Synthesis of Some Isotype Analogs of Vincamine, Eburnamonine and Eburnamine, and an Alternative Approach to Ethyl Apovincaminate[1)]

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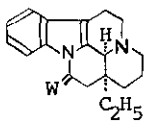
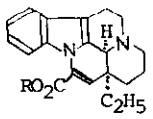
Abstract—— New synthetic analogs of Vinca minor alkaloids were described, together with a new total synthesis of ethyl apovincaminate.

Over the past twenty years, considerable attentions have been paid to vincamine [1] and its related alkaloids such as eburnamonine [2], eburnamine [3], apovincaminic acid esters [4a,4b] and so on because of their therapeutic potential as a cerebrovasodilator or an antihypertensive agent.[2)] A number of synthetic works on these alkaloids have been recorded and still now newer approaches are being recorded.[3)] In spite of their remarkable pharmacological activities, structure-modification studies on these pentacyclic indole molecules have been scarce, and thus synthesis of closly-related synthetic analogs seems very interesting from both a chemical and a medicinal point of view.

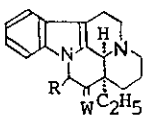
In this paper we wish to report some new analogs [5a,6a,7a] in which oxygen atoms are transpositioned from the 14-position of the corresponding natural alkaloids [1,2,3] into the neighboring position, and for the synthesis of this type of the compounds, N^1-acetic acid esters [9,10c] were used as key intermediates.



[1] W: CO_2CH_3, OH
[2] W: O
[3] W: OH, H



[4a] R: CH_3
[4b] R: C_2H_5



[5a] W: O, R:H
[6a] W: OH, H, R:H
[7a] W: OH, H, R: $CO_2C_2H_5$

Here is also described an alternative synthetic approach to ethyl apovincaminate [4b][4)] utilizing the present analogs as intermediates, and this novel synthesis involved dehydration process of β-hydroxyester as a key step whereas the already known chemical synthesis of these molecules [4] are all based on dehydration process of α-hydroxyester, vincamine itself.[4)]

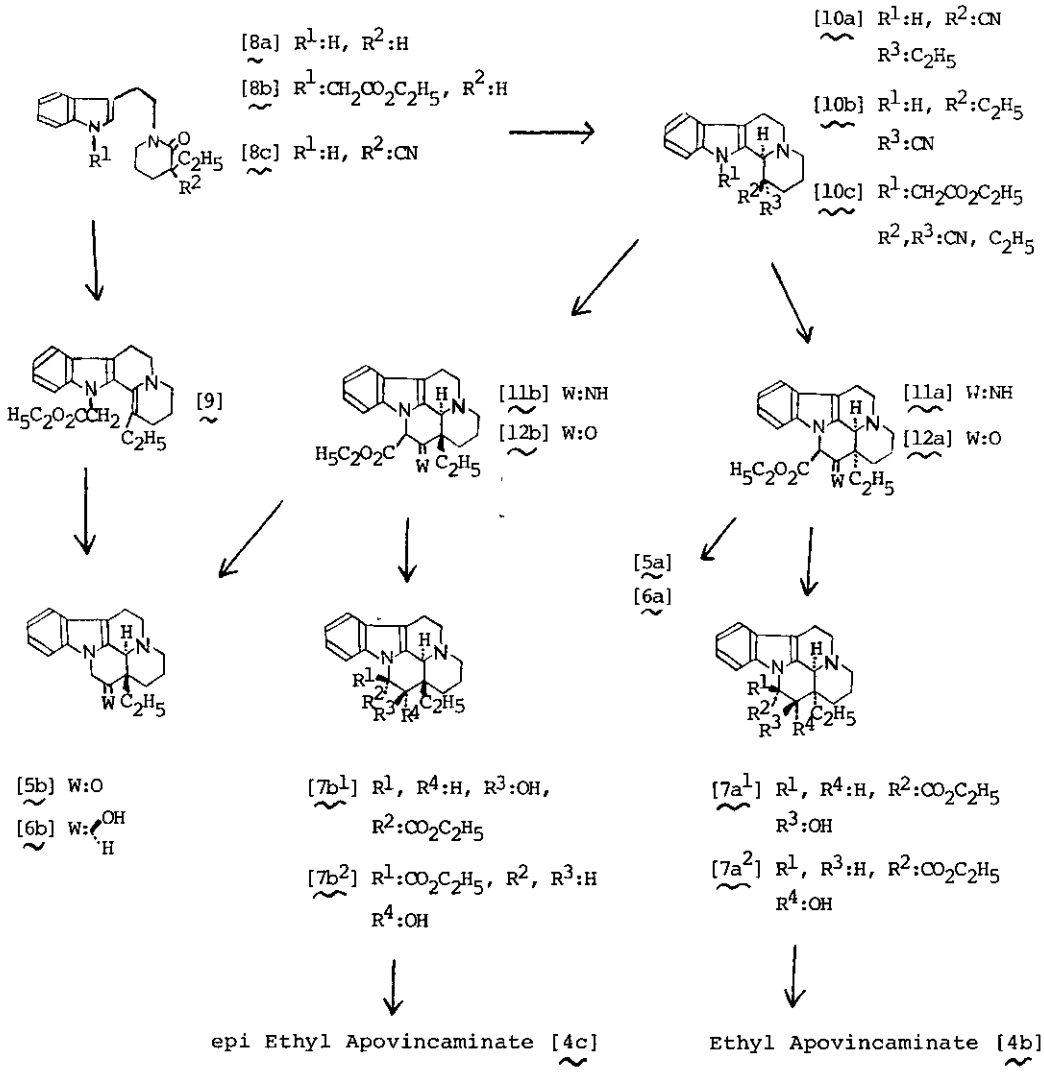
The synthesis of the first target compound, 15-oxo-14,15-dihydroeburnamenine [5a] was attempted by the intramolecular cyclization of the enamine [9]. The amide [8b], prepared by the alkylation of 8a[3c] with ethyl chloroacetate in the presence of sodium hydride at room temperature, was cyclized in refluxing acetonitrile containing phosphorus oxychloride ($POCl_3$) to give the enamine [9]. The crude enamine [9] was cyclized at 110° without solvent and then hydrogenated with 10% palladium on charcoal in ethanol solution to give only one stereoisomer [5b] [5.8% from 8a, mp 150-152°, NMR δ($CDCl_3$): 0.63(3H,t), 4.6(2H,AB quartet,J gem=19.4cps)]. Thus, we attempted to synthesize the cis isomer of 5b by means of the synthetic sequence using modified Ziegler cyclization[5] of 1-cyanoindroquinolizine [10a]. The cyano piperidone [8c] was cyclized in a acetonitrile with $POCl_3$ and subsequently reduced with $NaBH_4$ to yield only the trans [10b] [47.6%, mp 139-141°, NMR δ(d-pyridine): 0.81(3H,t), 3.71(1H,s), 9.95(1H,br)].

The trans [10b] readily epimerized[6] on treatment with conc. hydrochloric acid at reflux to a mixture containing 29% the trans and 71% the cis, which was recrystallized from methanol to afford pure 10a [50%, mp 231-233°, NMR δ(d-pyridine): 0.98 (3H,t), 3.50(1H,s), 11.07(1H,br)]. The nitriles were respectively converted via the esters [10c] to the imino esters by the reaction with ethyl chloroacetate at the presence of an excess of NaH [11a: 70%, mp 94-95°, NMR δ($CDCl_3$): 1.08(3H,t), 1.23 (3H,t), 6.28(2H,br), 11b: 64.4%, mp 180-180.5°, NMR δ($CDCl_3$): 0.64(3H,t), 1.26(3H, t), 6.46(2H,br)], and followed by hydrolysis of 11 to give the keto esters [12a, 12b] [12a: 80% mp 139-142.5°, NMR δ($CDCl_3$): 0.93(3H,t), 1.20(3H,t), 5.44(1H,s), 12b: 34.5%, mp 130-131.5°, NMR δ($CDCl_3$): 0.65(3H,t-like), 1.26(3H,t), 5.33(1H,s)]. The trans imino ester [11b] was quantitatively converted to the ketone [5b] by the hydrolysis in the conc. hydrochloric acid solution at room temperature.

On the other hand, the target, 15-oxo-14,15-dihydroeburnamenine [5a] was obtained from the keto ester by refluxing in the saturated HCl-ethanol solution [43.6%, NMR δ($CDCl_3$): 1.0(3H,t), 4.5(2H,AB quartet,J gem=19.5cps)].

The second target compound, 15-hydroxy-14,15-dihydroeburnamenine [6a] or its trans isomer was easily obtained by the reduction of 5a or 5b with $NaBH_4$ or L-selectride [6a: 84.6%, amorphous, NMR δ($CDCl_3$): 1.02(3H,t), 3.53(1H,t), 4.05-4.4(2H,M), 6b: 89%, mp 168.5-172.5°, NMR δ($CDCl_3$): 0.85(3H,t-like), 3.5-4.4(3H,M)]. The third target coupound, 15-hydroxy-14,15-dihydroapovincaminic acid ester [7a] was obtained as a mixture of diastereoisomers by the reduction of the keto ester [12a].

The reduction of 12b with $NaBH_4$ afforded a mixture of two diastereoisomers [7b[1],



7b^2] in the ratio of ca 4:1 which were separated by column chromatography and their structures were deduced from their NMR spectrum [7b^1: NMR δ($CDCl_3$): 0.87(3H, t-like), 1.30(3H,t), 4.61(1H,d,J=9-10cps), 7b^2: 0.81(3H,t), 1.10(3H,t), 5.10(1H,d, 8cps)].

By a similar procedure as described above were obtained the main product [7a^1] [about 85%, NMR δ($CDCl_3$): 1.03(3H,t), 1.32(3H,t), 4.23(1H,d,J=9cps), 4.53(1H,d,)] and its diastereoisomer [7a^2] [NMR δ($CDCl_3$): 0.93(3H,t), 1.37(3H,t), 4.3(1H,d,J= 3-4cps), 4.79(1H,d)] from 12a.

Some of the present isotype analogs (e.g., the ketones [5a,5b]) and their intermediates, the keto esters [12a,12b] are shown to have excellent pharmacological

activities.[7] The hydroxy esters [7a,7b] were also found to be useful for the synthesis of apovincaminic acid esters. That is, by the dehydration of 7a or 7b with a excess of NaH, ethyl apovincaminate [4b] or epi ethyl apovincaminate [4c] was readily obtained [4b: 42%, identified upon comparison with the authentic sample prepared according to the known procedure[4], 4c: 95%, mp 99.5-102°, NMR $\delta(CDCl_3)$ 0.73(3H,t-like), 1.37(3H,t), 4.41(2H,q), 6.27(1H,s)].

References and Notes

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7) Structure-activity relationship study on these compounds is now in progress.

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