Biomimetic Synthesis of Tropinone by the Oxidation of Hygrine with Mercury(II) Acetate

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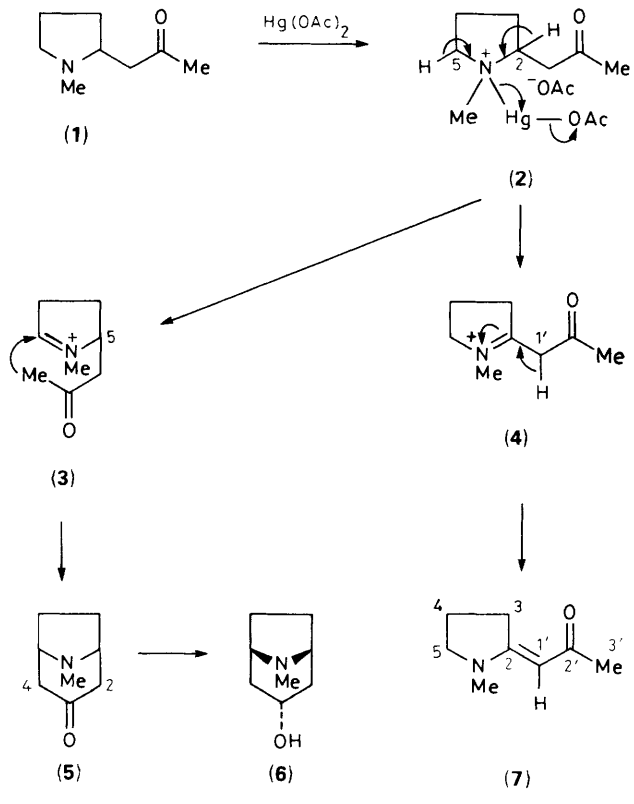
Tropinone and (*E*)-2,1′-dehydrohygrine were obtained by refluxing a solution of hygrine in dilute acetic acid with mercury(II) acetate.

Tropinone (**5**), the simplest tropane alkaloid, has been isolated from several plant species.[1] It is a key intermediate in the biosynthesis of more complex alkaloids, such as hyoscyamine and scopolamine.[2] It was first synthesized in 1901 by Willstätter[3] in 16 steps, starting with cycloheptanone. Since that time, numerous syntheses of tropinone have been reported,[4] the most exciting being that of Robinson[5] who obtained it from succindialdehyde, methylamine, and acetone-1,3-dicarboxylic acid in one step. In nature it has been established that hygrine (**1**) is the biological precursor of tropine (**6**), the alcohol moiety of the ester alkaloid hyoscyamine.[6] Tropine is formed biosynthetically by the reduction of tropinone.[2] An intermediate in the biosynthesis of tropinone is considered to be the 5-acetonyl-1-methyl-Δ^1-pyrrolinium salt (**3**). Iminium salts of this type have been produced by a variety of methods,[7] however the direct oxidation of *N*-alkylpyrrolidines with mercury(II) acetate is the most convenient.[8]

We have thus examined the oxidation of hygrine[9] (3 mM) with excess mercury(II) acetate (10 g) in boiling 2% acetic acid (500 ml). After 18 h, the reaction mixture was cooled, decanted from elemental mercury, and treated briefly (2 min) with sodium cyanoborohydride (2 g). The black mixture so formed was filtered through Celite, made basic with K_2CO_3, and extracted with CH_2Cl_2. The residue obtained on evaporation of this dried (Na_2SO_4) extract was subjected to preparative TLC on silica gel PF-254, developing with $CHCl_3$, EtOH, and conc. NH_3 (90:10:1) affording unreacted hygrine, R_f 0.45 (50—60%), tropinone, R_f 0.60 (10—15%), and 2,1′-dehydrohygrine (**7**), R_f 0.72 (20—30%). Initial treatment of the reaction mixture with $NaCNBH_3$ was crucial to the



Scheme 1

successful isolation of these products. It is probable that the products formed in the initial reaction mixture are complexed with the mercury(II) acetate. The identity of the tropinone was established by comparison with an authentic specimen (IR, ^{1}H and ^{13}C NMR, and mass spectra, GC retention time) and by the preparation of its 2,4-dipiperonal derivative.[5] The structure of (**7**), a colourless oil, was deduced spectroscopically. High resolution mass spectrometry (electron impact, 70 eV) yielded only two major peaks (rel. intensity): 139.1006 (30) [$C_8H_{13}NO$ requires 139.0997] (M^+), 124.0755 (100) [$C_7H_{10}NO$ requires 124.0762] (M – C-3′ Me); IR (neat) 1645, 1560 cm^{-1}; UV (95% EtOH) $\lambda_{max.}$ 304 nm (ε 26000), this intense absorption at this λ is predicted for such a vinylogous amide;[10] ^{1}H NMR ($CDCl_3$): δ (ref. Me_4Si) 1.87 (2H, p, 4-H), 1.99 (3H, s, 3′-H), 2.77 (3H, s, NMe) 3.12 (2H, t, 3-H), 3.32 (2H, t, 5-H), 4.91 (1H, s, 1′-H); nuclear Overhauser enhancement (NOE) experiments established the (*E*) stereochemistry for the double bond. When the hydrogen at C-1′ was saturated, the signals arising form the NMe and the hydrogens at C-3′ showed NOE, but the 3-H signals were not enhanced; ^{13}C NMR ($CDCl_3$): δ (ref. Me_4Si) 20.8 (4), 30.5 (3′), 33.2 (3 and NMe), 54.2 (5), 89.4 (1′), 165.6 (2), 194.0 (2′). The chemical shifts of the carbons in the vinylogous amide portion of the molecule are consistent with those of model compounds.[11]

Compound (**7**) has been unequivocally obtained[12] by Eschemoser's synthesis of vinylogous amides[13] from 1-methylpyrrolidine-2-thione. In this synthesis[12] the (*E*)-stereochemistry of the double bond was not established, but the reported spectral data for (**7**) are in good agreement with ours. The proposed mechanism for the formation of tropinone and 2,1′-dehydrohygrine is illustrated in Scheme 1. The quaternary ammonium compound (**2**) results from reaction of hygrine with mercury(II) acetate. Loss of a proton from C-5 and elimination of mercury (isolated in quantitative yield from the reaction) affords (**3**). A Mannich reaction occurs spontaneously to yield tropinone. Loss of a proton from C-2 of (**2**) affords the iminium salt (**4**) which by proton loss at C-1′ yields (**7**).

These experiments thus add credence to the proposed biosynthesis of tropine from hygrine *via* tropinone. The dehydrohygrine (**7**) has never been isolated from natural sources, but this may be due to the fact that it is a vinylogous amide, only weakly basic. Indeed it is readily extracted from acidic solutions with CH_2Cl_2.

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