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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—DLXIX[1]

ONE-STEP SYNTHESIS OF DIHYDROPYRIDOCARBAZOLE DERIVATIVES

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Abstract—Heating indole and 4,5-dibromomethyl-3-hydroxy-2-methylpyridine hydrobromide (**10**), followed by acetylation, gave the desired dihydropyrido[4.3-b]carbazole (**12**) and its structural isomer, dihydropyrido[3.4-b]carbazole (**13**). The structures of (**12** and **13**) were determined by UV spectral investigations of the corresponding dehydrogenated products, 4-acetoxy-3-methyl-6H-pyrido[4.3-b]carbazole (**11**) and 4-acetoxy-3-methyl-10H-pyrido[3.4-b]carbazole (**14**).

On the other hand, the same reaction in the presence of sodium iodide afforded **12** together with four other coupling products which were not cyclized, such as (**16**, **17**, **18**), and a dimer.

Since the first synthesis of the benzocyclobutene derivative by Finkelstein[2] was achieved by the reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene with sodium iodide, Cava[3] and Arnold[4] described a benzocyclobutene derivative to undergo many interesting reactions. Oppolzer *et al.*[5] applied this reaction to the total synthesis of (±)-chelidonine (**3**), one of the isoquinoline alkaloids, from the benzocyclobutene derivative (**1**) *via* the *o*-quinodimethane (**2**).

As an extension of this reaction, we have recently investigated the synthesis of heterocyclic compounds by use of indolylmagnesium bromide (**4**) and 1-cyano-4,5-dimethoxybenzocyclobutene (**5**) and achieved the synthesis of 6-cyano-8,9-dimethoxy-5H-benzo[b]carbazole (**7**) *via* 6-cyano-5a,6,11,11a-tetrahydro-8,9-dimethoxy-5H-benzo-[b]carbazole (**6**).[6] Since the structure (**7**) is related to olivacine (**8**) and ellipticine (**9**), 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-3-hydroxy-2 methylpyridine hydrobromide (**10**).[7]

Therefore, we carried out the reaction of indole with dibromide (**10**), which was obtained from pyridoxine and hydrobromic acid, and here wish to report a one-step synthesis of the dihydropyrido[4.3-b]carbazole ring system which is present in olivacine (**8**) and ellipticine (**9**).

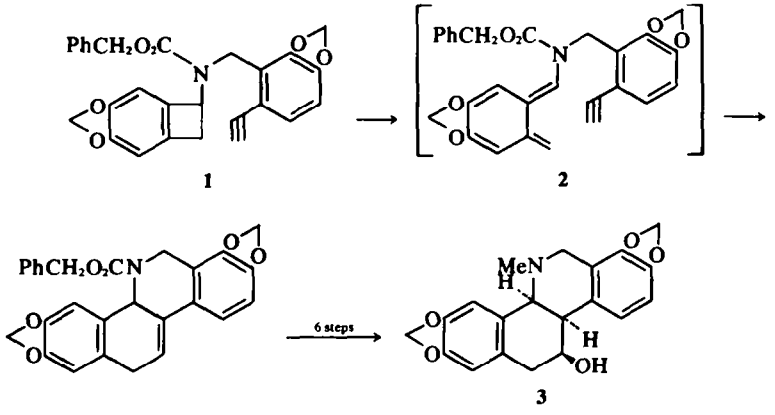
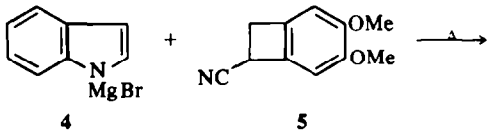


CHART 1

Heating indole with pyridoxyl dibromide (**10**) in dimethylformamide for 4 hr, followed by acetylation without purification, gave the expected dihydropyridocarbazole derivative (**12**) in 4% yield, and its structural isomer (**13**) in 15% yield.

It has been reported that the olivacine-type compound could be easily distinguished from its structural isomer by a comparison of UV spectral



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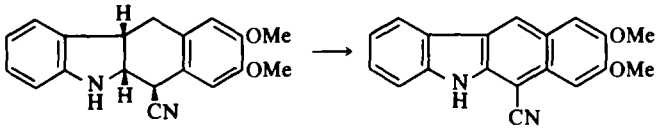

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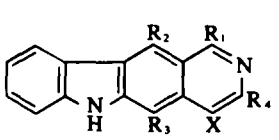
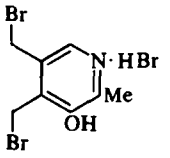


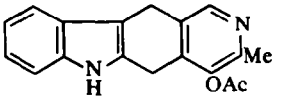
8: $R_1 = R_3 = Me$, $R_2 = R_4 = X = H$
9: $R_1 = R_4 = X = H$, $R_2 = R_3 = Me$
11: $R_1 = R_2 = R_3 = H$, $R_4 = Me$, $X = OAc$



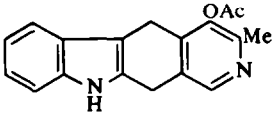
10

CHART 2

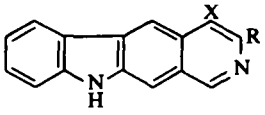
data.[8,9] Therefore, both dihydropyridocarbazoles (**12** and **13**) were converted to the pyridocarbazole derivatives (**11** and **14**), respectively, by dehydrogenation on 30% Pd-C, and the UV spectrum of (**11**) is similar to olivacine (**8**) and that of **14** is similar to 6H-pyrido[3.4-b]carbazole (**15**).[8-10] These facts suggest that the former compound (**12**) is an olivacine-type compound, whereas the latter compound (**13**) is its structural isomer.



12



13



14: R = Me, X = OAc
15: R = X = H

CHART 3

Regarding the mechanism for the formation of the dihydropyridocarbazoles, one should consider which Br atom would be preferentially removed. From the NMR data of α,β and γ-picolines [$\delta(CDCl_3)$ 2·54, 2·33 and 2·32, respectively], it was found that the electron densities of the methyl carbons at β and γ-positions are almost the same. But in case of pyridoxyl dibromide (**10**), the Br atom at the C_4-methylene position should be removed more easily than the Br atom at the C_5-Me position due to the OH group at the C_3-position. From this reasoning the reaction mechanism for the formation of **13** is considered to proceed through the route (a) as shown in Chart 4. This mechanism is also supported by the formation ratio (1:4) of compound **12** to compound **13**. The mechanism along with the route (b) would lead to the formation of the minor product (**12**).

On the other hand, this reaction in the presence of sodium iodide afforded a trace amount of dihydropyridocarbazole derivative (**12**) together with four other coupling products, which could be separated by chromatography on silica gel. Three of these were tentatively assigned structures **16**, **17** and **18** on the basis of spectral data. Furthermore, the **18** was easily converted to **17** by acetylation, but the coupling direction was uncertain. The fourth product was found to be a dimer by mass spectral analysis [m/e 596 (M^+)]. There are so many possibilities for the coupling direction that we could not assign the structure of the dimer from the spectral data.

Furthermore, the differences of π-electrons energy between **19** and **20** were calculated by semi-empirical SCF-MO method,[11,12] supposing both of transition states as **19** and **20**. As a result it was found that the transition-state **19** is more stable than **20** by 1·9 eV.

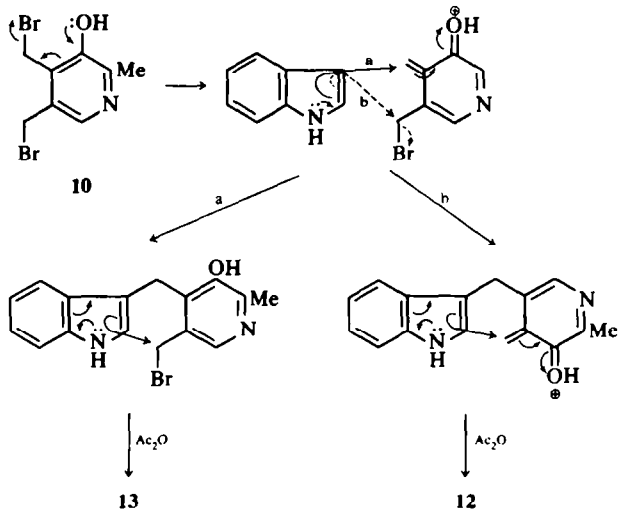
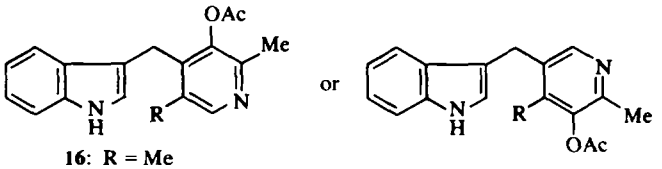


CHART 4



16: R = Me
17: R = CH_2OAc
18: R = CH_2OH

CHART 5

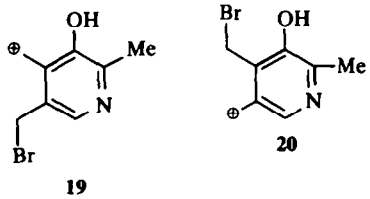


CHART 6

EXPERIMENTAL

M.p.s are uncorrected and were determined on Yanagimoto microapparatus (MP-S2). IR spectra were measured with a Hitachi EPI-3 spectrophotometer, NMR spectra with Hitachi H-60 and JEOL JNM-PS-100 spectrophotometers using TMS as an internal standard, and mass spectra were taken with a Hitachi RMU-7 spectrometer.

4-Acetoxy-3-methyl-10H-dihydropyrido[3.4-b]carbazole (**13**) *and 4-acetoxy-3-methyl-6H-dihydropyrido[4.3-b]carbazole* (**12**). A mixture of indole (0·96 g) and **10** (3·03 g) in 50 ml N,N-dimethylformamide was refluxed for 4 hr. After cooling, 3 ml Ac_2O and 5 drops pyridine were added and the mixture was set aside overnight at room temp. After the excess Ac_2O had been decomposed with sat $NaHCO_3$ aq, the resulting mixture was diluted with 500 ml water and then extracted with $CHCl_3$. The extract was washed with sat NaCl aq and dried over K_2CO_3. The solvent was distilled off under reduced pressure to afford a viscous syrup, which was chromatographed on 40 g silica gel. Elution with $CHCl_3$–MeOH (v/v 99 : 1) afforded a solid, which recrystallised from EtOH to give 87 mg of (**12**) as colourless needles; m.p. 238–240°; IR ($CHCl_3$) 3470 (NH) and 1755 cm^{-1} (CO); NMR 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, Ar–H), 8·37 (1H, s, the proton of α-position on pyridine ring), and 9·90–10·10 (1H, broad s, NH, exchanged with D_2O); mass (*m/e*) 292 (M^+). (Found: C, 74·14; H, 5·47; N, 9·86. Calc. for $C_{18}H_{16}N_2O_2$: C, 73·95; H, 5·52; N, 9·58%).

Elution with $CHCl_3$–MeOH (v/v 98:2) also afforded a solid (**13**), which was recrystallised from EtOH to give 350 mg of (**13**) as pale yellow needles; m.p. 245–247°; IR ($CHCl_3$) 3470 (NH) and 1755 cm^{-1} (CO); NMR 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 (4H, m, Ar–H), and 8·28 (1H, s, the proton of α-position on pyridine ring); mass (*m/e*) 292 (M^+). (Found: C, 73·92; H, 5·50; N, 9·44. Calc. for $C_{18}H_{16}N_2O_2$: C, 73·95; H, 5·52; N, 9·58%).

4-Acetoxy-3-methyl-6H-pyrido[4.3-b]carbazole (**11**). A mixture of **12** (30 mg) and 30% Pd–C (35 mg) was refluxed in xylene for 12 hr. After removal of the catalyst by filtration, the solvent was distilled *in vacuo* to leave a residue, which was chromatographed on 2 g of silica gel to give 15 mg of **11**. Recrystallisation from MeOH afforded

yellow needles; m.p. 271–272° (dec.); IR ($CHCl_3$) 3470 (NH), 1750 (CO), and 1600 cm^{-1} (C=C); UV (MeOH) 223 (ε 39170), 277 (57070), 286 (87690), 291 (79540), and 330 (7850) nm; UV (MeOH–conc HCl) 241 ((ε .32910), 306 (70590), and 351 (8350) nm; NMR δ ($CDCl_3$ + DMSO-d_6) 2·51 (3*H*, *s*, CH_3 *or* $OCOCH_3$), 2·53 (3*H*, *s*, CH_3 *or* $OCOCH_3$), 7·00–8·20 (4*H*, *m*, Ar–H), 8·59 (1H, s, C_5–H), 7·53 (1H, s, C_{11}–H), 9·15 (1H, s, C_1–H), and 10·40–10·60 (1H, broad s, NH, exchanged with D_2O); mass (*m/e*) 290 (M^+). (Found: C, 74·71; H, 4·85; N, 9·51. Calc. for $C_{18}H_{14}N_2O_2$: C, 74·47; H, 4·86; N, 9·65%).

4 - *Acetoxy* - 3 - *methyl* - 10H - *pyrido*[3.4-b]*carbazole* (**14**). A mixture of **13** (52 mg) and 30% Pd–C (55 mg) was heated in refluxing xylene for 12 hr. After filtration of the catalyst, the solvent was removed under reduced pressure to afford a residue, which was subjected to chromatography on 2 g of silica gel by elution with $CHCl_3$ to give a solid. Recrystallisation from MeOH gave **14** (25 mg) as yellow needles; m.p. 284–285° (dec); IR ($CHCl_3$) 3470 (NH), 1755 (CO), and 1600 cm^{-1} (C=C); UV (MeOH) 229 (ε 27750), 273 (59660), 280 (79940), 319 (9500), and 332 (11950) nm; UV (MeOH–conc HCl) 231 (ε 24550), 258 (18040), 293 (69380), and 352 (16010) nm; NMR δ ($CDCl_3$ + DMSO-d_6) 2·54 (3H, s, CH_3 or $OCOCH_3$), 2·56 (3H, s, CH_3 or $OCOCH_3$), 7·00–8·30 (4H, m, Ar–H), 8·33 (1H, s, C_{11}–H), 7·90 (1H, s, C_5–H), 9·15 (1H, s, C_1–H), and 10·50–10·70 (1H, broad s, exchanged with D_2O); mass (*m/e*) 290 (M^+). (Found: C, 74·25; H, 4·80; N, 9·56. Calc. for $C_{18}H_{14}N_2O_2$: C, 74·47; H, 4·86; N, 9·65%).

The reaction of indole with pyridoxyl dibromide (**10**) *in the presence of sodium iodide.* A mixture of indole (632 mg), **10** (2·02 g) and NaI (2·5 g) in 50 ml of N,N-dimethylformamide was heated for 4 hr at 95–100°. After cooling to room temp. 2 ml Ac_2O and 5 drops pyridine were added and the mixture was kept at room temp for 12 hr. After excess of Ac_2O had been decomposed with sat $NaHCO_3$ aq, the resulting mixture was diluted with 500 ml water and then extracted with $CHCl_3$. The extract was washed with sat NaCl aq and dried over K_2CO_3. The solvent was distilled off *in vacuo* to leave a residue, which was subjected to chromatography on 40 g of silica gel.

The first elution with $CHCl_3$–MeOH (v/v 99:1) afforded 5 mg of a solid, whose spectral data were superimposable with those of **12**.

The second elution with $CHCl_3$–MeOH (v/v 99:1) gave 50 mg of **16** as a syrup; IR ($CHCl_3$) 3480 (NH) and 1758 cm^{-1} (CO); NMR δ ($CDCl_3$) 2·07 (3H, s, $OCOCH_3$), 2·33 (3H, s, CH_3), 2·37 (3H, s, CH_3), 4·07 (2H, s, Ar–CH_2–Ar'), 6·60 (1H, s, the proton of α-position in indole ring) 8·20 (1H, s, the proton of α-position in pyridine ring), and 8·00–8·20 (1H, broad s, NH, exchanged with D_2O); mass (*m/e*) 294 (M^+).

The third elution with $CHCl_3$–MeOH (v/v 99:1) afforded 65 mg of **17** as a syrup; IR ($CHCl_3$) 3480 (NH), 1760 (CO) and 1735 cm^{-1} (CO); mass (*m/e*) 352 (M^+).

The fourth elution with $CHCl_3$–MeOH (v/v 99:1) gave 360 mg of the dimer as a syrup; IR ($CHCl_3$) 3480 (NH) and 1760 cm^{-1} (CO); mass (*m/e*) 586 (M^+).

The fifth elution with $CHCl_3$–MeOH (v/v 98:2) afforded 90 mg of **18** as a syrup which was easily converted to **17** as described later; IR ($CHCl_3$) 3480 (NH) and 1760 cm^{-1} (CO); NMR δ ($CDCl_3$) 2·20 (3H, s, $OCOCH_3$), 2·40 (3H, s, CH_3), 2·70–3·00 (1H, broad s, OH, exchanged with D_2O), 4·07 (2H, s, Ar–CH_2–Ar'), 4·60 (2H, s, Ar–CH_2–OH), 6·50 (1H, s, the proton of α-position in indole ring) 8·20–8·50 (1H, broad s, NH, exchanged with D_2O) and 8·30 (1H, s, the proton of α-position in pyridine ring); mass (*m/e*) 310 (M^-).

The conversion of **18** *to* **17**. A mixture of 20 mg of **18**, 2 drops of Ac_2O and 1 drop of pyridine was set aside at room temp for 12 hr. After decomposition of excess Ac_2O with 10% NH_4OH aq, the mixture was extracted with $CHCl_3$. The extract was washed with sat NaCl aq, dried over K_2CO_3, and evaporated to leave a residue, which was separated by preparative TLC on silica gel. Thus 18 mg of a syrup with IR and NMR spectral data superimposable with those of **17**, was obtained.

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REFERENCES

[1]T. Kametani, F. Satoh, K. Fukumoto, H. Sugi and K. Kigasawa, Part DLXVIII, *Chem. Pharm. Bull.* **22**, 1835 (1974)
[2]H. Finkelstein, *Ber. Dtsch. Chem. Ges.* **43**, 1528 (1910)
[3]M. P. Cava and D. P. Napier, *J. Am. Chem. Soc.* **78**, 500 (1956)
[4]B. J. Arnold and P. G. Sammes, *Chem. Comm.* 1034 (1972)
[5]W. Oppolzer, *J. Am. Chem. Soc.* **93**, 3833, 3834 (1971); W. Oppolzer and K. Keller, *Ibid.*, **93**, 3836 (1971)
[6]T. Kametani, T. Suzuki, T. Takahashi, and K. Fukumoto, *Heterocycles* **2**, 9 (1974)
[7]S. A. Harris and K. Fokers, *J. Am. Chem. Soc.* **61**, 1245 (1939)
[8]J. Schmutz and F. Hunziker, *Pharm. Acta Helv.* **33**, 341 (1958)
[9]G. V. Marini-Bettolo und J. Schmutz, *Helv. Chim. Acta* **42**, 2136 (1959)
[10]T. Kametani, Y. Ichikawa, T. Suzuki, and K. Fukumoto, *Heterocycles* **2**, 171 (1974)
[11]J. A. Pople, *Trans. Faraday Soc.* **49**, 1375 (1953)
[12]R. Pariser and R. G. Parr, *J. Chem. Phys.* **21**, 767 (1953)