Tetrahedron Letters No.30, pp. 2523-2525, 1969. Pergamon Press. Printed in Great Britain.

THE SYNTHESIS OF A RACEMIC STEREOISOMER OF ASPIDOSPERMINE

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(Received in Japan 6 May 1969; received in UK for publication 23 May 1969)

In the previous communications (1), the stereochemistry of the tricyclic ketones (I and II), the key intermediates in our published synthesis (2) of dl-aspidospermine(VIII), has been concluded to be Ia and IIa, respectively, which are apparently different from the stereochemistry required of the natural alkaloid. Previously, Stork (3b) proposed a plausible mechanism of the cyclization of III in the presence of acetic acid to proceed through (a) route pictured in FIG. 1, based upon the incorrect assignment of his starting ketone to IIa, which involves the fission and recombination of the bond between C(12) and C(19) as are shown in IV and V to finally furnish the most stable product(VII) by reduction of VI.

As has been revised by us (1), the structure of Stork's ketone(II) should be represented by IIb, that could be in situ satisfactory for the stereospecific synthesis of dl-aspidospermine (VIII). Therefore, we further investigated the Fischer indole synthesis with our ketone(IIa).

The corresponding o-methoxyphenylhydrazone(III) (2) was refluxed with anhydrous formic acid for 45 min. (4). The reaction mixture was worked up in the usual manner and submitted to the chromatography on silica-gel. Elution with benzene: ethyl acetate(6:1) yielded the stereoisomer(X) of vallesine (5) as colorless needles, m.p. 128.5-129.5°, [IR. $\nu(CHCl_3)$: 2790, 2710 (6), 1640 cm^{-1} (N-CHO); UV. λ_{max}^{EtOH} mμ (log ε): 259(4.12), 289(3.35); M^+=340(base peak, m/e 124)] in 11.8% yield. The other products were proved to be XIII (2) and N-formyl-o-anisidine, colorless needles, m.p. 83-84°. The product(X) was hydolyzed with N-HCl to XI, colorless prisms, m.p. 89.5-90.5°, [IR. $\nu(CHCl_3)$: 3365 (NH), 2790, 2710 cm^{-1} (6); UV. λ_{max}^{EtOH} mμ (log ε): 246(3.82), 290(3.32)] which was allowed to stand with acetic anhydride in benzene for 2 days to afford a stereoisomer(XII) of aspidospermine as colorless prisms, m.p. 102.5-103.5° (recrystallized from n-pentane), [IR. $\nu(CHCl_3)$: 2790, 2710 (6) and 1630 cm^{-1} (N-$COCH_3$): UV. λ_{max}^{EtOH} mμ (log ε): 256(4.05), 280-289(3.55-3.46); NMR. ($CDCl_3$,δ ppm), 4.92(triplet C_2-H), 3.91(singlet, CH_3O-), 2.23(singlet, N-$COCH_3$), 0.94(triplet, C_5-CH_2-CH_3). The chemical shifts of these signals should be compared with the corresponding ones [δ 4.50(quartet C_2-H) δ 0.67(triplet, C_5CH_2-CH_3)]

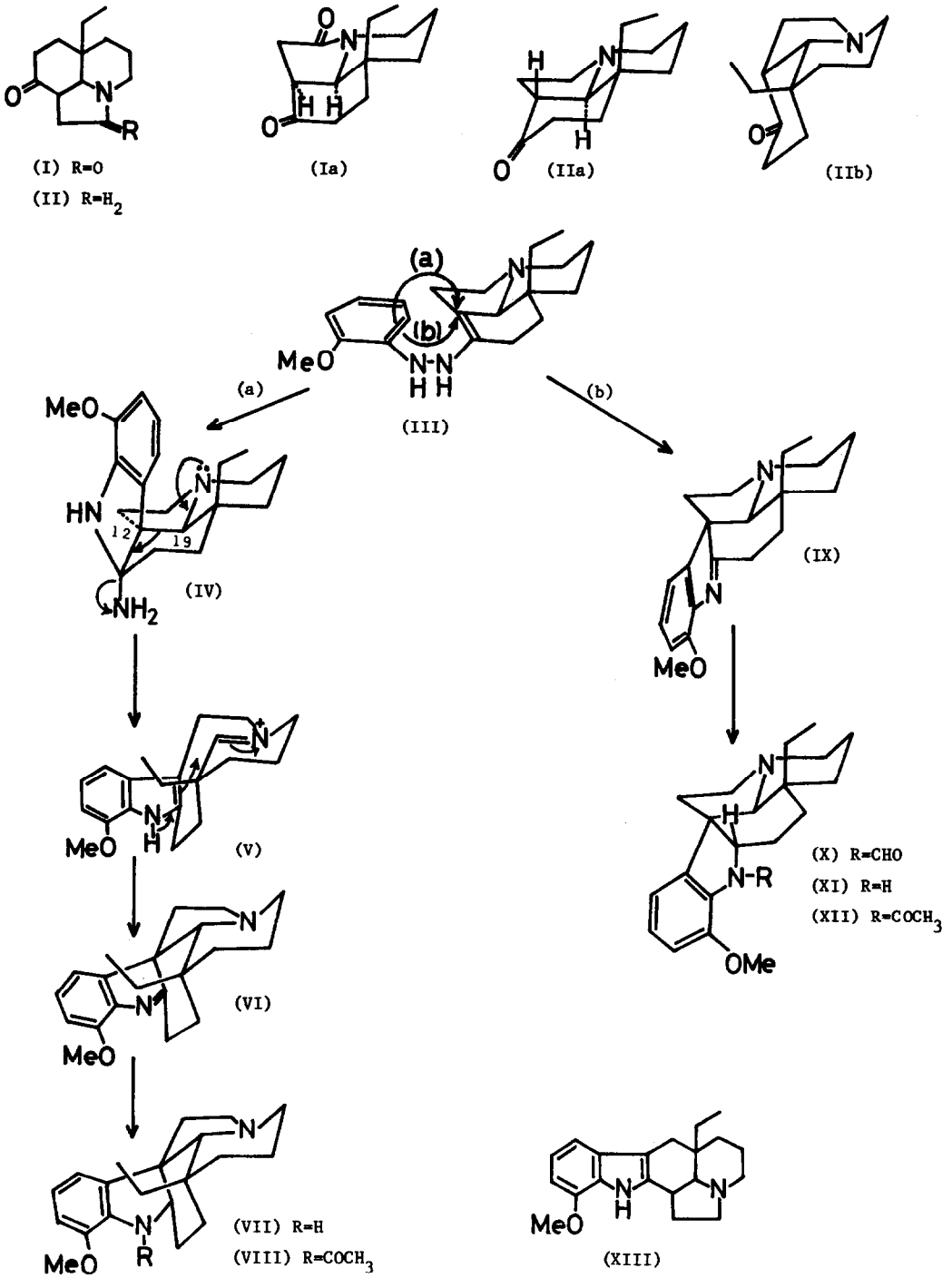
(I) R=O
(II) R=H2
(Ia)
(IIa)
(IIb)
(III)
(a)
(b)
(IV)
(V)
(VI)
(VII) R=H
(VIII) R=COCH3
(IX)
(X) R=CHO
(XI) R=H
(XII) R=COCH3
(XIII)

FIG. 1.

of the natural aspidospermine, and these results could be reasonably explained by the proposed structure(XII), which was finally established by X-ray analysis of the hydriodide, m.p. 245-246°, of XI (7). Thus the present synthetic product(XII) might be called "dl-pseudo-(C/D: trans)-aspidospermine", which could be formed under steric approach control (8) via (b) route.

The same product(XI) was obtained by heating III with acetic acid for 8 hrs together with deacetylaspidospermine(VII) of the natural stereochemistry. Satisfactory elemental analyses have been obtained on all crystalline compounds.

Acknowledgements: We would like to express our deep gratitude to Professor Gilbert Stork for his generosity in providing us many unpublished data. This research was supported by the PHS grant(5 RO1 MH 08187), National Institutes of Health, U. S. A., which is gratefully acknowledged.

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