SYNTHESIS OF ALKALOIDS, (±)-SCELETIUM ALKALOID A_4 AND (±)-N-ACETYLTORTUOSAMINE

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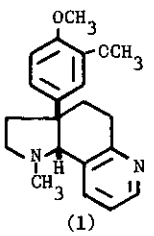
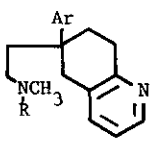
Abstract —— Synthesis of alkaloids, (±)-Sceletium alkaloid A_4 and (±)-N-acetyltortuosamine, was accomplished by application of a new method for constructing cycloalkenopyridines by thermal rearrangement of oxime O-allyl ethers.

Sceletium alkaloid A_4 (1)[1a-c] and N-acetyltortuosamine (2),[2] characterized by 5,6,7,8-tetrahydroquinoline structure, were isolated from Sceletium species and syntheses of the former have been completed by several groups.[3-6] We aimed at an alternative synthesis of these alkaloids by application of a new synthetic method[7] for constructing cycloalkenopyridine ring system.

(±)-Mesembrine, which was synthesized from 3,4-dimethoxyphenylacetonitrile by tracing the method reported by Stevens and Wentland,[8] was treated with O-allylhydroxylamine (4) in ethanol in the presence of sodium acetate to give (±)-mesembrine oxime O-allyl ether (5)[9] as an oil in 75% yield. Heating of the oxime O-allyl ether (5) in a sealed glass tube at 170-180°C (bath temperature) under air gave two products as expected, both of which were isolated in pure forms by preparative thin layer chromatography on silica gel. The less-polar one[10] was obtained in 18% isolated yield, and its spectral data and mp (153-155°C) exhibited good identity with those of (±)-Sceletium alkaloid A_4 reported in literature.[1a,b] The other was obtained as a colorless oil in 20% isolated yield, the spectroscopic properties of which suggested the structure (6)[11] as the regioisomer of (1). Hydrogenation (H_2/Pd-C) of (1) gave (±)-tortuosamine (7),[1b,c,12] the fact confirming, in turn, the synthesis of (1). Acetylation of (±)-tortuosamine (7) gave (±)-N-acetyltortuosamine (2)[13] in 83% yield. Spectroscopic properties of the latter showed good agreement with those described literature.[2]

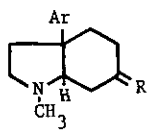


(1)



(2) R= $COCH_3$

(7) R= H



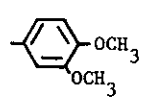
(3) R= O

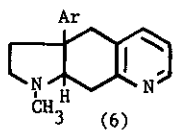
(5) R= $NOCH_2CH=CH_2$

$CH_2=CHCH_2ONH_2$

(4)

Ar=





(6)

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2) P. W. Jeffs, T. M. Capps, and R. Redfearn, J. Org. Chem., 1982, 47, 3611.

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9) IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630 (C=N); ^{1}H-NMR ($CDCl_3$) δ:2.35 (3H, s, NCH_3), 3.85 (6H, s, OCH_3 x2), 4.49 (2H, m, O-CH_2), 5.14 (2H, m, =CH_2), 6.00 (1H, m, -CH=); MS m/z 344 (M^+).

10) mp 153-155°C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1580; ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s, NCH_3), 3.72 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 6.51-6.60 (3H, aromatic-H), 7.17 (1H, dd, J=5 and 8Hz, 3-H), 7.56 (1H, dd, J=2 and 8Hz, 4-H), 8.47 (1H, dd, J=2 and 5Hz, 2-H); MS m/z: 324.1832 (M^+, calcd for $C_{20}H_{24}N_2O_2$, 324.1838).

11) IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1590; ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s, NCH_3), 3.79 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.72-6.79 (3H, m, aromatic-H), 7.03 (1H, dd, J=5 and 8Hz, 3-H), 7.27 (1H, dd, J=2 and 8Hz, 4-H), 8.41 (1H, dd, J=2 and 5Hz, 2-H); MS m/z: 324.1842 (M^+, calcd for $C_{20}H_{24}N_2O_2$, 324.1838).

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13) mp 122-124°C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.83 and 1.94 (3H, 2s, $COCH_3$), 2.76 and 2.81 (3H, 2s, NCH_3), 3.81, 3.84, and 3.86 (6H, 3s, OCH_3 x2)(2:1:1), 7.09 (1H, dd, J=5 and 8Hz, 3-H), 7.50 (1H, dd, J=2 and 8Hz, 4-H), 8.38 (1H, dd, J=2 and 5Hz, 2-H); ^{1}H-NMR (DMSO-D_6) at 90°C δ: 1.80 (3H, br.s, $COCH_3$), 2.62 (3H, br.s, NCH_3), 3.72 (6H, s, OCH_3 ×2), 7.10 (1H, dd, J=5 and 8Hz, 3-H), 7.56 (1H, dd, J=2 and 8Hz, 4-H), 8.26 (1H, dd, J=2 and 5Hz, 2-H); MS m/z: 368.2094 (M^+, calcd for $C_{22}H_{28}N_2O_3$, 368.2099).

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