A novel synthesis of the phenanthroindolizidine alkaloid ring system from phenanthrene

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A novel synthesis of the phenanthroindolizidine alkaloid ring system (16) from phenanthrene (2) is described.

In connection with our recent finding on the efficient synthesis of phenanthrene derivatives, its utility for the construction of the phenanthroindolizidine alkaloids was examined by synthesizing the ring system (16) from phenanthrene (2). Since there has been no example starting from 9,10-unsubstituted phenanthrene derivatives in the synthesis of the phenanthroindolizidine alkaloids, e.g., tylophorine (1), the attempt seemed to be worthwhile.

Chart 1

\[ \text{Chart 1} \]

\[ \text{(1) } R=\text{OMe} \]

\[ \text{(16) } R=\text{H} \]
Following Billups' method\(^4\), 7,7-dichlorodibenzo[\(\alpha,\gamma\)]bicyclo-[4.1.0]heptane(3)\(^5\), derived from phenanthrene(2) and dichlorocarbene, was treated with potassium \(\text{ter.butoxide}(2\text{eq.})\) in tetrahydrofuran at 0° to give an oily \(9-(\text{chloro-2-tetrahydrofuryl-methyl})\)-phenanthrene(5) in good yield \(\text{via}\) the chlorocarbene insertion to the solvent(Chart 2). Dehydrochlorination of 5 was effected by boiling with pyridine in dimethylformamide(1:8) to give the enol ether(6) as a stereoisomeric mixture which, without separation, on hydrolysis with ethanolic hydrochloric acid(2%) at room temperature afforded the ketol(7), mp 110°, \(\text{ir(nujol)}\) 3300, 1695 cm\(^{-1}\), \(\text{NMR}(\text{CDCl}_3)(\delta)\) 1.75(3H, m, disapp. 1H with \(\text{D}_2\text{O}\)), 3.47(2H, t, \(J=6\text{Hz}\)), 3.52(2H, t, \(J=7\text{Hz}\)), 4.09(2H, s), 7.45-7.95(7H, m), 8.50-8.75(2H, m), Mass(\(m/e\)) 278(\(M^+\)), in 30.1% yield from 5. The ketol(7) was converted to the benzylamino-alcohol(9), an oil, \(\text{ir(neat)}\) 3300 cm\(^{-1}\), \(\text{NMR}(\text{CDCl}_3)(\delta)\) 1.5-1.9 (4H, m), 3.15-4.25(8H, m, disapp. 1H with \(\text{D}_2\text{O}\)), 7.2-7.8(12H, m),
8.5-8.8(2H, m), 9.8-10.2(1H, br.s, disapp. with D₂O), in 55% yield, by treating with benzylamine, followed by reduction with sodium borohydride. After treatment of 9 with thionyl chloride in chloroform, the crude chloride(10) was stirred with ethanolic potassium carbonate at room temperature to give the N-benzyl-pyrrolidine derivative(11), an oil, NMR(CDC₃)(δ) 1.5-1.8(4H, m), 2.8-4.2(7H, m), 7.2-8.02(12H, m), 8.45-8.75(2H, m), Mass(m/e) 351(M⁺), in 91% from 9. The carbamate(12), an oil, ir(neat) 1680cm⁻¹, NMR(CDC₃)(δ) 1.6-2.1(4H, m), 2.7(1H, m), 3.5(2H, br.t), 4.0-4.5(2H, m), 5.2(2H, s), 7.15-7.9(12H, m), 8.5-8.75(2H, m), converted from 11 with carbobenzoxy chloride in the presence of potassium hydrogen carbonate in boiling chloroform, was heated at 120° in ethanolic hydrochloric acid(5%) to produce the secondary amine(13), mp 205-207°, ir(nujol) 3300cm⁻¹, NMR(CDC₃)(δ) 1.4-2.1(4H, m), 2.84(1H, br.s, disapp. with D₂O), 2.6-3.6 (5H, m), 7.4-8.2(7H, m), 8.5-8.73(2H, m), in total yield 73.6% from 11. Standard formic acid treatment of 13 yielded the formamide(14), an oil, which on cyclization with phosphorus oxychloride, followed by reduction with sodium borohydride, gave the required ring system(2,3,6,7-tetrademethoxytylophorine)(16), mp 167°(lit. 7°, 170°), NMR(CDC₃)(δ) 1.5-2.2(4H, m), 2.3-2.7(3H, m), 2.9-3.4(2H, m), 3.65(1H, d, J=18Hz), 4.7(1H, d, J=18Hz), 7.4-8.1(6H, m), 8.5-8.8(2H, m), Mass(m/e) 273(M⁺), 204(base peak), in 72% yield from 13.
Chart 3

(5) \rightarrow \begin{array}{c}
\text{H} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{4-phenyl}
\end{array} \rightarrow \begin{array}{c}
\text{N-Bz}
\end{array} \rightarrow \begin{array}{c}
\text{OH}
\end{array} \rightarrow \begin{array}{c}
\text{C1}
\end{array} \rightarrow \begin{array}{c}
\text{N-Bz}
\end{array} \rightarrow \begin{array}{c}
\text{OH}
\end{array} \rightarrow \begin{array}{c}
\text{N-Bz}
\end{array} \rightarrow \begin{array}{c}
\text{N-Bz}
\end{array}

(12) \rightarrow \begin{array}{c}
\text{CO}_2\text{Bz}
\end{array} \rightarrow \begin{array}{c}
\text{NH}
\end{array} \rightarrow \begin{array}{c}
\text{NH}
\end{array} \rightarrow \begin{array}{c}
\text{NH}
\end{array} \rightarrow \begin{array}{c}
\text{N}
\end{array}
The synthesis just described would be promising to the conversion of 9,10-unsubstituted phenanthrene derivatives into the phenanthroindolizidine alkaloids. Application of this method to the synthesis of an antitumor phenanthroindolizidine alkaloid, tylophorine (1), is currently being carried out in this laboratory.

REFERENCES

1 To be published elsewhere.

Received, 6th February, 1976