

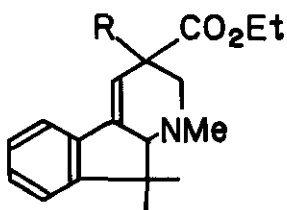
STUDIES ON INDENOPYRIDINE DERIVATIVES AND RELATED COMPOUNDS. V<sup>1</sup>.

A FACILE SYNTHESIS OF ETHYL 9,9-DIMETHYL-1,2,3,9a-TETRAHYDRO-9H-INDENO[2,1-b]PYRIDINE-3-CARBOXYLATE

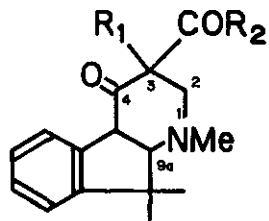
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**Abstract** — New synthetic methods for 1,2,3,9a-tetrahydro-9H-indeno[2,1-b]pyridine (1) are described. These methods involve the acidic de-t-butoxycarbonylation followed by base treatment of the diene (13) and mesylate (14).

In the previous paper, we have failed in synthesizing the title compound 1, which is a model compound for the synthesis of lysergic acid, via  $\beta$ -keto ester (3), because 3 is very susceptible to decomposition due to the effect of an active C-3 hydrogen.<sup>1</sup> This was readily proven by the fact that compound 4 lacking a C-3 hydrogen is sufficiently stable for isolation and was successfully converted to the tetrahydroindeno[2,1-b]pyridine (2). From these results, it was expected that the decrease of an acidity of a C-3 hydrogen such as  $\beta$ -keto amide (10) will make it possible to isolate.



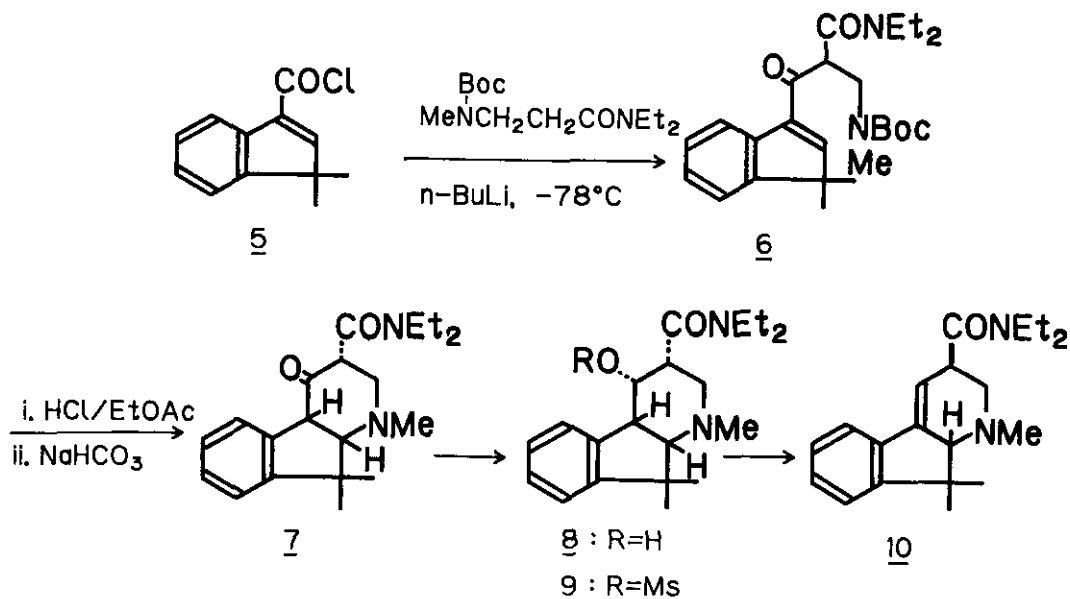
1 : R=H  
2 : R=Me



3 : R<sub>1</sub>=H, R<sub>2</sub>=OEt  
4 : R<sub>1</sub>=Me, R<sub>2</sub>=OEt  
10 : R<sub>1</sub>=H, R<sub>2</sub>=NEt<sub>2</sub>

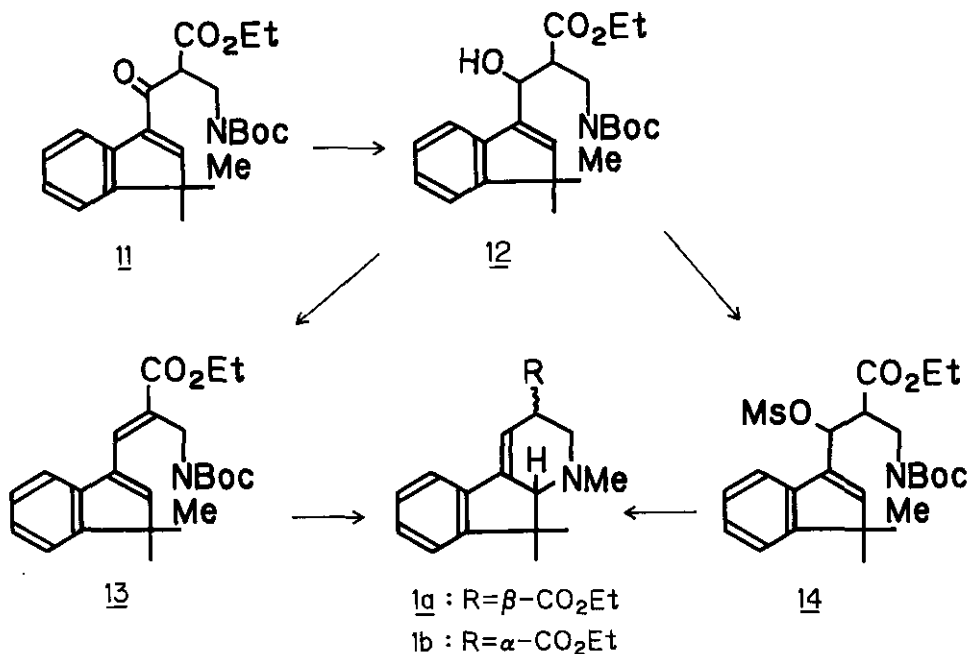
Treatment of the indenoyl chloride (5) with N,N-diethyl-3-(N-t-butoxycarbonyl-N-methyl)aminopropionamide in the presence of n-butyl lithium in tetrahydrofuran (THF) at -78 °C<sup>2</sup> afforded 6<sup>3</sup> in 45% yield after purification by column chromatography. Removal of the t-butoxycarbonyl (Boc) group with saturated hydrogen chloride in ethyl acetate (HCl-EtOAc) followed by treatment with sodium bicarbonate solution

gave  $\beta$ -keto ester (7) [high resolution ms : 328.2149 (theor. 328.2152)]. Without purification, reduction of 7 with sodium borohydride in ethanol afforded the alcohol (8) (mp 129-131°C) (57% overall yield from 6), which was found to be a single product from the  $^1\text{H}$ -nmr spectrum (300 MHz) [ $\delta$  ( $\text{CDCl}_3$ ) 2.63 (1H, dd,  $J=12, 11$  Hz, 2ax-H), 2.85 (1H, dd,  $J=11, 8$  Hz, 2eq-H), 4.16 (1H, bs, 4-H), 3.78 (1H, dd,  $J=9, 3$  Hz, 4a-H), 2.84 (1H, d,  $J=9$  Hz, 9a-H)]. The stereochemistry of 8, having an axially oriented hydroxyl group and an equatorially oriented diethylamide group in a stable B/C *cis*-fused form,<sup>4</sup> was deduced from its nmr spectrum on comparison with the data of the previously prepared compounds.<sup>1</sup> Treatment of 8 with methanesulfonyl chloride and triethylamine in dichloromethane gave the mesylate (9) in 96% yield which was then heated with a mixture of lithium bromide and lithium carbonate in dimethylformamide<sup>5</sup> to give N,N-diethyl-1,9,9-trimethyl-1,2,3,9a-tetrahydro-9H-indeno[2,1-b]pyridine-3-carboxamide (10)<sup>6</sup> in 51% yield.



Thus, another route was considered for the synthesis of compound 1. Reduction of 11<sup>1</sup> with sodium borohydride in ethanol gave the alcohol 12 quantitatively. Dehydration of 12 was performed with thionyl chloride and pyridine at room temperature to afford a dienic ester (13),<sup>7</sup> which showed a broad singlet at  $\delta$  6.46 due to a vinyl proton ( $\text{HC}=\text{C}-\text{CH}_2-$ ), in 38% yield. Acidolytic cleavage of the Boc group of 13 followed by treatment with sodium bicarbonate solution gave ethyl 1,9,9-trimethyl-1,2,3,9a-

tetrahydro-9H-indeno [2,1-b] pyridine-3-carboxylate in 92% yield, which was found to be a mixture of two unsaturated esters (1a and 1b) with the ratio of 5 : 4. Attempted separation of two unsaturated ester (1a and 1b) was unsuccessful except in the isolation of 1a<sup>5</sup> in low yield, which was found to isomerize to an equilibrium mixture of these two esters when standing at room temperature in ethanol for several hours.<sup>8</sup> The stereochemistries of 1a and 1b ( $\beta$ -CO<sub>2</sub>Et in 1a and  $\alpha$ -CO<sub>2</sub>Et in 1b) were determined from their <sup>1</sup>H-nmr spectra,<sup>9</sup> which exhibited a large coupling constant (11.5 Hz) between 2ax-H and 3-H in 1a and a small coupling constant (5 Hz) in 1b, upon comparison with those of despyrrololysergic acid derivatives reported by Ninomiya.<sup>10</sup> In order to improve the yield of the diene (13), 12 was treated with methanesulfonyl chloride to give the mesylate (14), which was subsequently treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethylsulfoxide (DMSO) to give the diene (13), but in low yield. However, the mesylate (14) was readily derived to the unsaturated ester (1) in satisfactory yield when worked up with HCl/EtOAc followed by treatment with DBU in DMSO at room temperature. The total yield of the product based on 11 was 45%.



In conclusion, we have developed new methods for the construction of 1,2,3,9a-tetrahydroindeno[2,1-b]pyridine skeleton having an ester group at C-3, and these will be applicable to the total synthesis of lysergic acid and its analogues.

REFERENCES AND NOTES

1. R. Yoneda, T. Terada, S. Harusawa, and T. Kurihara, *Heterocycles*, 1985, 23, 557.
2. N. Crouse and D. Seebach, *Chem. Ber.*, 1968, 101, 3113.
3.  $\nu_{\max}$  1690, 1640  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 1.12 (6H, m, 2 x  $\text{NCH}_2\text{CH}_3$ ), 1.38 (6H, s, 2 x  $\text{CH}_3$ ), 1.43 [9H, s,  $\text{C}(\text{CH}_3)_3$ ], 2.83 (3H, s,  $\text{NCH}_3$ ), 3.10-3.55 (4H, m, 2 x  $\text{NCH}_2\text{CH}_3$ ), 3.80 (2H, bd,  $\underline{J}=7$  Hz,  $\text{NCH}_2$ ), 4.80 (1H, m,  $\text{COCH}$ ), 7.30 (4H, m, Ar-H and =CH), 8.10 (1H, m, Ar-H); High-resolution ms : m/z 428.2673 (Theor. 428.2676 for  $\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_4$ ).
4. The projection used in this paper was depicted according to Z. Horii, et al, *Chem. Pharm. Bull.*, 1967, 15, 1641.
5. R.P. Holysz, *J. Am. Chem. Soc.*, 1953, 75, 4432.
6. oil (mp of picrate 195-197°C);  $\nu_{\max}$  1620  $\text{cm}^{-1}$ ;  $\lambda_{\max}$  (log  $\epsilon$ ) 252 (4.16), 286 (3.65), 295 (3.57) nm;  $\delta$  ( $\text{CDCl}_3$ ) 1.10 and 1.56 (each 3H, each s, 2 x  $\text{CH}_3$ ), 1.15 and 1.23 (each 3H, each t,  $\underline{J}=7$  Hz, 2 x  $\text{NCH}_2\text{CH}_3$ ), 2.52 (3H, s,  $\text{NCH}_3$ ), 2.79 (1H, t,  $\underline{J}=11$  Hz, 2ax-H), 3.0 (1H, dd,  $\underline{J}=11$ , 6 Hz, 2eq-H), 3.43 (4H, m, 2 x  $\text{NCH}_2\text{CH}_3$ ), 3.86 (1H, m, 3-H), 5.92 (1H, t,  $\underline{J}=2$  Hz, 4-H), 7.26 (3H, m, Ar-H), 7.45 (1H, m, 5-H); High-resolution ms : m/z 312.2200 (Theor. 312.2203 for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}$ ).
7. A similar aminodieneic ester functionalization is used to the total synthesis of lysergic acid by Ramage : R. Ramage, V.W. Armstrong and S. Coulton, *Tetrahedron*, 1981, 37, supplement 1, 157.
8. Complete hydrogen-deuterium exchange at the 3-position was observed when a mixture of 1a and 1b was refluxed in deuterium methoxide.<sup>10</sup>
9. 1a :  $\delta$  ( $\text{CDCl}_3$ ) 1.07 and 1.55 (each 3H, each s, 2 x  $\text{CH}_3$ ), 1.31 (3H, t,  $\underline{J}=7$  Hz,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 2.50 (3H, s,  $\text{NCH}_3$ ), 2.56 (1H, t,  $\underline{J}=11.5$  Hz, 2ax-H), 2.86 (1H, dd,  $\underline{J}=4$ , 3 Hz, 9a-H), 3.17 (1H, ddd,  $\underline{J}=11.5$  Hz, 5.5 Hz, 1 Hz, 2eq-H), 3.65 (1H, br m, 3-H), 4.21 (2H, q,  $\underline{J}=7$  Hz,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 6.13 (1H, td,  $\underline{J}=3$ , 1 Hz, 4-H), 7.22 (3H, m, Ar-H), 7.43 (1H, m, 5-H). High-resolution ms : m/z 285.1727 (Theor. 285.1730 for  $\text{C}_{18}\text{H}_{23}\text{NO}_2$ ).
- 1b :  $\delta$  ( $\text{CDCl}_3$ ) 1.02 and 1.53 (each 3H, each s, 2 x  $\text{CH}_3$ ), 1.23 (3H, t,  $\underline{J}=7$  Hz,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 2.45 (3H, s,  $\text{NCH}_3$ ), 2.54 (1H, dd,  $\underline{J}=11.5$  Hz, 5 Hz, 2ax-H), 2.79 (1H, t,  $\underline{J}=3$  Hz, 9a-H), 3.13 (1H, m, 3-H), 3.33 (1H, ddd,  $\underline{J}=11.5$ , 5, 1 Hz, 2eq-H), 4.18 (2H, m,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 6.15 (1H, m, 4-H), 7.30 (3H, m, Ar-H), 7.50 (1H, m, 5-H). (These data were obtained from the data of a mixture of 1a and 1b).
10. T. Kiguchi, C. Hashimoto, T. Naito, and I. Ninomiya, *Heterocycles*, 1984, 22, 1719.

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