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STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-RHYNCHOPHYLLINE AND (±)-ISORHYNCHOPHYLLINE

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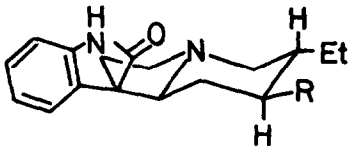
Rhynchophylline(I-A) and Isorhynchophylline(I-B) are alkaloids of Uncaria rhynchophylla MIQ. (Ouroparia rhynchophylla MATSUM.),[1] the structures of which were established as I-A and I-B,[2] respectively, in terms of absolute configuration.[2d] Although the partial synthesis of rhynchophylline from dihydrocorynantheine[2d] and the synthesis of (±)-rhynchophyllol(II-A) and (±)-isorhynchophyllol(II-B)[3] were reported, the total synthesis of these alkaloids has not yet been described, but only a brief reference to an incomplete work has appeared.[4] In this communication, we report the stereoselective total synthesis of (±)-rhynchophylline(I-A) and (±)-isorhynchophylline(I-B).

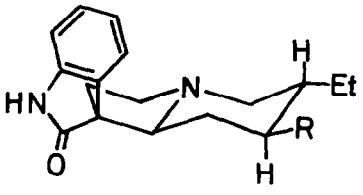


Rhynchophylline(I-A)

R= MeOOC-C=CHOMe

Rhynchophyllol(II-A)

R= CH_2CH_2OH



Isorhynchophylline(I-B)

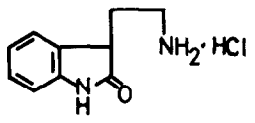
R= MeOOC-C=CHOMe

Isorhynchophyllol(II-B)

R= CH_2CH_2OH

[The normal series $\underset{\text{acid}^{2b)}}{\overset{\text{base}^{2a)}}{\rightleftharpoons}}$ The iso-series]

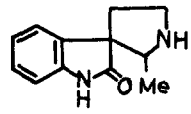
A mixture of 2-hydroxytryptamine hydrochloride(III) and ethyl sodium formyl acetate(IV) in the 1:1.8 molar ratio in 50% aqueous ethanol was kept at 48.5° for 2 days to afford almost exclusively VI as an oil(M^+=274; NMR($CDCl_3$) τ 8.88(3H, t. J=8Hz, $-CH_3$) and 6.07(2H, q., J=8Hz, OCH_2CH_3); UV λ_{max}^{EtOH} 252-253 and 283 nm) which formed the picrate, m.p. 187-188°, in 76.6%



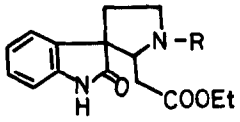
(III)

NaOCH=CH-COOEt

(IV)



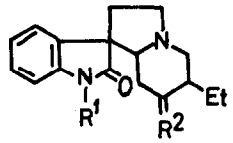
(V)



(VI) R=H

(VII) R=-CH=C(Et)-COOEt

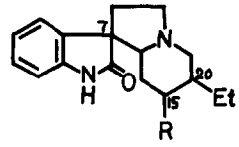
(VIIIa,b) R=-CH_2-CH(Et)-COOEt



(IXa,b) R^1=H, R^2= O

(X) R^1=H, R^2=>CH-COOMe

(XI) R^1=Et, R^2=>CH-COOMe



(XIIa,b,c) R=-CH_2COOMe

(XIII) R=-CH(CHO)-COOMe

(XIV) R=-C(CHO)=CHOMe

yield. In this reaction was observed generation of a neglegible amount of the decarboxylated compound(V) on tlc.[5] This compound[V, m.p. 150-151°, M^+=202; IR. no ester absorption; NMR ($CDCl_3$) τ8.97 (3H, d., J=7 Hz, -CH_3)] was produced as a sole product in 56.5% yield when the mixture was refluxed with sodium acetate in the same solvent for one day. The ester(VI) was condensed with ethyl α-formyl butyrate in benzene in a Dean-Stark apparatus to afford the enamine(VII) as an oil, which without isolation was hydrogenated with Adams' catalyst in acetic acid in a Parr apparatus to furnish the diester(VIII) as two isomers after chromatography on silica-gel. The first ether fraction furnished a minor isomer(VIIIa) as colorless needles, m.p. 113-114° (recrystallized from ether-n-hexane), and the subsequent fraction provided an oil in ca. 60% yield as a main product(VIIIb: the hydrochloride, m.p. 199-200°(decomp.) recrystallized from ethanol). The diester(VIIIb) was submitted to the Dieckmann condensation with sodium hydride in toluene heated at 110° under stirring for tow hours to afford the ketoester, which in turn, was heated in hydrochloric acid at reflux for 2.5 hrs. with evolution of carbon dioxide providing the ketone(IX) in 52% yield as a crude substance. A part of this product solidified on standing to provide one isomer(IXa, m.p. 162-163° recrystallized from ethyl acetate) and the material from the mother liquor on filtration of IXa was purified by silica-gel chromatography to give the other isomer(IXb, m.p. 153-154° recrystallized from ether-n-hexane) with a further crop of IXa.[6] The former ketone(IXa) was condensed with methyl diethylphosphonoacetate in the presence of sodium hydride in monoglyme kept at 50° for 5 hrs. to afford an oil(X, M^+=340) in

60.6% yield after purification by chromatography on alumina, in which a by-product that could assumed to be the N-ethyl derivative(XI) by the n.m.r. spectrum, was isolated as an oil in ca. 10% yield. The ester(X),[7] which was also obtained from IXb, was hydrogenated with palladium charcoal in ethanol to give the saturated ester(XII) in 80% yield, and the crude material was purified on silica-gel chromatography to afford two isomers, XIIa, m.p. 136-137°(M^+=342) and XIIb, oil (M^+=342), in an almost equal amount.[8] The latter(XIIb) was formylated with ethyl formate in the presence of sodium bistrimethylsilyl amide to provide the formyl derivative(XIII) as a yellow caramel (positive on $FeCl_3$ test), which was methylated with diazomethane in ether and methanol to yield (±)-isorhynchophylline[(±)-I-B] as colorless fine crystals, m.p. 225-227° (decomp.) after recrystallization from ether-n-hexane [M^+=384. Found: C, 68.47; H, 7.48; N, 7.15%. Calcd. for $C_{22}H_{28}N_2O_4$ (M=384.46): C, 68.72; H, 7.34: N, 7.29%]. The infrared($CHCl_3$), n.m.r.($CDCl_3$) and mass spectra of the synthetic sample were completely identical with those of the natural isorhynchophylline(I-B) on direct comparisons. Furthermore, the synthetic (±)-isorhynchophylline was converted to (±)-rhynchophylline[(±)-I-A], m.p. 197-199° (decomp.), colorless pillars, recrystallized from ethyl acetate-ether, on treatment with dilute acetic acid.[2b] The spectral data of the synthetic sample[(±)-I-A] were identical with those of the authentic specimen of the natural alkaloid(I-A). The present work is now being extended to syntheses of the other oxindole alkaloids. Satisfactory elemental analyses were obtained on all crystalline compounds.

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5) When the mixture was heated at higher temperatures than 60°, the ratio of V in the products increased. Also even when the relative amount of ethyl sodium formyl acetate(IV) was raised to 5 mol. eq. to III, the yield was not improved. Therefore, the condition described in the present paper should be strictly followed.

6) At the equilibration between the normal series(I-A) and the iso series(I-B), the former (I-A) is predominant in the resulting mixture(I-A:I-B = 7:3) on an acid catalyzed isomerization,[2b] and the latter(I-B) is preferential on a base treatment.[2a] The ratio of IXa and IXb in the products after the decarboxylation process heated with an acid is about 3:1, suggesting that the former(IXa) should be in the normal series and the other(IXb) must be in the iso seires.

7) The product(X) should be a mixture of geometric isomers related to the double bond (exo or endo cyclic and Z or E), as the O-methyl protons appear as two singlets at τ 6.46 and 6.51, which did not change at all under an equilibration condition heated with such a strong base as sodium methoxide. This experiment also suggests that the present product(X) should be in the iso series, since it was produced under an alkaline condition in the Wittig reactions of either IXa or IXb.

8) This hydrogenation was also carried out with Adams' catalyst in acetic acid to afford XII in 87.5% yield, which was submitted to chromatography on silica-gel to give another isomer(XIIc, m.p. 167-168°, M^+=342) as a major product along with XIIa and XIIb. When a solution of this isomer(XIIc) in methylene chloride was kept with alumina at room temperature overnight, it was converted to a mixture of XIIb and XIIc. Accordingly, XIIc should be in the normal series at the spiro position(C-7), and XIIb must be the corresponding iso base, which was led to the natural isorhynchophylline, indicating that the substituents C-15 and C-20 of XIIb and XIIc are in the trans configuration of diequatorial. The R_f values of these isomers are in the order of XIIa>XIIb>XIIc, and the values in the iso series are greater than those of the normal series without exception. Although the structure of XIIa has remained to be decided, it would be assumed to be the stereoisomer with the cis substituents at C-15 and C-20.