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THE REACTIONS OF ACTIVATED AMIDES. PART (II).
A NEW SYNTHETIC ROUTE TO ββ-DISUBSTITUTED INDOLINE DERIVATEVES.

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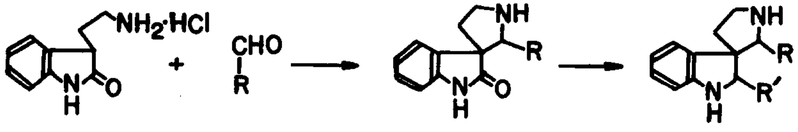
The conversion of readily obtainable ββ-disubstituted oxindoles(I)(1) into the corresponding indoline derivatives(II) having suitable substituents at the α-position is highly desirable, because the latters could be the common intermediates for syntheses of the natural bases such as strychnos and aspidosperma alkaloids.



(I) (II)

For this purpose, activation of a lactam carbonyl is necessary. Of many known reagents(2), the Meerwein's reagent(3) would be most promising, since this reagent is reported to convert a variety of amides under relatively mild condition to the corresponding iminoethers which are known to combine with several nucleophiles. However, their reactivity is still considerably less than that of the imidochlorides and only strong nucleophiles are expected to undergo smooth reactions with them(3,4). Moreover, it was found in the preliminary experiments(4) that the sterically hindered iminoethers failed to combine even with ethyl cyanoacetate. These difficulties could be overcome by arranging the two reaction centers on the same molecule; thus the compound(VII) was synthesized and subjected to the intramolecular condensation reaction in anticipation of obtaining vinylogous amide(VIII) (SCHEME I).

Condensation of 2-hydroxytryptamine hydrochloride in basic aqueous ethanol with 3-oxobutanal ethylene ketal(III)^{*1}, b.p.$_{11}$68-69.5°; semicarbazone, m.p.207°, which was obtained by the DMSO-DCC oxidation(5) of the corresponding alcohol afforded in 63% yield an approximately 1:2 mixture of epimeric secondary amines(IVa),m.p.129°, λ_{max}^{EtOH} 253mμ(logε 3.89); ν_{max}^{KBr} 3360 and 1705cm^{-1}; n.m.r.(CDCl$_3$) δ 1.25(s, 3H) and IVb, m.p.160-1°, ν_{max}^{KBr} 3360 and 1710cm^{-1}; n.m.r.(CDCl$_3$) δ 1.30(s, 3H). Treatment of IVa and IVb with acetyl chloride and pyridine, followed by mild hydrolysis of ketals, provided the keto-acetamide(Va), m.p.234-5°, λ_{max}^{EtOH} 252mμ(logε 3.91); ν_{max}^{KBr} 3230(broad), 1728, 1710, and 1615cm^{-1}, n.m.r.(DMSO-d6) δ 2.06(s, 3H) and 1.68(s, 3H) (75% from IVa) and Vb, m.p.199.5-201°, ν_{max}^{KBr} 3185(broad), 1728, 1715, and 1615cm^{-1}; n.m.r. (DMSO-d6) δ 2.10(s, 3H) and 2.03(s, 3H) (70% from IVb). The conversion of Va into the iminoether(VIIa), m.p.122-3.5°, λ_{max}^{EtOH} 260mμ(logε 3.83); ν_{max}^{KBr} 1718, 1638, and 1580cm^{-1}; n.m.r.(CDCl$_3$) δ 4.54(q, 2H), 2.17(s, 3H), 1.81(s, 3H), and 1.47(t, 3H) was achieved by refluxing it with five molar equivalents of the Meerwein's reagent (triethyloxonium tetrafluoroborate) in methylene chloride for fourteen hours, followed by the base treatment of the resultant salt^{*2} (71%). Similarly, VIIb, m.p.143-4°, λ_{max}^{EtOH} 260mμ(logε 3.85); ν_{max}^{KBr} 1714, 1644, and 1578cm^{-1}, n.m.r.(CDCl$_3$) δ 4.45(q, 2H), 2.17(s, 3H), 2.11(s, 3H), and 1.45(t, 3H) was obtained from Vb (60-70%)^{*2}. In compounds (Va and

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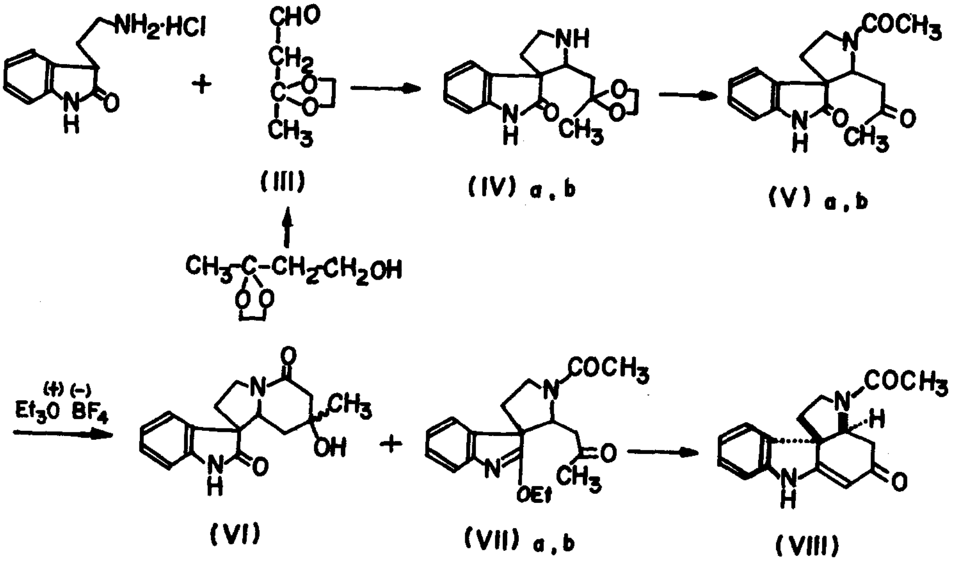
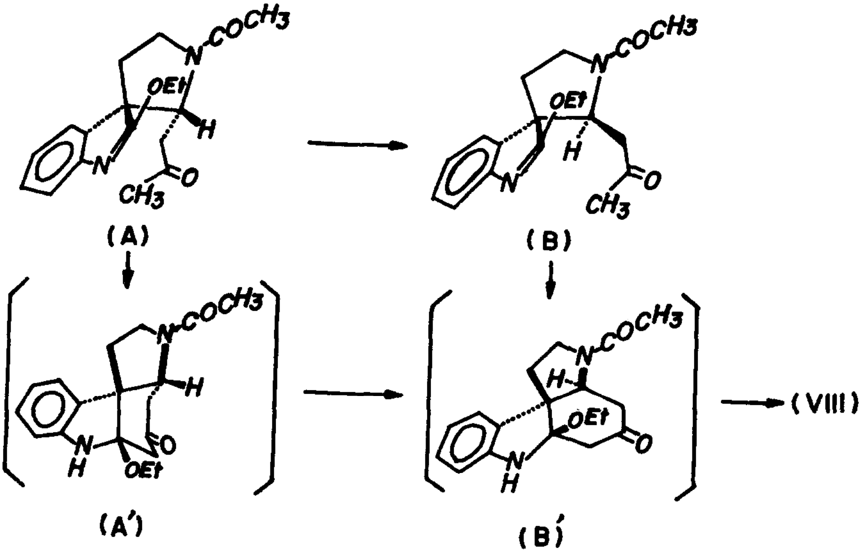
*1 Satisfactory elemental analytical data have been obtained for all new compounds.

*2 The compound(VI) was obtained in 5-10% yields in addition to VII. The structure and the mechanism of its formation will be discussed in the subsequent paper (Part III of this series).

SCHEME. I



F IG. I *3



VIIa), the methyl protons adjacent to keto-groups shifted upfield, whereas those of Vb and VIIb appear in the normal region. Therefore, the stereostructure of the <u>a</u> series could be represented by (A)(FIG.I),[*3] in which the methyl group lies nearly above the benzene ring. Accordingly, the corresponding structure of the <u>b</u> series should be illustrated as (B)(FIG.I)[*3].

The iminoethers(VIIa and VIIb) thus obtained were successfully converted into the desired vinylogous amide(VIII), m.p.266-7°, stereoselectively in 40-60% yield by treating them with NaH in DMSO under oxygen-free nitrogen at 70-75° for 4-5 hours. The structure of VIII was established by its elemental analysis, ultraviolet and infrared spectra, which include the characteristics of the vinylogous amides [λ_{max}^{EtOH} 235(log ε 4.27), 298(log ε 4.03), and 338mμ(log ε 4.35); ν_{max}^{KBr} 3150, 1630, and 1585cm^{-1}] and n.m.r. spectrum(DMSO-d6) δ 10.35(broad, 1H), 5.30(s, 1H), and 2.10(d, J=1.1 cps, 3H; collapsed to a sharp singlet when measured at 88°).

The Dreiding models show that the configuration of the C/D ring juncture of VIII should be "cis". Therefore, the stereoselective ring closure leading to VIII would be ascribed to the epimerization of the side chain from α to β either prior or after cyclization to the indoline derivatives (see A' and B'). However, the mechanism of this epimerization is not clear at present. Discussions in connection with the temperature dependent N-acetyl methyl signal will be presented in the forthcoming paper. Synthetic studies using this intermediate(VIII) are being continued.

[*3] Each delineated structure indicates one antipodal form of the dl-isomers.

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