A Simple Convenient Synthesis of *trans*-1,2,3,4,4a,5,6,10b-Octahydrophenanthridines

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trans-1,2,3,4,4a,5,6,10b-Octahydrophenanthridine, the 9-methoxy analog, and 5-methyl derivatives (**6a,6b**) of each have been synthesized from *trans*-phenylcyclohexylamines (**2a,2b**) and ethyl chloroformate followed by cyclization and reduction or by cyclization, *N*-methylation and reduction. The oximes (**1a,1b**) of 2-phenylcyclohexanone and the *m*-methoxy relative, a mixture of the *syn* and *anti* isomers, were reduced to **2a** and **2b** with sodium and ethanol. Hydrogenation (platinum oxide-acetic acid) of **1a** gave in addition to **2a**, a small yield of 2-cyclohexylcyclohexylamine. Similar hydrogenation of **1b** gave only this fully reduced compound.

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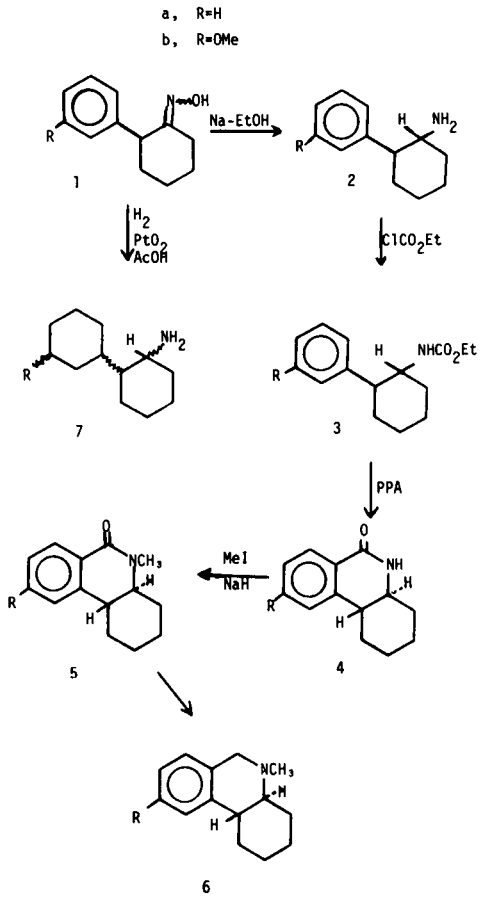
Phenanthridines and phenanthridones, basic structures in pharmacologically active compounds (1) have been synthesized by photocyclization of an *N*-substituted enamine of cyclohexanone, (2) Bischler Napieralski cyclization of the *N*-formyl derivative of 2-phenylcyclohexylamine (3,4) and related methods (5,6). In our project to make new heterocycles as pharmacologically active agents, we found a simple convenient synthesis of the title compound, it's 9-methoxy derivative and their 5-methyl homologs (**6a,6b**) *via* the respective phenanthridones, **5a,5b**, starting from 2-phenylcyclohexanones. While synthesizing these compounds, some interesting observations were made.

Masamune *et al.*, (4) reduced 2-phenylcyclohexanone oxime (**1**) in acetic acid with platinum oxide to a mixture of corresponding *cis* and *trans* amines (**2a**). When this experiment was repeated, the oxime prepared in the usual way (6) proved to be a mixture of *syn* and *anti* forms (tlc and glc analysis). Hydrogenation of **1** gave, in addition to **2a** and the corresponding *cis*-amine as reported before (4), at least two cyclohexylamines (**7a**), M^+ 181. Under similar conditions, oxime **2b** gave only fully reduced material, a mixture of 3-methoxycyclohexylcyclohexylamines (**7b**) M^+ 211. Thus the desired *trans*-amines, **2a** and **2b**, were made by reducing **1** with sodium in ethanol (4).

Compounds **2a** and **2b** and ethyl chloroformate gave carbamates **3a** and **3b** which were readily cyclized with polyphosphoric acid (PPA) to phenanthridones, **4a** and **4b** (ν CO 1660 cm^{-1}). Nmr data (δ 3.30, 2.70 - doublet of triplets, J = 11.5 Hz) indicated a *trans* B/C ring junction.



Reduction of **4** with lithium aluminum hydride gave the corresponding phenanthridines.

N-Methylphenanthridines **6** were prepared by methylation of **4** to **5** followed by lithium aluminum hydride reduction. The C-4 methylene hydrogens appear as an AB quartet, δ 3.80, 3.52 (J = 15 Hz).

EXPERIMENTAL

Melting points (uncorrected) were taken with a Thomas-Hoover apparatus. Ir spectra (chloroform) were determined on a Perkin-Elmer 257; nmr data were obtained from a 100 MHz Varian Model (TMS as internal standard). A Hitachi RMU 6E (70 eV) was used for mass spectra; a Beckamnn 55-model for glc.

Hydrogenation of **1a** and **1b**.

Acetic acid (100 ml.), **1a** (2 g.) and platinum oxide (150 mg.) were shaken under hydrogen until absorption had ceased (24 hours). After filtration of catalyst, acetic acid was removed under suction. The residue was made alkaline with 5% sodium hydroxide and the oil extracted with ether. Evaporation of the dried ether solution gave a viscous liquid (1.1 g.), a mixture of *cis* and *trans*-**2** (4). The aqueous layer gave, after 30 minutes, a white, crystalline solid (0.3 g.), m.p. 158°, M^+ 181. Tlc and glc indicated a mixture of two diastereoisomers of **7a**.

Anal. Calcd. for $C_{12}H_{23}N$: C, 79.49; H, 12.79; H, 7.73. Found: C, 79.70; H, 12.60; N, 7.88.

The benzoyl derivative of *trans*-**7a** has been reported (7).

Similarly, **1b** (1 g.), platinum oxide (100 mg.) and acetic acid (50 ml.) gave no **2b**, and 700 mg. of a diastereoisomeric mixture of 2-(3-methoxycyclohexyl)cyclohexylamine (**7b**), m.p. 143°, M^+ 211.

Anal. Calcd. for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 74.10; H, 11.76; N, 6.72.

trans-2-*m*-Methoxyphenylcyclohexylamine (**2b**).

To **1b** (8 g.) in 80 ml. of ethanol was added sodium (8 g.) in small pieces during 45 minutes. The solution was then refluxed for 1 hour, cooled, acidified with hydrochloric acid and filtered. The filtrate was extracted with ether. Drying and evaporation of the ether gave 6.2 g. (83%) of **2b**, b.p. 135°/2 mm.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.20; H, 9.48; N, 6.98.

Ethyl carbamates (**3a**, **3b**) of **2a** and **2b**.

To **2a** (4) (3.2 g.) in benzene (50 ml.) and anhydrous potassium carbonate (1.6 g.) was added gradually, ethyl chloroformate (2.2 g.) and the mixture refluxed for 1.5 hours. Filtration and removal of benzene *in vacuo* gave a thick oil which solidified on addition of petroleum ether (30-60°). Recrystallization from benzene-ether gave 3.1 g. (70%) of **3a**, m.p. 74-75°; ir (chloroform): 1710 cm^{-1}.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.62; H, 8.38; N, 5.82.

Similarly, **2b** (4 g.), ethyl chloroformate (2.6 g.), potassium carbonate (2.2 g.) and benzene (70 ml.) gave 3.2 g. of pure, liquid **3b**; ir (chloroform): 1710 cm^{-1}.

trans-1,2,3,4,4a,10b-Hexahydro-6(5*H*)phenanthridinone (**4a**).

Carbamate **3a** (3 g.) and PPA (25 g.) were heated (gently at first) on the steam bath. After 30 minutes (pink color), the mixture was treated (stirring) with 50 ml. of water and filtered. Recrystallization of the collected solid from benzene-chloroform gave 2.2 g. (90%) of **4a**, m.p. 219° [lit. (2), m.p. 218-220°]; ir (chloroform): 3390, 1660 cm^{-1}; nmr (deuteriochloroform): δ 8.10 (m, 1H, C-7, H), 7.58-7.20 (m, 3H, C-8, C-9, C-10H), 7.0 (b, 1H, NH), 3.30, 2.70 (doublets of triplets, 2H, *trans*-bridge protons, J = 11.5 Hz). The cyclohexyl protons are at δ 2.60-1.26.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.72; H, 7.32; N, 7.15.

trans-1,2,3,4,4a,10b-Hexahydro-9-methoxy-6(5*H*)phenanthridinone (**4b**).

Carbamate **3b** (2 g.) and PPA (20 g.) were kept on the steam bath for 1 hour. The red solution was diluted with water, filtered and recrystallized from chloroform-benzene to give 1.4 g. (83%) of **4b**, m.p. 205°; ir (chloroform): 3390, 1660 cm^{-1}; nmr (deuteriochloroform): δ 8.04 (d, 1H, C-7, H, J = 8 Hz), 6.90-6.60 (m, 2H, C-8, C-10H), 6.22 (b, 1H, NH), 3.82 (s, 3H, OCH_3), 3.24-3.64 (doublets of triplets, 2H, *trans*-bridge protons, J = 11.5 Hz), 2.44-1.24 (m, 8, CH_2 protons).

Anal. Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.58; H, 7.28; N, 6.22.

trans-1,2,3,4,4a,10b-Hexahydro-5-methyl-6(5*H*)phenanthridinone (**5a**).

Sodium hydride (800 mg.) was washed 3 times with petroleum ether (b.p. 30-60°). To this was added (stirring) dimethylformamide (DMF) then 2 g. of **4a** in 8 ml. of DMF. After 30 minutes, methyl iodide (1.8 g.) was added in small portions. Stirring was continued for another 20 minutes. Addition of water (50 ml.), filtration and drying and recrystallization of the precipitate from chloroform-ether gave 1.8 g. (81%) of **5a**, m.p. 143° [lit. (2), m.p. 141-143°]; ir (chloroform): 1660 cm^{-1}; nmr (deuteriochloroform): δ 3.10 (s, 3H, NCH_3). The remainder of the nmr spectrum is similar to that of **4a**.

trans-1,2,3,4,4a,10b-Hexahydro-9-methoxy-5-methyl-6(5*H*)phenanthridinone (**5b**).

Similar methylation of **4b** (2 g.) with sodium hydride (800 mg.), DMF (15 ml.) and methyl iodide (1.8 g.) gave 1.7 g. (81%) of **5b**, m.p. 113°; ir (chloroform): 1660 cm^{-1}; nmr (deuteriochloroform): δ 3.12 (s, 3H, NCH_3). The rest of the protons appear as in **4b**.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.16; H, 7.64; N, 5.86.

5-Methyl-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (**6a**).

Compound **5a** (2.5 g.) in 50 ml. of ether was added slowly to a stirred mixture of lithium aluminum hydride (1.4 g.) and 30 ml. of ether. It was stirred for 1 hour, treated carefully with ice-water and extracted with ether. The dried ether was distilled to give 1.0 g. (50%) of **6a**, b.p. 110°/2 mm. [lit. (4), b.p. 161-163°/15 mm.]; nmr (deuteriochloroform): δ 7.22-6.82 (m, 4H, aromatic), 3.80-3.52 (AB type q, 2H, J = 11.5 Hz, *trans*-bridge protons), 2.24 (s, 3H, NCH_3), 1.86-1.0 (m, 8H, C-1, C-2, C-3, C-4 H).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.38; H, 9.30; N, 7.12.

9-Methoxy-5-methyl-*trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (**6b**).

Reduction of **5b** (2 g.) with lithium aluminum hydride (1.4 g.) as described above gave 1.1 g. of liquid **6b**; nmr (deuteriochloroform): δ 6.91-6.47 (m, 3H, aromatic), 3.78-3.47 (AB type q, 2H, J = 15 Hz, C-6), 3.71 (s, 3H, OCH_3), 2.40-2.10 (doublets of triplets, 2H, J = 11.5 Hz, *trans*-bridge protons), 2.25 (s, 3H, NCH_3), 1.0-2.0

(m, 8H, C-1, C-2, C-3, C-4).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.76; H, 8.98; N, 6.20.

Reduction of **4a** and **4b**.

Compound **4a** (0.6 g.) in ether (30 ml.) was added slowly to a stirred mixture of lithium aluminum hydride (0.5 g.) and 30 ml. of ether. The mixture was stirred for 1.5 hours, then refluxed for 2.5 hours. After quenching carefully with ice-water, extraction with ether, and evaporation of the dried solution, a semisolid was obtained which crystallized from ether in a yield of 180 mg.; *trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine, m.p. 88-89° [lit. (4), m.p. 89.5-90.5°].

Similarly, **4b** (0.4 g.) gave 125 mg. of *trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine, m.p. 106°, M^+ 217.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.62; H, 8.46; N, 6.64.

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