## Communications to the Editor

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# A NEW SYNTHESIS OF EUPOLAURAMINE FROM A BENZ[f]INDOLE DERIVATIVE[1)]

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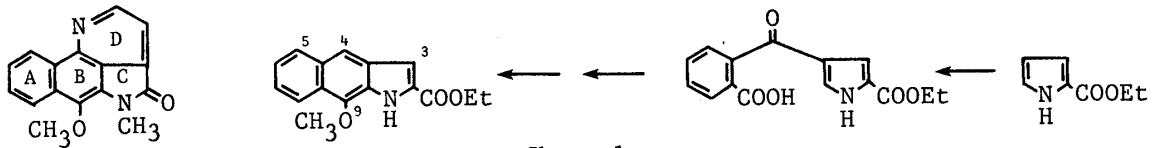
Eupolauramine (1), a structurally unique alkaloid having oxindole and pyridine nuclei, was synthesized from a benz[f]indole derivative easily prepared from a pyrrole derivative. The synthetic route involves one-pot construction of a pyridine ring *via* an enediamine moiety derived from the corresponding indole-2-carboxylic acid, and transformation of the enediamine to oxindole.

KEYWORDS——azaphenanthrene alkaloid; oxindole; pyridine; benz[f]-indole; enediamine; total synthesis; cyclization

Eupolauramine[2)] (1) is a structurally unique azaphenanthrene alkaloid, isolated from an Australian tree (*Eupomatia laurina*). This alkaloid (1) is regarded in one view as having benz[f]oxindole and pyridine nuclei. Recently we reported[4)] as a part of our studies of indole-2-carboxylic acid,[1,5)] the synthesis in a good total yield of the benz[f]indole (4) starting from ethyl pyrrole-2-carboxylate (2) *via* 4-acyl compound (3). As eupolauramine (1) contains the benz[f]indole (4) moiety (A-B-C rings and a methoxy group), we were interested in a convenient synthesis of 1 as an application of the above sequence. It was also expected that the presence of the 2-ethoxycarbonyl group could make the compound stable in the further elaboration, and give a clue for conversion to an oxindole nucleus. The two reported syntheses[6)] involved earlier construction of the A-B-D ring and later construction of the C ring. We report here a new synthesis of 1 on the basis of the above concept, being quite different from the reported ones.




1 4 3 2

Chart 1

Ethyl 1-methylpyrrole-2-carboxylate (5) was acylated with phthalic anhydride under Friedel-Crafts condition to give exclusively the corresponding 4-acylpyrrole derivative (6). Regioselective acylation at the $C_4$-position of ethyl pyrrole-2-carboxylate has been firmly established.[4,7)] Reduction of 6 with $Et_3SiH/CF_3COOH$, followed by cyclization and methylation gave the dimethyl compound (9a). Hydrolysis of the ester (9a) with KOH in EtOH, followed by nitration, gave the 4-nitro carboxylic acid (11), but not the 3-nitro acid. The nitration at the $C_4$-position

had been expected from the known fact that the Vilsmeier-Haack formylation of ethyl 1-benzyl-9-methoxybenz[f]indole-2-carboxylate (9b) took place[8] at the $C_4$-position. In the $^1$H-nuclear magnetic resonance ($^1$H-NMR) spectrum of 11, the $C_5$-H ($\delta$ 8.63) showed the most down-field shift of all of the aromatic protons in comparison with the $^1$H-NMR spectrum of 10. This supports the $C_4$-nitration. Successful nitration without destroying the skeleton may be attributed to the presence of the 2-carboxyl group.[5]

The reduction of the nitro group of 11 resulted in the formation of a complex mixture of products, probably because of the lability of the corresponding methoxy amine compound. Then the reduction of 11 in the presence of glyoxal was intended both to trap a resulting amino group and to construct a D-ring in a later step. Furthermore, the conversion of the $C_2$-carboxyl group to a carbamate group prior to the reduction was also intended for both activation of the $C_3$-position and later conversion of the $C_2$-substituent to an oxindole moiety. Thus, the carboxylic acid (11) was treated with diphenyl phosphorazidate (DPPA)/$Et_3N$ in tert-BuOH to yield the carbamate (12). The reduction of the nitro compound (12) with $H_2$/Pd-C in the presence of glyoxal gave two compounds, 13 and 14. The main product (13) had the formula, $C_{21}H_{21}N_3O_3$, as shown by elemental analysis and mass spectrum ($M^+$, 363). In the $^1$H-NMR spectrum of 13 the $C_3$-H disappeared and two aromatic protons appeared due to a newly born pyridine nucleus [$\delta$ 8.19 (1H, d, J=5.0 Hz) and 9.12 (1H, d, J=5.0 Hz)]. We thus concluded that 13 was an advantageously formed tetracyclic product. This compound (13) was probably formed as a result of the multistep reaction explained as follows. The reduction of the nitro compound (12) gave the amine (15), which was in turn condensed with glyoxal to give the Shiff base (16). Then the formyl group of 16 underwent intramolecular attack of the indolic $C_3$-position, whose reactivity was enhanced by the enediamine moiety of 16. The structure of the minor product (14) appeared to be the corresponding dihydro compound of 13 as shown by the mass spectrum ($M^+$, 365) corresponding to $C_{21}H_{23}N_3O_3$, and then determined by correlation of 14 with the cyclized product (13) by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). However, the position of the double bond was uncertain (or 14 might be a mixture of several regioisomers related to the double bond). Treatment of 13 with TsOH in AcOH removed the Boc group, followed by decarboxylation to give the imine (17). The hydrolysis of 17, which required rather drastic conditions, gave eupolauramine (1). The synthetic eupolauramine was found to be identical with the natural one. The synthetic sequence required 9 steps (7% of total yield from 5), which is comparable to the reported ones.[6]

The present total synthesis involved the interesting reaction of the enediamine moiety and its conversion to the oxindole nucleus as key steps. We are now investigating the synthetic utility of this sequence for various indole-2-carboxylic acids.

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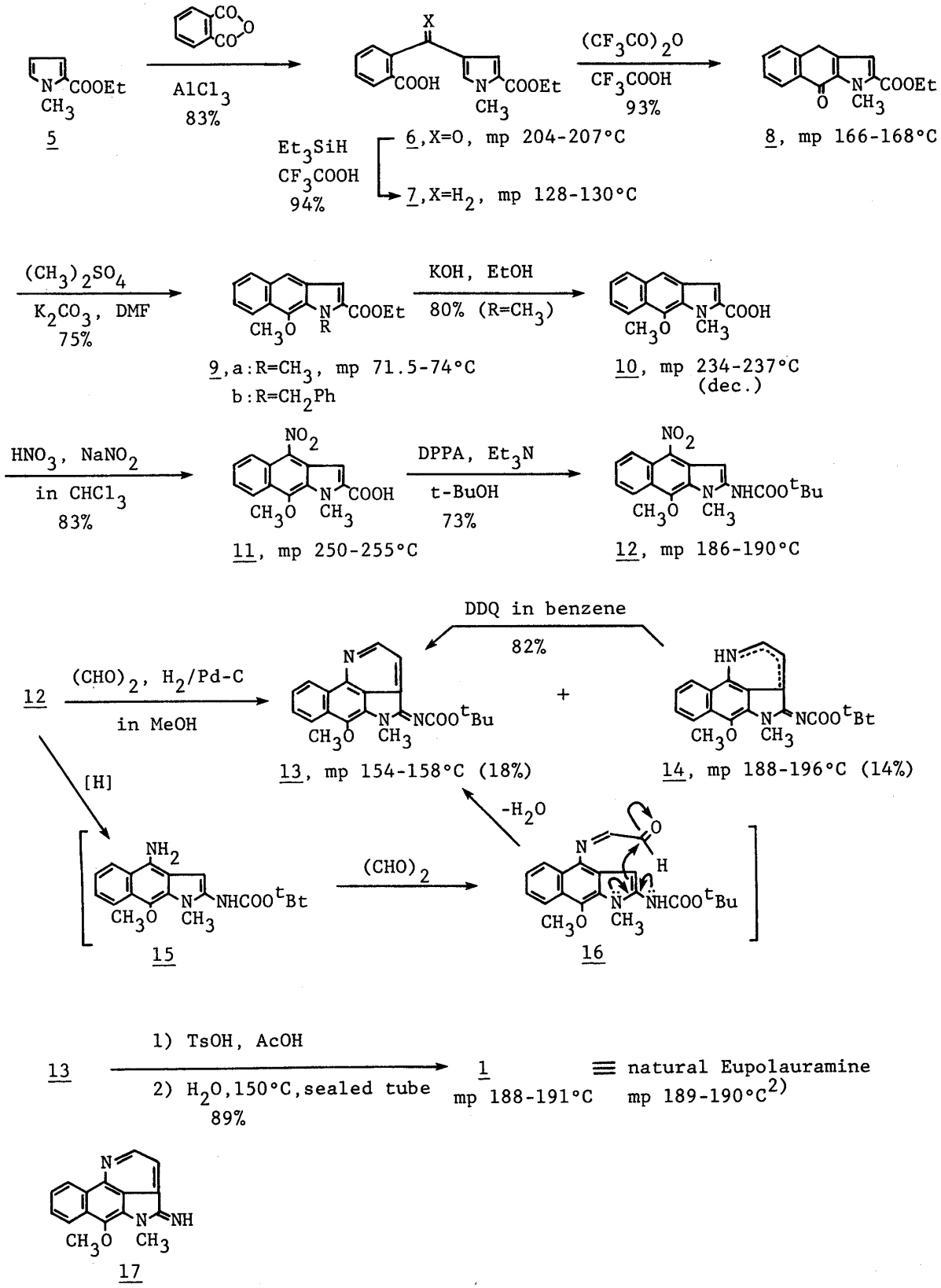


Chart 2

## REFERENCES AND NOTES

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