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AN APPROACH TO THE SYNTHESIS OF IBOGAINE

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IN view of the increasing interest in iboga alkaloids I should like to present some of the preliminary steps toward a total synthesis of ibogaine (I) (1). The successful, stereochemically controlled synthesis of the tetracyclic indole (XVIa) suggests a feasible pathway for the synthesis of I and some of its congeners. The cis-fused C/D rings of XVIa were constructed from the cis-enedione (IIa) (2), which, after suitable modifications (IIa ⟶ IIIa ⟶ VIa), was subjected to the Beckmann rearrangement to give VIIIa. The lactam was then reduced to the cis-aminoketal (Xa). The aminoketone derived from Xa underwent indole formation, producing the A-D ring system of XVIa and ibogaine (I).

Parallel transformations of the stereochemically more stable trans-enedione (IIb) were carried out, the availability of the trans series (IIIb-VIIIb and Xb) being helpful in determining the configurations during every step of the synthesis. Gas chromatography proved that the separately equilibrated IIa and IIb isomers reached a cis/trans ratio of 1:5.7. In spite of the stereochemical instability of IIa (3,4), it proved to be a useful starting material. The isolated double bond of both epimers (IIa,b) survived all the steps and was found to be particularly helpful in verifying the structures of VIa,b and VIIIa,b (vide infra).

In reproducing the preparation of the trans-enedione (IIb), as reported by Henbest, et al. (5), it was proved that the intermolecular chelate (XIV) [m.p. 159-160°; λ_{max}^{EtOH} 215, 292 mμ (ε7100, 3000); λ_{max}^{KBr} 3.08 (OH), 5.92 μ (>C=O)] was the actual product isolated. The two components of XIV were separated either by thin-layer chromatography (T.L.C.) (R_f 0.33 and 0.38)[a] or (in 90% yield) by solvolysis. The more puckered cis-dione (IIa) did not chelate with the planar hydroquinone derivative (XV) (6). This difference in behavior offered a means for the isolation of the trans-enedione (IIb) from an equilibrated epimer mixture in 75% over-all yield. The m.p. of IIb was found to be identical (95.5-96.5°) with that reported by Ireland and Marshall (3). The conspicuous differences between the nuclear magnetic resonance (n.m.r.) spectra[b] of the two epimers (IIa,b) established their conformations. The spectrum of IIa indicated non-equivalence for its four C_2, C_3-protons (sharp peaks at δ 2.77 and 2.80 p.p.m.). Contrary to this observation, equivalence of the protons in similar positions of IIb (δ 2.72 p.p.m., s), analogously to cyclohexane-1, 4-dione (7-9), suggested a twisted-boat conformation for its A ring. The axial-equatorial C_9, C_{10}-protons of IIa were easily distinguishable (δ 3.17 p.p.m., m) from the similar but diamagnetically shifted axial-axial protons of IIb (δ 2.59 p.p.m., m).[c]

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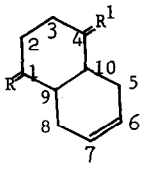
a) The T.L.C. systems were : Al_2O_3-G[ethyl acetate — n-hexane (2:3)] for XIV; neutral silica gel — starch (10) [ethyl acetate — n-hexane (2:3) for IIa,b to VIa,b and XXIIIa,b; Al_2O_3-G[chloroform] for VIIIa,b; Al_2O_3-G[chloroform — cyclohexane — diethylamine (7:2:1)] for XVIa,b and XVII.

b) Measured in deuteriochloroform at 60 Mc on a Varian, Model A-60, spectrometer and expressed as p.p.m. shift (δ) downfield from tetramethylsilane.

c) Details of the conformational analyses will be published elsewhere.



IIa,b*: $R=R^1=O$

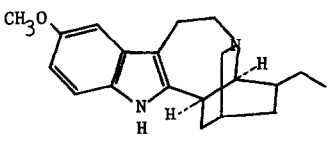
IIIa,b: $R=-O-(CH_2)_2-O-$; $R^1=O$

IVa,b: $R=R^1=-O-(CH_2)_2-O-$

Va,b: $R=O$; $R^1=\rangle NOH$

VIa,b: $R=-O-(CH_2)_2-O-$; $R^1=\rangle NOH$

VIIa,b: $R=-O-(CH_2)_2-O-$; $R^1=\rangle NOTs$



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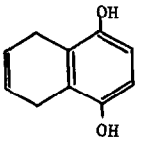

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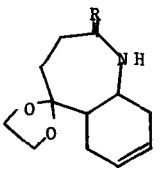
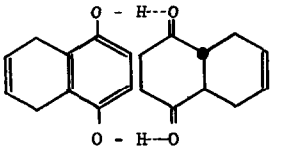
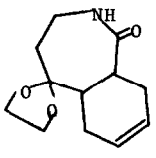




VIIIa,b: R=O

Xa,b: $R=H_2$

XIV



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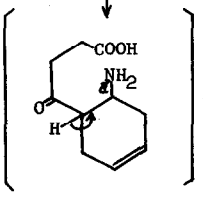
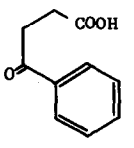
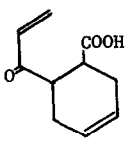


XI



XII



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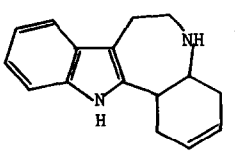
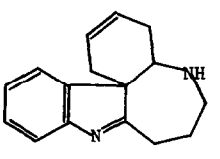


XVIa,b



XVII

* The ring systems of series a and b possess cis and trans configurations, respectively.

The cis-dione (IIa) failed to produce a satisfactory yield of the cis-monoxime (Va) [λ_{max}^{KBr} 3.15 (OH), 5.85 μ (>C=O); R_f 0.17[a]] and, furthermore, Va could not be rearranged to the corresponding lactam. To achieve a higher degree of stereostability before the oxime function was introduced, the monoketalization of IIa was studied (3,4). The ketalization, which was followed by quantitative T.L.C., led to a mixture of the cis-monoketal (IIIa, yield ca. 27%) [m.p. 62-64°; λ_{max}^{KBr} 5.85 μ; δ 2.30 (8H,m), 3.09 (2H,m), 4.0 (4H,d), 5.52 p.p.m. (2H,b); R_f 0.43] and the cis-bisketal (IVa, yield 10-15%) [m.p. 116-117° (4); δ 1.77 (4H,m), 2.13 (6H,b), 3.86 (8H,s), 5.54 p.p.m. (2H,b); R_f 0.53], as well as to the trans-monoketal (IIIb, yield ca. 22%) [m.p. 52-54° (4); λ_{max}^{KBr} 5.85 μ; δ 2.03 (8H,m), 2.56 (2H,m), 3.98 (4H,b), 5.53 p.p.m. (2H,b); R_f 0.48] and the trans-bisketal (IVb, yield 15-30%) [m.p. 97.5-98° (3); δ 1.71 (4H,s), 2.01 (6H,s), 3.86 (8H,b), 5.52 p.p.m. (2H,b); R_f 0.55]. Some starting material (IIa, ca. 5%) (R_f 0.24) and its epimer (IIb, ca. 10%) (R_f 0.35) were also detected. Thus, the T.L.C. and n.m.r. data revealed the concomitant epimerization and two-step ketalization of IIa. It was also proved that the cis-monoketal (IIIa) did not equilibrate with the trans-epimer (IIIb) during isolation from a Florisil column, as reported by others (4).

The two monoketals (IIIa,b) retained their configurations during oximation and gave rise to the cis-anti-oximeketal (VIa, yield 27% calculated on IIa) [m.p. 178-179°; λ_{max}^{KBr} 3.15 (OH), 5.98 (>C=N-), 6.03 μ (>C=C<); R_f 0.46] and trans-anti-oximeketal (VIb, yield 22% calculated on IIa) [m.p. 166-167°; λ_{max}^{KBr} 3.15 (OH), 5.98 (>C=N-), 6.03 μ (>C=C<); R_f 0.54]. The anti-oxime structure of VIa,b was verified by degradation (vide infra). On tosylation of the epimer ketaloximes (VIa,b) in warm pyridine, they exhibited a remarkable difference. While the trans-epimer (VIb) furnished the expected trans-tosyloxime ketal (VIIb) (m.p. 131-132°) in almost quantitative yield, the cis-epimer (VIa) spontaneously rearranged to the desired cis-lactamketal (VIIIa, yield 89%) [m.p. 211.5-212°; λ_{max}^{KBr} 3.15 (NH), 6.03 μ (>C=O); R_f 0.34[a]].

It is believed that the coplanarity of the participating centers of the intermediate cis-tosyloxime (VIIa) facilitate the Beckmann rearrangement. The trans-tosyloxime (VIIb) was ring expanded to the trans-lactamketal (VIIIb) [m.p. 200°; λ_{max}^{KBr} 3.15 (NH), 6.0 μ (>C=O); R_f 0.20] on a basic aluminum oxide column (11) in 78% yield.

The structures of the two lactams (VIIIa,b) were proved by consecutive acidic and alkaline treatment, which cleaved the ketal and lactam groups, respectively. The intermediate β-aminoketone (XI) lost ammonia and the unstable cyclohexadiene structure aromatized to β-benzoylpropionic acid (XII) [m.p. 113-114°; λ_{max}^{EtOH} 206,241 mμ (ε 13200, 12500)] in 80% yield. The n.m.r. spectrum of the crude degradation product (XII) showed no proton resonance signals between δ 5.6-6.3 p.p.m., expected for a vinyl ketone derivative (XIII). Thus, the formation of the "isolactam" structure (IX) during ring expansion could be excluded. Because the Beckmann rearrangement proceeds with anti-migration (12), the structure of the two lactams (VIIIa,b) retrospectively verified the anti-stereochemistry[d] of both oximes (VIa,b).

Lithium aluminum hydride reduction of the epimer lactams gave rise to the expected cis-aminoketal (Xa, yield 96%)[b.p.$_{0.001\ mm}$105-110°; δ 2.03 (10H, m), 3.14 (3H,m), 3.93 (4H,s), 5.64 p.p.m. (2H,b)] and trans-aminoketal (Xb) [b.p.$_{0.01\ mm}$98°; δ 2.20 (13H,m), 3.86 (4H,s), 5.50 p.p.m. (2H,b)]. As the closing step of this synthesis, a direct indolization of the cis-aminoketal (Xa) was achieved with sulfuric acid catalysis (13). Both theoretically possible enehydrazine intermediates (12) were apparently present, since the cis-tetracyclic indole (XVIa, yield 70-78%) [hydrochloride: m.p. 266-268°; λ_{max}^{EtOH} 226, 283, 291 mμ (ε 33500, 8400, 7200); free base: δ 2.25 (4H, m), 2.90 (4H, m), 3.45 (2H, m), 5.71 (2H, b), 7.10 (3H, m), 7.48 (1H, m), 7.83 p.p.m.

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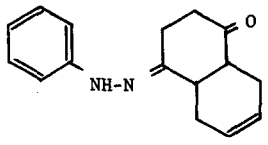
d) The oxime hydroxyl group is anti to the tertiary bridgehead carbon atom.

(1H, m); R_f 0.47[a]] and an indolenine derivative (XVII) [R_f 0.67] were observed. During the acidic cleavage of the ketal group of Xa, partial epimerization occurred and, as a third minor product, the trans-tetracyclic indole (XVIb) [R_f 0.32] was identified. The same indole (XVIb) was obtained by the direct indole-ring closure of the trans-aminoketal (Xb).

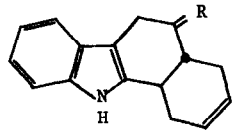
An alternative route for the synthesis of the ibogaine model (XVIa) was envisaged. The Fischer indole-ring closure of the cis-enedione-monophenylhydrazone (XVIII, yield 71%) [m.p. 162-163°; λ_{max}^{EtOH} 277 mμ (ε 19400); λ_{max}^{KBr} 5.85 μ (>C=O)] furnished the tetracyclic indole ketone (XIX, yield 80-90%) [m.p. 185-187°; λ_{max}^{EtOH} 225, 285, 292 mμ (ε 33100, 8900, 7500); λ_{max}^{KBr} 3.10 (NH), 5.91 μ (>C=O)]. During the indolization a complete inversion occurred, both IIa and IIb leading to the same trans-tetracyclic indole derivative (XIX). Although XIX smoothly underwent oxime formation to XX (yield 85%) [m.p. 224-225°; λ_{max}^{EtOH} 228, 283, 291 mμ (ε 29800, 8300, 7300); λ_{max}^{KBr} 3.0 μ (OH), no absorption between 5-6 μ], its Beckmann rearrangement produced the indolelactam (XXI) [m.p. 248-250°; λ_{max}^{KBr} 3.10 (NH), 6.05 μ (>C=O)] in low yield. Because the cis-configuration of the C/D ring could not be retained, there was no further exploration of this approach.

For the total synthesis of ibogaine (I), the Diels-Alder adduct (XXII) [m.p. 46-48°; λ_{max}^{KBr} 5.97 μ (>C=O); δ 0.86 (3H, t), 1.38 (2H, m), 2.30 (3H, m), 3.25 (2H, m), 5.75 (2H, m), 6.70 p.p.m. (2H, s)] was selected as a starting material. Selective zinc reduction of XXII provided the cis-enedione (XXIIIa) [m.p. 71-73°, λ_{max}^{KBr} 5.85 μ (>C=O); δ 0.99 (3H, t), 1.54 (2H, m), 2.33 (3H, m), 2.78 (4H, m), 3.16 (2H, m), 5.75 p.p.m. (2H, m); R_f 0.37[a]] in 66% over-all yield, calculated on the trans-1.3-hexadiene. From the endo-cis-formation of XXII, it is believed that the 5-ethyl group of XXIIIa occupies an equatorial position[c]. An isomerization of XXIIIa readily gave the trans-epimer (XXIIIb, yield 84%) [m.p. 78-78.6; λ_{max}^{KBr} 5.85 μ (>C=O); δ 0.95 (3H, t), 1.55 (2H, m),

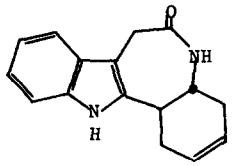
2.28 (3H, m) 2.94 (6H, m) 5.65 p.p.m. (2H, b); R_f 0.42]. The upfield shifted trans C_9, C_{10}-protons are partially hidden under the signal of the C_2, C_3-protons.



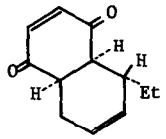
XVIIIa,b*



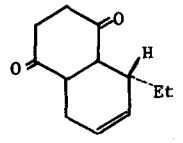
XIX: R=O
XX: R=>NOH



XXI



XXII



XXIIIa,b

* The ring systems of series a and b possess cis and trans configurations, respectively.

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