SYNTHESIS OF AN ALKALOID ONYCHINE AND RELATED COMPOUNDS: REVISED STRUCTURE OF ONYCHINE

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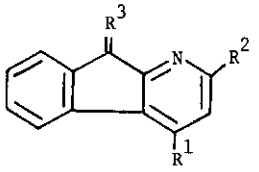
Abstract —— Synthesis of an alkaloid, onychine and related compounds by application of a new method for constructing pyridine ring was described and the synthesis revealed that the structure of the alkaloid should be revised to 4-aza-1-methyl-fluoren-9-one from 1-aza-4-methyl-fluoren-9-one.

In 1976, Gottlieb and his co-workers reported isolation and characterisation of an alkaloid, onychine (I) (m.p. 133-135°) occurring in Onychopetalum amazonicum (Annonaceae)[1]. In their report, they ruled out the alternative structure (II) for the alkaloid, since the signal of the methyl protons of dihydroonychine (III) showed a small high-field shift compared with that of the parent alkaloid. We aimed at the synthesis of onychine by application of a new synthetic method for constructing pyridine ring using oxidative thermal rearrangement of cycloalkanone oxime O-allyl ethers[2], revealing that the structure of onychine should be revised to 4-aza-1-methyl-fluoren-9-one (II). Treatment of 2-indanone (IV) with O-crotyl- (V) and O-α-methylallyl-hydroxylamine (VI)[2] gave 2-indanone oxime O-crotyl- (VII) and O-α-methylallyl ether (VIII)[3] in good yield, respectively. Thermolysis of each in a sealed tube under air at 170-180° (bath) for 48 hr. furnished the same mixture (38% yield) consisting of the two isomeric azafluorenes (IX) and (X), both of which were separated in pure form by preparative thin layer chromatography on silica gel. 1-Aza-4-methyl-fluorene (IX) showed the signals in its n.m.r. spectrum at δ ($CDCl_3$) 2.65 (3H, s, Me), 3.95 (2H, s, CH_2), and 8.33 (1H, d, J=5.5Hz. assigned to the α-proton of the pyridine ring), while the 2-methyl compound (X) showed no signal due to the α-proton of the pyridine ring, confirming the structures. Oxidation of (IX) and (X) with potassium permanganate in acetone gave the ketones (I) (m.p. 158-160°) and (XI) (m.p. 155-156°), respectively. The m.p. and n.m.r. data of the synthetic ketone (I) revealed nonidentity with those of onychine (see Table). Furthermore, the n.m.r. spectrum of the compound (III)[4] corresponding to dihydroonychine, prepared from (I) by hydrogenation, showed the signals having different chemical shift concerning α- and β-protons of pyridine moiety and the methyl protons, which were clearly observed in the spectrum (see Table).

In order to make the discrepancy clear, the synthesis of isomer (II) was made. 1-Indanone oxime O-crotyl- (XII) and O-α-methylallyl ether (XIII), obtained from 1-indanone and (V) and (VI), were

subjected to the oxidative thermal rearrangement in the same manner as mentioned above to give a mixture of 4-aza-1-methyl-fluorene (XIV) and 4-aza-3-methyl-fluorene (XV). Oxidation of the aza-fluorene (XIV) and (XV) with potassium permanganate yielded 4-aza-1-methyl-fluoren-9-one (II) and 4-aza-3-methyl-fluoren-9-one (XVI) in good yield, respectively. The m.p. (133-135°) and the n.m.r. spectral data of the former (II) exhibited good identity with those of onychine reported by Brazilian group. The n.m.r. spectral data of the dihydro derivative (XVII) prepared from (II) by reduction (H_2/Pd or $NaBH_4$) showed also good identity with those of dihydoonychine reported. Based on the above results, it is highly plausible that the structure of onychine should be revised to (II) from (I), although the direct comparison of our synthetic specimen with onychine has not been carried out.

After completing the synthesis, we realised that Australian group[5] has synthesised the aza-fluorenone (II), which showed good identity with onychine in m.p. (133-135°) and its spectroscopic properties.



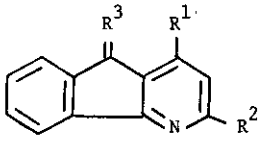
(I) R^1= Me; R^2= H; R^3= O

(III) R^1= Me; R^2= H; R^3=

(IX) R^1= Me; R^2= H; R^3= H_2

(X) R^1= H; R^2= Me; R^3= H_2

(XI) R^1= H; R^2= Me; R^3= O



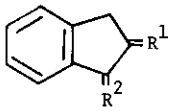
(II) R^1= Me; R^2= H; R^3= O

(XIV) R^1= Me; R^2= H; R^3= H_2

(XV) R^1= H; R^2= Me; R^3= H_2

(XVI) R^1= H; R^2= Me; R^3= O

(XVII) R^1= Me; R^2= H; R^3= 



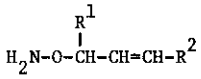
(IV) R^1= O; R^2= H_2

(VII) R^1= N-O-CH_2-CH=CH-Me; R^2= H_2

(VIII) R^1= N-O-  ; R^2=H_2

(XII) R^1= H_2; R^2= N-O-CH_2-CH=CH-Me

(XIII) R^1= H_2; R^2= N-O- 



(V) R^1= H; R^2= Me

(VI) R^1= Me; R^2= H

Table Comparison of the physical and spectral data of the synthetic compounds (I, II, III, and XVII) with those of onychine

onychine[1] m.p. 133-135°	1-aza-4-methyl-fluoren-9-one (I) m.p. 158-160°	4-aza-1-methyl-fluoren-9-one (II) m.p. 133-135°
8.39 (1H, d, α-H)	8.51 (1H, d, α-H) Δ + 0.12	8.44 (1H, d, α-H) Δ + 0.05
7.81 (1H, dt)	7.82 + 0.01	7.86 + 0.05
7.67 (1H, dt)	7.71 + 0.04	7.73 + 0.06
7.57 (1H, td)	7.60 + 0.03	7.62 + 0.05
7.40 (1H, td)	7.40 ± 0.00	7.44 + 0.04
6.96 (1H, d, β-H)	7.18 (1H, d, β-H) + 0.22	6.98 (1H, d, β-H) + 0.02
2.61 (3H, s, Me)	2.63 (3H, s, Me) + 0.02	2.62 (3H, s, Me) + 0.01

2H-onychine[1] m.p. 156-158°	1-aza-4-methyl-fluoren-9-ol (III) m.p. 154-156°[4]	4-aza-1-methyl-fluoren-9-ol (XVII) m.p. 156-157°
8.03 (1H, d, α-H)	8.39 (1H, d, α-H) Δ + 0.36	8.03 (1H, d, α-H) Δ ± 0.00
7.78-7.54 (2H, m)	7.89-7.62 (2H, m)	7.80-7.56 (2H, m)
7.35 (1H, td) 7.36 (1H, dt)	7.56-7.39 (2H, m)	7.47-7.30 (2H, m)
6.75 (1H, d, β-H)	7.13 (1H, d, β-H) + 0.38	6.74 (1H, d, β-H) - 0.01
5.57 (1H, s, -CH-O)	5.64 (1H, s, -CH-O) + 0.07	5.53 (1H, s, -CH-O) - 0.04
2.49 (3H, s, Me)	2.67 (3H, s, Me) + 0.18	2.47 (3H, s, Me) - 0.02

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2. H. Irie, I. Katayama, Y. Mizuno, J. Koyama, and Y. Suzuta, Heterocycles, 1979, 12, 771.
3. Satisfactory analyses and spectra were obtained for the new compounds cited here.
4. The compound was reasonably air-sensitive, giving the ketone (I) after determination of m.p. (thin layer chromatography examination), and sintered at 130°.
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Received, 14th May, 1979