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SYNTHESIS IN THE INDOLE SERIES VIII (1) : A NOVEL APPROACH TO INDOLOQUINOLIZIDINES THROUGH ALKYLATION-CYCLIZATION OF AN ENAMINE DERIVED FROM TRYPTAMINE

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Summary : A short access to enamide 1 and enamine 2 from tryptamine is described. Alkylation of 2 is followed by Mannich cyclization. This new route to indoloquinolizidines is applied to a short vincamone synthesis.

A recent paper by Takano et al (2) prompts us to report some of our results concerning the preparation and chemistry of enamide 1 and of the related enamine 2.

Compound 1, a crystalline solid, m.p. 88°, was obtained in a single step (Y=92%) by heating equimolecular quantities of tryptamine and methyl 4-formyl hexanoate under neutral conditions (toluene, 4 hours of reflux, Dean-Stark trap). The structure of 1 (3) was supported by its spectroscopic properties (^{1}H NMR : singlet at 5.65 ppm ; doublet, J=1.5Hz at 6.9 ppm). Traces of acid induced its cyclization to the known indoloquinolizidines 8a,b (4) through the intermediacy of an α-acylimmonium ion.

Reduction of 1 with a THF solution of LAH at 0°C proceeded quantitatively to the highly unstable enamine 2 (5) (IR vibration at 1670 cm^{-1} ; ^{1}H NMR singlets at 5.75 and 6.65 ppm). Treatment of 2 with TFA in $CHCl_3$ yielded the expected mixture of indoloquinolizidines 9a,b (6). It was tempting to check if alkylation of 2 could be similarly followed by a Mannich cyclization, thus forming two carbon-carbon bonds in a single operation. Actually, treatment of 2 with allyl bromide in acetonitrile, in the presence of powdered K_2CO_3 at 60°C, gave the mixture of alkylated compounds 10a,b (Y=60%), which were not separated. Compounds 10a,b are close to intermediates in Harley-Mason's synthesis of *Aspidosperma* alkaloids (7). In an analogous fashion alkylation with prenyl bromide was followed by cyclization yielding a mixture of regioisomers 11 and 12. All these reactions are thought to proceed *via* intermediate immonium ions 3 - 6.

Synthesis of (±) vincamone and (±) epivincamone

In an effort to apply the above sequence to a straightforward total synthesis of vincamone 14a, 2 was treated with ethyl iodoacetate (1 equivalent, CH_3CN,K_2CO_3,60°C) to yield a crude mixture of ethylvincamonates 13 which were directly converted to (±)-14a (m.p.201°,10%) (6) and (±)-14b (m.p.130°,10%) (6) by saponification followed by acidification. No improvement was gained by use of t-butyl bromoacetate.

Oxidation of enamine 2

Action of other electrophiles i.e. methyl acrylate, acrylonitrile, ethyldiazoacetate, onto enamine 2 resulted in complex mixtures. However, two products 15 and 16 could be isolated from all these reactions in yields up to 25% (15) and 21% (16) (in the acrylonitrile reaction). The same products were obtained in comparable yields by just swirling 2 at 60°C (CH_3CN, K_2CO_3) in an opened flask.

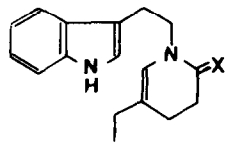
The more polar compound ($M^{+\cdot}$270) was attributed structure 15 on the basis of its spectral properties (^{13}C and 400 MHz ^1H NMR,MS)(8). Salient features of the ^{13}C NMR spectrum are the oxygen bearing carbons at 101.0 (d) and 83.7 ppm (s) ; the other carbons show up at expected values. In the ^1H NMR spectrum a signal at 5.5 ppm (broad singlet H(2)) is coupled to the exchangeable N-H(1) (broad singlet at 4.75 ppm). Compound 15 rearranged in acidic medium to a mixture of indoles 17, (UV). Their mass spectra exhibited a molecular ion at m/z 270, accompanied by a strong $M^{+\cdot}$-1 ion, typical of indoloquinolizidines.

The less polar compound ($M^{+\cdot}$286) had structure 16 (9). Its IR spectrum showed vibrations at 1715 (ketone) and 1665 cm^{-1} (amide) ; most of its resonances in the NMR spectrum appeared as doublets due to the amide group, including the formyl protons (singlets at 7.80 and 8.05 ppm). In order to get supplementary proofs regarding the structure of 16, this compound was reduced (LAH,THF) to a single aminoalcohol 18 ($M^{+\cdot}$274 ; ^1H NMR 3-H singlet at 2.3 ppm).

Whereas obtention of compound 16 is a clear-cut example of enamine oxidation (10,11), the origin of compound 15 is not obvious. It could arise through addition of oxygen to the terminal carbon atom of the enamine followed by trapping by the C(3) of indole. Final cyclization is accompanied by loss of OH^+, possibly captured by the solvent or by another molecule of enamine 2.

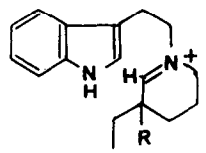
Oxidation of enamide 1

Treatment of enamide 1 by potassium t-butoxide in DMSO led to an unique oxidation product 19 (12) ($M^{+\cdot}$266). Its structure was based on its ^1H NMR spectrum, which displayed separate signals at 60MHz for all the protons of the molecule. Although air-oxidations mediated by



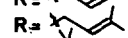
1 X= O

2 X= H_2



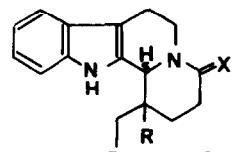
3 R=H

R= 

R= 

R= 

$R = CH_2CO_2C_2H_5$



8 a,b R=H, X = O

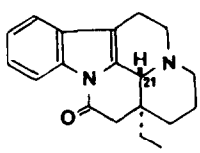
9 " R=H, X = H_2

4, 10 " "

5, 11 " "

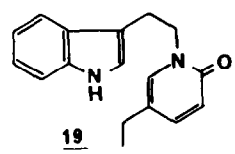
6, 12 " "

7, 13 " "



14a 21α H

14b 21β H



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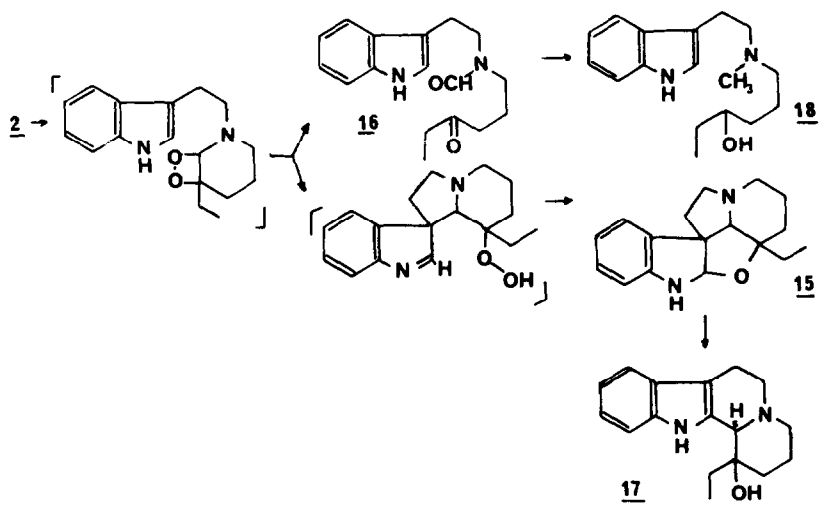
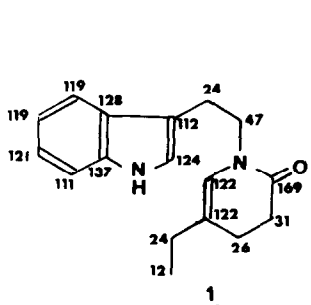
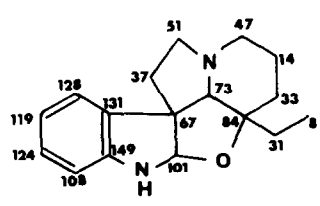


16 18 15 17



1



15

^{13}C NMR of derivatives 1 and 15

DMSO/^{t}BuOK are well precedented (13) it is the first time this reaction is applied to the synthesis of pyridones. This reaction appears as a general property of this type of enamides as no such reaction takes place with saturated lactames.

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(3) Compound 1 : m.p.88° (ether-hexane) ; UV λ_{max}^{EtOH}(log ε) : 225(4.56),270(3.97),282(3.92), 292(3.78) ; IR:3420,3300,1650cm^{-1} ; MS(rel.int.):268($M^{+\cdot}$),144,143,130(100%) ; ^{1}H NMR ($CDCl_3$;60MHz):8.80(s,1H),7.60(m,1H),7.20(m,2H),7.05(m,1H),6.90(d,J=1.5Hz,1H),5.65(bs,1H), 3.70(t,2H),3.00(t,2H),2.50-1.70(m,6H),0.90(t,J=7Hz,3H).

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(5) Compound 2 : UV λ_{max}^{EtOH} : 225,275,282,290nm ; IR:3430,3290,3070,1670,1455cm^{-1} ; MS:254, 252(impurity),144(100),124,122 ; ^{1}H NMR($CDCl_3$,60MHz):8.05(s,1H),7.55(m,1H),7.10(m,3H), 6.65(s,1H),5.75(s,1H),2.95(bs,6H),1.95(m,6H),0.95(t,7Hz,3H).

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(8) Compound 15 : UV λ_{max}^{EtOH} : 212,222(sh),245,282(sh),290,300nm ; IR:3330,1610,1480,1460 cm^{-1}; MS:270($M^{+\cdot}$,100%),241,213,171,144,143,140 ; ^{1}H NMR(400MHz):7.20(d,1H,8Hz),7.10(t,1H,8Hz),6.75(t,1H,8Hz),6.55(d,1H,8Hz),5.50(bs,1H), 4.75(bs,1H),4.40(s,1H),4.20(ddd;1H;6,10,12Hz),4.05(bd,1H,14Hz),3.95(dd,1H;6,8Hz), 3.80(dd;1H;12,10Hz),3.30(dt;1H;7,12Hz),3.10(bd,1H,14Hz),2.95(dd,1H;5,12Hz),2.80(m,1H), 1.30(m,1H),1.20(m,1H),1.0(t,3H,7Hz).

(9) Compound 16 : UV λ_{max}^{EtOH} : 225,275,282,291 ; IR:3340,1715,1665cm^{-1} ; MS:286,270,254,231, 143(100%),130,124 ; ^{1}H NMR(60MHz):8.80(s,N-H),8.05 and 7.80(2s,1H),1.0(t,7Hz,3H).

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(12) Compound 19 : UV λ_{max}^{EtOH} : 222,282,290,315nm ; IR:3400,3240,1660,1570,1540cm^{-1} ; MS:266($M^{+\cdot}$) 160,143(100%),130 ; ^{1}H NMR(60MHz):9.55(s,1H),7.7-7.0(m,4H),6.90(s,1H),6.65(s,1H),6.55 (d,6Hz,1H),4.20(t,7Hz,2H),3.20(t,7Hz,2H),2.20(q,7Hz,2H),0.95(t,7Hz,3H).

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