ABNORMAL HOFMANN DEGRADATION OF TETRAHYDROPROTOBERBERINIUM SALTS

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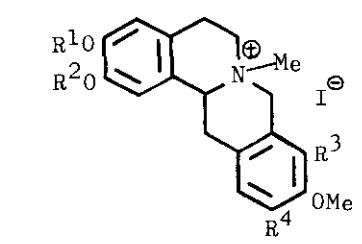
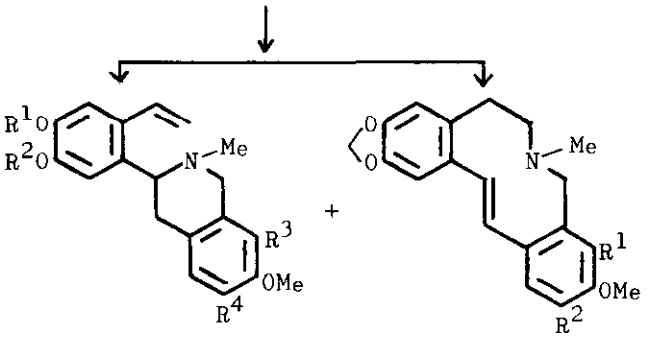
Hofmann degradation of 7,8,13,13a-tetrahydro-9-hydroxy-2,3,10-trimethoxy-7-methylprotoberberinium iodide (2) with methanolic potassium hydroxide gave 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxy-2-methoxymethylbenzyl)-6,7-dimethoxy-2-methylisoquinoline (13) in addition to the normal methine base (7). Abnormal Hofmann degradation was observed with nandinine methiodide (4) and its isomer (5). Moreover, this communication discusses the reaction mechanism of the abnormal Hofmann degradation and the biogenesis of the protoberberine alkaloid mecambridine (19).

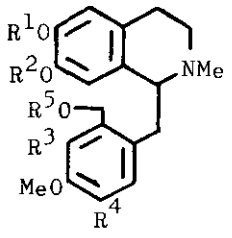
Hofmann degradation of the protoberberinium salt (1) gives the methine base (6) and in some cases, the second methine base (11) is formed as a minor product in addition to 6.[1] A second type of methine base is needed for the synthesis of a protopine alkaloid[2] and we carried out a Hofmann degradation of schefferine methiodide (2) to form an abnormal product (13) along with a normal methine base (7). Here we wish to report on this result.



(1) $R^1+R^2=CH_2$, R^3=H, R^4=OMe
(2) $R^1=R^2$=Me, R^3=OH, R^4=H
(3) $R^1=R^2$=Me, R^3=OMe, R^4=H
(4) $R^1+R^2=CH_2$, R^3=OH, R^4=H
(5) $R^1+R^2=CH_2$, R^3=H, R^4=OH



(6) $R^1+R^2=CH_2$, R^3=H, R^4=OMe
(7) $R^1=R^2$=Me, R^3=OH, R^4=H
(8) $R^1=R^2$=Me, R^3=OMe, R^4=H
(9) $R^1+R^2=CH_2$, R^3=OH, R^4=H
(10) $R^1+R^2=CH_2$, R^3=H, R^4=OH
(11) R^1=H, R^2=OMe
(12) R^1=OH, R^2=H



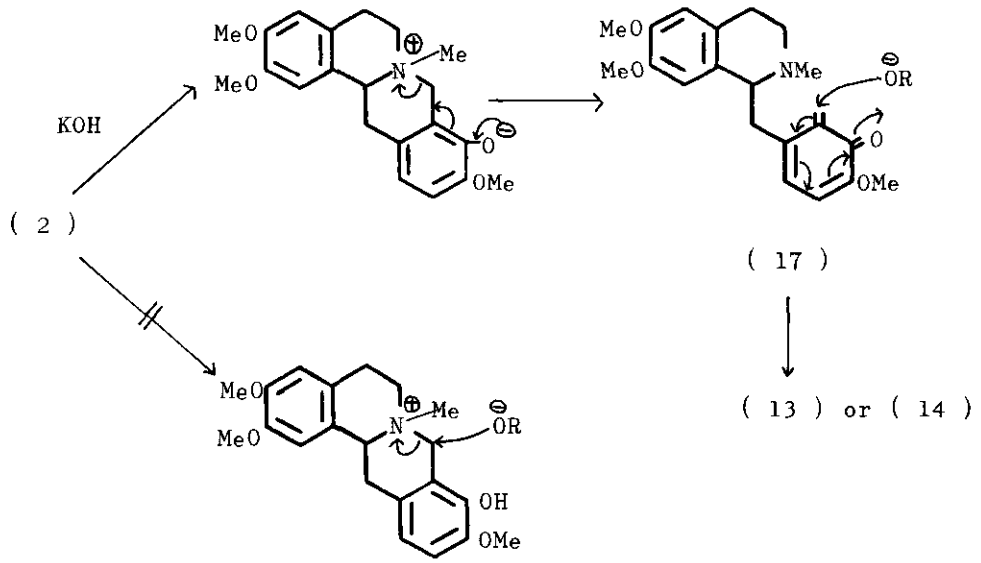
(13) $R^1=R^2=R^5$=Me, R^3=OH, R^4=H
(14) $R^1=R^2$=Me, R^3=OH, R^4=H, R^5=Et
(15) $R^1+R^2=CH_2$, R^3=OH, R^4=H, R^5=Me
(16) $R^1+R^2=CH_2$, R^3=H, R^4=OH, R^5=Me

Heating 2, prepared by our method,[3] with 20 % methanolic potassium hydroxide for 0.5 h on a water bath gave the normal methine base (7) in 47 % yield [ν ($CHCl_3$) 3590 cm^{-1} (OH); δ ($CDCl_3$) 5.12 (1H, dd, J 2 and 9 Hz, $^{H}\!>\!C\!=\!C\!<^{H}_{H}$), 5.44 (1H, dd, J 2 and 17 Hz, $^{H}\!>\!C\!=\!C\!<^{H}_{H}$), and 7.18 (1H, dd, J 9 and 17 Hz, $-CH\!=\!CH_2$)] and an unexpected compound (13) in 7.5 % yield [ν ($CHCl_3$) 3580 cm^{-1} (OH); λ (MeOH) 287 nm], which showed an aliphatic O-methyl (δ3.35), methylene protons (4.27 and 4.52, each 1H, each d, J 11 Hz) between an aromatic ring and O-function, and an aromatic proton (5.80, s) resonating at an abnormal higher field in addition to one N-methyl (2.52), three aromatic O-methyl [3.47 (3H) and 3.82 (6H)] and three aromatic proton [6.47 (1H, d, J 8 Hz), 6.55 (1H, s), and 6.72 (1H, d, J 8 Hz)]. The mass spectrum revealed a fragment ion as a base peak at m/e 206, which suggested a product with the 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline system. The same treatment of 2 with ethanolic potassium hydroxide afforded 7 in 43.6 % yield and the O-ethyl analogue (14) in 8.4 % yield [δ ($CDCl_3$) 1.20 (3H, t, J 7 Hz, CH_2CH_3)]. The ir, uv and nmr spectra of 14 were closely similar to those of the product from the treatment with methanolic potassium hydroxide. Thus, the unexpected compounds could be assigned the secoprotoberberine structures 13 and 14, respectively.

The formation mechanism of 13 from 2 is that involving a quinonoid intermediate (17), but does not involve an S_N2 type reaction as shown in 18. This fact was proved by the formation of only methine base (8) in a Hofmann degradation of the non-phenolic quaternary base (3) under the same reaction condition.

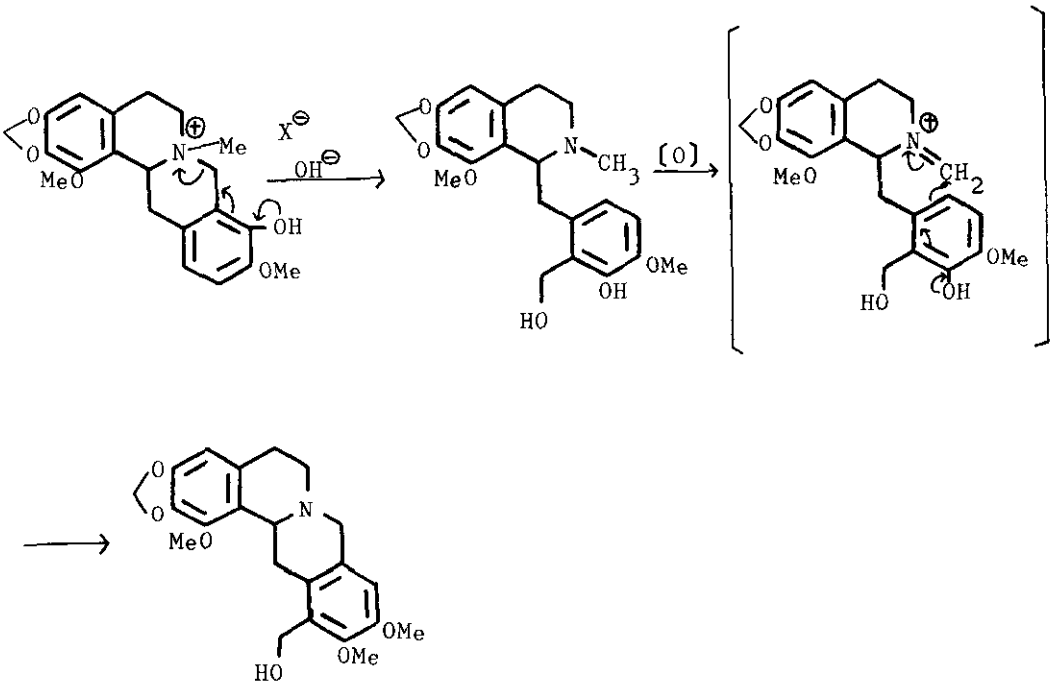
Similarly, nandinine[4] methiodide (4) gave the methine base (9) in 38.6 % yield [δ ($CDCl_3$) 5.12 (1H, dd, J 2 and 10 Hz), 5.42 (1H, dd, J 2 and 17 Hz), and 7.17 (1H, dd, J 10 and 17 Hz)] and the secoprotoberberine (15) in 5 % yield [δ ($CDCl_3$) 3.38

(3H, s, $ArCH_2OCH_3$)], 4.38 and 4.59 (each 1H, each d, J 11.5 Hz, $ArCH_2OMe$), and 5.98 (1H, s, 8 - H)], but not the second methine base (12) as reported by



Giacopello and co-worker.[5] Isomer (5)[4] of nandinine methiodide afforded the methine base (10) in 18.8 % yield [δ ($CDCl_3$) 5.15 (1H, dd, J 2 and 10 Hz), 5.43 (1H, dd, J 2 and 16 Hz), and 7.21 (1H, dd, J 10 and 16 Hz)] and the secoprotoberberine (16) in 58.8 % yield [δ ($CDCl_3$) 3.28 (3H, s, $ArCH_2OCH_3$), 4.13 (2H, s, $ArCH_2OMe$) and 5.99 (1H, s, 8 - H)].

The formation of the secoprotoberberine type base from the quaternary tetrahydroprotoberberinium salt would provide a strong evidence for the biogenesis of mecambridine (19) as shown in the following scheme.



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