Efficient Synthesis of 1-Ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine: a Key Precursor to Eburnane Alkaloids

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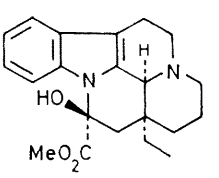
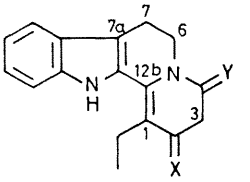
Summary The title compound has been conveniently synthesized from the imine (**3**) by cyclisation with acrylic acid followed by reduction

RECENTLY the development of new synthetic routes to eburnane alkaloids has attracted interest culminating in several total syntheses of vincamine (**1**), an excellent cerebral vasodilator drug, and other pharmacologically active eburnamonine-like compounds [1] As outlined in Wenkert's pioneering work, 1-ethyl-2,3,4,6,7,12-hexahydroindolo-[2,3-*a*]quinolizine (**2**) can serve as a precursor to the eburnane skeleton in some stereo- and enantio-selective approaches [2] We now describe a short and highly efficient synthesis of the 'Wenkert enamine' (**2**) starting from the easily available compound (**3**) [3]

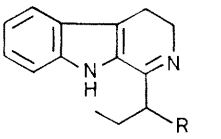
Utilizing the ability of the imine–enamine (**3**) to act as an ambident nucleophile (N- *vs* C-attack),[4] we treated (**3**) with 1·1 equiv of acrylic acid in refluxing anhydrous *p*-xylene (1·5 h) under N_2, to give the presumed intermediate (**4**) which underwent intramolecular cyclization to give the enamide (**5**) (91%), m p 235 °C [λ_{max} (MeOH) 229, 307, and 318 nm, ν_{max} ($CHCl_3$) 3500, 1665, and 1645 cm^{-1}, δ ($CDCl_3$) 1·26 (t, *J* 7 Hz, *Me*CH_2), 2·24—2 60 (4H, m, C_2H_2 + C_3H_2), 2·60 (q, *J* 7 Hz, MeCH_2), 2·86 (t, *J* 6 Hz, C_7H_2), and 4 06 (t, *J* 6 Hz, C_6H_2)] † Compound (**5**) was converted (75%) by $LiAlH_4$ in tetrahydrofuran (THF) at room temperature into the target molecule [isolated as its perchlorate, m p 175 °C, λ_{max} (MeOH) 207, 244, and 351 nm, ν_{max} (Nujol) 3320 and 1635 cm^{-1}] or, more efficiently, by sequential thionation (P_4S_{10}, refluxing C_6H_6) into (**6**) [λ_{max} (MeOH) 212, 248, 253, and 303 nm, δ ($CDCl_3$) 1·28 (t, *J* 7 Hz, *Me*CH_2), 2 28 (t, *J* 7 Hz, C_2H_2), 2 98 (t, *J* 5·5 Hz, C_7H_2), 3·04 (t, *J* 7 Hz, C_3H_2), and 4·76 (t, *J* 5 5 Hz, C_6H_2)] followed by desulphurisation with acetone–deactivated Raney nickel in MeOH at room temperature (81% yield) The suggested intermediacy of (**4**) was supported by N_b-acryloylation of (**3**) either with acrylic acid–diphenylphosphoryl azide[5] [dimethylformamide (DMF), room temperature] or with acryloyl chloride in the presence of 4-(dimethylamino)pyridine (MeCN, room temperature) [6‡] In both cases we obtained the enamide (**5**) as the sole isolable product in 95 and 63% yields, respectively



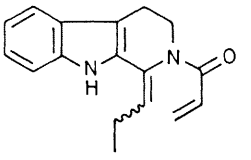
(1)



(2) X = Y = H_2
(5) X = H_2, Y = O
(6) X = H_2; Y = S
(8) X = O , Y = H_2



(3) R = H
(7) R = $[CH_2]_2CO_2Me$



(4)

Alternatively, regiospecific *C*-alkylation of (**3**) was achieved by refluxing with methyl acrylate in C_6H_6–MeOH (1; 1) (48 h) to give (**7**) [ν_{max} ($CHCl_3$) 3475, 3320, and 1725 cm^{-1}, δ ($CDCl_3$) 0·90 (t, *J* 7 Hz, *Me*CH_2) and 3·73 (s, CO_2*Me*), devoid of olefinic protons] which, on further heating (96 h) in *p*-xylene, gave (**5**) in 52% overall yield §

These routes constitute a considerable improvement in the synthesis of (**2**) and appear to be flexible for the preparation of either ring D-functionalised eburnanes or corynantheine-related alkaloids

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† The same product was recently observed by Le Men amongst the solvolysis products of the 7a-chloroindolenine from 1,12b-dihydro-(**5**), Y-Y Laronze, J Laronze, D Royer, J Levy, and J Le Men, *Bull Soc chim France*, 1977 1215

‡ These conditions are known to enhance reactivity at the carbonyl group of the acrylic acid unit

§ By refluxing (**3**) and methyl acrylate in C_6H_6–MeOH (1 1) for 96 h Szantay (ref 3) obtained in 12 6% yield a product to which structure (**8**) was assigned [m p 242—243 °C, ν_{max} (KBr) 3310 and 1668—1620 cm^{-1}, δ ($CDCl_3$) 1 26 (3H t Me), 4 05 (2H t $COCH_2$), 6 96—7 58 (4H m aromatic H), and 8 38 (1H s indole NH)] Compound (**8**) was inefficiently converted into (**2**) by a harsh Wolff–Kishner reduction It is especially difficult to check structure (**8**) in the absence of u v data and on the basis of the reported 4·05 p p m triplet for $COCH_2$

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[2] E Wenkert and B Wickberg, *J Amer Chem Soc*, 1965, **87**, 1580, C Thal T Sevenet, H P Husson, and P Potier, *Compt rend*, 1972, **275**, 1295, A Buzas, C Herisson, and G Lavielle *ibid*, 1976, **283**, 763, C Szantay, L Szabó, and G Kalaus, *Tetrahedron*, 1977, **33** 1803 A Buzas, C Retourne, J P Jacquet and G Lavielle, *ibid*, 1978, **34**, 3001

[3] Obtained by melting tryptamine and butyric acid at 190 °C followed by $POCl_3$-induced cyclization of the resulting N_b-butyryltryptamine, G Kalaus, P Gyory, L Szabó, and C Szántay, *Acta Chim Acad Sci Hung*, 1978, **97**, 429 (*Chem Abs*, 1979, **90**, 39093)

[4] Atta-ur-Rahman, *J C S Perkin I*, 1972, **94**, 731

[5] T Shioiri, K Ninomiya, and S Yamada, *J Amer Chem Soc*, 1972, **94**, 6203

[6] G Hofle, W Steglich, and H Vorbruggen, *Angew Chem Internat Edn*, 1978, **17**, 569