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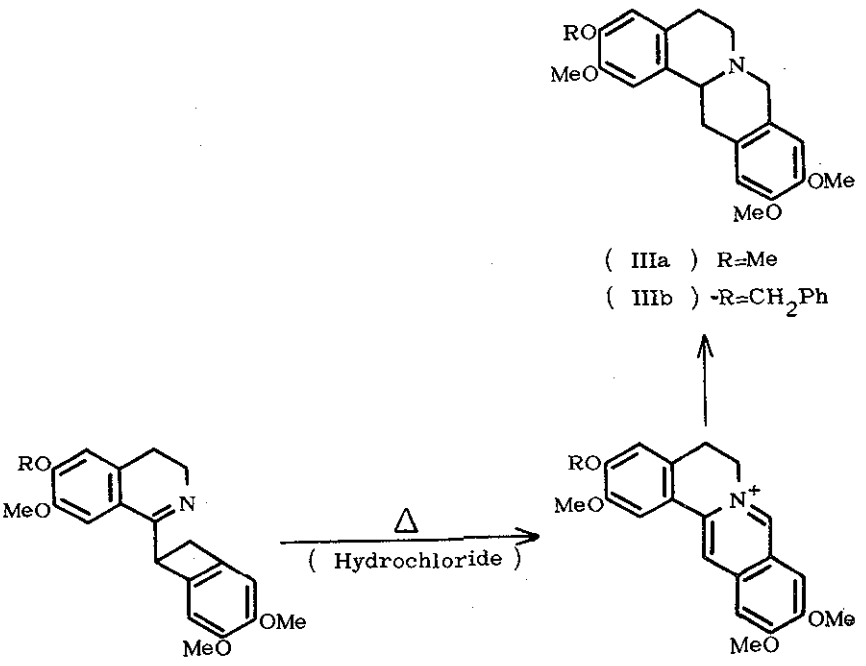
A FACILE SYNTHESIS OF THE SPIROBENZYLISOQUINOLINES AND THE SPIROBENZYLCARBOLINES

Tetsuji Kametani*, Yoshiro Hirai, Hiromitsu Takeda, Masahiro Kajiwara, Tamiko Takahashi, Fumio Satoh, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

1',2,2',3,3',4'-Hexahydro-5,6,6',7'-tetramethoxy-1-keto-spiro[indene-2,1'-isoquinoline] (IVa) and its 7'-benzyloxy analogue (IVb) are synthesized from 3,4-dihydro-1-(4,5-dimethoxybenzocyclobutenyl)isoquinolines (I). 1-Ketospiro[indene-2,1'-β-carbolines] (XIa and XIb) are also obtained by the same method from the corresponding benzocyclobutene derivatives (IXa and IXb).

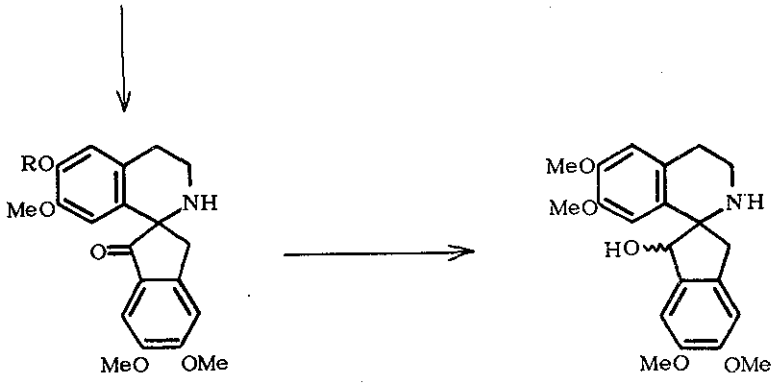
Previously, we reported a novel synthesis of the benzoquinolizidines such as protoberberines (IIa and IIb)[1,2] and dehydroyohimbane (X),[3] by an intramolecular cycloaddition of the o-quinodimethanes derived from the 1-benzocyclobutenyl-3,4-dihydroisoquinolines (Ia and Ib) and 3,4-dihydro-β-carboline (IXb), and achieved a simple total synthesis of xylopinine (IIIa)[1] and discretine (IIIb)[2] from the benzoquinolizidines (IIa and IIb), respectively. In this communication, we wish to report a facile conversion of the 1-benzocyclobutenylisoquinolines (Ia and Ib) into the spirobenzylisoquinolines (IVa and IVb), whose structures are related to the alka-



(IIIa) R=Me
(IIIb) R=CH_2Ph

(Ia) R=Me
(Ib) R=CH_2Ph

(IIa) R=Me
(IIb) R=CH_2Ph



(IVa) R=Me
(IVb) R=CH_2Ph

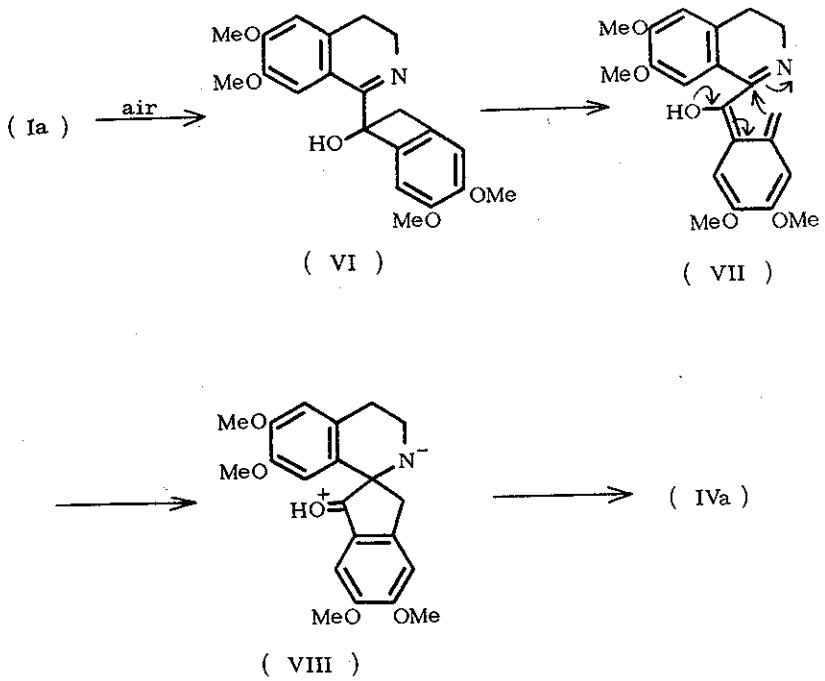
(V)

loid, ochotensine, and the formation of the ketospiro[indene-2,1'-β-carbolines] (XIa and XIb) from the 1-benzocyclobutenyl-3,4-dihydro-β-carbolines (IXa and IXb) is also described.

Although the hydrochloride of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline (Ia)[1] is stable at room temperature in organic solvents, the free base (Ia), mp 135 - 136° (decomp.) [$\nu_{max}^{CHCl_3}$ 1620^{sh} cm^{-1} (C=N); m/e 353 (M^+); δ ($CDCl_3$) 2.58 (2H, t, J 7.5 Hz, $ArCH_2CH_2$), 3.35 - 3.72 (4H, m, 2 x CH_2), 3.82 (6H, s, 2 x OMe), 3.85 (3H, s, OMe), 3.90 (3H, s, OMe), 4.72 br (1H, >CH-), 6.70 (3H, s, 3 x ArH) and 7.07 (1H, s, ArH)] is converted into the ketospirobenzylisoquinoline (IVa), mp 204 - 205° (lit.,[5] mp 203 - 204°), in good yield when the above free base is allowed to stand in chloroform at room temperature for 48 h. The structure (IVa) of this product was determined by spectroscopic methods. Mass spectrum [m/e 369 (M^+)] showed that one more oxygen is introduced in this transformation, and ir [ν_{max}^{KBr} 3305 (NH) and 1690 cm^{-1} (C=O)] and uv [λ_{max}^{MeOH} 275 and 321 nm] spectra revealed this product to have the 1,2,3,4-tetrahydroisoquinoline and aroyl groups. Nmr spectrum (δ) showed four methoxyl resonances at 3.59, 3.82, 3.91 and 3.97 as singlets and benzyl methylene protons at 3.37 as a singlet in addition to four aromatic protons (6.11, 6.58, 6.89 and 7.24, each singlet) and two pairs of methylenes protons (2.60 - 2.95 and the lower part is obscured by other resonances), thus indicating the new oxygen to form the carbonyl group. The presence of a methoxyl and an aromatic proton resonanced at relatively high field suggested this product to have the spirobenzylisoquinoline system.[4] Reduction of IVa with sodium borohydride gave the alcohol (V), the nmr (δ in $CDCl_3$) of which showed a methine proton at 4.95 as a singlet that was assigned to the carbinol methine between aromatic ring and the quaternary carbon. On the ground of these facts, the isomerization product could be assigned to the structure IVa, which was proved by spectral com-

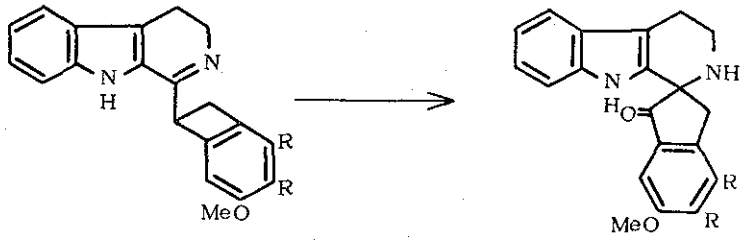
parison with the authentic sample prepared by Irie.[5]

A possible mechanism is shown in the following chart; thus the autooxidation of free base (Ia)[6] gave the benzocyclobutenol (VI), whose ring-opening according to Woodward-Hoffmann rule,[7] followed by electrocyclic changes in E-formed o-quinodimethane (VII) as indicated, formed the ketospirobenzylisoquinoline (IVa) through the intermediate (VIII).



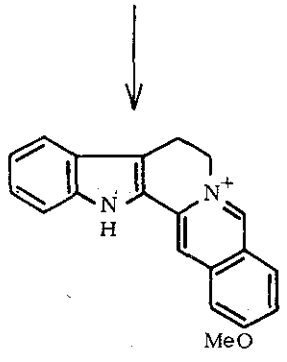
Similarly, 6-benzyloxy analogue (Ib)[2] of Ia rearranged to the ketospirobenzyl-isoquinoline (IVb), mp 158 - 160° [ν_{max}^{KBr} 3325 (NH) and 1680 cm^{-1} (C=O); δ ($CDCl_3$) 3.41 ($ArCH_2$), 3.59 (C_7-OMe), 6.15 (C_8-H)].

1-(3,4,5-Trimethoxybenzocyclobutenyl)-3,4-dihydro-β-carboline (IXa) was converted into the ketospirobenzyl-1,2,3,4-tetrahydro-β-carboline (XIa), mp 227°, quantitatively after 3 days, [$\nu_{max}^{CHCl_3}$ 3450 (indole NH), 3350 (NH) and 1697 cm^{-1} (C=O); λ_{max}^{MeOH} 320^{sh}, 290^{sh}, 282 nm; δ ($CDCl_2$ + $(CD_3)_2SO$) 3.43 ($ArCH_2$)]. Similar type of the spiro compound XIb formed from the benzocyclobutene (IXb).[3]



(IXa) R=OMe
(IXb) R=H

(XIa) R=OMe
(XIb) R=H



(X)

This transformation represents a convenient synthesis of the spirobenzylisoquinolines and the spirobenzylcarbolines and a total synthesis of the ochotensine type alkaloids by this method is under examination.

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