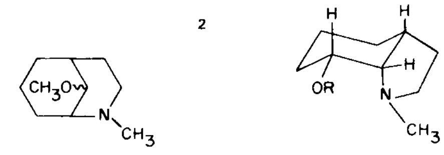
Commercial 7-methoxyindole was *N*-methylated by the general method of Potts and Saxton (3) to give 1-methyl-7-methoxyindole (**1**) in essentially quantitative yield (4). Hydrogenation (platinum oxide) of **1** in aqueous acetic acid afforded two products, initially identified by mass spectrometry as 1-methyl-*cis*-octahydroindole (**2**) and 1-methyl-7(e)-methoxy-*cis*-octahydroindole (**3**), in a ratio of 2:3, respectively. Partial purification of the mixture was achieved by preparative thin layer chromatography (tlc), enabling the isolation of **3** as its picrate salt. The nmr spectrum of **3**, as the free base, showed the C-7a proton as a triplet (J = 4 Hz) at δ 2.67 and the width at half-height ($W_{1/2}$ = 10 Hz) established this as an equatorial proton and thus the ring juncture must be *cis* fused.

In order to facilitate the separation of **2** and **3** as well as to establish the complete stereochemistry of **3**, the mixture was refluxed with hydriodic acid to give recovered **2** and the alcohol **4**. Again separation was difficult and a small sample of pure **4** was obtained by preparative tlc. The nmr spectrum of **4** again confirmed the *cis*-ring juncture (C-7a proton at δ 3.27 as a doublet of doublets, $J_{7a\text{-}7}$ = 4.5 Hz, $J_{7a\text{-}3a}$ = 6 Hz, $W_{1/2}$ = 12 Hz) but did not establish the stereochemistry at C-7. Acetylation of the mixture of **2** and **4** enabled the separation of pure **2** and the acetate **5**. Compound **2** was established as 1-methyl *cis*-octahydroindole by conversion to the previously reported (5) picrate and methiodide. Similarly, hydrogenation of 1-methylindole under identical conditions as above gave only one product, the picrate of which was identical to **2**.

Hydrogenolysis of methoxyl from an aromatic ring has been recorded in the literature (6). The cleavage presumably occurs through an intermediate reduction state; most probably *via* an allylic ether (6). The hydrogenolysis does not occur from the completely reduced



1 2 3



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4 R = H
5 R COCH₃

state since hydrogenation of **3** yields only recovered starting material. Hydrogenation of 1-methyl-5-methoxyindole also afforded the hydrogenolysis product **2** in better than a 50% yield, as well as the expected 1-methyl 5-methoxyoctahydroindole, no attempt being made to assign the stereochemistry of the latter compound (7).

Mertes and co-workers (5) have assigned the preferred conformation of **2** as the *cis* compound with the nitrogen axial based on the observation of a low-field multiplet at δ 3.13 in the nmr, assigned to an equatorial C-7a proton. We have examined this compound at 250 MHz and observed a one proton signal at δ 3.12 ($W_{1/2}$ = 23 Hz) mostly as a triplet (J = 10 Hz), each part being further split into a doublet (J = 4 Hz). We feel that this observed resonance is not consistent with an equatorial proton and suggest that instead this is due to one of the C-2 protons. This downfield position for a C-2 proton is unusual but has been observed in the nmr spectra of several alkaloids (8) which have the octahydroindole nucleus. Indeed, other workers (9) have reported similar findings in the decahydroquinoline series. Furthermore, we have prepared (2) other octahydroindole derivatives in which both C-2 protons have been replaced with deuterium and have observed the disappearance of complex one-proton resonances in this δ 3.1 region. At the same time, we cannot locate the C-7a proton in **2** with accuracy and thus choose to refer to it as the *cis* structure based on comparison to earlier derivatives reported in the literature (5). It is interesting to note that this anomalous low-field position for one of the C-2 protons is also observed in

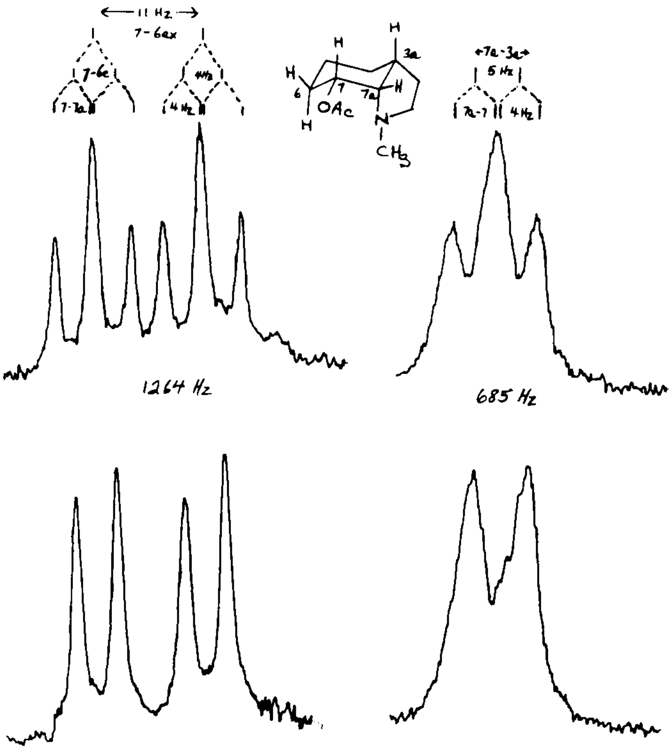

Figure 1. Double resonance decoupling experiment of **5** at 250 MHz in deuteriochloroform.

the nmr spectra of compounds **3**, **4**, and **5**.

However, detailed nmr analysis at 250 MHz of acetate **5** enabled the assignment of the acetate group as equatorial, the C-7a proton as equatorial and thus the ring juncture must be *cis*-fused. The C-7 proton was observed as a doublet of triplets centered at δ 5.05 (J = 4 Hz, $W_{1/2}$ = 20 Hz), in good agreement with axial protons (10). The C-7a proton was observed as an apparent triplet centered at δ 2.74 (J = 4 Hz, $W_{1/2}$ = 10 Hz), in good agreement with equatorial protons (10). Double resonance experiments enabled us to confirm these assignments (see Figure 1). Irradiation at C-7a caused the downfield proton to collapse to a doublet of doublets, with coupling constants of J = 4 Hz for axial-equatorial coupling (7ax-6eq) and J = 11 Hz for diaxial coupling (7ax-6ax) (11). Similarly, irradiation at C-7 allowed the upfield triplet to collapse to a doublet with a coupling constant of J = 5 Hz for equatorial-axial coupling (7a eq-3a ax) (8a). Thus, the coupling of C-7a with C-7 is 4 Hz due to an equatorial-axial interaction. Therefore, the C-7 functional group in **3** and **4** must have been in the equatorial conformation.

In further support of the assigned stereochemistry of **4** is the observation of *N*-methyl resonance in the nmr at δ 2.95, about 0.6 ppm downfield from the value of δ 2.36 for the simple model, *N*-methylpyrrolidine. This is in agreement with the assignment wherein there is strong OH-N interaction (8c). In **3** and **5** where there is no intramolecular H-bonding, the *N*-methyl resonances are observed at δ 2.48 and 2.40, respectively.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are not corrected. Nmr spectra were recorded on a Varian A-60D and the Mellon Institute 250 MHz spectrometer in deuteriochloroform with tetramethylsilane as internal standard. Thin layer chromatography (Analtech, Inc.) and preparative tlc (1.0 mm, Quantum Industries) were carried out with silica gel GF and spots were located by spraying with a 4% solution of iodine in ethanol. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan and Galbraith Laboratories, Inc., Knoxville, Tennessee. Mass spectra were determined on an LKB model 9000 spectrometer at 70 eV. All concentrations were done under reduced pressure. Drying of the organic layers was accomplished with anhydrous sodium sulfate. 7-Methoxyindole was purchased from Aldrich Chemical Company, Inc.

1-Methyl-7-Methoxyindole (**1**).

In a 300 ml. 3-necked flask, fitted with a dry-ice condenser, drying tube and cooled in dry ice were placed 70-75 ml. of liquid ammonia and 10 mg. of ferric nitrate nonahydrate. Sodium metal (1.0 g., 0.043 g.-atom) was added in small portions, while stirring (magnetic bar), always maintaining the blue color. 7-Methoxyindole (1.0 g., 6.8 mmoles) was dissolved in anhydrous ether (7 ml.) and slowly added to the mixture. After 25 minutes methyl iodide (3.0 ml., 48 mmoles) was added dropwise and the mixture stirred for an additional 30 minutes. The dry-ice and condenser were removed and the mixture allowed to stir at room temperature until all the ammonia evaporated. The resulting residue was partitioned between water and dichloromethane. The organic layer was washed once with water and dried. The solution was concentrated to give **1** as a tan solid, which appeared homogenous on tlc (benzene as eluant), weight 1.03 g. (94%). This solid was suitable for the next reaction, or could be crystallized from petroleum ether (b.p. 63-75°) to give crystalline **1**, m.p. 50-51° (reported m.p. 54.5-55.5°); mass spectrum m/e 161 (M^+).

1-Methyl-7(e)-methoxy-*cis*-octahydroindole (**3**).

A solution of the indole **1** (1.06 g., 6.6 mmoles) in 25 ml. of glacial acetic acid was diluted with 3 ml. of water, platinum oxide (0.40 g., 81% Englehard) was added and the mixture was hydrogenated at one atmosphere until no more hydrogen was consumed. The catalyst was removed by filtration, washed with water, and the combined filtrate concentrated to a small volume. The aqueous solution was made alkaline with 25% sodium hydroxide solution and the liberated oil extracted into dichloromethane. The dichloromethane layer was washed with saturated salt solution, dried and the solvent removed by distillation through a small Vigreux column. The remaining brown oil (0.97 g.) consisted of two components, 1-methyl-*cis*-octahydroindole (**2**) and **3**, in the approximate ratio of 2:3, according to the gc tracing (6' x 1/8" 3% OV-1, 115° isothermally), as well as tlc estimation. A small sample of **3** was obtained by preparative tlc (15% methanol-chloroform + 1.5% NH_4OH), nmr δ 2.48 (s, 3, N-CH_3), 3.2 (m, 1, C-2 H), 3.38 (almost s, 4, O-CH_3, C-7 H); mass spectrum m/e (relative intensity), 169 (52, M^+), 154 (66, $M^+ - CH_3$) 96 (100, $M^+ - C_4H_9O$), 83 (48, $M^+ - C_5H_{10}O$), 82 (38, 83 - H); an analytical sample of **3** was obtained by conversion to its picrate salt and recrystallization from ether, m.p. 158-160°.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.06. Found: C, 48.27; H, 5.47; N, 14.13.

1-Methyl-7(e)-hydroxy-*cis*-octahydroindole (**4**).

A portion (0.50 g.) of the crude mixture of **2** and **3** was dissolved in 1.0 ml. of concentrated hydriodic acid solution (Fisher, 57%) and refluxed for 75 minutes. The brown solution was cooled and diluted with 5 ml. of water and made alkaline with 25% sodium hydroxide solution. The liberated oil was extracted into dichloromethane, the organic layer separated and washed one time with saturated salt solution, dried, and the solvent removed by distillation through a small Vigreux column. The remaining brown oil (0.45 g.) consisted of two components, unreacted amine **2** and the alcohol **4**, as shown by combined gc-mass spectrometry. A portion of this mixture was purified by preparative tlc (15% methanol-chloroform + 1.5% ammonium hydroxide) thus enabling the isolation of the alcohol **4** as a clear oil; nmr δ 2.95 (s, 3, N-CH_3), 3.77 (m, 1, C-2H), 4.22 (m, 1, C-7 H), 6.20 (m, 1, OH); mass spectrum m/e (relative intensity) 155 (15, M^+), 96 (100), 83 (27), 82 (21).

1-Methyl-*cis*-octahydroindole (**2**) and 1-Methyl-7(e)-acetoxy-*cis*-octahydroindole (**5**).

(a) A portion (0.28 g.) of the crude mixture of **2** and **4** was dissolved in 3 ml. of acetic anhydride and then concentrated sulfuric acid (0.05 ml.) was added. This solution was stirred and heated at 60° for 65 minutes and at room temperature for 55 minutes. A small amount of ice was added to the solution and then while cooling in ice it was made alkaline with 25% sodium hydroxide solution and the product extracted into dichloromethane. The organic layer was washed once with saturated salt solution, dried and concentrated to a brown oil (0.22 g.), whose tlc showed major spots for the acetate **5** and amine **2**, as well as a small spot corresponding to the alcohol **4**. The oil was purified on four preparative tlc plates (10% methanol-chloroform + 1.5% ammonium hydroxide). The upper acetate band yielded 93 mg. of an oil whose tlc indicated about 15% hydrolysis back to the alcohol **4**. Pure acetate **5** was obtained by preparative gc (12' x 3/8" 3% OV-1, 160° isothermally), nmr δ 2.03 (s, 3, $COCH_3$), 2.40 (s, 3, N-CH_3), 3.27 (m, 1, C-2 H). An analytical sample of **5** was obtained by conversion to its picrate salt and recrystallization from isopropyl alcohol, m.p. 140-142°.

Anal. Calcd. for $C_{17}H_{22}N_4O_9$: C, 47.87; H, 5.20; N, 13.14. Found: C, 47.83; H, 5.00; N, 13.00.

The lower band from the preparative tlc afforded 13 mg. of amine **2**, which was converted to its picrate and methiodide salts. The picrate was crystallized from benzene, m.p. 205-209° (reported (5) m.p. 204° from ethanol). The methiodide was prepared by allowing an ethereal solution of **2** and methyl iodide to remain in the refrigerator overnight; recrystallization from acetone-ether gave colorless crystals, m.p. 208-209° (reported (5) m.p. 208°).

(b) 1-Methylindole (3) (2.00 g., 15.3 mmoles) was dissolved in 50 ml. of glacial acetic acid and 6 ml. of water added. Platinum oxide (0.60 g., 81% Englehard) was added and the mixture hydrogenated at one atmosphere pressure until no more hydrogen was consumed. Workup as described for the preparation of **2** and **3** gave 1.69 g. (80%) of a yellow oil, one spot on tlc corresponding to amine **2**, b.p. 57° (8 mm). A 50 mg. aliquot of **2** was converted to its picrate salt, 0.11 g., and crystallized from benzene, m.p. 204-208°; identical ir (potassium bromide) to **2**-picrate obtained by hydrogenolysis.

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