THE FIRST SYNTHESES OF ANTIVIRAL, CYTOTOXIC 6-CYANO-5-METHOXY- AND -12-METHYLINDOLO[2,3-*a*]CARBAZOLES, AND RELATED INDOLO[2,3-*a*]CARBAZOLES FROM INDIGO[1]

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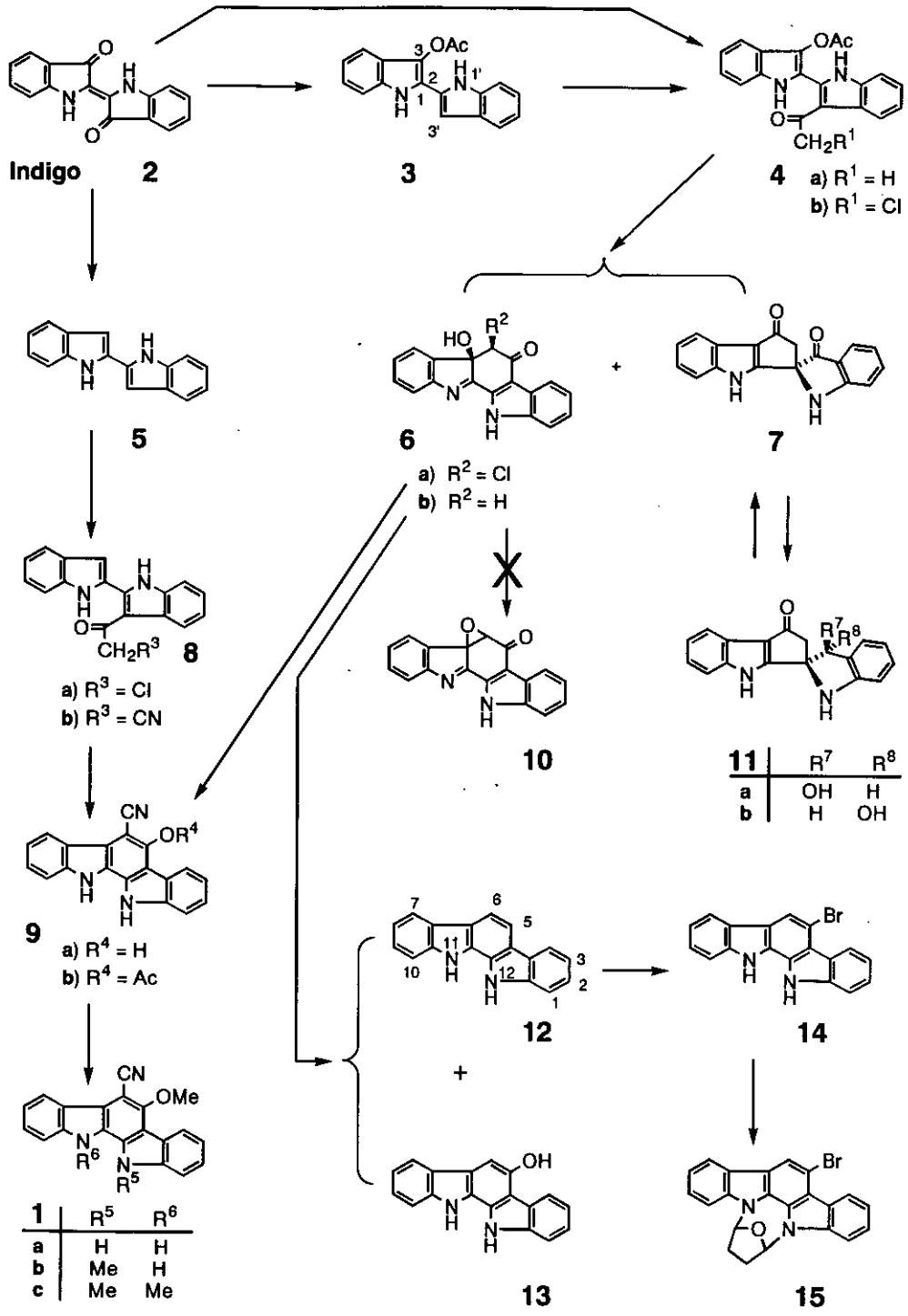
Abstract ——————The first simple total syntheses of 6-cyano-5-methoxy- (**1a**) and -12-methylindolo[2,3-*a*]carbazole (**1b**) are attained from indigo (**2**) in only five and six steps, respectively. Preparations of 5-hydroxy- (**13**), 5-bromoindolo[2,3-*a*]carbazole (**14**), and a novel spiro compound (**7**) are also included.

Indolo[2,3-*a*]carbazoles[2] such as staurosporine,[2a] tjipanazoles,[2b] BE-13793C,[2c] etc. have attracted much attention from the point of developing medicines for psoriasis, hypertension, cancer, and HIV-infection. As members of this interesting class of compounds, Moore and co-workers[3] isolated cytotoxic and antiviral 6-cyano-5-methoxy- (**1a**, Scheme 1) and -12-methylindolo[2,3-*a*]carbazole (**1b**) from blue-green alga *Nostoc sphaericum* (strain EX-5-1) and determined their structures. In our synthetic project for finding a new biologically active indolo[2,3-*a*]carbazoles,[4] we have been interested in **1a** and **1b**. Now, we wish to report the first and simple total syntheses of **1a** and **1b**, and the related useful building blocks, such as 5-hydroxy- (**13**) and 5-bromoindolo[2,3-*a*]carbazole (**14**), for various derivatives.

In the previous papers,[4] we have established a convenient one step and selective syntheses of 3-acetoxy- (**3**), -3'-acetyl-2,2'-biindolyl (**4a**), 2,2'-biindolyl (**5**), or 1-acetyl-2,3-dihydro-2,2'-biindolyl from indigo (**2**) in 88, 49, 46, and 82% yields, respectively. To meet our end, **3** reacted with chloroacetyl chloride to afford 3-acetoxy-3'-chloroacetyl-2,2'-biindolyl (**4b**) in 90% yield. Subsequent reaction of **4b** with aqueous ammonia in MeOH generated indolo[2,3-*a*]carbazole (**6a**) and a novel spiro compound (**7**) in 54 and 29% yields, respectively. Further treatment of **6a** with NaCN in DMF-H_2O produced 6-cyano-5-hydroxyindolo[2,3-*a*]carbazole (**9a**) in 63% yield. Methylation of **9a** with diazomethane afforded **1a** in

Scheme 1


Indigo
2
3
4
a) R^1 = H
b) R^1 = Cl
5
6
a) R^2 = Cl
b) R^2 = H
7
8
a) R^3 = Cl
b) R^3 = CN
9
a) R^4 = H
b) R^4 = Ac
10
11
12
13
14
15
1
a H H
b Me H
c Me Me
11
a OH H
b H OH

90% yield. Although the methylation of **1a** with MeI and NaH in DMF formed 11,12-dimethyl compound (**1c**) in 73% yield, use of K_2CO_3 instead of NaH discerned the difference in the reactivity of nitrogens at the 11 and 12 positions to produce **1b** as major product in 55% yield together with 34% yield of **1c**. Thus, the first and simple five steps synthesis of **1a** and six steps synthesis of **1b** from **2** were achieved. The spectral data of synthetic samples (**1a** and **1b**) are in good agreement with those of the natural products.[3] The originality rates[5] for **1a** and **1b** are 67 and 57%, respectively.

The compound (**9a**) was alternatively prepared from **5** as follows. Chloroacetylation of **5** gave 87% yield of **8a**, which was then converted to **8b** in 77% yield by the reaction with NaCN in NH_2CHO-MeOH. Subsequent treatment of **8b** with refluxing Ac_2O-AcOH in the presence of 10% Pd/C produced **9b** in 35% yield. Finally, alkaline hydrolysis of **9b** afforded **9a** in 97% yield.

The structure of **6b**, which was obtained in 46% yield upon treatment of **4a** with Na_2CO_3 in DMF, was determined by X-Ray single crystallographic analysis and the results are shown in Figure 1. Although R values (R=0.145, Rw=0.175) are large because the reflection data were collected at room temperature, the skeleton is confirmed unequivocally. The structure of **6a** was determined by comparing its spectral data with those of **6b**. The *cis* stereochemistry of the hydroxy and chloro substituents on **6a** was deduced by the fact that its alkaline treatment did not form the corresponding epoxy compound (**10**). While, the structure of **7** was determined as follows. Reduction of **7** with $NaBH_4$ led to diastereomers (**11a**) and (**11b**) in 82 and 17% yields, respectively. On oxidation with PCC in pyridine, **11a** and **11b** afforded **7** in 42 and 26% yields, respectively, showing that they are stereoisomers at the carbon bearing the hydroxy group. The results of X-Ray single crystallographic analysis of the diastereomer (**11a**), shown in Figure 2, and the above mentioned experimental data finally proved the structures of **7**, **11a**, and **11b**.

Figure 1
ORTEP Drawing of **6b**

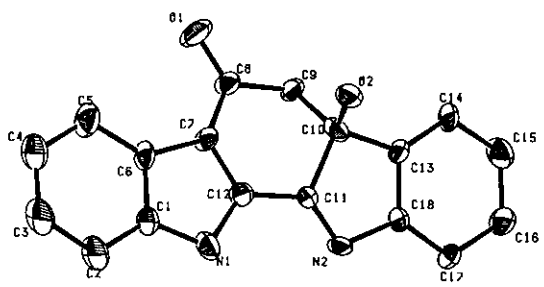
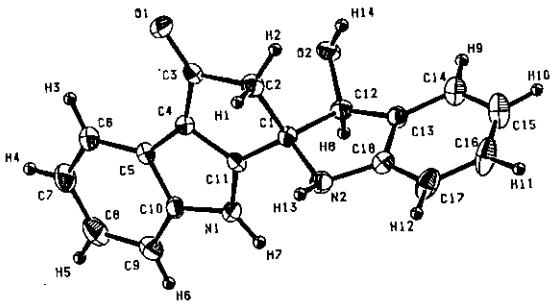


Figure 2
ORTEP Drawing of **11a**



On the other hand, **13** and **14**, useful building blocks for various indolo[2,3-*a*]carbazoles, were obtained as follows. The sequential reaction of **6b** with $NaBH_4$ and then with 2N-HCl provided indolo[2,3-*a*]carbazole (**12**) and its 5-hydroxy derivative[6a] (**13**) in 70 and 12% yields, respectively. Exclusive production of **13** in 79% yield was realized upon treatment of **6a** with Zn-NH_4Cl in MeOH. 5-Bromo derivative[6b] (**14**) was obtained in 69% yield together with 17% yield of recovery by reacting **12** with 1.0 mol of Br_2 in AcOH. Further treatment of **14** with 2,5-dimethoxytetrahydrofuran in AcOEt-trifluoroacetic acid (9:1, v/v) gave 77% yield of **15**.

Based on the present methodology suitable for the preparative scale production of indolo[2,3-*a*]carbazoles from **2**, we are preparing various related derivatives in order to develop new lead compounds.

REFERENCES AND NOTES

1. This is Part 84 of a series entitled "The Chemistry of Indoles". Part 83: F. Yamada, T. Hashizume, and M. Somei, *Heterocycles*, 1998, **47** (No. 1), in press. All new compounds gave satisfactory spectral data and elemental analyses. **1a**: mp >300°C; **1b**: mp 299-301°C; **1c**: mp 200-201°C; **4b**: mp 233-235°C; **6a**: mp 236-238°C (decomp); **6b**: mp 263-264°C (decomp); **7**: mp >300°C; **8a**: mp 166-167°C; **8b**: mp 246-252°C; **9a**: mp >300°C; **9b**: mp >300°C; **11a**: mp 244-245°C (decomp); **11b**: mp 236-237°C (decomp); **12**: mp >300°C; **13**: mp >300°C; **14**: mp 62-64°C; **15**: mp 240-245°C.

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