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ONE-STEP SYNTHESIS OF DIHYDROPYRIDOCARBAZOLE DERIVATIVES

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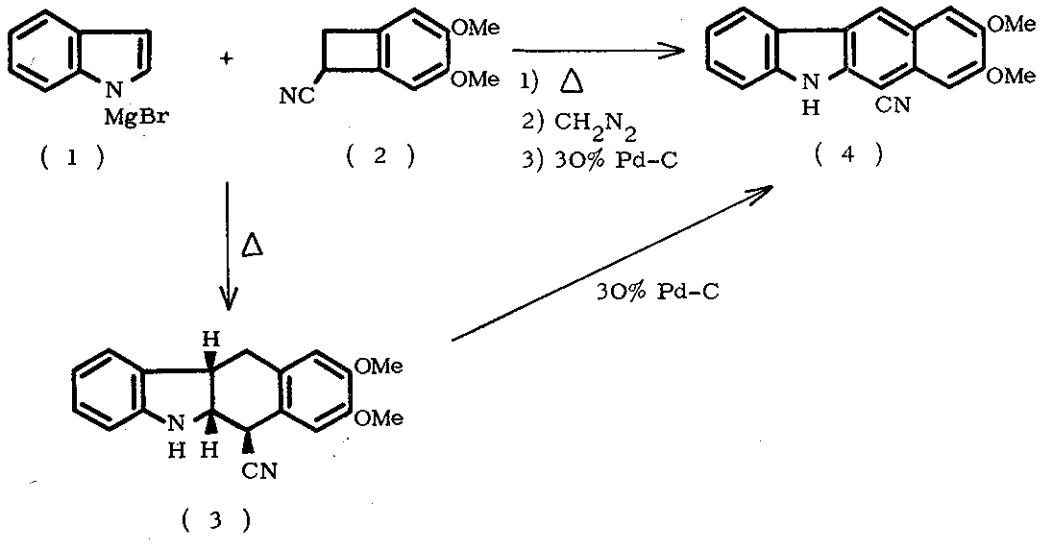
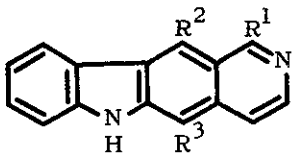
Heating indole and 4,5-dibromomethyl-3-hydroxy-2-methylpyridine hydrobromide (7) in the presence of sodium iodide, followed by acetylation, gave the dihydropyrido[3,4-b]carbazole derivative (9) along with four other coupling but not cyclized products (14), (15), (16), and a dimer. On the other hand, the same reaction without sodium iodide afforded the desired dihydropyrido[4,3-b]carbazole (8) and its structural isomer (9). The structures of 8 and 9 were determined by ultraviolet spectral investigations of the corresponding dehydrogenated products, 4-acetoxy-3-methyl-6H-pyrido[4,3-b]carbazole (12) and 4-acetoxy-3-methyl-10H-pyrido[3,4-b]carbazole (13).

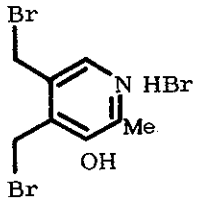
Recently we have investigated the synthesis of heterocyclic compounds from indolylmagnesium bromide (1) and 1-cyano-4,5-dimethoxybenzocyclobutene (2) and achieved the synthesis of 6-cyano-8,9-dimethoxy-5H-benzo[b]carbazole (4) via 6-cyano-5a,6,11,11a-tetrahydro-8,9-dimethoxy-5H-benzo[b]carbazole (3).[1] Since structure (4) is related to olivacine (5) and ellipticine (6), indole alkaloids having antitumor activity, we expected to get compounds closely related to these alkaloids when this type of reaction was applied to indole and 4,5-dibromomethyl-





(5) R^1=Me, R^2=H, R^3=Me

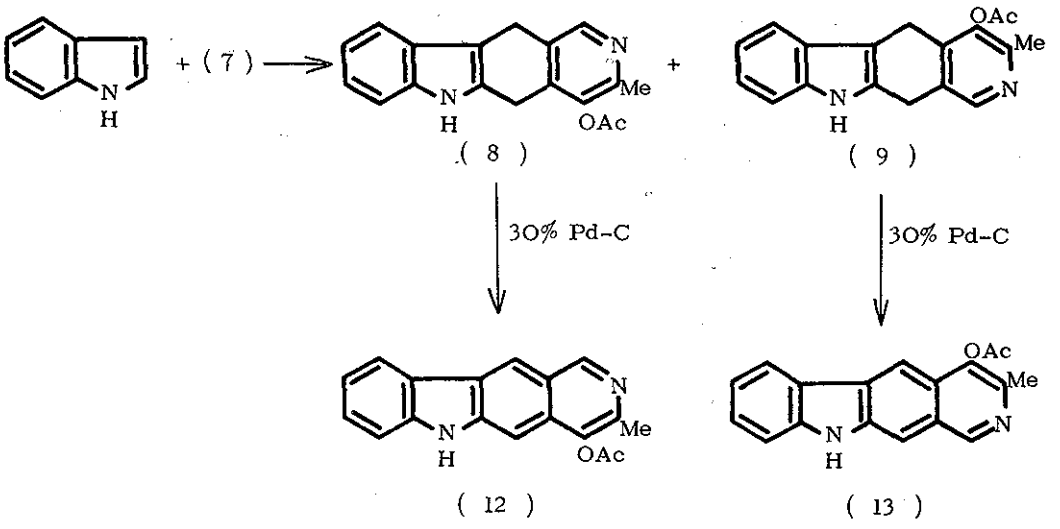
(6) R^1=H, R^2=Me, R^3=Me

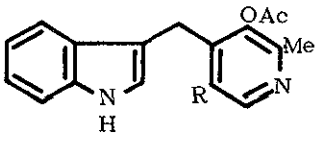


(7)

3-hydroxy-2-methylpyridine hydrobromide (7).[2]

We carried out the reaction of indole with dibromide (7), which was obtained from pyridoxine and hydrobromic acid. Here we wish to report a one-step synthesis of the dihydropyrido[4,3-b]carbazole ring system which is present in olivacine (5) and ellipticine (6).





(14) R=Me
(15) R=CH_2OAc
(16) R=CH_2OH

Heating indole with pyridoxyl dibromide (7) in dimethylformamide at 150 - 160° for 4 h, followed by acetylation of the reaction mixture without purification, gave the expected dihydropyridocarbazole derivative (8) in 4 % yield, mp 238 - 240° [$\nu_{max}^{CHCl_3}$ 3470 (NH) and 1755 cm^{-1} (C=O); m/e 292 (M^+) δ ($CDCl_3$ + DMSO - d_6) 2.39 (6H, s, CH_3 and $OCOCH_3$), 3.88 (2H, m, Ar-CH_2-Ar'), 4.05 (2H, m, Ar-CH_2-Ar'), 6.95 - 7.60 (4H, m, aromatic protons), 8.37 (1H, s, C_1-H), 9.90 - 10.10 (1H, broad s, NH, exchange with D_2O)] and its structural isomer (9) in 15 % yield, mp 245 - 247° [$\nu_{max}^{CHCl_3}$ 3470 (NH) and 1755 cm^{-1} (CO); m/e 292 (M^+); δ($CDCl_3$ + DMSO - d_6), 2.36 (3H, s, $OCOCH_3$), 2.43 (3H, s, CH_3), 3.80 (2H, m, Ar-CH_2-Ar'), 4.10 (2H, m, Ar-CH_2-Ar'), 6.90 - 7.60

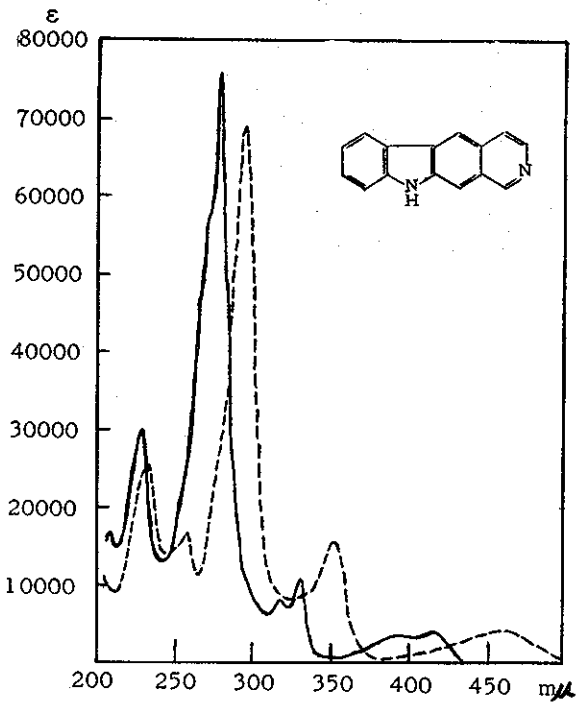


Fig. 1 6H-Pyrido[3,4-b]carbazole

—— UV spectrum in MeOH

---- UV spectrum in MeOH + conc.HCl (1 drop)

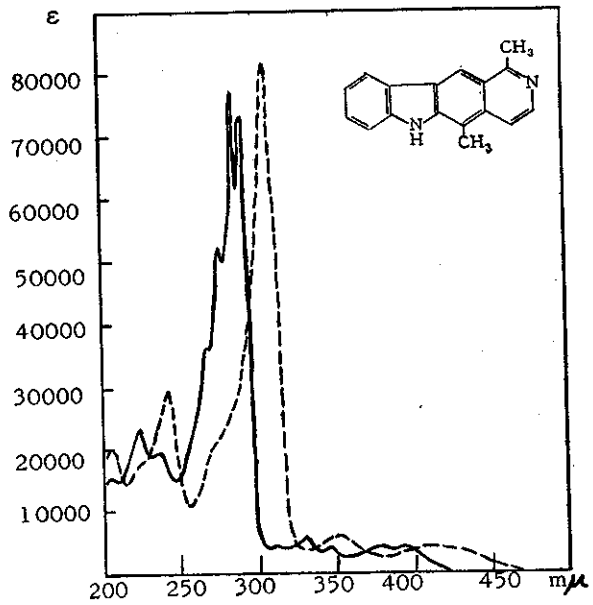


Fig. 2 Olivacine

—— UV spectrum in MeOH

---- UV spectrum in MeOH + conc.HCl (1 drop)

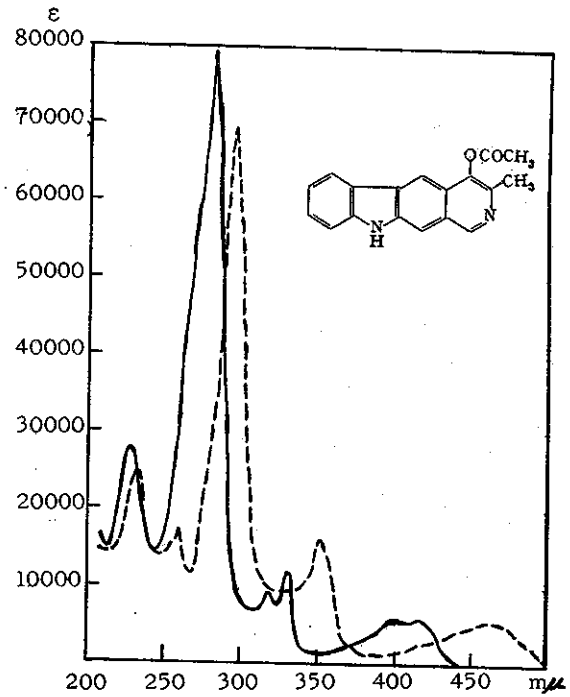


Fig. 3 4-Acetoxy-3-methyl-10H-pyrido[3,4-b]carbazole (13)

—— UV spectrum in MeOH

---- UV spectrum in MeOH + conc.HCl (1 drop)

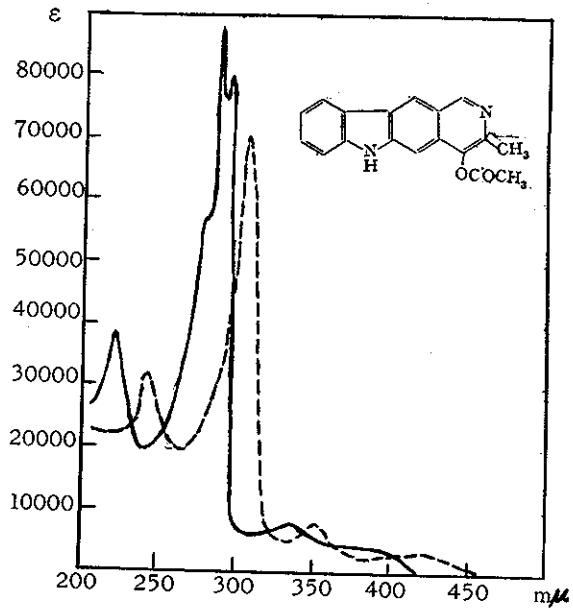


Fig. 4 4-Acetoxy-3-methyl-6H-pyrido-[4,3-b]carbazole (12)

—— UV spectrum in MeOH

---- UV spectrum in MeOH + conc.HCl (1 drop)

(4H, m, aromatic protons), 8.28 (1H, s, C_1-H)]. However, the two structural isomers (8) and (9) could not be distinguished from these spectral data.

It has been reported that the olivacine-type compound could be easily distinguished from its structural isomer by a comparison of ultraviolet spectral data as shown in figures 1 and 2.[3,4]

Therefore, both of the dihydropyridocarbazoles (8) and (9) were converted to the pyridocarbazole derivatives (12) and (13) respectively by dehydrogenation on 30 % Pd-C in refluxing xylene for 12 h, and the ultraviolet spectra were measured. As a result, the following figures 3 and 4 were obtained.

These facts suggest that the former compound (8) is an olivacine-type compound, whereas the latter compound (9) is its structural isomer.

On the other hand, this reaction in the presence of sodium iodide afforded a trace amount of dihydropyridocarbazole (9) together with four other coupling products, which were separated by chromatography on silica gel. Three of the compounds were tentatively assigned as structures (14), (15) and (16) on the basis of spectral data. Furthermore, compound (16) was easily converted to (15) by acetylation. The fourth product was found to be a dimer by mass spectral analysis [*m/e* 586 (M^+)]. There are so many possibilities of coupling directions that we could not assign the structure of the dimer from the spectral data.

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