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A TOTAL SYNTHESIS OF N_a-METHYL SECODINE

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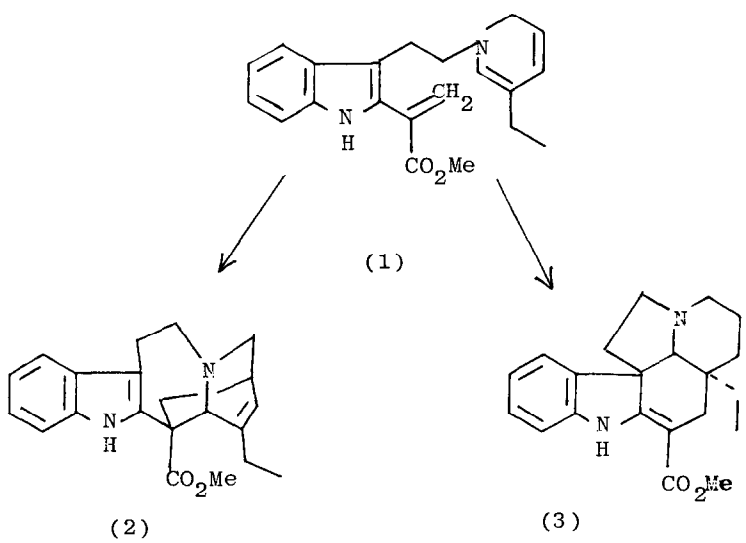
Abstract: A short synthetic route to N -methyl secodine and its subsequent conversion to the carbazole derivative (11) via a postulated dehydrosecodine intermediate (9) is described.

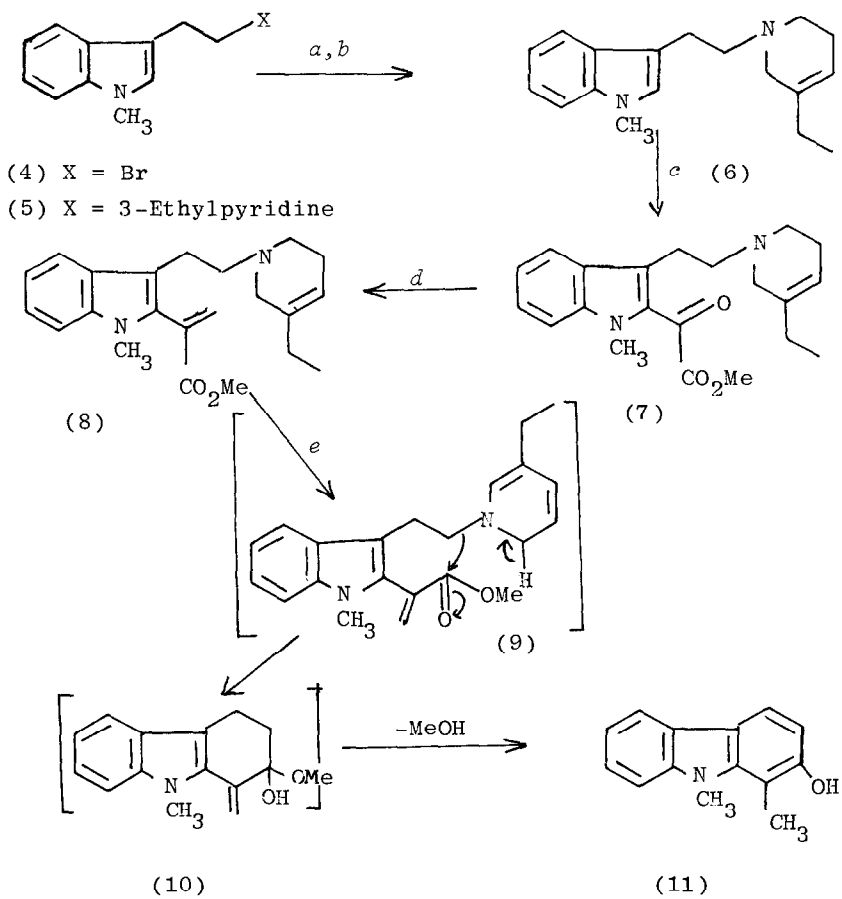
The currently accepted biosynthetic route to the indole alkaloids envisages the intermediacy of 14, 21-dehydrosecodine (1) which can undergo intramolecular Diels-Alder reactions in two different ways to afford either the *Iboga* alkaloids catharanthine (2) or the *Aspidosperma* alkaloid tabersonine (3)[1,2] (Scheme 1). Inspite of intensive efforts by several groups the synthesis of dehydrosecodine has still not been accomplished on account of its high susceptibility to oxidation dimerization and polymerization; the synthesis of N-benzyldehydrosecodine has recently been reported.[3] Secodine has however been synthesised[4-7] and a number of approaches to the indole

Scheme 1



alkaloids involving the intermediacy of the secodine system have been studied.[8,9] We report here a short and high yield synthesis of N-methyl secodine based on a facile Friedel-Crafts acylation reaction at the indole 2-position.

Scheme 2



[e] 3-Ethylpyridine, ethyl acetate, 120°C. [b] $NaBH_4$, Et_3N, MeOH, 0°C, 2 hrs.
[c] Cl.C(=O).C(=O).OMe, $AlCl_3$, CH_2Cl_2, 30°C, 25 hrs. [d] $CH_3\overset{+}{P}(C_6H_5)_3$ $B\bar{r}$, CH_3Li, ether, -20°C, 72hr
[e] CH_3CN, refluxed, 8 hrs.

N-methyl tryptophyl bromide (4) was obtainable in 75% overall yield by N-methylation of indole acetic acid (NaH, MeI, THF, 24 hrs., 30°C), esterification (MeOH/H_2SO_4, 21 hrs., 30°C), reduction (LAH, ether, 2 hrs., 30°C) and bromination (PBr_3, reflux in benzene, 5 hrs.). Model reactions were first explored and reaction parameters optimised by carrying out the reactions, with tetrahydropyridine instead of 3-ethyl pyridine to afford the respective des-ethyl analogues. Subsequent condensation of (4) with 3-ethyl pyridine afforded the salt (5) in 80% yield, m.p. 75-76°C (decomp); UV (MeOH) λ_{max}225, 285 nm, λ_{min}250 nm; I.R. (KBr): 2880-3082 cm^{-1}, 1630 cm^{-1}; N.M.R. ($CDCl_3$): 1.04 (3H, t, J = 7.5Hz, $-C\underline{H}_3-CH_2$), δ 2.55 (2H, q, J = 7.5Hz, $CH_3-C\underline{H}_2$), δ 3.48 (2H, t, J = 6.4Hz, $C\underline{H}_2-CH_2-N$), δ 3.69 (s, 3H, $N-C\underline{H}_3$), δ 5.17 (t, 2H, J = 6.4Hz, $CH_2-C\underline{H}_2N$), δ 7.04 (s, 1H, indole-2 (H)). Careful reduction of (5) gave the tetrahydropyridine (6) as a pale orange gum (65% yield); UV (MeOH): λ_{max}225, 280 nm, λ_{min}250 nm; I.R. ($CHCl_3$): 1600 cm^{-1} (>C=C): MS: m/e 268.1942 (M^+, 22%, calcd. for $C_{18}H_{24}N_2$: 268.1933); 144 (8%), 124 (100%); NMR ($CDCl_3$): δ 1.03 (t, 3H, J = 7.4 Hz, $-CH_2-C\underline{H}_3$), δ 2.02 (q, 2H, J = 7.4Hz, $-C\underline{H}_2-CH_3$), δ 3.72 (s, 3H, $N-C\underline{H}_3$), δ 5.5 (m, 1H, >C=CH), δ 6.8 (s, 1H, ind-2 (H)).

Friedel-Crafts acylation of (6) with monomethyl oxalyl chloride and aluminium chloride afforded a yellowish product (7) (55% yield); UV (MeOH): λ_{max}210, 240, 322 nm, λ_{min}235, 270 nm; I.R. ($CHCl_3$): 1740 cm^{-1} (ester C=O), 1640 cm^{-1} (keto); MS: m/e 354.3945 (M^+, 3%, calcd. for $C_{21}H_{26}N_2O_3$: 354.3992), 144 (66%), 124 (100%); NMR ($CDCl_3$): δ 1.03 (3H, t, J = 7.7Hz, $-CH_2-C\underline{H}_3$), δ 2.00 (q, 2H, J=7.7Hz, $-C\underline{H}_2-CH_3$), δ 4.00 (3H, s, $N-C\underline{H}_3$), δ 4.05 (3H, s, $CO_2C\underline{H}_3$), δ 5.17 (1H, m, >C=C$\underline{H}$). A Wittig reaction on the α-keto ester (7) afforded the desired N-methyl secodine (8) in 45% yield as a pale yellow amorphous solid. UV (MeOH): λ_{max}220, 259, 275, 295 nm, λ_{min}250, 260, 280 nm; I.R. ($CHCl_3$): 1740 cm^{-1} (ester C=O); MS: m/e 352.2153 (M^+, 3%, calcd. for $C_{22}H_{28}N_2O_2$: 352.2150), 277 (12%), 215.0923 (100%, calcd. for $C_{13}H_{13}N$: 215.0946, 201 (84%), 124 (56%); NMR ($CDCl_3$): δ 1.02 (t, 2H, J = 7.4 Hz, $-CH_2-C\underline{H}_3$), δ 2.09 (q, 3H, J = 7Hz, $-C\underline{H}_2-CH_3$), δ 3.61 (s, 3H, $N-C\underline{H}_3$), δ 3.81 (s, 3H, $CO_2C\underline{H}_3$), δ 5.49 (1H, m, >C=C$\underline{H}$), δ 5.91 (1H, d, J=1.7Hz, C-17H), δ 6.99 (1H, d, J=1.7Hz, C-17H).

N-methyl secodine (8) when refluxed in acetonitrile for 8 hrs. afforded the 2-hydroxy carbazole (11) as a major product (yield 80%). UV (MeOH): λ_{max}205, 240, 260, 300 nm, λ_{min}275, 255, 225 nm; MS: m/e 211.0991 (M^+, 100%, calcd. for $C_{14}H_{13}NO$ 211.0995). The facile conversion of the secodine derivative to the carbazole system (11) (Scheme 2) suggests the intermediacy of N-methyl dehydrosecodine (9) in the reaction which may have been formed through aerial oxidation. The generation of carbazole derivatives have previously been reported[3,10] and it has been proposed that 2-hydroxy carbazole is formed via dehydro-secodine by an intramolecular rearrangement and hydrogen transfer mechanism.

This synthesis represents the shortest route reported uptodate to the secodine system. Attempts are presently underway to generate the corresponding dehydro-secodines for biomimetic transformations to the Aspidosperma and Iboga alkaloids.

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