Tetrahedron Letters,Vol.26,No.24,pp 2925-2928,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF ISOINDOLOISOQUINOLINE ALKALOIDS. A REVISION OF THE STRUCTURE OF (±)-NUEVAMINE

Ricardo Alonso, Luis Castedo and Domingo Domínguez

Departamento de Química Orgánica de la Facultad de Química y
Sección de Alcaloides del CSIC. Santiago de Compostela (Spain)

Abstract: An easy and efficient method for the synthesis of isoindoloisoquinolines, and the assignment of a new structure for the alkaloid (±)-nuevamine are reported.

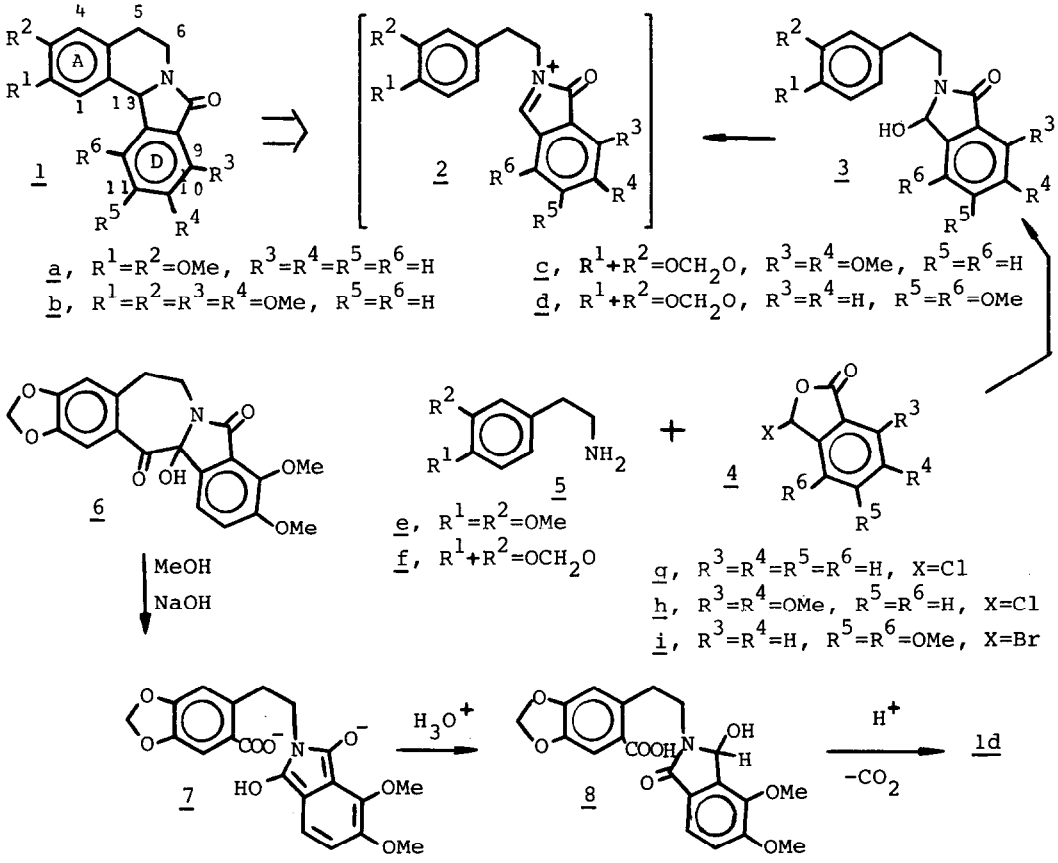
(±)-Nuevamine 1c is an alkaloid recently isolated from Berberis darwinii Hook,[1] and is the first isoindoloisoquinoline reported from natural sources. The novelty of its skeleton prompted us to seek a synthetic route to this type of isoquinoline alkaloids.

To this end a strategy was designed which rests upon the construction of the C-C bond linking the C-13 position with the aromatic ring A. Formation of this bond was conceived as being possible by an intramolecular arylation of α-acyliminium cations[3] of type 2, which can be easily generated by mild acid treatment of the corresponding γ-hydroxylactams. In our case the latter are the phthalimidols 3, which can be prepared by a regioselective reduction[3] of the corresponding phthalimide or, more conveniently, by condensation[4] of a primary amine with a suitably substituted 3-halophthalide. This latter procedure allows access to compounds 3 by simple treatment of an acetone solution of a 3-halophthalide 4 with triethylamine and a readily available phenethylamine 5. After 4 days of stirring at room temperature the triethylamine hydrochloride is filtered off and the product isolated by preparative TLC on silicagel. Compounds 3a-c were obtained in this way in good yield.[5]

When a methylene chloride solution of phthalimidols 3a-c was treated with trifluoroacetic acid at room temperature, followed by aqueous

bicarbonate washings, isoindoloisoquinolines 1a-c were obtained in quantitative yield.[5,6] Synthetic 1c thus obtained has the structure assigned to the alkaloid (±)-nuevamine.[7] However its mp and spectral data are significantly different from those reported for the natural compound[1], thus suggesting reconsideration of the latter's structure to be necessary.

Upon examination of the chemical conversion of chilenine 6 into (±)-nuevamine,[2] it ocurred to us that this alkaloid might have the isomeric structure 1d, which would result by cyclization of the phthalimidol 8, formed by an alternative protonation to that proposed for the intermediate anion 7.[2] The synthesis of 1d was accordingly carried out following the above procedure. Condensation of 3-bromopseudomeconine 4i[8] and phenethylamine 5f gave phthalimidol 3d (55% yield), which was quantitatively transformed into 1d by TFA treatment. Compound 1d thus prepared had



identical mp and spectral data to those reported for (±)-nuevamine, so the structure 1c initially proposed should now be changed to that represented by 1d.[9]

Phthalimidol 3d, the immediate precursor of (±)-nuevamine 1d, has also been synthesized by ortho-metalation[10] of the amide derived from amine 5f and 3,4-dimethoxybenzoic acid, followed by DMF addition and aqueous work-up (28% yield). This new approach provides a much quicker path to (±)-nuevamine 1d, although in lower yield.

Acknowledgement. We thank the Comisión Asesora (CAICYT) for its financial support.

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5. All new compounds were fully characterized by IR, NMR and mass spectra and gave satisfactory elemental analyses.

6. 2,3-Dimethoxyisoindoloisoquinoline 1a. mp 173º (ether), IR ν_{max} (KBr) 1680 cm^{-1}, MS m/e (%) 295(M^+, 94), 294(88), 280(31) and 264(100), H-NMR(250 MHz, $CDCl_3$, δ) 2.78, 3.02 and 3.43(m each, 1H each), 3.85(s, 3H, OMe), 3.94(s, 3H, OMe), 4.52(m, 1H), 5.64(s, 1H, H-13), 6.67(s, 1H, H-4), 7.13(s, 1H, H-1), 7.50, 7.62 and 7.86(m each, 4H, Ar-H).

2,3,9,10-Tetramethoxyisoindoloisoquinoline 1b. mp 162º (MeOH), IR 1680, MS 355(M^+, 93), 354(80), 340(37) and 324(100), H-NMR 2.74, 3.01 and 3.36(m each, 1H each), 3.86(s, 3H, OMe), 3.91(s, 3H, OMe), 3.94(s, 3H, OMe), 4.08(s, 3H, OMe), 4.47(m, 1H), 5.53(s, 1H, H-13), 6.66(s, 1H, H-4), 7.08(s, 1H, H-1), 7.16 and 7.46(ABq, J.8.2, 2H, H-11 and H-12).

2,3-Methylendioxy-9,10-dimethoxyisoindoloisoquinoline 1c. mp 194-196º

(MeOH), IR 1680, MS 339(M^+, 100), 338(93), 324(22), 310(31), 309(24), 308(71), and 280(17), H-NMR 2.75, 2.98 and 3.39(m each, 1H each), 3.91(s, 3H, OMe), 4.07(s, 3H, OMe), 4.32(m, 1H), 5.46(s, 1H, H-13), 5.90 and 5.96(ABq, J.1, 2H, OCH_2O), 6.66(s, 1H, H-4), 7.04(s, 1H, H-1), 7.15 and 7.44(ABq,J.8.3, 2H, H-11 and H-12).

7. The structure of our synthetic 1c is quite certain given the method employed in its preparation, and was further confirmed by NOE difference spectroscopy, which showed strong enhancements between protons H-12 and H-1.

8. Compound 4 i was obtained by NBS bromination of pseudomeconine, which was in turn obtained by ortho-metalation of N-phenyl-3,4-dimethoxybenzamide, followed by passage of formaldehyde and final acidic work-up.

9. The structure of 1d was further confirmed by NOEDS studies, which under irradiation of H-1 did not show any enhancement in the remote protons H-9 and H-10, and viceversa.

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(Received in UK 10 April 1985)