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

A SYNTHESIS OF BENZOCARBAZOLE DERIVATIVES BY THERMOLYSIS[2]

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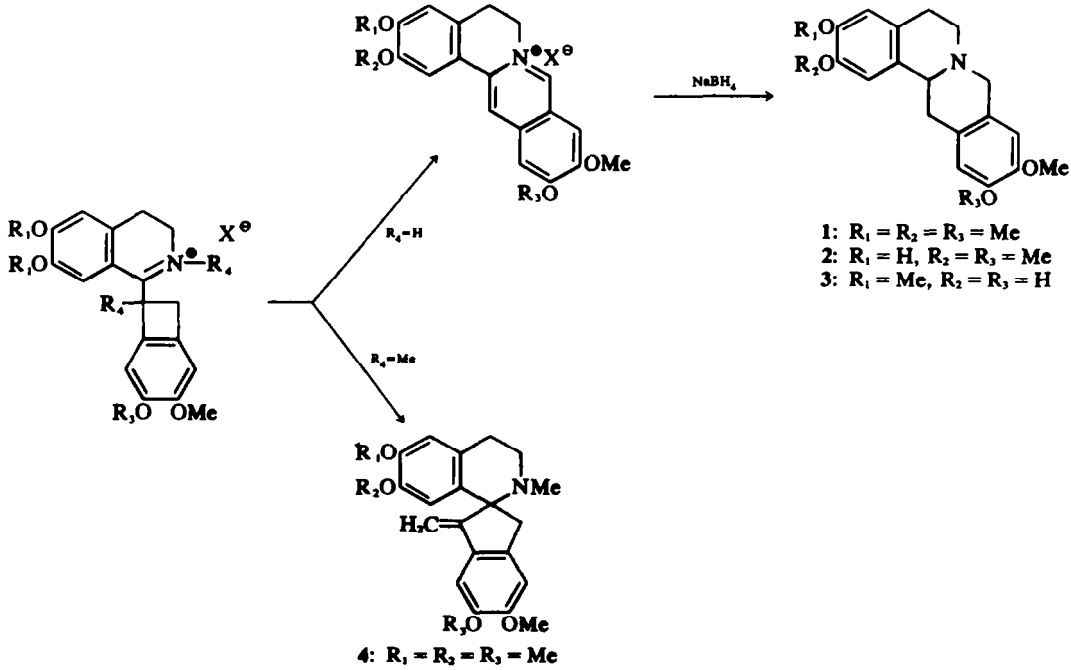
Abstract—A thermal reaction of indolylmagnesium bromide (5) with 1-cyano-4,5-dimethoxybenzocyclobutene (6) gave a mixture of 6-cyano-5a, 6,11,11a-tetrahydro-8,9-dimethoxy-5H-benzo [b] carbazole (8a) and 6-cyano-5a, 6, 11, 11a-tetrahydro-9-hydroxy-8-methoxy-5H-benzo[b] carbazole (10). Compound 8a was easily converted to 6-cyano-8, 9-dimethoxy-5H-benzo [b] carbazole (12) by dehydrogenation on 30% Pd–C.

The benzocyclobutene has a long history in organic and in physical organic chemistry. The first reported synthesis of the benzocyclobutene ring system was that of Finkelstein.[3]

Since a benzocyclobutene derivative has been shown to undergo many interesting reactions,[4-6] we have achieved the synthesis of the protoberberine-type alkaloids [xylopinine (1),[7] discretine (2),[8] and coreximine (3)[9]] and a ochotensine-type compound (4).[10] As an extension of this method, we now wish to report an intermolecular cycloaddition of indolylmagnesium bromide (5) with 1-cyano-4, 5-dimethoxybenzocyclobutene (6).

If the indole reacts with 6 by the pathway shown in Chart 2, the formation of a cycloaddition product is supposed.

Therefore, at first, a reaction of indole with 6 was tried, but only 5, 6-dicyano-2, 3, 8, 9-tetramethoxydibenzo [a,e] cyclooctene (7)[11] was obtained; subsequently indolylmagnesium bromide



1: $R_1 = R_2 = R_3 = Me$
2: $R_1 = H$, $R_2 = R_3 = Me$
3: $R_1 = Me$, $R_2 = R_3 = H$

4: $R_1 = R_2 = R_3 = Me$

CHART 1.

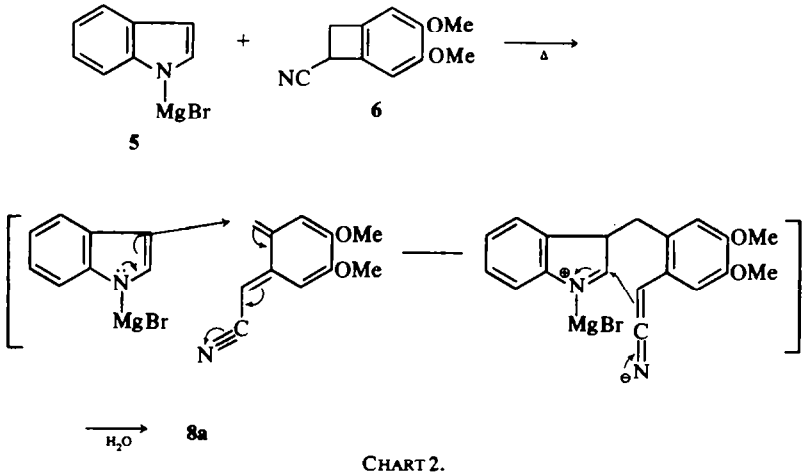


CHART 2.

(5) instead of indole was used to enhance the nucleophilicity of indole.

A fusion of 5 and 6 in dichlorobenzene at 160° for 10 min gave a mixture of 6-cyano-5a-, 6, 11, 11a-tetrahydro - 8, 9 - dimethoxy - 5H - benzo[b] - carbazole (**8a**), m.p. 169–170° [ν_{max} ($CHCl_3$) 3430 (NH) and 2250 cm^{-1} (CN)] as a major product in 83% yield and 6 - cyano - 5a, 6, 11, 11a - tetrahydro - 9 - hydroxy - 8 - methoxy - 5H - benzo [b] - carbazole (**10**) [ν_{max} ($CHCl_3$) 3550 (OH) and 2250 cm^{-1} (CN)] in 5% yield, both of which were easily separated by chromatography on silica gel. The latter compound (**10**) was converted to **8a** on treatment with diazomethane. On the other hand, the former mixture, without purification, was treated with excess of diazomethane, followed by dehydrogenation on 30% Pd–C, to afford 6 - cyano - 8, 9 - dimethoxy - 5H - benzo [b] carbazole (**12**), m.p. 290° [ν_{max} ($CHCl_3$) 3460 (NH) and 2210 cm^{-1} (CN)] in 60% yield.

The structure of **8a** was confirmed by mass and NMR spectroscopy [*m/e* 306 (M^+); δ($CDCl_3$) 2·96 (2H, d, *J* 5·4 Hz, C_{11}–H_2), 3·80 (3H, s, OCH_3), 3·88 (3H, s, OCH_3), 4·08 (1H, t, d, *J* 5·4 Hz, and 4·6 Hz, C_{11a}–H), 4·74 (1H, d, d, *J* 10·8 and 4·6 Hz, C_{5a}–H), 6·59 (1H, s, C_{10}–H). The proton at C_6-position was obscured by two OMe resonances.

The above structure was also characterized not only by the spectral data of acetylation product (**9**) [ν_{max} ($CHCl_3$) 2230 (CN) and 1642 cm^{-1} (C=O); δ ($CDCl_3$) 2·52 (3H, s, $COCH_3$), 6·84 (1H, s, C_{10}–H)] but also by conversion to the **12** obtained by direct dehydrogenation of **8a**.

The structure **10** was also confirmed by the spectral data of acetylation product **11** [ν_{max} ($CHCl_3$) 2250 (CN), 1760 and 1650 cm^{-1} (C=O); *m/e* 376 (M^+); δ ($CDCl_3$) 2·32 and 2·54 (each 3H, s, $COCH_3$), 6·95 and 7·0 (each 1H, s, C_7–H or C_{10}–H). The position of the OH group of **10** was determined by the fact that the chemical shift of C_{10}-proton in **11** resonances further downfield than those of **8a** and **9**. In general, the cleavage of ether bond by Grignard reagent[12] is well known.

The other possible structure (**8b**) was ruled out not only by the fact that the methylene protons did not couple with the benzylic methine proton but coupled instead with the lowest methine proton assigned to C_{5a}–H. Furthermore the reaction mechanism as shown in Chart 2 favors structure **8a** over **8b**. The configuration of **8a** was also determined to be *cis* by the coupling constants described above.

It is supposed that this reaction would proceed *via* a two step cycloaddition for the following reasons; these types of reactions are always more effective with localized systems and regioselective.[7,10,11]

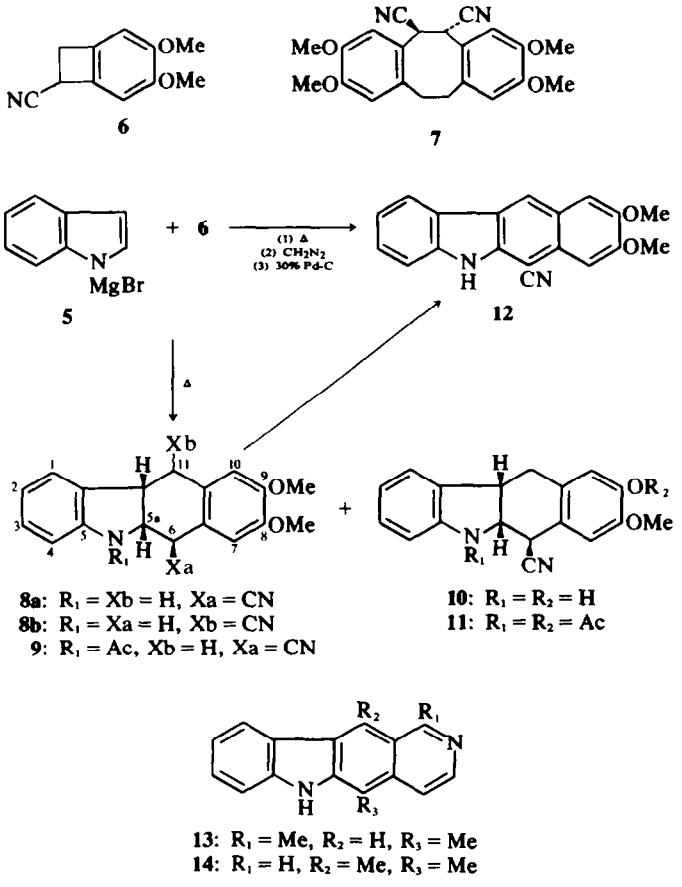
Since the structure **12** is closely related to olivacine (**13**) and ellipticine (**14**), the indole alkaloids having an antitumor activity,[13] the synthesis of these types of alkaloids by this method is under investigation.

EXPERIMENTAL

M.ps are uncorrected and were determined on a 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.

5, 6, - *Dicyano* - 2, 3, 8, 9 - *tetramethoxydibenzo* [a, e] *cyclobutene* (**7**). A mixture of indole (120 mg) and **6** (200 mg) was refluxed in dichlorobenzene for 4 h. Evaporation of the solvent gave a residue, which was chromatographed on 10 g of silica gel to afford a solid, which was recrystallised from MeOH to give 166 mg of **7** as colourless prisms, m.p. 103–105° (lit.[11] m.p. 100–102·5°).

6 - *Cyano* - 5*a*, 6, 11, 11*a* - *tetrahydro* - 8, 9 - *dimethoxy* - 5H - *benzo* [b] *carbazole* (**8a**), 6 - *cyano* - 5a, 6, 11, 11a - *tetrahydro* - 9 - *hydroxy* - 8 - *methoxy* - 5H - *benzo*[b] - *carbazole* (**10**), *and* 6 - *cyano* - 8, 9 - *dimethoxy* - 5*H* - *benzo* [b] *carbazole* (**12**) gasic (a) A soln of indole (330 mg) in 30 ml THF was added to a soln of EtMgBr (prepared by



8a: R_1 = Xb = H, Xa = CN
8b: R_1 = Xa = H, Xb = CN
9: R_1 = Ac, Xb = H, Xa = CN

10: $R_1 = R_2$ = H
11: $R_1 = R_2$ = Ac

13: R_1 = Me, R_2 = H, R_3 = Me
14: R_1 = H, R_2 = Me, R_3 = Me

CHART 3.

the reaction of EtBr (330 mg) with Mg turning (70 mg) at − 10° for 10 min]. The mixture was stirred at room temp for 30 min, and then 50 ml methylene dichloride was added in order to bring the complex into solution. After evaporation of the solvent in a current of N_2, a soln of 260 mg of **6** in 20 ml distilled dichlorobenzene was added to the resultant residue. After heating at 160° for 10 min under N_2, 30 ml of water was added to the mixture, which was extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave a residue, which was subjected to chromatography on 10 g of silica gel.

The first elution with benzene–$CHCl_3$ (v/v 4 : 1) afforded 350 mg of **8a** as brownish prisms from MeOH; m.p. 169–170°; IR ($CHCl_3$) 3430 (NH) and 2250 cm^{-1} (CN); NMR ($CDCl_3$) δ 2·96 (2H, d, *J* 5·4 Hz, C_{11}–H_2), 3·0–3·2 (1H, broad s, NH, exchanged with D_2O), 3·80 (3H, s, OCH_3), 3·88 (3H, s, OCH_3), 4·08 (1H, t, d, *J* 5·4 Hz and 4·6 Hz, C_{11a}–H), 4·74 (1H, d, d, *J* 10·8 and 4·6 Hz, C_{5a}–H), 6·59 (1H, s, C_{10}–H), 7·00 (1H, s, C_7–H), 6·38–7·12 (4H, m, aromatic protons). The proton at C_6-position was obscured by two OMe resonances; mass (*m/e*) 306 (M^+), 189 ($M^+ - C_8H_7N$), 146 (189 − Ac), and 117 (C_8H_7N). (Calc. for $C_{19}H_{18}N_2O_2$: C, 74·49; H, 5·92. Found: C, 74·07; H, 5·92%). It was also characterised as hydrochloride, m.p. 141–142° (Calc. for $C_{19}H_{18}N_2O_2$. HCl: C, 66·53; H, 5·58; N, 8·17. Found: C, 66·43; H, 5·60; N, 7·92%).

The second elution with $CHCl_3$ gave 20 mg of **10** as a brownish syrup; IR ($CHCl_3$) 3550 (OH) and 2250 cm^{-1} (CN), which was transformed to **8a** by treatment with diazomethane as described later.

(b) The mixture which was obtained by the same procedure as described above, without purification, was treated with an excess diazomethane, followed by dehydrogenation on 500 mg of 30% Pd–C in refluxing xylene for 2 h. After filtration of the catalyst, the solvent was distilled off under reduced pressure to leave a residue, which was chromatographed on 10 g of silica gel by elution with benzene to afford 154 mg of **12** as yellow prisms after recrystallisation from $CHCl_3$–MeOH; m.p. 290°; IR ($CHCl_3$) 3460 (NH) and 2210 cm^{-1} (CN); NMR δ ($CDCl_3$ + DMSO–d_6) 4·02 (3H, s, OCH_3), 4·08 (3H, s, OCH_3), 7·20–8·80 (8H, including NH in indole ring and seven aromatic protons consisting of three sharp singlets and unresolved multiplet); mass (*m/e*) 302 (M^+). (Calc. for $C_{19}H_{14}N_2O_2$: C, 75·48; H, 4·67; N, 9·27. Found: C, 75·29; H, 4·91; N, 9·19%).

(c) A mixture of 35 mg of **8a** and 50 mg of 30% Pd–C was refluxed in xylene for 2 h. After filtration of catalyst, the solvent was distilled *in vacuo* to leave a residue, which was chromatographed on 3 g of silica gel to give 25 mg of **12**, identical with the above sample.

Conversion of **10** *to* **8a**. To a soln of **10** (5 mg) in MeOH was added an excess of a slution of diazomethane in ether, and then kept aside at room temp overnight. Evaporation of the solvent afforded a residue, which was chromatographed on silica gel to give 4 mg of **8a**, which

was identical with the authentic sample prepared by the above method.

Acetylation of **8a**. A mixture of 20 mg of **8a**, 0·5 ml of $(Ac)_2O$, and 2 drops of pyridine was allowed to stand overnight at room temp. The mixture was poured into an excess of water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to leave a residue, which was chromatographed on 3 g of silica gel by elution with $CHCl_3$ to afford 19 mg of a yellowish syrup (**9**); IR ($CHCl_3$) 2230 (CN) and 1642 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2·52 (3H, s, $COCH_3$), 6·84 (1H, s, C_{10}–H).

Acetylation of **10**. A mixture of **10** (10 mg), 0·5 ml of $(Ac)_2O$, and 2 drops of pyridine was set aside overnight at room temp. The mixture was poured into an excess of water, which was extracted with $CHCl_3$. The extract was dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was subjected to chromatography on 2 g of silica gel. Elution with $CHCl_3$–MeOH (v/v 99:1) gave 10 mg of diacetate (**11**); IR ($CHCl_3$) 2250 (CN), 1760 and 1650 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2·32 and 2·54 (each 3H, s, $COCH_3$), 6·95 and 7·0 (each 1H, s, C_7–H or C_{10}–H). Mass (*m/e*) 376 (M^+), 334 ($M^+ - C_2H_2O$), 292 ($M^+ - 2 \times C_2H_2O$) 175 ($C_{10}H_9NO_2$), and 117 (C_8H_7N).

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