HETEROCYCLES. V.[1] KEY INTERMEDIATES FOR CORYNOLINE ANALOGUES[2]

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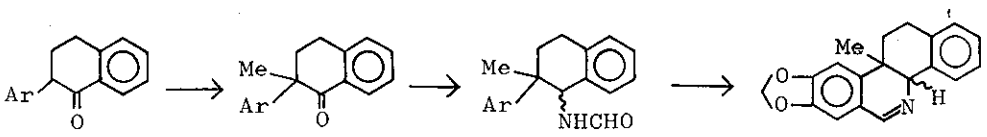
The 2-aryl-2-methyl-1-tetralone (2), which is derived from the 2-aryl-1-tetralone (1), affords the cis (5) and trans tetrahydrobenzo/c/phenanthridine (6) by the Leuckart and Bischler-Napieralski reactions. The methiodide (7) of 5 is converted into the cis lactam (10) via oxidation of the pseudo cyanide (9). On bromination and successive dehydrobromination 2 gives the enone (13) which affords the cis (16) and trans dihydrobenzo/c/phenanthridine (17) by the same procedures as above. The methiodide (18) of 16 is reduced to give the cis tetrahydrobenzo/c/phenanthridine (19). The compounds (10) and (19) can be connected with the synthetic methods of corynoline analogues, which were already known.

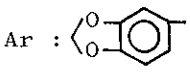
The synthetic method of benzo/c/phenanthridines, which started from condensation of aromatic aldehydes and acetophenones, was

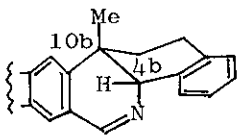
established as an useful one.[3] We have attempted to apply it to syntheses of corynoline and its analogues. Fortunately, since the syntheses of corynoline and its analogues have been achieved,[4] the objective of the present work is to obtain key intermediates for them by the above method.

The 2-aryl-1-tetralone (1), mp 135-136.5°, was smoothly prepared by starting from piperonal and acetophenone. On methylation with methyl iodide in the presence of sodium hydride 1 afforded the 2-aryl-2-methyl-1-tetralone (2), mp 104.5-105°, in 84 % yield, whose NMR spectrum (60 MHz) showed a three-protons singlet for the newly introduced methyl group at δ 1.50. The Leuckart reaction of 2 gave a mixture of the cis (3) and trans amide (4) in 71 % yield, whose purification by recrystallization and alumina chromatography provided 3 and 4 as oil and colorless prisms of mp 247-248°, respectively. The structures of 3 and 4 are assigned on the basis of those of the compounds obtained by the next reaction. The Bischler-Napieralski reaction of 3 and 4 gave the cis (5), mp 164-165°, and trans tetrahydrobenzo/c/phenanthridine (6), mp 157-158.5°, in 74 and 82 % yields, respectively. Their structures are examined by the NMR spectroscopy. From the allylic coupling constants ($J_{4b,6}$), the 4b-H's in both compounds are considered to be axial to the B ring.[5] As can be seen from the cis conformer (5a), the 4b-H and 10b-Me group lie in the deshielding zones of the D and A rings, respectively. As a result, downfield shifts of their chemical shifts are predictable. On examination of the stereostructure (6a) a downfield shift of the 4-H is

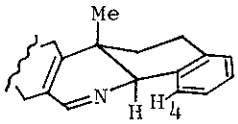


1 2 3: cis 4: trans 5: cis 6: trans

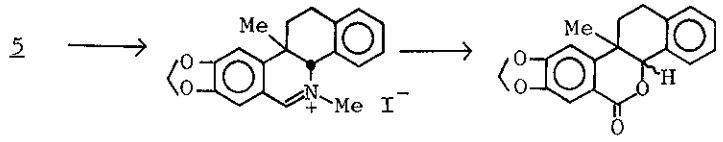




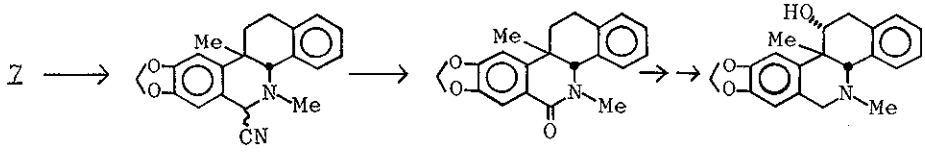
5a



6a



7 8



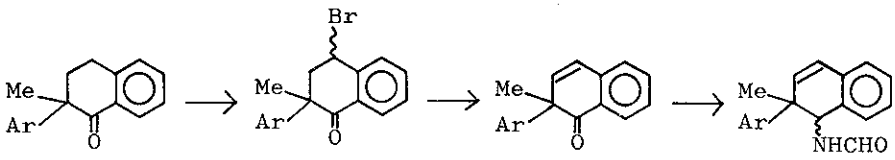
9 10 11

Chart 1

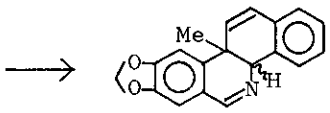
anticipated for the trans isomer owing to interaction of the nitrogen lone pair.[6] Their NMR data (100 MHz) are the follows: 5; δ 7.51 (1H, q, J 8 and 3 Hz, 4-H), 4.56 (1H, d, J 3 Hz, 4b-H), 1.30 (3H, s, 10b-Me). 6; δ 8.07 (1H, q, J 8 and 3 Hz, 4-H), 4.28 (1H, d, J 3 Hz, 4b-H), 0.85 (3H, s, 10b-Me). From the above considerations and NMR data, 5 and 6 can be assigned to be the cis and trans isomers, respectively. The Bischler-Napieralski reaction of the above mixture of 3 and 4 without separation gave 5 and 6 in an approximate ratio of 2.3:1.

On treatment of 5 with methyl iodide the methiodide (7), mp 227-228°, was quantitatively obtained. Oxidation of 7 with potassium ferricyanide in the presence of potassium hydroxide, unexpectedly, gave the lactone (8), mp 220°, having no nitrogen atom in 53 % yield. Its IR spectrum (KBr) showed the carbonyl band of the lactone group at 1715 cm^{-1}. After conversion of 7 with sodium cyanide into the pseudo cyanide (9) (87 %), mp 172-175°, successive oxidation of 9 gave the cis lactam (10), mp 250°, in 91 % yield. IR ($CHCl_3$): 1638 cm^{-1} (C=O of lactam). NMR (100 MHz): δ 7.40 (1H, s, 7-H), 7.27-6.87 (4H, m, D ring-H's), 6.71 (1H, s, 10-H), 5.90 (2H, q, J 1.5 Hz, OCH_2O), 4.25 (1H, s, 4b-H), 3.46 (3H, s, 5-Me), 2.82 (2H, m, 12-H_2), 2.44 (1H, m, 11-H_A), 2.00 (1H, m, 11-H_B), 1.35 (3H, s, 10b-Me). The synthetic pathway from 10 to the corynoline analogue (11) was reported.[4a]

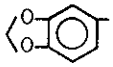
Bromination of 2 (→ 12) with N-bromosuccinimide and successive treatment with 1,5-diazabicyclo/5.4.0/undecene-5 afforded the enone (13) as oil in 57 % yield. Its NMR spectrum (100 MHz)

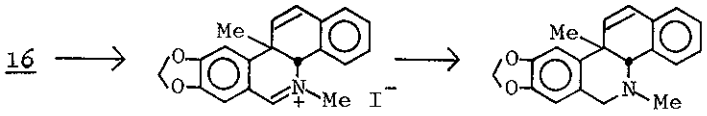


2 12 13 14: cis 15: trans

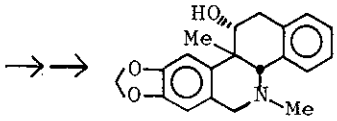


16: cis
17: trans

Ar: 



18 19



11

Chart 2

showed two one-proton doublets (J 10 Hz) at δ 6.70 and 6.22, the presence of the double bond being supported. The Leuckart reaction of 13 gave the cis (14) and trans amide (15) as oil in 52 and 30 yields, respectively. Their structures are assigned on the basis of the compounds obtained by the next reaction. The cis amide (14) afforded the cis dihydrobenzo/c/phenanthridine (16) as oil in 58 % yield by the Bischler-Napieralski reaction. NMR (100 MHz): δ 7.39 (1H, q, J 9 and 3 Hz, 4-H), 6.71 (1H, s, 10-H), 5.83 (1H, d, J 10 Hz, 11-H), 4.76 (1H, d, J 3 Hz, 4b-H), 1.37 (3H, s, 10b-Me). The trans amide (15) gave the trans dihydrobenzo/c/phenanthridine (17), mp 131-132°, in 43 % yield. NMR (100 MHz): δ 8.14 (1H, q, J 6 and 2 Hz, 4-H), 6.90 (1H, s, 10-H), 6.60 (1H, d, J 10 Hz, 11-H), 4.59 (1H, d, J 3 Hz, 4b-H), 0.82 (3H, s, 10b-Me). From examinations of the Dreiding models and similar considerations to those in the cases of 5 and 6, downfield shifts of the 4b-H and 10b-Me protons in 16 and the 4-H in 17 are predicted. Further, since the 11-H in 16 lies in the shielding zones of the A ring, this proton must be shielded. Owing to steric effect, the 10- and 11-H in 17 are expected to shift to lower fields. The NMR data of 16 and 17 are in accord with the above considerations.

The methiodide (18), mp 241-242°, (81 %), obtained from 16 was reduced with sodium borohydride to give the cis tetrahydrobenzo/c/phenanthridine (19), mp 152-153°, in 84 % yield. NMR (100 MHz): δ 7.38-7.02 (4H, m, D ring-H's), 6.91 (1H, s, 10-H), 6.49 (1H, s, 7-H), 6.40 (1H, d, J 10 Hz, 12-H), 5.92 (1H, q, J 10 and 2 Hz, 11-H), 5.92 (2H, s, OCH_2O), 3.81 (1H, d, J 15 Hz,

6-H_A), 3.65 (1H, d, J 15 Hz, 6-H_B), 3.24 (1H, d, J 2 Hz, 4b-H), 2.05 (3H, s, 5-Me), 1.23 (3H, s, 10b-Me). The cis tetrahydrobenzo/c/phenanthridine (19) can be, also, connected with the synthesis of 11.[4b]

REFERENCES AND NOTES

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Received, 13th April, 1977