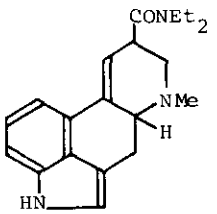
STUDIES ON INDENOPYRIDINE DERIVATIVES AND RELATED COMPOUNDS. IV[1] SYNTHESIS AND STEREOCHEMISTRY OF ETHYL 9,9-DIMETHYL-1,2,3,9a-TETRAHYDRO-9H-INDENO[2,1-b]PYRIDINE-3-CARBOXYLATE AND ITS DERIVATIVES

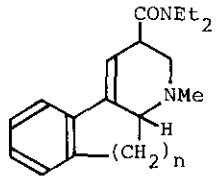
Ryuji Yoneda, Tatsuya Terada, Shinya Harusawa, and Takushi Kurihara*
Osaka College of Pharmacy, 2-10-65, Kawai, Matsubara, Osaka 580, Japan

Abstract —— The simplified analogs of lysergic acid, namely ; 4-diethylphosphoryl or 3-methyl derivatives (15a, 15b, and 22) of ethyl 1,9,9-trimethyl-1,2,3,9a-tetrahydro-9H-indeno[2,1-b]pyridine-3-carboxylate are synthesized. The structure and stereochemistry of these products as well as some intermediates are also discussed.

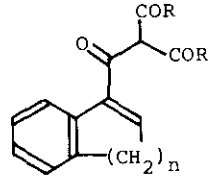
In view of the pharmacological interests, the synthesis of simplified analogs of ergot alkaloids has been extensively studied.[2,3] Craig and his co-workers reported the synthesis of the indan analog (3) from indene via a ten steps sequence, which is highly effective in reversing guinia pig ideal contractions induced by the standard oxytocic agents.[4] The indan analog 3 is the closely related compound to the despyrrole analog (2) of lysergic acid diethylamide, which is prepared by the Mannich condensation of 4 (n=2).[5] Craig demonstrated in his report that an analogous method using the Mannich reaction of 4 (n=1) for the synthesis of 3 failed because of the high reactivity of the allyllic protons in the indene nucleus and the resulting side reactions. Recently we reported the synthesis and stereochemistry of 9-hydroxy-9-phenylhexahydro-9H-indeno[2,1-b]pyridines.[1] In continuation of our studies on indenopyridines, we now report a convenient synthetic method of indenopyridine nucleus using 1,1-dimethylindene-3-carboxylic acid (8) as a model compound.



1



2 : n=2 ; 3 : n=1



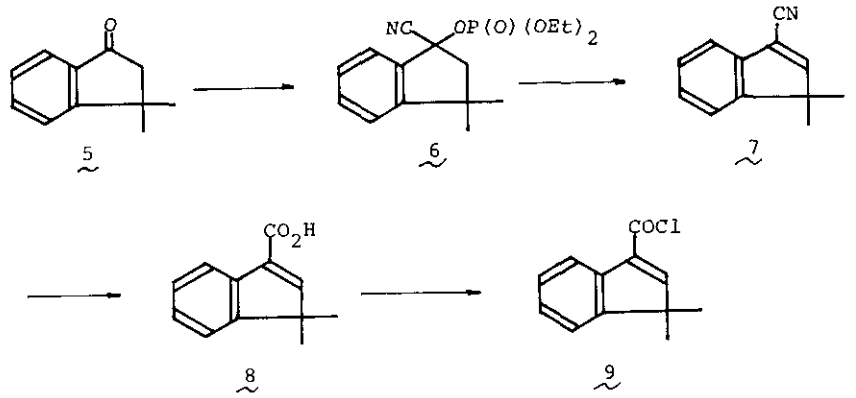
4 (n=1 or 2)

Chart 1

Synthesis

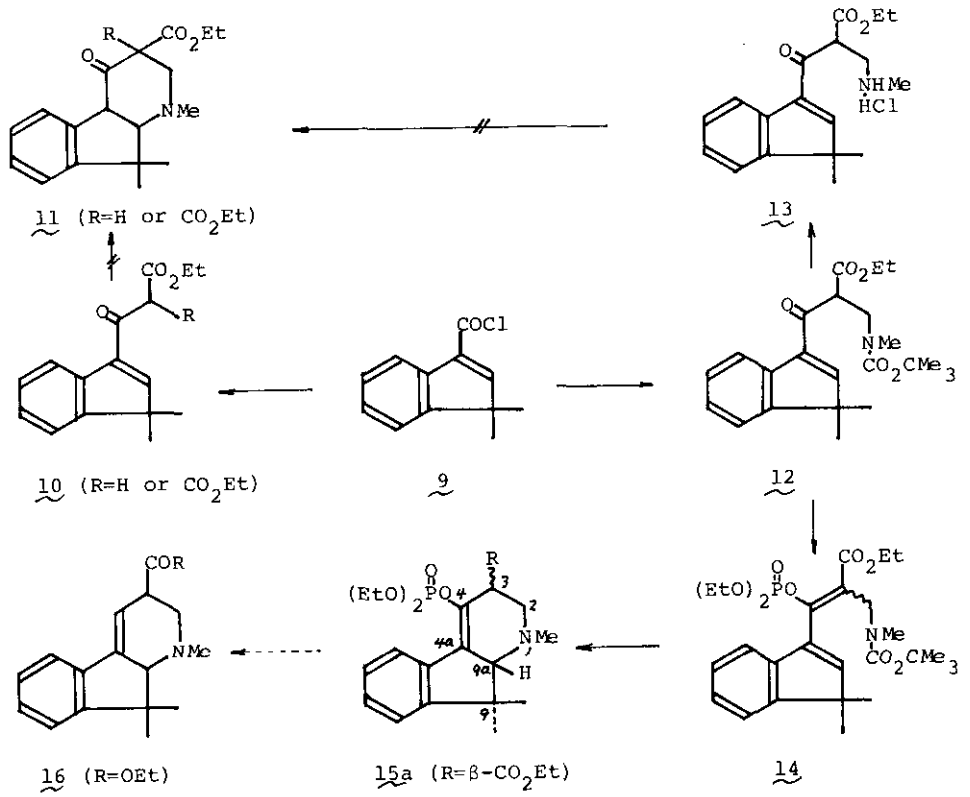
Previously we have developed a new synthetic method of α,β-unsaturated nitriles from aromatic ketones via cyanophosphates.[6] Reaction of 1-indanone (5)[7] with diethyl phosphorocyanidate (DEPC) and lithium cyanide in tetrahydrofuran afforded the cyanophosphate (6), which was treated with borontrifluoride etherate in benzene at room temperature to afford the indene-3-carbonitrile (7). Hydrolysis of 7 with potassium hydroxide in ethanol gave 8 in 92.4% yield from 5. Chlorination of 8 with thionyl chloride gave the indenoyl chloride (9) in quantitative yield which was purified by distillation (bp_3 104 ℃). Reaction of 9 with ethyl acetate[8] in the presence of lithium diisopropylamide (LDA) or with diethyl ethoxymagnesiummalonate afforded the β-ketoester [10 (R=H) in 86% yield] or the β-ketodiester [10 (R=CO_2Et) in 98% yield]. Mannich condensations of 10 with methylamine and formalin were unsuccessful in spite of the lack of the allyllic protons in the indene nucleus. Therefore another route to prepare the piperidine ring was considered. Condensation of 9 with ethyl 3-(N-t-butoxycarbonyl-N-methyl)aminopropionate in the presence of LDA yielded the β-ketoester 12 in 74% yield. Removal of the protective group of 12 with hydrogen chloride gas in ethyl acetate gave the hydrochloride of 13 quantitatively. However, attempts to obtain the product 11 (R=H) failed, probably due to the susceptibility to Retro-Mannich cleavage induced by the active C-3 hydrogen, thus giving only the complex mixture. In order to remove an active C-3 hydrogen, 12 was converted to the dienolphosphate (14) by treatment with diethyl phosphorochloridate. Cyclization was successfully achieved after removal of the protective group followed by the workup with sodium bicarbonate to give a mixture of two enolphosphates (15a and 15b), which were separated by column chromatography, in a ratio of 1:1 in 73% combined yield from 12. Reductive cleavage of the phosphate function[9] to 16 is now under investigation. In order to make sure the Retro-Mannich cleavage cited above, 9 was condensed with ethyl 3-(N-t-butoxycarbonyl-N-methyl)amino-2-methylpropionate in the presence of LDA at -78 ℃ to give the β-ketoester (18) in 68% yield. In this case, single product, namely ethyl 4-oxo-1,3,9,9-tetramethyl-1,2,3,4,4a,9a-hexahydro-9H-indeno[2,1-b]pyridine-3-carboxylate (19), was obtained by base treatment 18 in 75% yield after cleavage of t-butoxycarbonyl group. Sodium borohydride reduction of 19 gave the alcohol (20) as sole product in 83% yield. Dehydration of 20 with thionyl chloride and pyridine gave the complex products

from which 22 was *not isolated*. Thus mesylation of 20 with mesyl chloride afforded 21, which was subsequently treated with 1,8-diazabicyclo[5.4.0]undec-7-ene[10] to give the unsaturated ester (22) in 69% yield. Synthesis of 16 and 17 by the alternative method is now under progress.



5 6 7 8 9

Chart 2



11 (R=H or CO_2Et)

13

10 (R=H or CO_2Et)

9

12

14

16 (R=OEt)

17 (R=NEt_2)

15a (R=β-CO_2Et)

15b (R=α-CO_2Et)

Chart 3

Stereochemistry

The stereochemistry of 15a and 15b was deduced from their nmr spectra. The 2ax-proton of 15a appears as a triplet (J=11 Hz) coupled with 2eq- and 3-protons, while 2ax-proton of 15b appears as a doublet of doublets coupled with

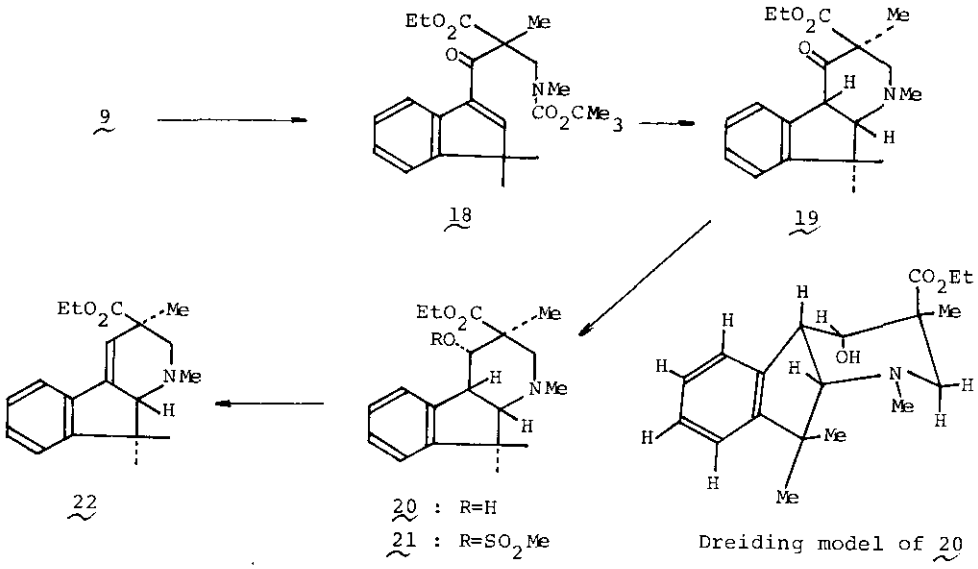
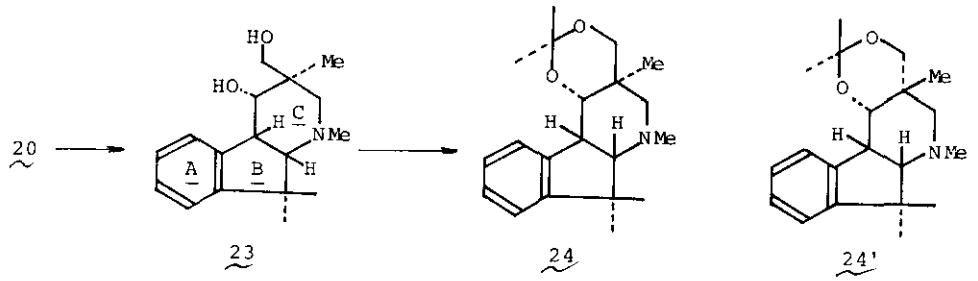
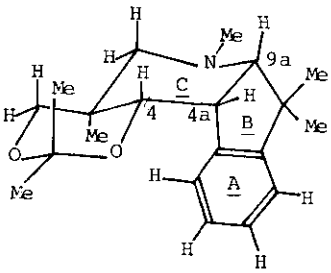


Chart 4





Dreiding model of 24

Chart 5

Table. ^{1}H-nmr Data for Unsaturaeted Esters

Compd.	2ax-H	2eq-H	3-H
15a (3β-CO_2Et)	2.63 t J=11 Hz	3.22 dd J=11 and 6 Hz	*
15b (3α-CO_2Et	2.78 dd J=12 and 4.5 Hz	3.25 dd J=12 and 2 Hz	3.76 m

* Signals for this proton are ambiguous due to the overlapping to other protons at δ 4.0-4.2

2eq-proton (J=12 Hz) and with 3-proton (J=4.5 Hz). Another proton signals, summarized in the Table, closely resembled with those of protons in the benzo[f]quinoline groups.[11] Therefore, it was concluded that the ethoxycarbonyl group of 15a is in a β-equatorial orientation, while that of 15b is an α-axial orientation. Contrary to the case of benzo[f]quinoline groups[11] which isomerized to an equilibrium mixture when standing neat at room temperature for 2 days or in methanol for 5 h, the oily unsaturated esters (15a) and (15b) were found not to isomerize under the conditions as above due to the inductive effect of the phosphate functions. Next we investigated the stereochemistry of the alcohol 20 and its analogs. As Craig demonstrates,[4] the strong deschielding of the aromatic C-5 proton in the hexahydroindeno[2,1-b]pyridine system is caused whenever a substituent at C-4 is equatorial in an unstable B/C cis-fused form in which a C4a-C4b bond is axial with respect to the piperidine ring.[12] In the nmr spectrum of 20, the deshielded signal due to 5-proton was not observed. Further the 9a-proton and 4-proton of 20 appear as a doublet with a coupling constant of 9 Hz and 2 Hz, respectively, thus indicating an axial orientation of C-4 hydroxyl group with a B/C cis-ring junction. Lithium aluminum hydride reduction of 20 afforded the diol (23), which reacted with 2,2-dimethoxypropane[13] to afford a cyclic 1,3-dioxane derivative (24). The nmr spectrum of 24 showed one aromatic proton signal at δ7.70 clearly deshielded from the other. This fact strongly suggests the proximity of 5-proton and C-4 oxygen function of 24 caused by ring-flipping to an unstable B/C cis-fused system. If an equatorial orientation of hydroxymethyl group be assigned, the structure 24' would be considered for the structure of a cyclic 1,3-dioxane derivative. However this is very unlikely since there is severe crowding between the methyl group on 1,3-dioxane ring and A-ring. On the basis of these results, the preferred structure of 24 was assigned as drawn in Chart 5. Therefore, a stable B/C cis-fused form was given to 20 as shown in Chart 4.

ACKNOWLEDGEMENT

We thank Dr. A. Numata and Miss M. Nabae for the measurements of nmr spectra. We also thank Miss S. Satoda for the technical assistance.

REFERENCES AND NOTES

1. T. Kurihara, K. Kawamura, and R. Yoneda, Chem. Pharm. Bull., submitted.
2. J.C. Craig and S.D. Hurt, J. Org. Chem., 1979, 44, 1108.
3. Z. Horii, T. Watanabe, T. Kurihara, and Y. Tamura, Chem. Pharm. Bull., 1965, 13, 420.
4. J.C. Craig, A. Dinner, and P.J. Mulligan, J. Org. Chem., 1974, 39, 1669.
5. Z. Horii, T. Kurihara, S. Yamamoto, and I. Ninomiya, Chem. Pharm. Bull., 1967, 15, 1641.
6. S. Harusawa, R. Yoneda, T. Kurihara, Y. Hamada, and T. Shioiri, Tetrahedron Lett., 1984, 25, 427.
7. C.F. Koelsch and C.D. LeClaire, J. Org. Chem., 1941, 6, 516.
8. M.W. Rathke and J. Deitch, Tetrahedron Lett., 1971, 2953.
9. R.E. Ireland, D.C. Muchmore, U. Hengartner, J. Am. Chem. Soc., 1972, 94, 5098 ; G. Majetich, P.A. Grieco, and M. Nishizawa, J. Org. Chem., 1977, 42, 2327.
10. P.Wolkoff, J. Org. Chem., 1982, 47, 1944.
11. T. Kiguchi, C. Hashimoto, T. Naito, and I. Ninomiya, Heterocycles, 1984, 22, 1719 ; I. Ninomiya, C. Hashimoto, T. Kiguchi, and T. Naito, J. Chem. Soc. Perkin I, 1984, 2911.
12. The projection used in this paper were depicted according to the reference 5.
13. K. Hayakawa, Y. Kamikawaji, A. Wakita, and K. Kanematsu, J. Org. Chem., 1984, 49, 1985.

Received, 17th December, 1984