A NOVEL SYNTHESIS OF THE PHENANTHROINDOLIZIDINE ALKALOID RING SYSTEM FROM PHENANTHRENE

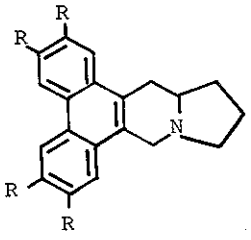
Seiichi Takano,* Kohtaro Yuta, and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

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[1], its utility for the construction of the phenanthroindolizidine alkaloids[2] 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)[3], the attempt seemed to be worthwhile.

Chart 1

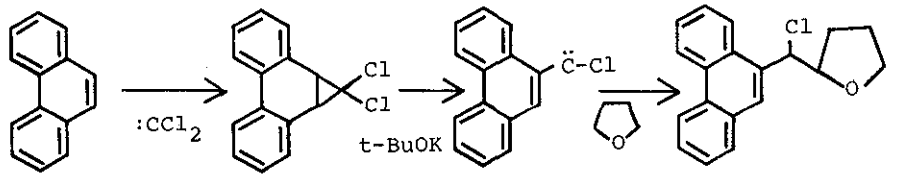


(1) R=OMe

(16) R=H

Following Billups' method[4], 7,7-dichlorodibenzo[*a*,*e*]bicyclo-[4.1.0]heptane(3)[5], derived from phenanthrene(2) and dichlorocarbene, was treated with potassium *ter*.butoxide(2eq.) in tetrahydrofuran at 0° to give an oily 9-(chloro-2-tetrahydrofuryl-methyl)-phenanthrene(5) in good yield *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,

Chart 2

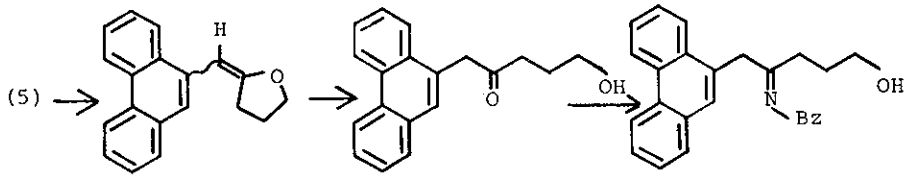


(2) (3) (4) (5)

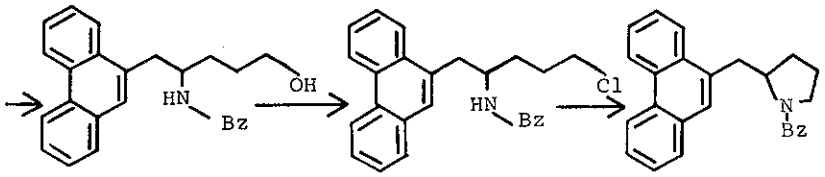
without separation, on hydrolysis with ethanolic hydrochloric acid(2%) at room temperature afforded the ketol(7), mp 110°, ir(nujol) 3300, 1695cm^{-1}, NMR($CDCl_3$)(δ) 1.75(3H, m, disapp. 1H with D_2O), 3.47(2H, t, J=6Hz), 3.52(2H, t, J=7Hz), 4.09(2H, s), 7.45-7.95(7H, m), 8.50-8.75(2H, m), Mass(m/e) 278(M^+), in 30.1% yield from 5. The ketol(7) was converted to the benzylamino-alcohol(9), an oil, ir(neat) 3300cm^{-1}, NMR($CDCl_3$)(δ) 1.5-1.9 (4H, m), 3.15-4.25(8H, m, disapp. 1H with D_2O), 7.2-7.8(12H, m),

8.5-8.8(2H, m), 9.8-10.2(1H, br.s, disapp. with D_2O), in 55% yield, by treating with benzylamine, followed by reduction with sodium borohydride. After treatment of 9 with thionyl chloride in chlorofoum, the crude chloride(10) was stirred with ethanolic potassium carbonate at room temperature to give the N-benzyl-pyrrolidine derivative(11), an oil, NMR($CDCl_3$)(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($CDCl_3$)(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[6], was heated at 120° in ethanolic hydrochloric acid(5%) to produce the secondary amine(13), mp 205-207°, ir(nujol) 3300cm^{-1}, NMR($CDCl_3$) (δ) 1.4-2.1(4H, m), 2.84(1H, br.s, disapp. with D_2O), 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($CDCl_3$)(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.

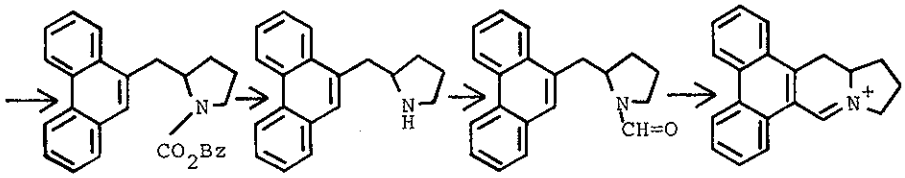
Chart 3



(6) (7) (8)



(9) (10) (11)



(12) (13) (14) (15)

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.

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