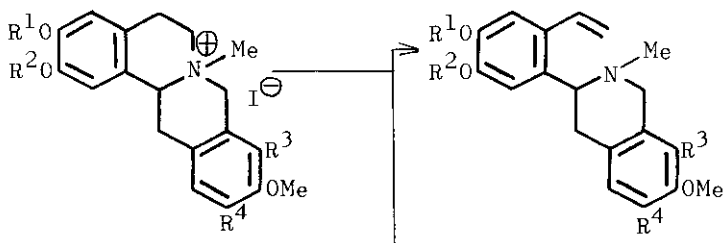
THE NOVEL FORMATION OF A DIBENZOCYCLOHEPTA[b]PYRIDINE BY AN ABNORMAL HOFMANN DEGRADATION OF A DIPHENOLIC TETRAHYDROPROTOBERBERINIUM SALT

Tetsuji Kametani,* Makoto Takemura, Keiichi Takahashi, Mitsuhiro Takeshita, Masataka Ihara, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

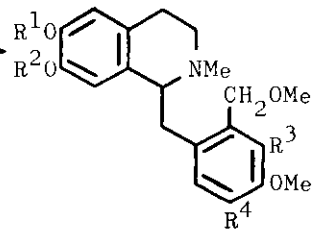
Heating coreximine methiodide (5) with methanolic potassium hydroxide gave the secoprotoberberine (14) and 5,5a,6,7,8-pentahydro-3,11-dihydroxy-2,10-dimethoxybenz[b,e]-4H-azuleno[3,2,1-ij]isoquinoline (15), but not the methine base (10) usually formed by Hofmann degradation. The possible biogenesis of these two abnormal Hofmann degradation products from protoberberine alkaloids is discussed.

Previously, we reported that Hofmann degradation of the 9- and 11-hydroxy-7,8,13,13a-tetrahydroprotoberberinium salts (1 and 2) by treatment with methanolic potassium hydroxide afforded the secoprotoberberines (11 and 12) in addition to the methine bases (6 and 7) while the nonphenolic substrate (3) gave only the methine base (8).[1] This type of abnormal Hofmann degradation has been further investigated and we now wish to report on the reaction of discretine methiodide (4) and coreximine methiodide (5) with methanolic potassium hydroxide.

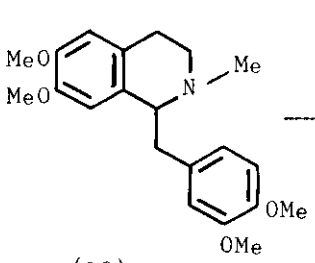


(1) $R^1+R^2=CH_2$, $R^3=OH$, $R^4=H$
(2) $R^1+R^2=CH_2$, $R^3=H$, $R^4=OH$
(3) $R^1=R^2=Me$, $R^3=OMe$, $R^4=H$
(4) $R^1=R^3=H$, $R^2=Me$, $R^4=OMe$
(5) $R^1=Me$, $R^2=R^3=H$, $R^4=OH$

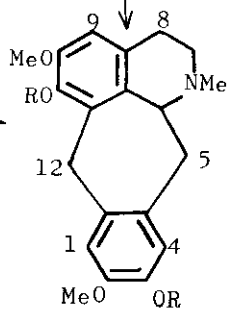
(6) $R^1+R^2=CH_2$, $R^3=OH$, $R^4=H$
(7) $R^1+R^2=CH_2$, $R^3=H$, $R^4=OH$
(8) $R^1=R^2=Me$, $R^3=OMe$, $R^4=H$
(9) $R^1=R^3=H$, $R^2=Me$, $R^4=OMe$
(10) $R^1=Me$, $R^2=R^3=H$, $R^4=OH$



(11) $R^1+R^2=CH_2$, $R^3=OH$, $R^4=H$
(12) $R^1+R^2=CH_2$, $R^3=H$, $R^4=OH$
(13) $R^1=R^3=H$, $R^2=Me$, $R^4=OMe$
(14) $R^1=Me$, $R^2=R^3=H$, $R^4=OH$



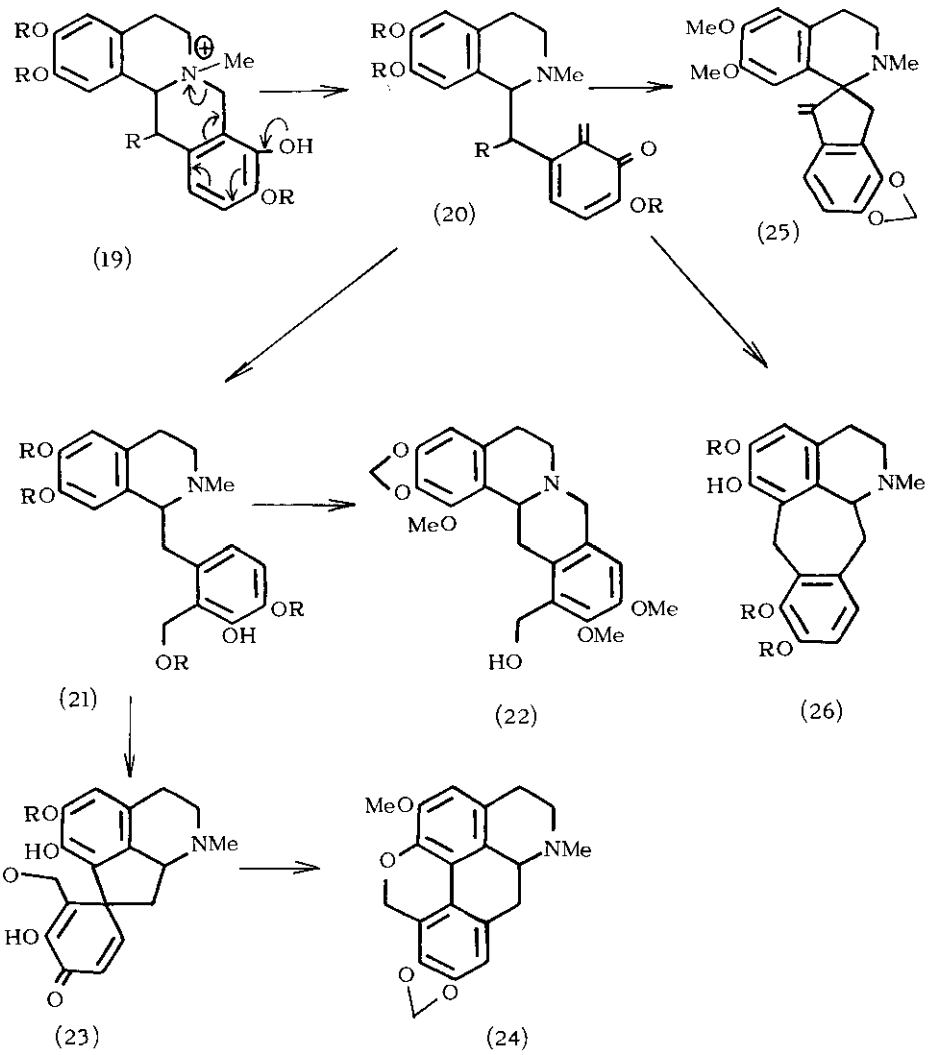
(18)



(15) R=H
(16) R=Ac
(17) R=Me

Heating discretine[2] methiodide (4) with 20 % methanolic potassium hydroxide for 4 hr on a water bath gave only the methine base (9) [δ ($CDCl_3$) 5.05 (1H, dd, J 2 and 10 Hz, $^{H}\!>\!C\!=\!C\!<^{H}_{H}$), 5.37 (1H, dd, J 2 and 17 Hz, $^{H}\!>\!C\!=\!C\!<^{H}_{H}$) and 7.11 (1H, dd, J 10 and 17 Hz, $-CH\!=\!CH_2$)] in 43 % yield. None of the secoprotoberberine (13) was detected by tlc. This fact is consistent with our suggested mechanism on the formation of the secoprotoberberine which involves a phenolic hydroxyl group either at the C - 9 or C - 11 position in the protoberberine system.[1]

On the other hand, treatment of coreximine[3] methiodide (5) with 20 % methanolic potassium hydroxide for 4 hr gave no methine base (10) but afforded instead a separable mixture of the secoprotoberberine (14) in 30 % yield [δ ($CDCl_3$) 3.25 (3H, s, $ArCH_2OCH_3$) and 4.11 (2H, s, $ArCH_2OCH_3$) and the novel compound (15) in 15 % yield, mp 182 - 183°. The latter compound (15) [m/e 341 (M^+)], containing a phenolic 1,2,3,4-tetrahydroisoquinoline system [ν max ($CHCl_3$) 3530 cm^{-1}; λ max (MeOH) 288 nm] was acetylated to furnish the corresponding diacetate (16) [m/e 425 (M^+); ν max ($CHCl_3$) 1730 cm^{-1} (ArOAc); δ ($CDCl_3$) 2.24 and 2.35 (each 3H, each s)] and methylated with diazomethane to afford the tetramethoxy derivative (17) [m/e 369 (M^+)], mp 116 - 118°. The nmr spectrum (δ in $CDCl_3$-DMSO) of the diphenolic base (15) showed the presence of methylene protons between two aromatic rings at 4.0 as a broad singlet and three isolated aromatic protons as singlets at 6.45, 6.46, and 6.63 in addition to an N-methyl (2.53) and two O-methyl resonances (3.78, 6H). Heating the secoprotoberberine (14) with the above reagent for 24 hr also gave compound (15), identical with the product obtained directly from 5. Furthermore, treatment of 5 with the same reagent for 40 hr afforded 14 and 15 in 10 % and 60 % yield, respectively. The structural assignment of the dibenzocyclohepta-[b]pyridine (15) was confirmed by an alternative synthesis of the tetramethoxy derivative (17). Refluxing laudanosine (18) with 37 % formalin and acetic acid in the presence


RO
RO
N
Me
R
OH
OR
(19)
NMe
O
(20)
MeO
MeO
(25)
(21)
OR
OH
(22)
MeO
OMe
HO
(26)
HO
(23)
(24)

of hydrochloric acid for 14 hr[4] gave (17) in 53 % yield, whose ir and nmr spectra were identical with those of the tetramethoxy derivative obtained from the Hofmann degradation product (15).

The novel dibenzocyclohepta[b]pyridine type compound may be considered as a potential alkaloid, derivable from the protoberberine alkaloids by the addition of one more carbon unit and therefore related to mecambridine (22)[1] and de-N-methylthalphenine (24).[5] On this basis, the quinonoids (20), derived from the protoberberinium salts (19), would occupy an important role in the biogenesis of certain benzylisoquinoline alkaloids. Thus, nucleophilic attack to the quinonoid methylene would generate the secoprotoberberines (21)[1] followed by oxidation to mecambridine (22)[1] or the proaporphine (23). The latter could then rearrange to de-N-methylthalphenine (24).[5]

On the other hand, coupling between the quinonoid methylene and the carbon at the C - 1 position of the isoquinoline ring would give the spirobenzylisoquinoline alkaloids (25),[6] while coupling at the C - 8 position would afford the dibenzocyclohepta[b]-pyridines (26) when a phenolic hydroxyl group is present at the C - 7 position.

REFERENCES

1 T. Kametani, M. Takemura, K. Fukumoto, T. Terui, and A. Kozuka, Heterocycles, 1974, 2, 433.

2 T. Kametani, M. Takeshita, and S. Takano, J. Chem. Soc. Perkin I, 1972, 2834.

3 T. Kametani and M. Ihara, J. Pharm. Soc. Japan, 1967, 87, 174.

4 A. von Baeyer, Ber., 1872, 5, 280; L. H. Baekland, Ind. and Eng. Chem., 1909, 1, 149.

5 M. Shamma and D.-Y. Hwang, Heterocycles, 1973, 1, 31.

6 M. Shamma and C. D. Jones, J. Amer. Chem. Soc., 1969, 91, 4009; 1970, 92, 4943.

Received, 5th August, 1974