Tetrahedron Letters No.20, pp. 2425-2428, 1968. Pergamon Press. Printed in Great Britain.

THE TOTAL SYNTHESIS OF (±)-OCHOTENSIMINE

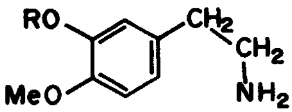
Stewart McLean, Mei-Sie Lin and John Whelan
Department of Chemistry, University of Toronto
Toronto 5, Ontario 5, Ontario

(Received in USA 19 January 1968; accepted for publication 14 February 1968)

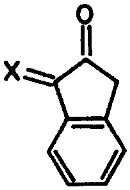
Ochotensimine (Vd), the structure of which we have recently established (1), incorporates a spiro ring junction that is a novel feature in this class of alkaloids. Although the Pictet-Spengler reaction has been widely used in the synthesis of benzylisoquinoline alkaloids, it does not seem to have been given much attention in cases where a ketone rather than an aldehyde is one of the reaction components. Since a reaction of this sort with the appropriate ketone offered a direct route to the ochotensimine skeleton, we decided to approach the synthesis of the alkaloid from this direction.

We established first that when homoveratrylamine (Ia) and 2-indanone (IIa) were heated to 90° with 85% phosphoric acid under nitrogen for 21 hours (2), a 16% yield of the desired tetracyclic product IIIa was obtained. This did not crystallize, but formed a crystalline N-acetyl derivative, m.p. 152-153°, $C_{21}H_{23}O_3N$ (Found: C, 74.80; H, 6.91; N, 4.22). Under the same conditions, 1,2-indanedione (IIb) (3) reacted with Ia to form the ketone IIIb (i.r. $\lambda_{max}^{CHCl_3}$ 5.84 μ) in 30% yield. No product resulting from reaction at position 1 of IIb was found. Compound IIIb, which was non-crystalline, was converted quantitatively under Eschweiler-Clarke conditions (4) to its yellow N-methyl derivative (IIIc), m.p. 136-138°, $C_{20}H_{21}O_3N$ (Found: C, 74.11, H, 6.57; N, 4.34), i.r. $\lambda_{max}^{CHCl_3}$ 5.85 μ, u.v. $\lambda\lambda_{max}^{MeOH}$ 242 (ε, 14,200), 286 (ε, 5,200), 366 (ε, 90) mμ. A Wittig reaction of IIIc employing methylenetriphenylphosphorane in tetrahydrofuran (5) converted it in 44% yield to (±)-des(methylenedioxy)ochotensimine (IIId) which was non-crystalline but which exhibited an n.m.r. spectrum almost identical with that of ochotensimine (1) except for the absence of the methylenedioxy signal and the presence of signals corresponding to two additional protons as part of a complex multiplet in the region τ 2.10-2.76 (total area corresponding to 4 protons). The methiodide of IIId, $C_{21}H_{23}O_2N.CH_3I$ (Found: C, 56.77; H, 5.92; N, 2.95; I, 24.78, 25.16), was crystalline, m.p. 130-134°.

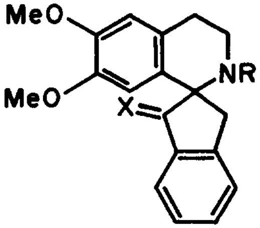
4,5-Methylenedioxy-1-indanone (IVa), the required precursor of ochotensimine itself, was prepared by a lengthy sequence starting from 2,3-dihydroxybenzoic acid. The corresponding methylenedioxycinnamic acid was prepared by the method described by Perkin (6) with the modification that lithium aluminum hydride was used to reduce the methylenedioxybenzoic acid and the resulting alcohol was oxidized to the aldehyde with chromium trioxide in pyridine. The methylenedioxycinnamic acid was reduced to its dihydro derivative with sodium amalgam, and this was cyclized by phosphorus pentoxide (7) to the indanone IVa, m.p. 165-168°, $C_{10}H_8O_3$ (Found: C, 68.38; H, 4.39), i.r. $\lambda_{max}^{CHCl_3}$ 5.89 μ, in 25% yield. The oximinoketone IVb was prepared by the method used in the synthesis of the indanedione IIb (3), but, in contrast to the situation in the model series, IVb resisted hydrolysis under a variety of conditions and it became necessary to convert IVa to the dione IVc by an alternative route. This was accomplished in best yield (about 70%) by the acetoxylation of IVa with lead tetraacetate (8) followed by careful hydrolysis of the ester with 2% sodium hydroxide at 0°, and oxidation with the Jones reagent of the resulting hydroxyketone to give IVc, m.p. 158-168°, $C_{10}H_6O_4$ (M. Wt. 190 by mass spectrometry), i.r. $\lambda\lambda_{max}^{CHCl_3}$ 5.66 (m), 5.82 (s). Unfortunately, when the Pictet-Spengler conditions used in the model series were applied to IVc and Ia, no recognizable product was obtained and IVc did not survive the reaction. We then found that IVc reacted with the phenolic amine Ib in the presence of 2.5% hydrochloric acid at 50° to form the desired product Va, m.p. 104-107°, $C_{19}H_{17}O_5N$ (M. Wt. 339 by mass spectrometry), i.r. $\lambda_{max}^{CHCl_3}$ 5.85 μ; reaction was very slow, but the yield of Va based on unrecovered IVc was excellent (over 80%). Diazomethane converted Va almost quantitatively to its O-methyl derivative Vb, m.p. 176-179°, i.r. $\lambda_{max}^{CHCl_3}$



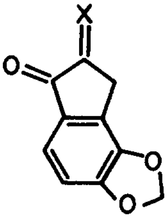
(I) a : R = Me
b : R = H



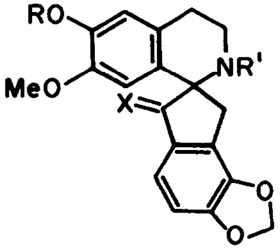
(II) a : X = H_2
b : X = O



(III) a : R = H ; X = H_2
b : R = H ; X = O
c : R = Me; X = O
d : R = Me; X = CH_2



(IV) a : X = H_2
b : X = NOH
c : X = O



(V) a : R = H ; R' = H ; X = O
b : R = Me ; R' = H ; X = O
c : R = Me ; R' = Me ; X = O
d : R = Me; R' = Me ; X = CH_2

5.85 μ, with OMe signals at τ 6.15 and 6.44 in the n.m.r. N-Methylation of Vb under the conditions used in the model series afforded Vc, m.p. 162-165°, $C_{21}H_{21}O_5N$ (M. Wt. 367 by mass spectrometry), i.r. $\lambda_{max}^{CHCl_3}$ 5.85 μ, with an NMe signal at τ 7.72 in the n.m.r.; the yield was 85%. Finally the Wittig reaction under the conditions already described converted Vc to Vd, $C_{22}H_{23}O_4N$ (M. Wt. 365 by mass spectrometry), in 60% yield. Neither natural ochotensimine nor the racemic synthetic material have been obtained crystalline but they exhibit the same behavior on t.l.c. and their i.r., u.v., and n.m.r. spectra are superimposable.

Acknowledgement. We are grateful to the National Research Council for financial support.

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