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TOTAL SYNTHESIS AND STEREOCHEMICAL REASSIGNMENT OF THE INDOLE ALKALOID VINOXINE

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The first total synthesis of the indole alkaloid vinoxine and the reassignment of the relative configuration at carbon-16 in this alkaloid is reported.

Vinoxine[1] is a minor indole alkaloid isolated in 1967 from *Vinca minor* L. Its planar structure 6, lacking the characteristic tryptamine unit present in the greater part of indole alkaloids and having, as pleiocarpamine,[2] a bridged 2,7-diazabicyclo[3.3.1]nonane moiety and an exocyclic *E*-ethylidene substituent, was established some years later.[3] The relative configuration at C-16[4] depicted in 6a was assigned to vinoxine from the chemical shift of the H-16 proton in the ^{1}H-nmr spectrum (δ4.84), coincident with that of 16-epipleiocarpamine (δ4.74) but different from the one reported for pleiocarpamine (δ5.26).

In contrast to pentacyclic alkaloids of the C-mavacurine group[5] related to vinoxine, no synthesis for this alkaloid has been described yet. In previous papers we reported the synthesis of the fundamental tetracyclic framework of vinoxine.[6] Our synthetic approach implied closure of ring C by formation of the C_2-C_3 bond in the key synthetic step through intramolecular cyclization of an appropriate piperidinium salt upon the indole 2-position. The same methodology was used to synthesize a 19,20-dihydro derivative of vinoxine.[7]

We present here the first total synthesis of vinoxine. The synthesis is based on the intramolecular cyclization of a suitably substituted dihydropyridinium salt upon the indole 2-position. On the other hand, due to its high stereoselectivity, among the numerous methods of generating the exocyclic C-20 *E*-ethylidene substituent developed in alkaloid synthesis[8] we selected that based on the hydrolysis and decarboxylation followed by sodium borohydride reduction of β-(1,4,5,6-tetrahydro-3-pyridyl)acrylate systems[9] such as 4.

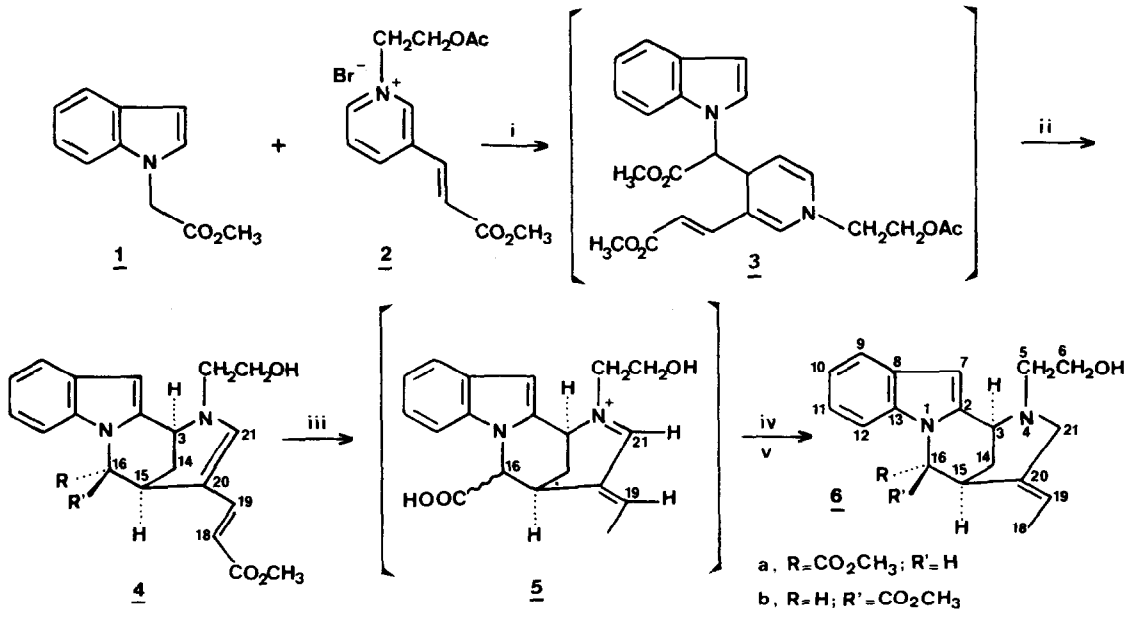
The required doubly vinylogous urethane 4 was prepared in 12% yield as a mixture of C-16 epimers[10] in a two step "one pot" synthesis by reaction of ester 1[11] with pyridinium bromide 2[12] in the presence of LDA, followed by treatment of the intermediate 1,4-dihydropyridine 3 with hydrogen chloride in benzene. The ability of *N*-alkylpyridinium salts having electron-withdrawing substituents at the 3-position to react with ester α-anions at the γ-position of the pyridine ring has been previously applied in alkaloid synthesis.[13] On the other hand, it is worth mentioning that the cyclization proceeded regiospecif-

ically since protonation occurs at the β-carbon of the unsubstituted enamine function rather than at the doubly vinylogous urethane moiety.

The structure of 4a and 4b was inferred from its ^{1}H and ^{13}C-nmr data.[10] Thus, a singlet for the indole 3-proton and an apparent triplet due to the bridgehead C-3 methine proton clearly indicated that cyclization had occurred. The observed coupling constant of the doublet due to the C-16 methine proton was 1.2 Hz in the major isomer 4a and 5.4 Hz in the minor C-16 epimer 4b. These values are those expected for the relative stereochemistry of this center depicted in 4a (H-15/H-16 *trans*-relationship) and 4b (H-15/H-16 *cis*-relationship), in which the approximate dihedral angles in the H-C^{15}–C^{16}-H bond system are 80° and 40°, respectively.

As expected, treatment of 4a with refluxing 4N hydrochloric acid accomplished the hydrolysis of the two ester groups and the decarboxylation of the acrylic acid moiety to give a conjugated iminium salt 5, which was not isolated. Direct reesterification of the 16-carboxy group followed by sodium borohydride reduction of the carbon-nitrogen double bond afforded a mixture of vinoxine and 16-epivinoxine in 22% yield. This synthetic vinoxine was identical in all respects (tlc, ir, ^{1}H-nmr, ^{13}C-nmr) with the natural product.[14] When the same reaction sequence was carried out from 4b, vinoxine was isolated as the major product.

The natural *E*-configuration of the ethylidene chain in both isomers was evident from the observation of a positive NOE effect for the signal corresponding



Reagents: (i) LDA, THF, -30°C, 1h; (ii) C_6H_6-HCl, pH=3.5-4; (iii) 4N HCl, 100°C, 2h; (iv) 1.5N MeOH-HCl, r.t., 18h; (v) $NaBH_4$, MeOH, 0°C, 1h.

to H-15 on irradiation of the doublet of doublets due to the C^{19}-CH_3 group.[15] This configuration was not unexpected since the steric interactions between C^{21}-H and C^{19}-H in the iminium salt 5 with an *E*-configuration are lower than those between C^{21}-H and C^{19}-CH_3 in the corresponding *Z* iminium salt.[16]

Comparison of the ^{1}H-nmr spectra of vinoxine[3] and 16-epivinoxine[17] with those of pleiocarpamine and 16-epipleiocarpamine allows the reassignment[3b] of the relative orientation of the 16-methoxycarbonyl substituent of vinoxine. Thus, the J_{15-16} coupling constant in 16-epipleiocarpamine[2] (H-15/H-16 *trans*-relationship) is 1.5 Hz, a value similar to that observed for 16-epivinoxine (J=1.14 Hz), whereas that reported for pleiocarpamine[2] (H-15/H-16 *cis*-relationship) is 4 Hz, similar to that observed in vinoxine (J=6.14 Hz). Accordingly, vinoxine has the same relative configuration at C-16 than pleiocarpamine, so it can be depicted as 6b. Furthermore, the observed J_{15-16} coupling constant of vinoxine is in fair agreement with that expected from the Karplus relationship for the stereochemical disposition in 6b.

The above stereochemical assignments are in good agreement with the shielding of C-14 in the ^{13}C-nmr spectra of 4a and 6a, as compared with 4b and vinoxine (6b),[3] by a γ-effect induced by the methoxycarbonyl group. Related γ-effects at C-20 caused by the methoxycarbonyl group are observed in 4b and vinoxine (6b) when compared with their 16-epimers.

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REFERENCES AND NOTES

1. J. Mokrý, I. Kompiš, and G. Spiteller, *Coll. Czech. Chem. Commun.*, 1967, *32*, 2523.
2. M. Hesse, W. v. Philipsborn, D. Schumann, G. Spiteller, M. Spiteller-Friedmann, W. I. Taylor, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1964, *47*, 878.
3. (a) Z. Votický, E. Grossmann, J. Tomko, G. Massiot, A. Ahond, and P. Potier, *Tetrahedron Lett.* 1974, 3923; (b) Z. Votický, E. Grossmann, and P. Potier, *Coll. Czech. Chem. Commun.*, 1977, *42*, 548.
4. The biogenetic numbering is used throughout this paper. J. Le Men and W. I. Taylor, *Experientia*, 1965, *21*, 508.
5. (a) D. D. O'Rell, F. G. H. Lee, and V. Boekelheide, *J. Am. Chem. Soc.*, 1972, *94*, 3205; (b) S. Sakai and N. Shinma, *Chem. Pharm. Bull.*, 1974, *22*, 3013; (c) S. Sakai and N. Shinma, *Heterocycles*, 1976, *4*, 985; (d) S. Sakai and N. Shinma, *Yakugaku Zasshi.*, 1978, *98*, 950; (e) M. J.Calverley,J. B. Banks, and J. Harley-Mason, *Tetrahedron. Lett.*, 1981, *22*, 1635.
6. (a) J. Bosch, M. Feliz, and M.-L. Bennasar, *Heterocycles*, 1982, *19*, 853; (b) J. Bosch, D. Mauleón, M. Feliz, and R. Granados, *J. Org. Chem.*, 1983, *48*, 4836; (c) J. Bosch, M. Feliz, and M.-L. Bennasar, *Tetrahedron*, 1984, *40*, 000.
7. J. Bosch, M.-L. Bennasar, and E. Zulaica, Third European Symposium on Organic Chemistry, Canterbury, England, 1983.
8. J. Bosch and M.-L. Bennasar, *Heterocycles*, 1983, *20*, 2471.

9. This procedure has been applied to the synthesis of the *E*-ethylidene bearing indole alkaloids deplancheine[9a] and geissoschizine[9b]. (9a) R. Besselièvre, J.-P. Cosson, B. C. Das, and H.-P. Husson, *Tetrahedron Lett.*, 1980,*21*, 63; (9b) E. Wenkert, Y. D. Vankar, and J. S. Yadav, *J. Am. Chem. Soc.*, 1980, *102*, 7971.

10. The 4a/4b ratio was 5:1. 4a: m.p. 109-110°C (ether-acetone). Ir (KBr, cm^{-1}): 3100-3600, 1750, 1690, 1580. ^{1}H-nmr ($CDCl_3$, δ): 2.0 (dt,J=3.6 and 13.2 Hz,1H,H-14β), 2.4 (dt,J=3.0 and 13.2 Hz,1H,H-14α), 3.18 (dt,J=5.2 and 15Hz,1H,H-5), 3.24 (br,1H,H-15), 3.56 (dt,J=6.5 and 15Hz,1H,H-5), 3.68-3.86 (masked,2H,H-6), 3.75 (s,3H,OCH_3), 3.77 (s,3H,OCH_3), 4.64 (t,J=1Hz, 1H,H-3), 5.04 (d,J=1.2Hz,1H,H-16), 5.67 (d,J=15Hz,1H,H-18), 6.40 (s,1H,H-7), 6.47 (s,1H, H-21), 7.02-7.16 (m,3H,H-indole), 7.26 (d,J=15Hz,1H,H-19), 7.58 (dt,J=1 and 7Hz,1H,H-12). ^{13}C-nmr ($CDCl_3$,δ): 22.95 C-14, 29.11 C-15, 48.93 C-3, 51.10 OCH_3, 52.71 OCH_3, 55.50 C-5, 59.14 C-16, 60.65 C-6, 99.5 C-7, 103.34 C-18, 105.45 C-20, 109.09 C-12, 120.55 C-11, 120.93 C-9, 122.42 C-10, 127.77 C-8, 135.09 C-2, 136.58 C-13, 145.18 C-19, 145.59 C-21, 169.15 C=0, 170.76 C=0. 4b: ir ($CHCl_3$, cm^{-1}): 3100-3600, 1750, 1690, 1580. ^{1}H-nmr ($CDCl_3$, δ): 2.04 (br,2H,H-14), 3.16 (dt,J=5 and 15Hz,1H,H-5), 3.42-3.84 (m,4H,H-5,H-6,H-15), 3.70 (s,3H,OCH_3), 3.73 (s,3H,OCH_3), 4.57 (t,J=1Hz,1H,H-3), 4.99 (d,J=5.4Hz,1H,H-16), 5.39 (d, J=15Hz,1H,H-18), 6.41 (s,1H,H-7), 6.63 (s,1H,H-21), 7.04-7.20 (m,3H,H-indole),7.26 (d, J=15Hz,1H,H-19), 7.58 (m,1H,H-12). ^{13}C-nmr: 26.00 C-14, 27.5 C-15, 48.64 C-3, 50.98 OCH_3, 52.72 OCH_3, 56.11 C-5, 60.62 C-6, 61.99 C-16, 99.88 C-7, 102.98 C-20, 103.11 C-18, 110.45 C-12, 120.65 C-11, 120.90 C-9, 122.25 C-10, 128.13 C-8, 136.34 C-2, 136.86 C-13, 145.46 C-19, 147.03 C-21, 169.29 C=0, 170.35 C=0.

11. Methyl 1-indoleacetate (1) was prepared by condensation of indole with methyl bromoacetate followed by esterification of the resulting 1-indoleacetic acid.

12. Salt 2 was obtained by alkylation of methyl β-(3-pyridyl)acrylate[13b] with 2-bromoethyl acetate.

13. (a) E. Wenkert, C. J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J.C. King, and K. Orito, *J. Am. Chem. Soc.*, 1976, *98*, 3645; (b) E. Wenkert, T. D. J. Halls, G. Kunesch, K. Orito, R. L. Stephens, W. A. Temple, and J. S. Yadav, *J. Am. Chem. Soc.*, 1979, *101*, 5370; (c) M. J. Wanner, G. J. Koomen, and U. K. Pandit, *Heterocycles*, 1981, *15*, 377; (d) M. J. Wanner, G. J. Koomen, and U. K. Pandit, *Heterocycles*, 1982, *19*, 2295 ; (e) M. Lounasmaa and A. Koskinen , *Tetrahedron Lett.*, 1982, *23*, 349.

14. We are indebted to Professor Pierre Potier of the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, for the gift of a sample of vinoxine.

15. J. C. Nouls, G. Van Binst, and R. H. Martin, *Tetrahedron Lett.*, 1967,4065.

16. M. R. Uskoković, R. L. Lewis, J. J. Partridge, C.W. Despreaux, and D. L. Pruess, *J. Am. Chem. Soc.*, 1979, *101*, 6742.

17. 6a: ir ($CHCl_3$, cm^{-1}): 3300-3600, 1750, 1730. ^{1}H-nmr ($CDCl_3$,δ): 1.79 (dd,J=2.1 and 6.8Hz, 3H,H-18), 2.11 (dt,J=4 and 12Hz,1H,H-14), 2.35 (m,2H,H-14,H- 5), 2.51 (br d,J=14Hz,1H, H-21ax), 2.83 (ddd,J=4.8,7.8 and 13.2Hz,1H,H-5), 3.02 (d,J=14Hz,1H,H-21eq), 3.58 (br,1H, H-15), 3.68 (m,2H,H-6), 3.72 (s,3H,OCH_3), 4.10 (t,J=1Hz,1H,H-3), 4.85 (d,J=1.14Hz,1H,H-16), 5.45 (qd,J=2.1 and 6.8Hz,1H,H-19), 6.35 (s,1H,H-7), 7.09-7.20 (m,3H,H-indole),7.61 (m,1H, H-12). ^{13}C-nmr ($CDCl_3$,δ): 12.59 C-18, 27.76 C-14, 31.8 C-15, 51.82 C-3, 52.71 OCH_3, 54.34 C-5, 56.49 C-21, 57.93 C-6, 59.9 C-16, 101.42 C-7, 108.61 C-12, 120.35 C-11, 120.74 C-9, 120.86 C-10, 121.77 C-19, 127.79 C-8, 131.95 C-2, 135.08 C-20, 136.27 C-13, 170.11 C=0.

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