HETEROCYCLES, Vol 20, No 2, 1983

A NEW SYNTHESIS OF PHENANTHRIDINE DERIVATIVES

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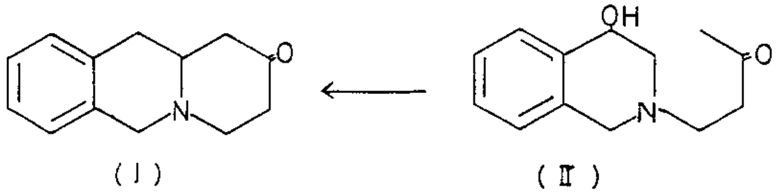
Abstract ---Reduction of 4-(3-oxobutyl)isocarbostyril derivatives gave 4-(3-oxobutyl)-1,2-dihydroisoquinolines which were treated with 12 N hydrochloric acid to give *cis*-phenanthridine derivatives.

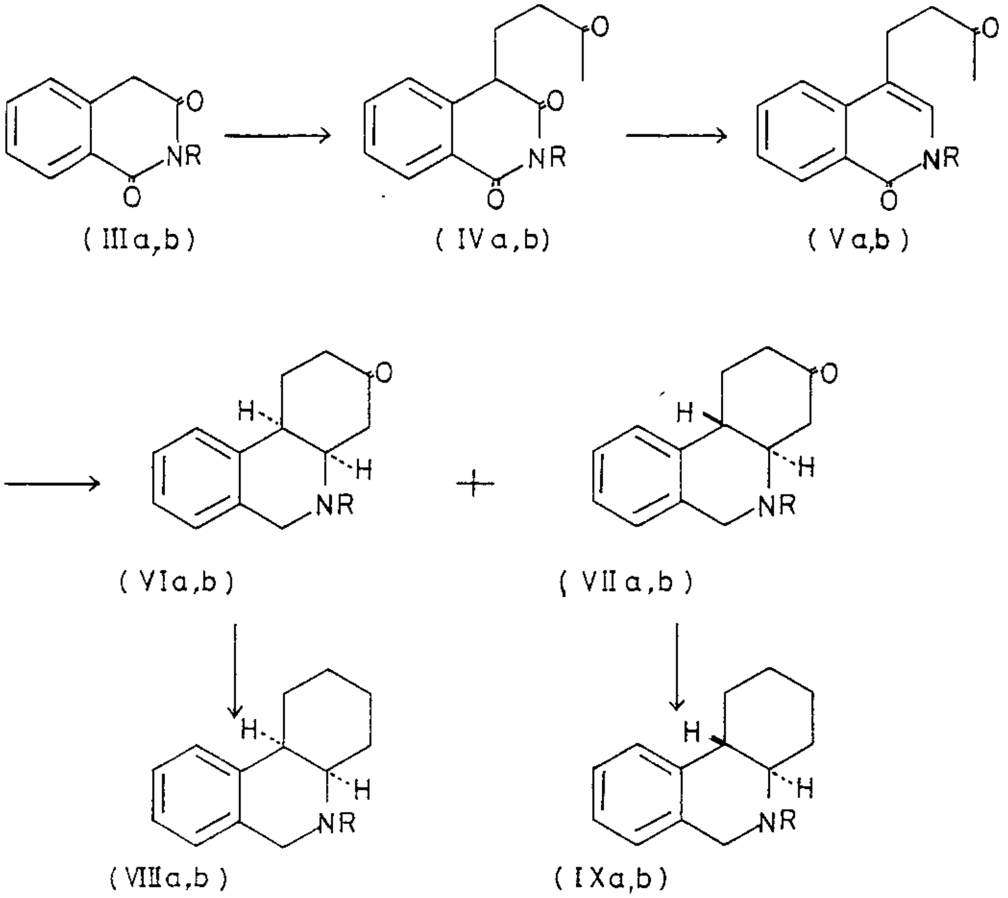
Bobbitt et al. reported the synthesis of benzo[b]quinolizine derivative (I) from the N-(3-oxobutyl)-1,2-dihydroisoquinoline derivative (II).1) We have now investigated the reactivity of position 3 in 1,2-dihydroisoquinoline derivative, which was prepared from isocarbostyril derivative,2) and have developed the synthesis of phenanthridine derivative from 4-(3-oxobutyl)isocarbostyril 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, $-CH_3$), 3.30 (3H, s, $N-CH_3$), 3.95 (1H, m, C_4-H), 8.20 (1H, dd, J = 12, 2 Hz, C_8-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, $-CH_3$), 3.90 (1H, m, C_4-H), 5.20 (2H, s, $-CH_2Ph$), 8.21 (1H, dd, J = 12, 2 Hz, C_8-H); MS m/e 321 (M^+).

Ketalization of IVa,b with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene gave the ketal in 90% yield, whose reduction with sodium borohydride followed by treatment with hydrochloric acid gave the 4-(3-oxobutyl)isocarbostyril (Va,b) in 80-90% yield. N-Methylisocarbostyril derivative (Va) showed mp 105-107°C; IR(nujol) cm^{-1}: 1700 and 1640; ^1H NMR($CDCl_3$) δ 2.10 (3H, s, $-CH_3$) 3.52 (3H, s, $-NCH_3$), 6.95 (1H, s, C_3-H),8.43 (1H, dd, J = 12, 2 Hz, C_8-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)　(VIIa,b)

(VIIIa,b)　(IXa,b)

a: R = Me
b: R = CH_2Ph

^{1}H NMR($CDCl_3$) δ 2.10 (3H, s, $-CH_3$), 2.81 (4H, m, $-CH_2$x2), 5.20 (2H, s, $-CH_2Ph$), 6.95 (1H, s, C_3-H), 8.50 (1H, dd, J = 12, 4 Hz, C_8-H); MS m/e 305 (M^+).

Compound (Va) was converted in the usual manner in 90% yield to the ketal which was reduced wuth 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 standerd 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 57-59°C; IR(nujol) cm^{-1}: 1700; ^{1}H NMR($CDCl_3$) δ 2.39 (3H, s, $-NCH_3$), 2.60 (2H, m, C_2-H_2), 3.10 (2H, m, C_4-H_2), 3.52, 3.85 (2H, ABq, J = 15 Hz, C_6-H_2); MS m/e 215 (M^+). The minor product (VIIa) showed mp 101-104°C; IR(nujol) cm^{-1}: 1700; ^{1}H NMR($CDCl_3$) δ 2.32(3H, s, $-NCH_3$), 3.60, 3.90 (2H, ABq, J = 15Hz, C_6-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 82-85°C; IR(nujol) cm^{-1} 1700; ^{1}H NMR($CDCl_3$) δ 3.52, 3.95 (2H, ABq, J = 13 Hz, C_6-H_2), 3.70 (2H, d, J = 8 Hz, $-CH_2Ph$); MS m/e 291 (M^+). The minor product (VIIb) showed mp 127-129°C; IR (nujol) cm^{-1}: 1700; ^{1}H NMR($CDCl_3$) δ 3.40, 3.85 (2H, ABq, J = 13 Hz, C_6-H_2), 3.70 (2H, d, J = 8 Hz, $-CH_2Ph$); 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.

REFERENCES

1) J. M. Bobbitt and T. E. Moore, *J. Org. Chem.*, 1968, **33**, 2958.

2) H. Iida, K. Takahashi, and T. Kikuchi, *Heterocycles,* 1976, **4**, 1497.

3) T. Masamune, M. Ohno, M. Koshi, S. Ohuchi, and Iwadare, *J. Org. Chem.*, 1964 **29**, 1419.

4) I. Ninomiya, T. Naito, and T. Kiguchi, *J. Chen. Soc. Perkin I,* 1973, 2257.

Received, 12th July, 1982