Communications to the Editor

[Chem. Pharm. Bull.
30(4)1521—1524(1982)]

1,6-DIHYDRO-3(2*H*)-PYRIDINONES AS SYNTHETIC INTERMEDIATES. TOTAL SYNTHESIS OF (±)-EBURNAMONINE

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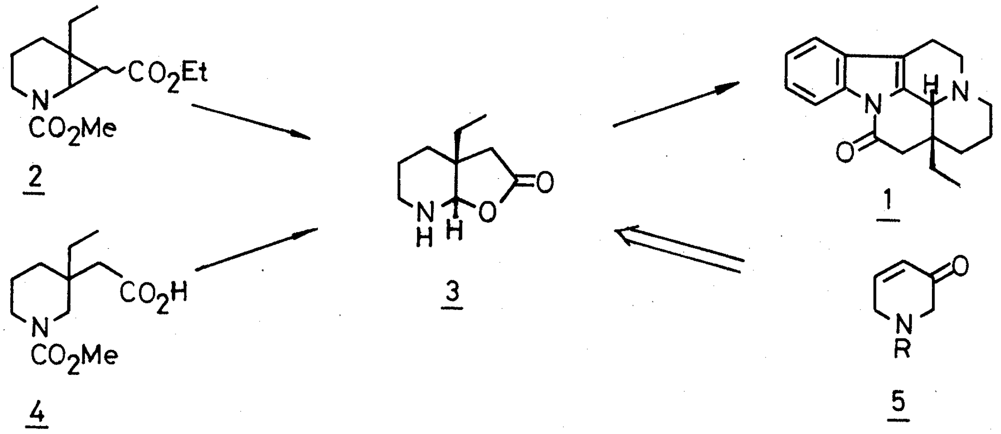
The allyl alcohol (11) derived from the dihydropyridinone (8) by a few steps was transformed into the ester (15) *via* the Claisen rearrangement, oxidation, esterification, and then hydrogenation. N-Chlorination of 15 followed by a basic hydrolysis afforded the lactone (3) exclusively which was converted into (±)-eburnamonine (1) by the known sequence.

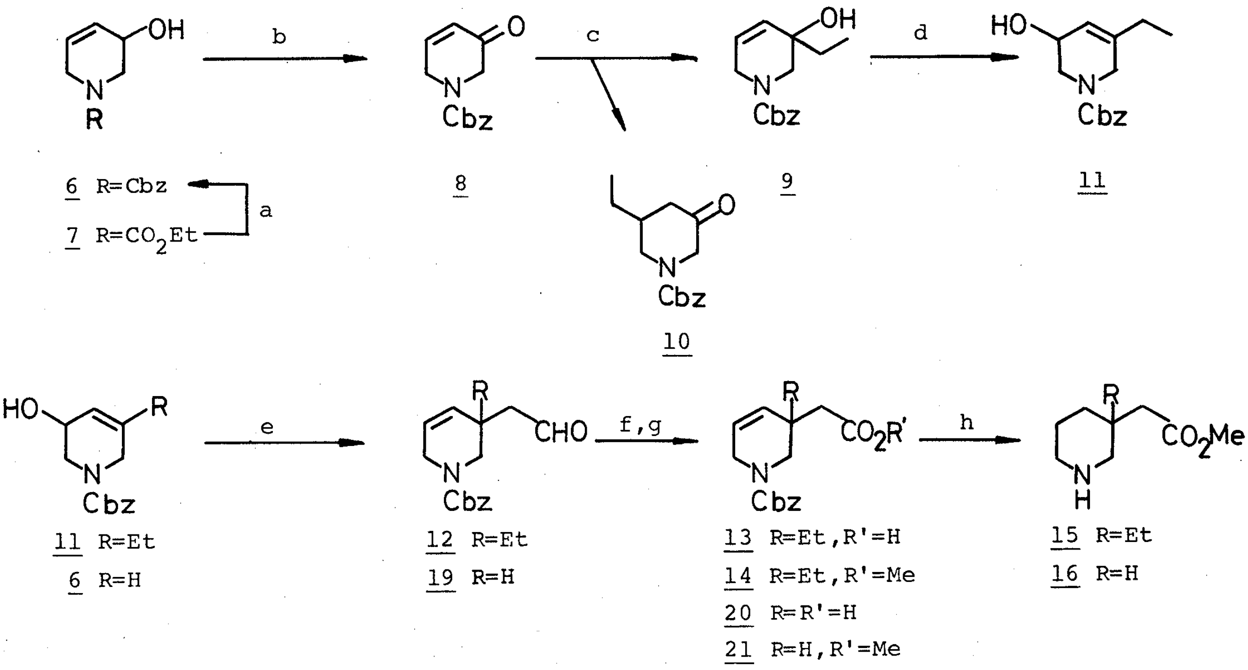
KEYWORDS—— allylic rearrangement; the Claisen rearrangement; dihydropyridinone; indole alkaloid; eburnamonine; total synthesis; amine oxidation; lactone formation; isomerization of imine

Eburnamonine (1), an indole alkaloid possessing the 1,2,3,3-tetrasubstituted piperidine unit, has been synthesized by many groups to date.1) Recently, Wenkert and his co-workers1f) reported an elegant synthesis of (±)-1 through a crucial conversion of the cyclopropanecarboxylate (2) into the amino lactone (3) by basic hydrolysis. On the other hand, Irie and Ban1i) demonstrated an alternative synthesis of the same lactone (3) by anodic oxidation of the urethane (4).

We have been investigating various natural product syntheses starting from a common synthon, the 1,6-dihydro-3(2*H*)-pyridinone (5),2) and report here a novel synthesis of the lactone (3), the key intermediate for (±)-1, using the same synthon (5) through a facile amino lactone formation method.

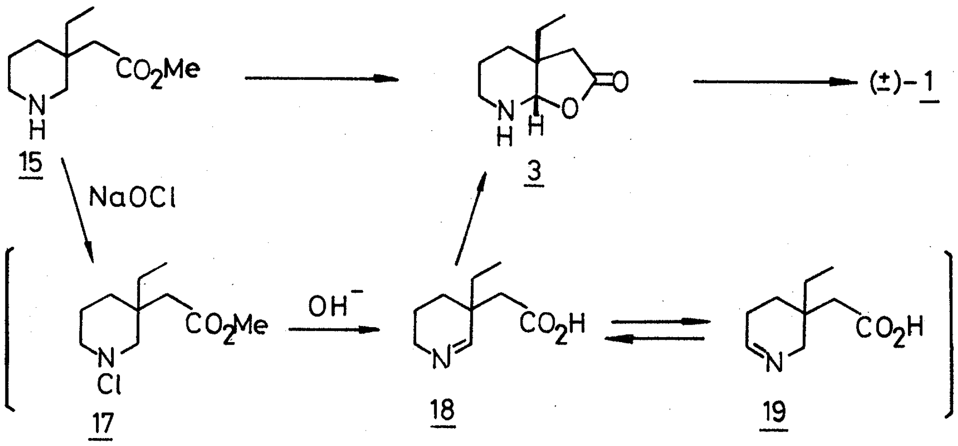


Benzyl 3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (6), prepared from 7[3)] by basic hydrolysis and subsequent condensation with carbobenzoxy chloride in 94% yield, was subjected to the Jones oxidation to give the dihydropyridinone (8) [89% yield; ν 1695, 1622; δ 4.12 (2H, s), 4.22 (2H, t, J=3), 5.10 (2H, s), 6.05 (1H, dt, J=10, 3), 6.92 (1H, dt, J=10, 3), 7.25 (5H, s)]. Treatment of 8 with 2.5 molar equivalent of ethylmagnesium bromide in ether afforded the 1,2-adduct (9) [57% yield; ν 3560, 1680, 1650; δ 0.93 (3H, t, J=7), 1.60 (2H, q, J=7), 5.70 (2H, s)] along with a small amount of the 1,4-adduct (10). The allylic rearrangement of the hydroxyl group in the former (9) was accomplished under the condition of heating with 1% aqueous hydrochloric acid in acetone to afford the secondary alcohol (11) [61% yield; δ 1.03 (3H, t, J=7), 2.02 (2H, q, J=7), 5.57 (1H, m)]. A solution of 11 in a large excess of ethyl vinyl ether containing mercuric acetate was heated in a sealed tube at 200°C for 48 h to yield the labile aldehyde (12), which was immediately oxidized with silver (I) oxide[4)] to give the carboxylic acid (13) [46% yield from 11; δ 0.87 (3H, t, J=7.5), 1.42 (2H, q, J=7.5), 2.33 (2H, s), 5.62 (2H, s), 8.72 (1H, broad s)]. The methyl ester (14), obtained from 13 on reaction with ethereal diazomethane in 84% yield, was hydrogenated in methanol over 5% palladium on carbon providing the saturated amine (15) [49% yield; ν 3350, 1720; δ 0.83 (3H, t, J=6.5), 2.35 (2H, s); m/e 185 (M^+), 44 (base)]. Its deethyl analogue (16) was prepared in the same way as shown in the chart [6 → 19 → 20 → 21 → 16].



Reagents: (a) KOH, H_2O, EtOH; $PhCH_2OCOCl$; (b) Jones oxidation; (c) EtMgBr, Et_2O; (d) 1%HCl, acetone; (e) $EtOCH=CH_2$, $Hg(OAc)_2$; (f) $AgNO_3$, KOH, H_2O, EtOH; (g) CH_2N_2, Et_2O; (h) 5%Pd-C, H_2, MeOH

N-Chlorination [5% aqueous sodium hypochlorite in dichloromethane,5) r.t., 6 h] of 15 and the subsequent hydrolysis [potassium hydroxide in aqueous dioxane, reflux, 2.5 h] resulted in direct formation of the desired amino lactone (3) [85% yield, mp 73-75°C (lit.1*i*) mp 74-75°C); ν 3400, 1745; δ 0.91 (3H, t, *J*=7.5), 2.21 and 2.42 (2H, AB-q, *J*=16.5), 2.58 (1H, s), 5.13 (1H, s); *m/e* 169 (M^+), 96 (base)], whereas the same treatment of 16 gave no lactonic compound. The successful formation of the lactone (3) from 15 is interpreted as follows: the initially formed chloramine (17) is subjected to ester hydrolysis and elimination of hydrogen chloride under the basic condition employed to give the interconvertible6,7) imino acids (18 and 19),8) and then only the isomer (18) cyclizes to the lactone (3) *via* the quasi-axial conformation of the carboxylmethyl group. Owing to little contribution of the requisite quasi-axial conformation, compound 16 could afford no corresponding lactone.



According to the known method1*f*,*i*) the amino lactone (3) was converted into (±)-eburnamonine (1) [mp 202-204°C (lit.1*i*) mp 202-205°C)], which was proved to be identical with natural eburnamonine by spectral comparison.

Scope, limitation, and further application of this novel method for amino lactone formation are in progress.

ACKNOWLEDGEMENT We wish to thank Prof. E. Wenkert, University of California, San Diego, for a generous supply of natural eburnamonine.

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6) Isomerization of 18 and 19 to each other is easily explicable from the excellent yield of the lactone (3) without any detectable compounds expected from 19.

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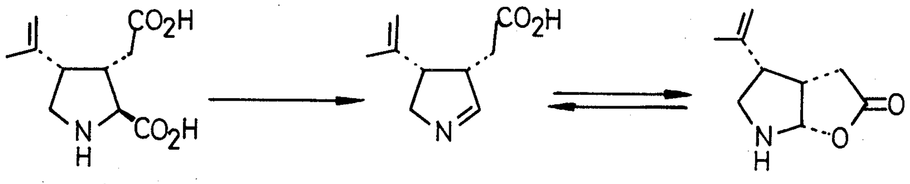

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(Received February 19, 1982)