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SYNTHESIS AND TRANSFORMATIONS OF A 20-DEETHYL 3-OXO VINCADIFFORMINE.

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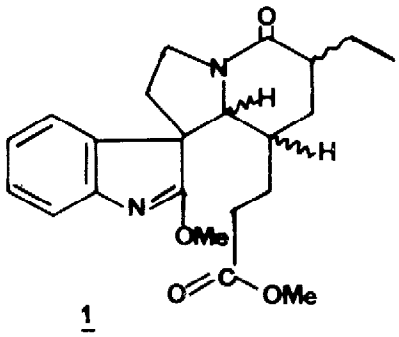
Summary : A 20-deethyl 3-oxo vincadifformine 3 was synthetized via condensation of 2-hydroxy tryptamine with synthon 9. It was further alkylated to the oxo-pseudovincadifformine 2. The given relative configurations remain hypothetical.

In continuation of the syntheses of vincadifformine[1] and tabersonine[2], the iminoether 1 was prepared[3]. However, attempts of ring closure yielded only very little of the desired oxo-pseudovincadifformine 2. It was therefore decided to synthetize first 20-deethyl 3-oxo vincadifformine 3[4], a substrate amenable to further alkylation to 2.



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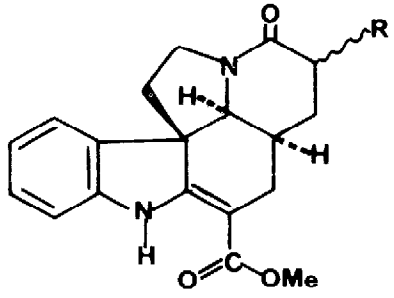


2 R = Et
3 R = H

The synthesis of 4-formyl dimethyl pimelate 4 - a valuable synthon for the non tryptaminic moiety of 2 - has been attempted through the alkylation of 4-oxo dimethyl pimelate with trimethyl sulfoxonium as well as methoxymethylene triphenyl phosphorane. In each case, hydrolysis of the adduct gave only a poor yield of 4.

A more lengthy synthesis of compound 9 (TABLE) was then devised : nitrile 6, prepared from 4-chlorobutyl benzoate[5] 5 (KCN, DMSO, 100°C 1h, 99%), was first hydrolyzed (1.1 eq of 2M NaOH in EtOH.H_2O, 1:1; refl., 10 min.) to 7 (96%), then oxidized to aldehyde 8 (PCC, COREY's procedure, 81%), the pyrrolidino enamine of which was alkylated with methylacrylate to compound 9 (45%).

Condensation of 9 with 2-hydroxytryptamine gave (76%) a mixture of (four?) epimers, detectable as two spots only on t.l.c. The more polar component (m.p.=209°C ; UV : 212,258,295 nm ; IR : 2230,1710,1640 cm^{-1}; $M^{+\cdot}$ 309, $C_{18}H_{19}O_2N_3$) was predominant (6:1) when condensation was performed between 2-hydroxytryptamine and 9 (benzene, azeotropic distillation, AcOH refl. 2h), while the less polar one was more abundant when using 2-hydroxytryptamine,HCl (AcOH refl. 20h).

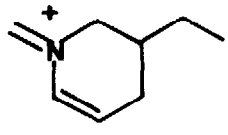
Only the more polar component of the mixture 10 was able to suffer the following ring closures . when treated with trimethyloxonium fluoroborate it gave the iminoether 11 ($M^{+\cdot}$ 323, $C_{19}H_{21}O_2N_3$; IR : 2240,1640,1580 cm^{-1} ; NMR : s.3H:4.08 ppm),along with some amide 12 ($M^{+\cdot}$ 355, $C_{20}H_{25}O_3N_3$; IR : 1660,1640,1585 cm^{-1} ; NMR : s.3H:4.03, s.3H:2.6 ppm).

The ring closure of 11 (HNa : 2.5 eq in DMF ; 25°C 10 min.,115°C 1h) yielded the pentacyclic nitrile 13 ($M^{+\cdot}$ 291, $C_{18}H_{17}ON_3$; UV : 222,288,320 nm ; IR : 2200 cm^{-1}).

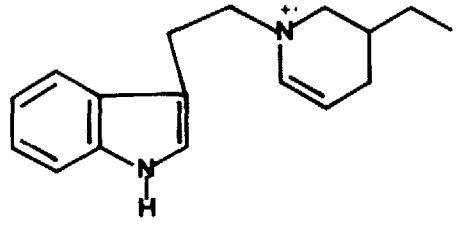
Upon methanolysis (MeOH, HCl, -20°C, overnight) 10 gave the ester 14 (m.p.=228°C; $M^{+\cdot}$ 342, $C_{19}H_{22}O_4N_2$; IR : 1740,1715,1640 cm^{-1} ; NMR : s.3H:3.55 ppm), the cyclisation of which through iminoether 15 (Me_3OBF_4 : 2.8 eq in CH_2Cl_2,20°C, 4 days, 89%) ($M^{+\cdot}$ 356, $C_{20}H_{24}O_4N_2$; IR : 1735, 1635,1575 cm^{-1} ; NMR : s.3H:4.05, s.3H:3.55 ppm) yielded (53%) 20-deethyl 3-oxo vincadifformine 3 (m.p.=238°C ; $M^{+\cdot}$ 324, $C_{19}H_{20}O_3N_2$; UV : 222,292,327 nm , IR : 1680,1650,1605 cm^{-1} ; NMR : s.3H:3.72 ppm).

The dianion (LDA : 2.1 eq in THF, HMPA : 1.1 eq, -80°C) was treated with 1.1 eq EtI (-80°C, 1h ; -20°C, 12h then 25°C,1h) to yield less than 1% of dialkylated derivative 16 ($M^{+\cdot}$ 380, $C_{23}H_{28}O_3N_2$; UV : 225,293,327 nm) together with 55% of monoalkylated derivative 2 (m.p.=212°C ; $M^{+\cdot}$ 352, $C_{21}H_{24}O_3N_2$; UV : 225,293,327 nm ; IR : 1675,1635,1605 cm^{-1} ; NMR : s.1H:8.96, s.3H:3.72, t.3H:1.04 ppm).

In order to afford supplementary proofs of its structure, 2 was reduced with $NaBH_3CN$ / AcOH to its dihydroderivative 17 ($M^{+\cdot}$ 354, $C_{21}H_{26}O_3N_2$; UV : 215,245,305 nm ; IR : 1735,1635 cm^{-1}), which was itself treated with lithium aluminium hydride in THF at 20°C to give the alcohol 18 The mass spectrum of 18 showed peaks at m/e 124 (100%) and 254 (20%), strongly indicative of the postulated structure[6].

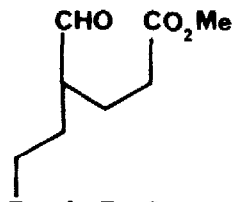


m/e 124

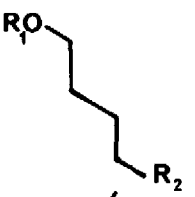


m/e 254

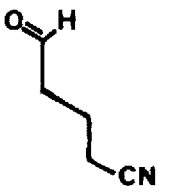
The synthesis of vincadifformine under similar lines[1] strongly suggests the relative configuration of the asymmetric centers in 2,3,13 and 16-18 to be as depicted on the formulae. This point awaits further configuration.



4 : R = CO_2Me
9 : R = CN



5 : R_1 = COØ R_2 = Cl
6 : R_1 = COØ R_2 = CN
7 : R_1 = H R_2 = CN



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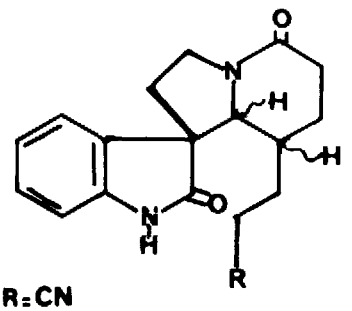
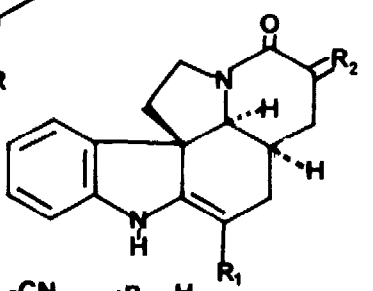
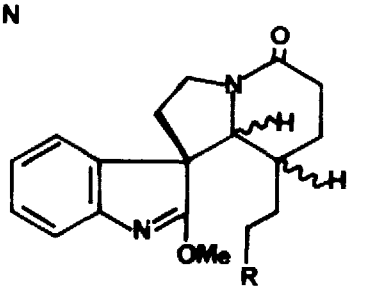


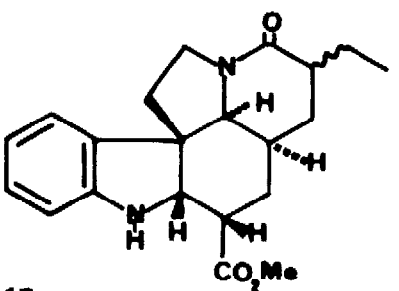
10 : R = CN
14 : R = CO_2Me



13 : R_1 = CN ; R_2 = H_2
16 : R_1 = CO_2Me ; R_2 = Et,Et



11 : R = CN
12 : R = $CONHCH_3$
15 : R = CO_2Me



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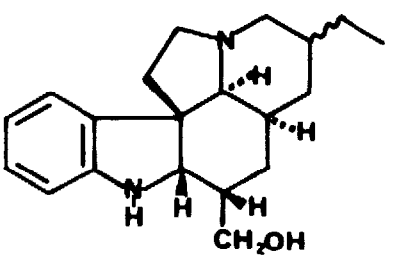

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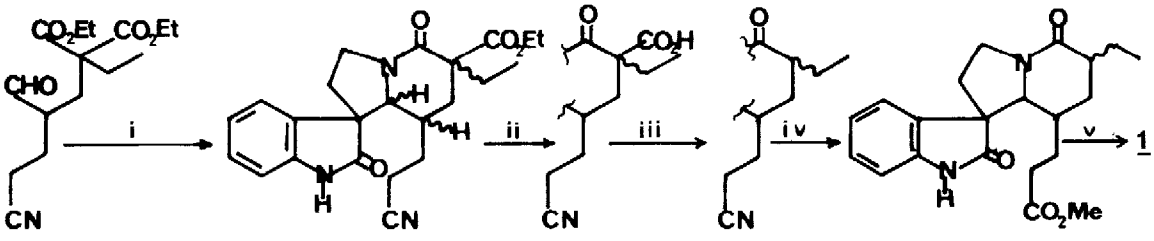
TABLE

Notes and references

1. J-Y. LARONZE, J. LARONZE-FONTAINE, J. LEVY and T. LE MEN, Tetrahedron Lett., 491 (1974).
2. J. LEVY, J-Y. LARONZE, J. LARONZE and J. LE MEN, Tetrahedron Lett., 1579 (1978).
3. Main steps of the synthesis of derivative 1 :



i:2-hydroxytryptamine,AcOH,refl. ; ii.NaOH/H_2O ; iii:200°C, 0,02 torr ; iv:MeOH/HCl ; v:Me_3OBF_4

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