NEW ROUTE TO PHTHALIDEISOQUINOLINE ALKALOIDS: SYNTHESIS OF (±)-CORDRASTINE I AND II

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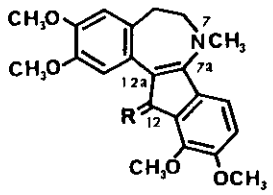
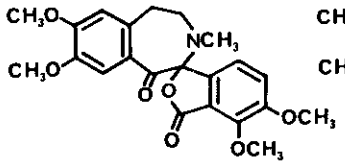
Abstract——Acid-catalyzed isomerization of the keto-lactone (3) provided the immonium salt (6), sodium borohydride reduction of which gave (±)-cordrastine I (7) and II (8) after acid treatment.

Benz[d]indeno[1,2-b]azepine is of interest as a possible ring system of key-intermediates for the isoquinoline alkaloid syntheses. In 1970, Irie reported the first synthesis of rhoeadine alkaloid, in which the alkaloid skeleton was brought about by the oxidative creavage reaction of the Δ^{12}-tetrahydrobenz[d]indeno[1,2-b]-azepine.[1] On the other hand, our studies starting with the $\Delta^{7a,12a}$-isomers[2] have led to the syntheses of rhoeadine, spirobenzylisoquinoline and protopine alkaloids.[3] In this paper, we wish to report an alternative utility of the latter type of the



1 R=H$_2$
2 R=O



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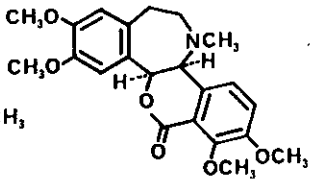

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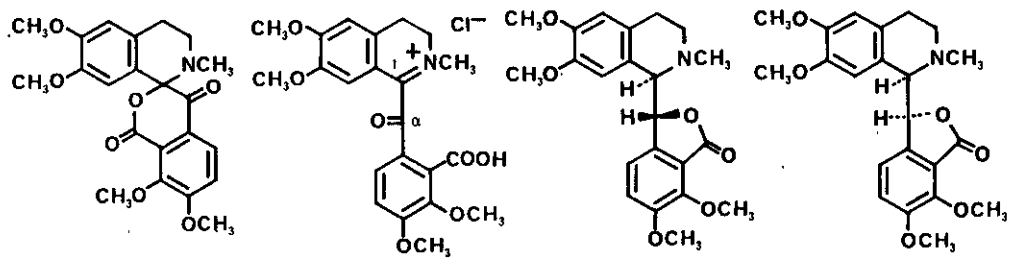
azepine (1) for synthesis of phthalideisoquinoline alkaloids, (±)-cordrastine I (7) and II (8).

The reaction course of 1 → 2 → 3 → 4 has served as key steps in the synthesis of the rhoeadine alkaloid, (±)-cis-alpinine. The lactone (4), which has the alkaloid skeleton, is readily obtained by $NaBH_4$ reduction of the keto-lactone (3), followed by the acid-catalyzed lactonization of the hydroxy-carboxylic acid.[3a]

It is assumed that the application of this two-step reaction sequence to the keto-lactone (5), one of the plausible isomers of 3, may provide a new entry into the phthalideisoquinoline alkaloid syntheses. Thus, 3 was heated in boiling 0.5N-HCl solution for 30 min. The product isolated was not 5 but its equivalent, yellow crystalline immonium salt (6) (98%), monohydrate mp 160-162°C (MeOH-ether), whose spectral data [ν max (nujol) 3600-2200, 1725, 1670cm^{-1}; λ max (EtOH) 217(ε 14,300), 244(ε 13,200), 314(ε 12,900), 377nm(ε 6900); ^1H nmr (DMSO-D_6) δ 2.5-4.7 (4H, m, C_3- and C_4-H's), 3.63, 3.66, 3.84, 3.99, 4.03(15H, each s, OCH_3×4 and N-CH_3), 6.82 (1H, s, C_5-H), 7.35(1H, s, C_8-H), 7.26, 7.95(2H, AB-q, J=9.0 Hz, ring D aromatic H's) were in good accordance with the assigned structure.

Subsequent reduction of this salt (6) with excess $NaBH_4$ in MeOH cooled on ice-water bath followed by treatment with diluted HCl solution, led to the formation of (±)-cordrastine II (8, 93%), mp 117-118°C(MeOH)(lit.[5] mp 117-118°C, lit.[6] mp 118-119°C), accompanied by a trace of (±)-cordrastine I (7). It is noted that this remarkable stereoselectivity is similar to the one that Shamma and his co-workers have observed on the conversion of oxyberberine into (±)-β-hydrastine.[4]



5 6 7 8

On the other hand, when $NaBH_4$ reduction of 6 was attempted in MeOH containing 5% $NaHCO_3$ solution, and worked up in the same manner as the above, (±)-cordrastine I

(7), mp 156-157°C (MeOH)(lit.[6] mp 155-156°C), was obtained as a predominant product in a 3:2 ratio of 7 and 8 (94%).[7] Spectral and physical data of both compounds were identical with the data published for (±)-cordrastines,[5,6] and ir spectra of 7 and 8 were superimposed with those of the corresponding authentic samples prepared by MacLean et al.[5]

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7. The uv spectrum of 6 measured in basic medium [λ max (MeOH-5% $NaHCO_3$) 235 (ε 10,000) and 284nm(ε 9,000)] revealed the absence of the aforementioned strong bands characteristic of conjugated immonium system of the original salt (6). This may suggest the presence of sp^3 C_1-carbon, which is generated by interaction of the immonium double bond with ^-OH provided by addition of $NaHCO_3$ solution. The first attack of hydride anion, therefore, takes place on C_α-carbonyl carbon [-CO-C(OH)-N< $\xrightarrow{H^-}$ -CH(OH)-C(OH)-N< $\rightleftharpoons$ -CH(OH)-C=N<], and, on the contrary, the aforementioned stereoselective transformation of 6 into 8 may commence with the hydride reduction of the immonium double bond (see ref. 4).

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