

A NEW SYNTHESIS OF PHENANTHRIDINE DERIVATIVES

Hideo Iida,* Toshiyuki Takahashi, Mamoru Narimiya, Hiroshi Takayanagi,
and Toyohiko Kikuchi

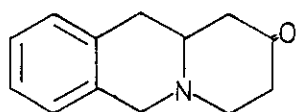
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03
Japan

Abstract ---Reduction of 4-(3-oxobutyl)isocarbostyryl derivatives
gave 4-(3-oxobutyl)-1,2-dihydroisoquinolines which were treated with
12 N hydrochloric acid to give cis-phenanthridine derivatives.

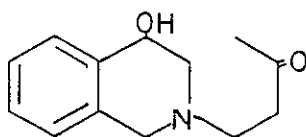
Bobbitt et al. reported the synthesis of benzo[b]quinolizine derivative (I)
from the N-(3-oxobutyl)-1,2-dihydroisoquinoline derivative (II).¹⁾ We have now
investigated the reactivity of position 3 in 1,2-dihydroisoquinoline derivative,
which was prepared from isocarbostyryl derivative,²⁾ and have developed the
synthesis of phenanthridine derivative from 4-(3-oxobutyl)isocarbostyryl derivatives
(Va,b), which were prepared from 4-(3-oxobutyl)homophthalimides (IVa,b).

Michael reaction of the homophthalimides (IIIa,b) with methyl vinyl ketone in
the presence of Triton-B gave the compounds (IVa,b) in 80-90% yield. N-Methyl
derivative (IVa) showed mp 65-67°C; IR(nujol) cm^{-1} : 1710, 1700 and 1650; ^1H NMR
(CDCl_3) δ 2.10 (3H, s, $-\text{CH}_3$), 3.30 (3H, s, $\text{N}-\text{CH}_3$), 3.95 (1H, m, $\text{C}_4\text{-H}$), 8.20 (1H, dd,
 $J = 12, 2 \text{ Hz}$, $\text{C}_8\text{-H}$); MS m/e 245 (M^+). N-Benzyl derivative (IVb) showed mp 110-112°C;
IR(nujol) cm^{-1} : 1710, 1700 and 1650; ^1H NMR(CDCl_3) δ 2.00 (3H, s, $-\text{CH}_3$), 3.90
(1H, m, $\text{C}_4\text{-H}$), 5.20 (2H, s, $-\text{CH}_2\text{Ph}$), 8.21 (1H, dd, $J = 12, 2 \text{ Hz}$, $\text{C}_8\text{-H}$); MS m/e 321
(M^+).

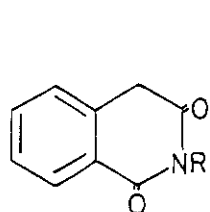
Ketalization of IVa,b with ethylene glycol and p-toluenesulfonic acid in reflux-
ing benzene gave the ketal in 90% yield, whose reduction with sodium borohydride
followed by treatment with hydrochloric acid gave the 4-(3-oxobutyl)isocarbostyryl
(Va,b) in 80-90% yield. N-Methylisocarbostyryl derivative (Va) showed mp 105-
107°C; IR(nujol) cm^{-1} : 1700 and 1640; ^1H NMR(CDCl_3) δ 2.10 (3H, s, $-\text{CH}_3$) 3.52 (3H,
s, $-\text{NCH}_3$), 6.95 (1H, s, $\text{C}_3\text{-H}$), 8.43 (1H, dd, $J = 12, 2 \text{ Hz}$, $\text{C}_8\text{-H}$); MS m/e 229 (M^+).
N-Benzyl derivative (Vb) showed mp 115-117°C; IR(nujol) cm^{-1} : 1700 and 1650;



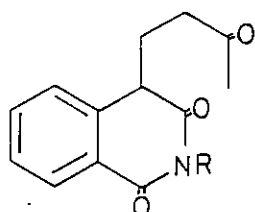
(I)



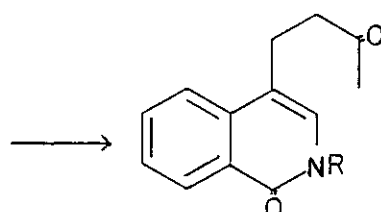
(II)



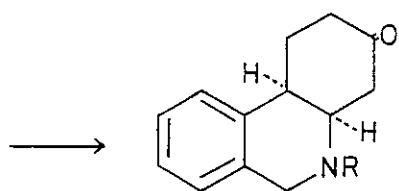
(IIIa,b)



(IVa,b)

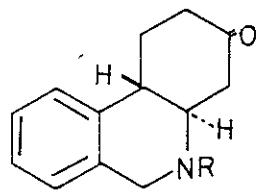


(Va,b)

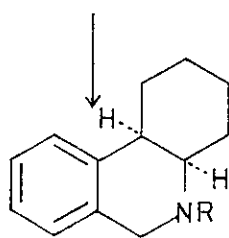


(VIa,b)

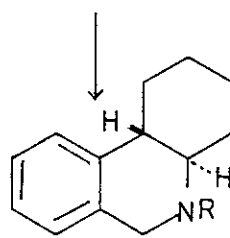
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(VIIa,b)



(VIIIa,b)



(IXa,b)

a: R = Me

b: R = CH₂Ph

^1H NMR(CDCl_3) δ 2.10 (3H, s, $-\text{CH}_3$), 2.81 (4H, m, $-\text{CH}_2 \times 2$), 5.20 (2H, s, $-\text{CH}_2\text{Ph}$), 6.95 (1H, s, $\text{C}_3\text{-H}$), 8.50 (1H, dd, $J = 12, 4$ Hz, $\text{C}_8\text{-H}$); MS m/e 305 (M^+).

Compound (Va) was converted in the usual manner in 90% yield to the ketal which was reduced with lithium aluminum hydride to give 1,2-dihydroisoquinoline derivative and the resulting product was immediately treated with 12 N hydrochloric acid at 100°C for 1 h, followed by a standard work-up, gave a mixture consisting of two products by thin layer chromatography. Column chromatography (basic alumina, benzene elution) gave 1,2,4a,5,6,10b-hexahydrophenanthridin-3(4H)-one (VIa) as colorless needles and VIIa as colorless prisms in a ratio of 18:1 in 90% yield. The major compound (VIa) showed mp $57\text{--}59^\circ\text{C}$; IR(nujol) cm^{-1} : 1700; ^1H NMR(CDCl_3) δ 2.39 (3H, s, $-\text{NCH}_3$), 2.60 (2H, m, $\text{C}_2\text{-H}_2$), 3.10 (2H, m, $\text{C}_4\text{-H}_2$), 3.52, 3.85 (2H, ABq, $J = 15$ Hz, $\text{C}_6\text{-H}_2$); MS m/e 215 (M^+). The minor product (VIIa) showed mp $101\text{--}104^\circ\text{C}$; IR(nujol) cm^{-1} : 1700; ^1H NMR(CDCl_3) δ 2.32 (3H, s, $-\text{NCH}_3$), 3.60, 3.90 (2H, ABq, $J = 15\text{Hz}$, $\text{C}_6\text{-H}_2$); MS m/e 215 (M^+). The above spectral data suggested that two products VIa and VIIa differ in their B/C-ring fusion.

Under analogous condition, N-benzyl derivative (Vb) led to the 5-benzyl-1,2,4a,5,6,10b-hexahydrophenanthridin-3(4H)-one (IVb) and VIIb in a ratio of 30:1 in 90% yield respectively. The major product (VIb) showed mp $82\text{--}85^\circ\text{C}$; IR(nujol) cm^{-1} : 1700; ^1H NMR(CDCl_3) δ 3.52, 3.95 (2H, ABq, $J = 13$ Hz, $\text{C}_6\text{-H}_2$), 3.70 (2H, d, $J = 8$ Hz, $-\text{CH}_2\text{Ph}$); MS m/e 291 (M^+). The minor product (VIIb) showed mp $127\text{--}129^\circ\text{C}$; IR(nujol) cm^{-1} : 1700; ^1H NMR(CDCl_3) δ 3.40, 3.85 (2H, ABq, $J = 13$ Hz, $\text{C}_6\text{-H}_2$), 3.70 (2H, d, $J = 8$ Hz, $-\text{CH}_2\text{Ph}$); MS m/e 291 (M^+).

The stereochemistry of the products unequivocally established by conversion into the known compounds, cis-1,2,3,4,4a,5,6,10b-octahydrophenanthridine derivative (VIIIa)³⁾ and trans-1,2,3,4,4a,5,6,10b-octahydrophenanthridine derivatives (IXa),³⁾ (IXb).⁴⁾ Namely, the hydrazone prepared from (VIa) and tosyl hydrazine was reduced with sodium borohydride to the VIIIa, which was identical by spectral (IR) comparison with the authentic samples of B/C-cis-compound (VIIIa). Under analogous condition, VIIa and VIIb led to IXa and IXb, which were identical by spectral (IR) comparison with the authentic samples of B/C-trans-compounds (IXa) and (IXb) respectively.

The synthesis of phenanthridine derivative has been applied to that of natural products.

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