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STEREOSPECIFIC SYNTHESES OF rac.-N-METHYLRHYNCHOPHYLLANE FOR STEREOCHEMISTRY OF RHYNCHOPHYLLINE

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RHYNCHOPHYLLINE ($C_{22}H_{28}O_4N_2$) is an alkaloid of Uncaria rhynchophylla MIQ. (Ouroparia rhynchophylla MATSUM.), which was first isolated and named by Kondo[1]. In recent years, Marion et al.[2] proposed the formula (I) for rhynchophylline, and Nozoye[3] suggested the partial stereo-formula (IV) for the same alkaloid. This alkaloid in acetic acid readily isomerizes to isorhynchophylline[3,4,2b] which has also been found to occur in nature and has the same plane formula (I).[2b,3] Rhynchophylline is converted with dilute hydrochloric acid into rhynchophyllal (II), and then by the Wolff-Kishner reduction to rhynchophyllane* (III, R=H), which is readily derived to N-methylrhynchophyllane (III, $R=CH_3$).[2b]

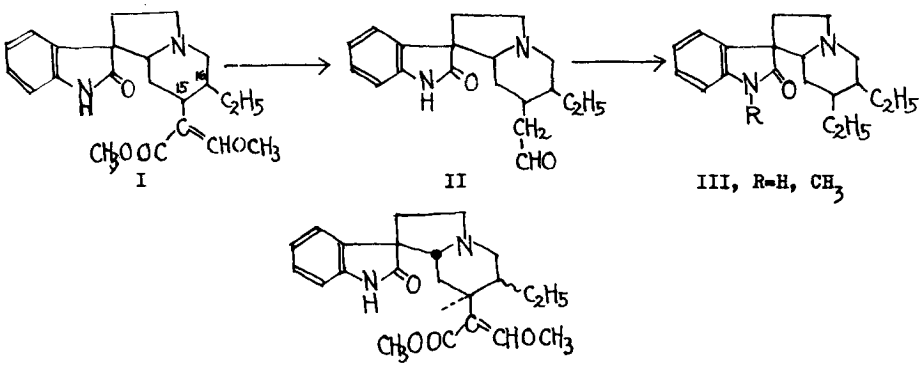
* Marion et al. prefer the name "isorhynchophyllane" to "rhynchophyllane" for this compound, because the same compound is obtained from isorhynchophylline and the isobase always predominates at the equilibrium of isomerization between rhynchophylline and isorhynchophylline.[2b] But we adopt the name "rhynchophyllane" till the stereochemistry of this base is elucidated.

1 H. Kondo, T. Fukuda and M. Tomita, J.Pharm.Soc.Japan 48, 321 (1928).

2a J.C. Seaton and L. Marion, Canad.J.Chem. 35, 1102 (1957); b J.C. Seaton and L. Marion, Ibid. 38, 1035 (1960).

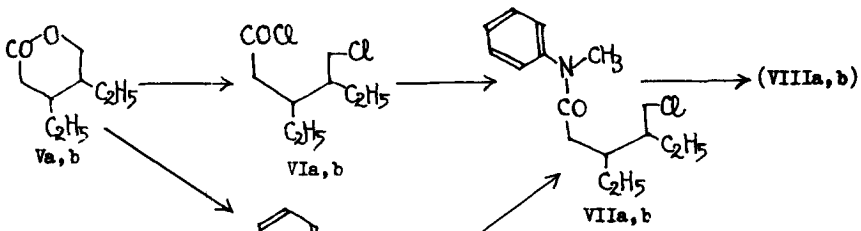
3 T. Nozoye, Chem. & Pharm.Bull.Japan 6, 309 (1958).

4 H. Kondo and T. Ikeda, J.Pharm.Soc.Japan 57, 881 (1937).

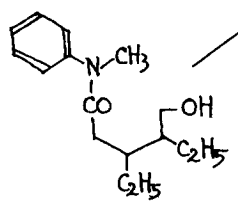


I II III, R=H, CH_3

IV

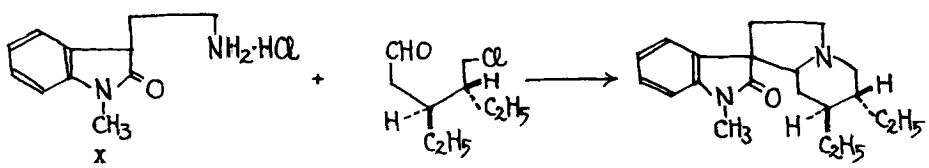


Va,b VIa,b VIIa,b (VIIIa,b)

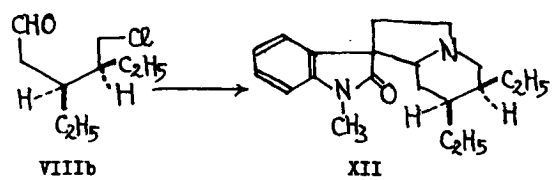


IXa,b

a: threo series
b: erythro series



X VIIIa XI



X VIIIb XII

In this paper, we wish to report stereospecific syntheses of four stereoisomers of rac.-N-methylrhynchophyllane, which established the trans configuration of the substituents at C(15) and C(16) of rhynchophylline and isorhynchophylline. The synthetic scheme is shown in the Chart.

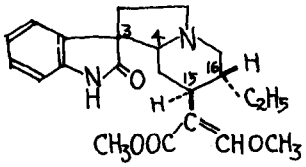
The lactone of threo-3:4-diethyl-5-hydroxyvaleic acid (Va)[5] was treated with phosphorus pentachloride to yield threo-3:4-diethyl-5-chlorovaleic acid chloride (VIa). This acid chloride, without purification, was condensed with methylaniline in pyridine to afford the anilide (VIIa, b.p. 158°/2.5 mm, Yield, 24.4% from Va) which in turn, was reduced with lithium aluminium hydride to give threo-3:4-diethyl-5-chlorovaleraldehyde (VIIIa, b.p. 110-112°/14 mm, Yield, 14.2%). The compound (Va) was reacted with methylanilinomagnesium iodide to yield IXa (b.p. 170-173°/3-4 mm, Yield, 60%) which, with thionyl chloride, gave VIIa, identical with the product obtained via the above route. The aldehyde (VIIIa) was condensed with N-methyloxytryptamine hydrochloride (X) in ethanolic solution of sodium hydroxide at room temperature for 7 days to afford pale yellow oil (yield, 56.7%), which was chromatographed on alumina. Elution with benzene yielded a main fraction of the free base (XI), colourless oil (called trans-A hereafter), giving the picrate, pale yellow prisms of m.p. 182-183°. Also, ether elution afforded the free base (XI), colourless oil (trans-B), yielding the picrate, orange yellow prisms of m.p. 184°.

On the other hand, the lactone of erythro-3:4-diethyl-5-hydroxyvaleic acid[5b] gave erythro-3:4-diethyl-5-chlorovaleic acid chloride (VIb), which was condensed with methylaniline to give the erythro-anilide (VIIb, b.p. 156-157°/2 mm, Yield, 57.5% from Vb). This anilide (VIIb) was reduced with

[5a] E.E. van Tamelen, P. Aldrich and T.J. Katz, J.Amer.Chem.Soc. 79, 6426 (1957); [b] A.R. Battersby and S. Garrett, J.Chem.Soc. 3512 (1959); Cf. C.F. Koelsch and C.H. Stratton, J.Amer.Chem.Soc. 66, 1881 (1944).

lithium aluminium hydride to yield erythro-3:4-diethyl-5-chlorovaleraldehyde (VIIIb, b.p. 105-108°/12 mm, Yield, 28%). The Grignard reaction of Vb gave the erythro-derivative (IXb, b.p. 173-174°/3-4 mm) in 60% yield, which was treated with thionyl chloride to afford the erythro-anilide (VIIb). Condensed with N-methyloxytryptamine hydrochloride (X) in ethanolic solution of sodium hydroxide, the aldehyde (VIIIb) gave the pale yellow oil (yield, 67.7%), which was purified by chromatography on alumina. Elution with benzene yielded a main fraction of the free base (XII), colourless needles, m.p. 94° (called cis-A hereafter), yielding the picrate, pale yellow scales of m.p. 173-174°. Similarly, benzene-ether (1:1) elution gave the colourless needles, m.p. 143-144° (XII, cis-B) which gave the picrate, orange yellow prisms, m.p. 168°. The infra-red spectra of these free bases (XI, trans-A and -B; XII, cis-A and -B) are very similar, but not identical particularly in 1150-1050 cm^{-1} region.

N-Methylrhynchophyllane (III, R=CH_3) derived from the natural alkaloid, was carefully chromatographed and obtained as colourless oil* which had the infra-red absorption in solution identical with that of the synthetic trans-A, but different from those of cis-A, cis-B and trans-B. The trans-arrangement at C(15) and C(16) of N-methylrhynchophyllane is thus established, which means that the relative configuration of the same positions of rhynchophyl-



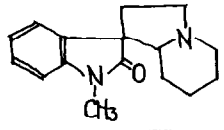
XIII

* This base gave the picrate, m.p. 185-186°, whose infra-red spectrum was completely identical with that of N-methylisorhynchophyllane, kindly supplied by Professor Marion.

line and isorhynchophylline are trans, because these alkaloids giving the same N-methylrhynchophyllane (III, R=CH_3) are considered to be different only in the configurations at C(3) and/or C(4),* and the above changes may be understood to take place without conversion of the configuration at C(15) and C(16).[5,6] Thus, rhynchophylline and isorhynchophylline are illustrated as the partial stereo-formula (XIII), in which the configurations at C(3) and C(4) of each alkaloid remain to be determined. Satisfactory elemental analyses have been obtained on every recrystallized product.

Acknowledgements - We are indebted to Professor Em.E. Ochiai and Dr. T. Nozoye for an authentic sample of rhynchophylline, and to Professor L. Marion for a I.R. chart of N-methylisorhynchophyllane.

* This interpretation was also supported by the fact that one of two isomers of the base (XIV) with no substituents at C(15) and C(16), recently synthesized by us, readily isomerizes to the other under the same conditions as the isomerization described above.[2b]



XIV

6 M.-M. Janot, R. Goutarel, A.Le Hir, G. Tsatsas and V. Prelog, Helv.Chim.Acta 38, 1073 (1955).