SYNTHETIC STUDIES ON THE LYCOPODIUM ALKALOIDS. A FORMAL TOTAL SYNTHESIS OF (±)-LYCODOLINE[1)]

Sang-Won Kim,* Ikuo Fujii, Keishiro Nagao and Yutaka Ozaki
Faculty of Pharmaceutical Sciences, Josai University
1-1 Keyakidai, Sakado, Saitama 350-02, Japan

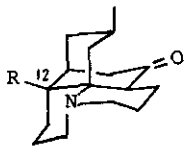
Abstract----The tricyclic amine (10) was reacted with the acid chloride (17) to afford the amide (18), which was converted in 3 steps into the amino-alcohol (16). Its preparation constitutes a formal total synthesis of (±)-lycodoline.

Among the Lycopodium alkaloids known today,[2)] lycodoline (1; alkaloid L.8) is an attractive synthetic target because it is one of the 12-hydroxylated alkaloids as determined by Ayer and Iverbach[3)] and the most widely distributed of the minor bases in the family.[2a)] Our previous paper dealt with the total synthesis of anhydrolycodoline via the acrylamide (2), but this did not cyclize to the lactam (3) under Michael conditions for a stereoelectronic reason.[4)]

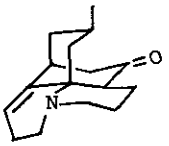
It is of interest that Heathcock and his coworkers reported an elegant synthesis of lycopodine by constructing the fourth ring via the intramolecular aldol cyclization of the aldehyde (4).[5)] In addition, they have accomplished very recently[6)] the first total synthesis of 1 via the aldehyde (5) in the similar manner. This prompted us to describe herein our work on 1.

Our initial objective was the aldehydes (5) and (6), or their equivalents (11-14) as shown in Chart 1. For this purpose, at first, the acid chlorides (7), (8) and (9) with protected aldehyde group were synthesized as follows. The Reformatskii reaction of ethyl bromoacetate with ethyl orthoformate gave a 2:1 mixture of ethyl 3,3-diethoxypropionate and ethyl 3-ethoxyacrylate.[7)] This mixture was heated in the presence of $NaHSO_4$ to afford pure 3-ethoxyacrylate, which on hydrolysis with base and treatment with oxalyl chloride in dry C_6H_6 gave the acid chloride (7).[8)] The ester mixture mentioned above was heated with ethylene glycol

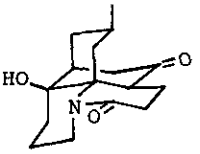
or ethanedithiol in the presence of $NaHSO_4$, followed by the sequence of reactions employed for 7, to afford the acid chlorides (8) and (9), respectively.



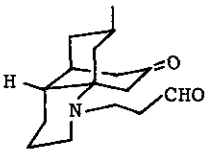
lycodoline (1; R=OH)
lycopodine (R=H)



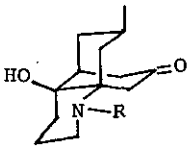
anhydrolycodoline



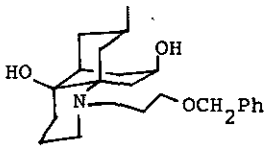
(3)



(4)



(2) R = $COCH=CH_2$
(5) R = CH_2CH_2CHO
(6) R = $COCH_2CHO$
(10) R = H
(11) R = COCH=CHOEt
(12) R = $COCH_2CH$



(19)

(13) R = $COCH_2CH$
(14) R = CH_2CH_2CH
(15) R = $COCH_2CH_2OH$
(16) R = $CH_2CH_2CH_2OH$
(18) R = $COCH_2CH_2OCH_2Ph$
(20) R = $CH_2CH_2CH_2OCH_2Ph$

(7) EtOCH=CHCOCl
(8)  $CHCH_2COCl$
(9)  $CHCH_2COCl$
(17) $PhCH_2OCH_2CH_2COCl$

Chart 1

The tricyclic amine (10) reported previously[4] was reacted with 7, 8 and 9 in the presence of Et_3N in $CHCl_3$ to afford the corresponding amides (11), (12) and (13), respectively.[9] Deprotection of 11, 12 and 13 was carried out fruitlessly under various conditions; i.e.; acid treatment of 11 and 12 gave either 10, the unchanged starting material or a complex mixture of undefined components depending on the conditions used, and treatment of 13 with either $HgCl_2/CH_3CN$,[10] $Tl(NO_3)_3$,[11] or CH_3I/aq. CH_3CN-THF[12] also gave a complex mixture. Deketalization of the dioxolane (14), obtained by reduction of 12 with $LiAlH_4$ followed by Jones oxidation, did not take place under acidic conditions at room temperature, but treatment with 10% HCl in acetone at 50° yielded 10.[13]

Unfeasibility of the deprotection described above let us synthesize the alcohols (15) and (16) as the aldehyde equivalents. By the reaction of 10 with the acid chloride (17), prepared from β-propiolactone in 2 steps, was obtained

the amide (18). Reduction of 18 with $LiAlH_4$ (to give 19) followed by Jones oxidation (to give 20) and hydrogenolysis over 10% Pd-C afforded 16. Hydrogenolysis of 18 over 10% Pd-C gave 15. Oxidation of 15 and 16, in our hands, was unsuccessful under various conditions, for example, Jones, PDC, PCC, Moffatt and Oppenauer (benzophenone[5] or fluorenone[14]/ KOBu-t in boiling $PhCH_3$) oxidations. Oppenauer oxidation of 15 with benzophenone/KH, Heathcock's successful condition, gave 2, identified with an authentic sample. The preparation of 16 constitutes an additional approach towards the synthesis of 1.

Acknowledgment----The authors thank Prof. Z. Horii, President of Josai University, for his encouragement throughout this work.

References and footnotes

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9) Selected data for new compounds, which were analyzed satisfactorily, except 14 and 20, are as follows. 11(mp 170-171°): IR 3400, 1700, 1650, 1580cm^{-1}; NMR δ0.93 (3H, fused d), 1.32 (3H, t, J=7.2Hz), 3.89 (2H, q, J=7.2Hz), 5.50 (1H, d, J=12Hz), 7.40 (1H, d, J=12Hz). 12(mp 152-153°): IR 3400, 1700, 1630cm^{-1}; NMR δ0.93 (3H, fused d), 2.72 (2H, d, J=4.2Hz), 3.73-4.06 (4H, m), 5.20 (1H, t, J=4.2Hz). 13(mp 150-153°): IR 3400, 1700, 1630cm^{-1}; NMR δ0.93 (3H, fused d), 2.89 (2H, d, J=7.2Hz), 3.20 (4H, s), 4.83 (1H, t, J=7.2Hz). 14(oil): MS 323(M^+); IR 3430, 1698cm^{-1}; NMR δ0.93 (3H, fused d), 3.73-4.06 (4H, m), 4.85

(1H, t, J=4.2Hz). 15(mp 152-153°): IR 3400, 1700, 1620cm^{-1}; NMR δ0.93 (3H, fused d), 2.54 (2H, t, J=5Hz), 3.82 (2H, t, J=5Hz). 16(mp 139°; lit.[6] mp 140-140.5°): IR 3400, 1700cm^{-1}; NMR δ0.93 (3H, fused d), 3.73 (2H, t, J=5Hz). 18(mp 124-125°): IR 3400, 1700, 1630cm^{-1}; NMR δ0.93 (3H, fused d), 2.63 (2H, t, J=6.2Hz), 3.76 (2H, t, J=6.2Hz), 4.51 (2H, s), 7.30 (5H, s). 19(mp of the $HClO_4$salt 185-190°): IR 3400cm^{-1}; NMR δ0.93 (3H, d, J=6.4Hz), 3.50 (2H, t, J=6Hz), 4.50 (2H, s), 7.34 (5H, s). 20(oil): MS 371 (M^+); IR 3400, 1700cm^{-1}; NMR δ0.93 (3H, fused d), 3.50 (2H, t, J=6.4Hz), 4.50 (2H, s), 7.34 (5H, s).

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13) This result may indicate that the desired 5 was formed and it was decomposed to 10 by a retro-Michael reaction.

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Received, 28th May, 1981