Convenient and Expeditious Synthesis of Some Indoloquinolizine Alkaloids

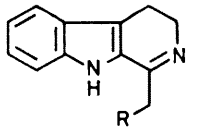
By BRUNO DANIELI,* GIORDANO LESMA, and GIOVANNI PALMISANO

(Istituto di Chimica Organica della Facoltà di Scienze, Università degli Studi di Milano, Centro di Studio per le Sostanze Organiche Naturali del C.N.R., Via Saldini 50, 20133 Milano, Italy)

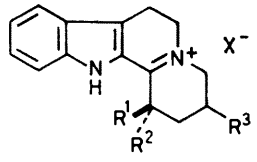
Summary The ambident reactivity of the imine-enamines (**1**) and (**2**) towards 1,3-dihalogenopropanes leads to an expeditious and efficient synthesis of some indoloquinolizines.

IN a previous communication we reported the reaction of the imine-enamine (**1**) with an electron-deficient three-carbon acrylic acid unit which, in conjunction with specific reduction, provided an efficient route to (**3**), a pivotal intermediate for preparation of clinically useful anti-hypertensive eburnane alkaloids.[1]

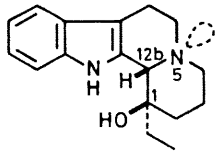
A straightforward one-step sequence is now reported for the conversion of (**1**) into (**3**) which exploits the predictable reactivity of the *C,N*-ambident nucleophile (**1**) towards 1,3-dihalogenopropanes *via* a favoured 'exocyclic' displacement.[2] Thus, refluxing for 7—8 h of a partial suspension of (**1**) (0·2 mol l^{-1}) and 1,3-dibromopropane or 1-bromo-3-chloropropane (0·4 mol) in acetonitrile in the presence of the non-nucleophilic proton acceptor ethyldi-isopropylamine[3] (0·2 mol) provided a 68 or 75% yield, respectively, of Wenkert's enamine, isolated as its perchlorate (**3**; X = ClO_4), m.p. 175 °C. Contrary to our expectation, the reaction of (**1**) with freshly distilled 1,3-di-iodopropane under similar conditions failed to give (**3**) but instead afforded in 52% yield the corresponding 1-hydroxy derivative as the hydriodide (**4**; X = I), m.p. 254 °C (from MeCN) [λ_{max} (MeOH) 245 and 360 nm; ν_{max} ($CHCl_3$) 3340,



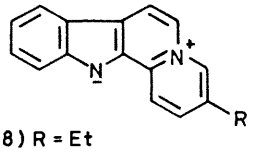
(1) R = Et
(2) R = H



(3) R^1 = Et, R^2 = R^3 = H
(4) R^1 = OH, R^2 = Et, R^3 = H
(5) R^1 = R^2 = H, R^3 = Et
(6) R^1 = R^2 = R^3 = H



(7)



(8) R = Et
(9) R = H

3200, and 1628 cm^{-1}].† The structure of (**4**) followed from its reduction ($NaBH_4$, MeOH) to the (±)-(1*R**, 5*R**, 12b*S**)[4]-dihydro-derivative (**7**), m.p. 172 °C [λ_{max} (MeOH) 223, 273(sh), 280, and 287 nm; *m/z* 270($M^{+\cdot}$)]. The depicted relative stereochemistry is suggested by i.r. absorptions [ν_{max} ($CHCl_3$) 3571 and 3418 (intramolecular $HO \cdots HN^a$ bonding), 2808 and 2747 cm^{-1} (*trans*-quinolizidine Bohlmann bands)] and n.m.r. ($CDCl_3$) signals [δ_H 0·82 (3H, t, *J* 7 Hz, $MeCH_2$), 1·96 (2H, q, *J* 7 Hz, $MeCH_2$), and 3·26 (1H, s, 12b-H); δ_C *inter alia* 69·5 (d, C-12b) and 75·0 p.p.m. (s, C-1)]. Compound (**7**) was in turn obtained from Wenkert's enamine (**3**) by electrophilic acetoxylation [thallium(III) acetate, chloroform, under argon] followed by treatment with $NaBH_4$.[5]

In order to test the utility of this annelation approach, we attempted the regiospecific synthesis of (**5**), an obvious precursor of the fully dehydrogenated alkaloid flavopereirine (**8**).[6] Refluxing (**2**) with 1-bromo-2-(bromomethyl)butane in MeCN and ethyl di-isopropylamine for 9 h led to (**5**; X = ClO_4) [λ_{max} (MeOH) 223, 248, and 353 nm; ν_{max} (Nujol) 3250 and 1625 cm^{-1}] which, after dehydrogenation with Pd–C (280 °C; 10 min) furnished flavopereirine (**8**) isolated as its perchlorate, m.p. 308 °C (from EtOH) [λ_{max} (EtOH–HCl) 237, 294, 350, and 391 nm] in 57% overall yield.

Likewise, the rare alkaloid (**9**)[7] was isolated in 68% yield as its picrate, m.p. 253 °C (MeOH–dimethylformamide), starting from (**2**) and 1,3-dibromopropane *via* the iminium salt (**6**; X = ClO_4),[8] m.p. 218 °C, and subsequent stepwise aromatization (Pd–C, maleic acid; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing acetic acid).

The high yields observed here along with the simple experimental procedure and the easy availability of starting materials make this approach more attractive than the previously reported syntheses of 1- and/or 3-(di)substituted indoloquinolizines.

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† T.l.c. provided evidence for the formation of (**3**) which was able to survive the work-up procedure only in trace amounts. The formation of (**4**) is presumed to proceed by a free-radical chain oxidation process initiated by iodine generated by thermal decomposition of 1,3-di-iodopropane and this process is consistent with the intermediacy of a 1-hydroperoxide which undergoes reduction by iodide ions present. Conversely, if the reaction was carried out under carefully controlled conditions in an inert atmosphere, after metathesis with $LiClO_4$, (**3**; X = ClO_4) was isolated in 54% yield.

‡ The high stereoselectivity may be rationalized in terms of intramolecular participation of the hydroxy group by co-ordination of tetrahydroborate anion (see T. Kametani, S. Hibino, and S. Takano, *J. Chem. Soc., Perkin Trans.* 1, 1972, 391). Dissolving-metal reduction [Zn, AcOH–H_2O (6 : 4), 6 h, room temperature] of (**4**), gave a more polar (t.l.c.) compound in 10% yield. This has been identified as the 12b-epimer of (**7**) on the basis of its i.r. [ν_{max} ($CHCl_3$) 3500(NH) and 3300 (br, OH) cm^{-1}; weak Bohlmann bands] and ^1H n.m.r. spectra [δ ($CDCl_3$) 0·96 (3H, t, *J* 7 Hz, $MeCH_2$) and 4·14 (1H, s, 12b-H)].

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[2] L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, 1970, **53**, 2059.
[3] S. Hünig and M. Kiessel, *Chem. Ber.*, 1958, **91**, 380. Other bases gave no better and sometimes considerably poorer results.
[4] IUPAC Tentative Rules for Nomenclature of Organic Chemistry, Section E, *J. Org. Chem.*, 1970, **35**, 2849.
[5] P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, and P. Potier, *J. Am. Chem. Soc*, 1979, **91**, 2243.
[6] Flavopereirine is one of the simplest biogenetically related bases to heteroyohimbane; it has been the object of several regio- and non-regio-specific syntheses and was generally obtained in multistep procedures in low overall yields: E. Wenkert and B. Vickberg, *J. Am. Chem Soc.*, 1962, **84**, 4914, and references quoted therein; Cs. Szántay and L. Töke, *Acta Chim. Acad Sci. Hung.*, 1963, **39**, 249 (*Chem. Abs.*, 1964, **60**, 5575); I. Ninomiya, Y. Tada, T. Kiguchi, O. Yamamoto, and T. Naito, *Heterocycles*, 1968, **9**, 1527.
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[8] R. N. Schut and T. J. Leipzig, *J. Heterocycl. Chem.*, 1966, **3**, 101.